The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia

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BACKGROUND: Fetal growth restriction is a common complication of preeclampsia. Expectant management for qualifying patients has been found to have acceptable maternal safety while improving neonatal outcomes. Whether fetal growth restriction influences the duration of latency during expectant management of preeclampsia is unknown.

OBJECTIVE: The objective of the study was to determine whether fetal growth restriction is associated with a reduced interval to delivery in women with preeclampsia being expectantly managed prior to 34 weeks.

STUDY DESIGN: We performed a retrospective cohort of singleton, live-born, nonanomalous deliveries at the University of Cincinnati Medical Center between 2008 and 2013. Patients were included in our analysis if they were diagnosed with preeclampsia prior to 34 completed weeks and if the initial management plan was to pursue expectant management beyond administration of steroids for fetal lung maturity. Two study groups were determined based on the presence or absence of fetal growth restriction. Patients were delivered when they developed persistent neurological symptoms, severe hypertension refractory to medical therapy, renal insufficiency, nonreassuring fetal status, pulmonary edema, or hemolysis elevated liver low platelet syndrome or when they reached 37 weeks if they remained stable without any other indication for delivery. Our primary outcome was the interval from diagnosis of preeclampsia to delivery, measured in days. Secondary outcomes included indications for delivery, rates of induction and cesarean delivery, development of severe morbidities of preeclampsia, and select neonatal outcomes. We performed a multivariate logistic regression analysis comparing those with fetal growth restriction with those with normally grown fetuses to determine whether there is an association between fetal growth restriction and a shortened interval to delivery, neonatal intensive care unit admission, prolonged neonatal stay, and neonatal mortality.

RESULTS: A total of 851 patients met the criteria for preeclampsia, of which 199 met inclusion criteria, 139 (69%) with normal growth, and 60 (31%) with fetal growth restriction. Interval to delivery was significantly shorter in women with fetal growth restriction, median (interquartile range) of 3 (1.6) days vs normal growth, 5 (2.12) days, $P < .001$. The association between fetal growth restriction and latency less than 7 days remained significant, even after post hoc analysis controlling for confounding variables (adjusted odds ratio, 1.66 [95% confidence interval, 1.12−2.47]). There were no differences in the development of severe disease (85.9 vs 91.7%, $P = .26$), need for intravenous antihypertensive medications (47.1 vs 46.7%, $P = .96$), and the development of severe complications of preeclampsia (51.1 vs 42.9%, $P = .30$) in normally grown and growth-restricted fetuses, respectively. Fewer women with fetal growth restriction attained their scheduled delivery date, 3 of 60 (5.0%), compared with normally grown fetuses,12 of 139 (15.7%), $P = .03$. Admission to the neonatal intensive care unit, neonatal length of stay, and neonatal mortality were higher when there was fetal growth restriction; however, after a logistic regression analysis, these associations were no longer significant.

CONCLUSION: Fetal growth restriction is associated with a shortened interval to delivery in women undergoing expectant management of preeclampsia when disease is diagnosed prior to 34 weeks. These data may be helpful in counseling patients regarding the expected duration of pregnancy, guiding decision making regarding administration of steroids and determining the need for maternal transport.

Key words: expectant management of preeclampsia, fetal growth restriction, preeclampsia

Preeclampsia and fetal growth restriction (FGR) are common complications of pregnancy. Preeclampsia complicates approximately 6-8% of all pregnancies.[1,2] Additionally, the rate of preeclampsia is expected to rise, given increasing rates of pregnancies complicated by advanced maternal age, obesity, and multiple gestation.[3]

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Preeclampsia is associated with a number of adverse maternal and fetal-neonatal outcomes and remains a leading cause of maternal death in the United States.[4] Maternal complications include abruption, disseminated intravascular coagulopathy, eclampsia, acute renal failure, liver hemorrhage and failure, intracranial hemorrhage, hemolysis elevated liver enzymes, and low platelet (HELLP) syndrome, pulmonary edema, and death.[5,6] Fetal-neonatal complications include preterm delivery, FGR, hypoxia with subsequent acidosis, neurological injury, and death.[5]

In a recent study of pregnancies complicated by preeclampsia, the relative risk of stillbirth was 8- to 6-fold higher at 26 weeks and 7-fold higher at 34 weeks' gestation.[7] Because delivery is the only known definitive management of preeclampsia, when patients have early-onset preeclampsia, the risks of expectant management must be balanced with the risks of preterm delivery.

Historically, delivery was indicated once the diagnosis of preeclampsia was established. However, subsequent studies have demonstrated acceptable maternal safety and improved neonatal outcomes with expectant management of selected patients with preeclampsia.[8,9] Currently in patients less than 34 weeks' gestation with preeclampsia, expectant management is recommended in the

absence of contraindications.[10] The absolute contraindications to expectant management are eclampsia, pulmonary edema, disseminated intravascular coagulopathy, uncontrolled severe hypertension, nonviable fetus, nonreassuring fetal status, or fetal demise.[10]

FGR, as defined in most recent American College of Obstetricians and Gynecologists practice bulletin, is a fetus with an estimated fetal weight (EFW) less than the 10th percentile for gestational age.[11] Thus, by definition FGR occurs in 10% of all pregnancies, but hypertensive disorders in pregnancy including preeclampsia have been shown to substantially increase the risk of FGR with subsequent small-for-gestational-age newborns.[12-15]

The relationship between preeclampsia and FGR is not completely understood and is likely multifactorial, but both are thought to be the end result of placental insufficiency.[11,12] Placental insufficiency and resultant FGR has been reported to be secondary to failed conversion of the spiral arteries, in which failed remodeling at the decidual level of the spiral arteries leads to reduced uteroplacental arterial flow and episodes of irregular placental perfusion.[16,17] Reduced perfusion leads to generation of reactive oxygen species and oxidative stress, a generalized hyperinflammatory state and necrotic disruption of syncytial archtecture.[17] Fetal surveillance is therefore indicated in the setting of preeclampsia to screen for fetal growth restriction.[18] If surveillance studies are suggestive of growth restriction, Doppler velocimetry is recommended.

The development of absent or reversed end-diastolic flow in the umbilical artery is associated with increased risk of perinatal mortality, and these alterations in Doppler measurements often affect delivery planning.[11,19,20] Despite the complicated relationship between growth restriction and hypertensive disorders in pregnancy, there are very limited studies looking at how FGR has an impact on the expectant management of preeclampsia. The aim of this study was to assess the impact FGR has on the latency period during expectant management of all preeclampsia patients diagnosed prior to 34 weeks.

Materials and Methods

We performed a retrospective cohort study of all patients who delivered between January 2008 and January 2013 at the University of Cincinnati Medical Center. The study was approved by local institutional review board. All data were collected from patient charts by trained abstractors from the electronic medical record.

The study was performed prior to the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy[10] guidelines, and therefore, the diagnosis was based on a combination of elevated blood pressures greater than 140/90 mm Hg on at least 2 measures and proteinuria (0.3 g total urinary protein excreted over a 24 hour period). Factors that also were considered in diagnosing preeclampsia and determining severity as well as candidacy for expectant management were presence of neurological symptoms, epigastric pain, the HELLP syndrome, pulmonary edema, and renal compromise. All patients diagnosed with preeclampsia were considered for inclusion in our study.

We excluded multiple pregnancies, given the strong effect this may have on latency. We also excluded anomalous fetuses and stillbirths. We considered only those with a diagnosis prior to 34 weeks, the point in which expectant management is more aggressively pursued. Finally, we included only patients who had a management plan that explicitly stated expectant management was going to be attempted, excluding those who had a plan for delivery upon admission or after completion of the steroid window.

Two study groups were determined based on the presence or absence of fetal growth restriction at the time of diagnosis. Determination of the sonographic estimation of the fetal weight (EFW) was performed by registered sonographers, and the Hadlock 84 formula was used.[21] Patients were considered to have FGR if the estimated fetal weight was less than the 10th percentile.[11]

In addition, patients were included in the FGR study group if they had an isolated abdominal circumference less than the fifth percentile and also had abnormal umbilical artery (UA) Doppler findings, defined as a pulsatility index greater than the 95th percentile or absent/reversed end diastolic flow. This categorization was chosen to best distinguish those fetuses with poor growth secondary to placental insufficiency from constitutionally small fetuses. Doppler of the UA was performed on any patient with an EFW less than the 10th percentile or an abdominal circumference less than the fifth percentile but was not otherwise performed, according to institutional protocol.

Patients admitted with suspected preeclampsia were admitted and treated with magnesium for 24 hours while undergoing evaluation. Patients were given betamethasone to induce fetal lung maturity if they were less than 34 weeks, and rescue steroids were given if they were greater than 2 weeks from an initial course of steroids and under 32 weeks. The majority of patients remained inpatient until delivery once a diagnosis of preeclampsia was made. The decision to proceed forth with delivery was made for either worsening maternal or fetal status at the discretion of the managing obstetrical team, or women were delivered when they reached 37 weeks' gestation.

Our primary outcome was interval to delivery between diagnosis of preeclampsia and delivery (days), measured as a continuous variable. Delivery timing is dictated by departmental protocol but is ultimately at the discretion of the managing physician. Common indications for delivery included attainment of 37 weeks, inability to control blood pressures, persistent neurological symptoms, development of the HELLP syndrome, worsening fetal status, onset of labor, or rupture of membranes.

Secondary outcomes included development of severe morbidities of preeclampsia including the development of severe hypertension, the need for intravenous antihypertensive

medication, and the development of a composite of severe morbidities of preeclampsia that included neurological symptoms, HELLP syndrome, renal insufficiency, pulmonary edema, or eclampsia. In addition, we analyzed the indication for delivery, rate of attempted induction, and rate of cesarean delivery when FGR was present vs absent. Neonatal outcomes evaluated included the rate of neonatal intensive care unit (NICU) admission and neonatal length of stay (days).

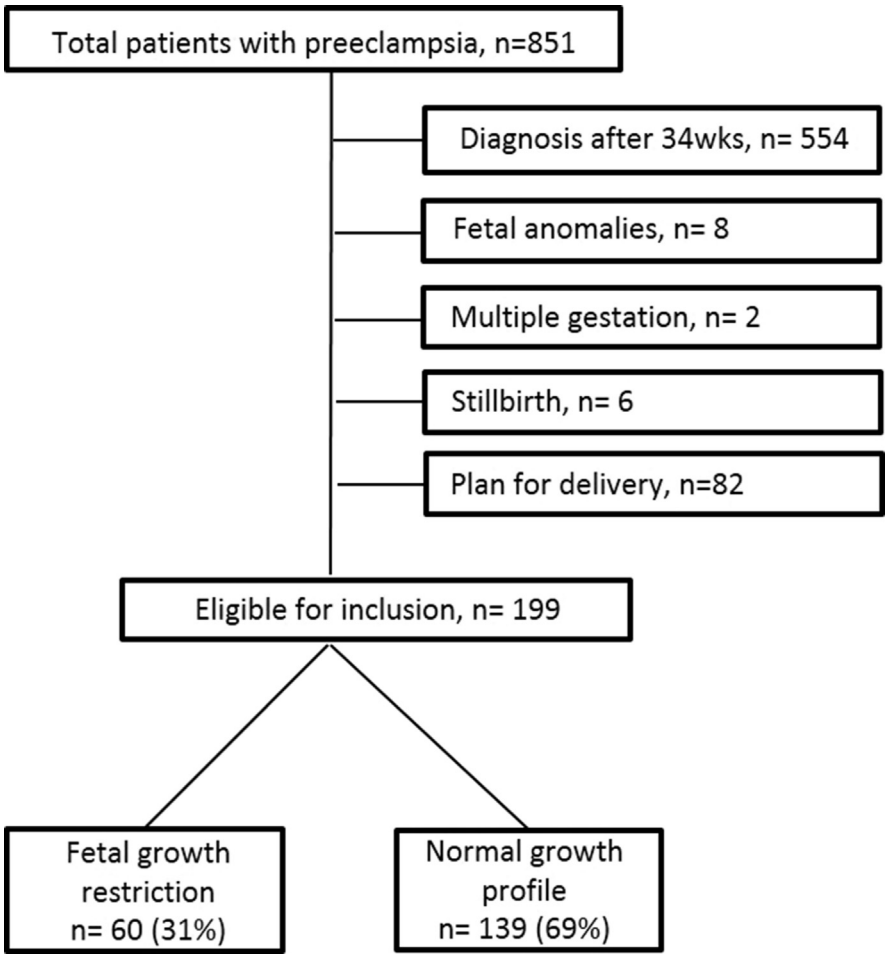
A multivariate logistic regression was performed to estimate the crude odds ratio and the adjusted ORs with 95% confidence intervals after inclusion of pertinent covariates assessing the following categorical outcomes: interval to delivery of less than 1 week, NICU admission, prolonged neonatal hospitalization over 4 days, and neonatal mortality. A stepwise backward regression analysis was used to evaluate the impact of multiple potential confounding variables. After backward elimination maternal race, tobacco use, chronic hypertension, gestational age at delivery, severe preeclampsia, and fetal sex were included in the final regression model.

Study data were collected and managed using Redcap electronic data capture tools posted at the University of Cincinnati.[22] Categorical variables were compared using a χ^2 analysis or a Fisher exact test when any cell in a 2×2 table contained fewer than 10 subjects. Continuous variables were compared using a Student t test when normally distributed, a Wilcoxon rank sum when nonnormally distributed. Data normally distributed are presented as mean ± SD, nonnormally distributed data are presented at median (25th and 75th percentile). A two-sided value of $P < .05$ or 95% confidence interval not inclusive of the null value 1.0 was considered statistically significant. All data analyses were performed using NCSS 8 statistical software (release 8; NCSS LLC, Kaysville, UT).

Results

Of 851 patients with preeclampsia, 199 met inclusion criteria and were included in the analyses. The most common reasons for exclusion were a diagnosis beyond 34 weeks (n = 554), multiple pregnancy (n = 2), major fetal anomaly (n = 8), stillbirth (n = 6), and plan for immediate delivery or delivery once the patient received betamethasone to induce fetal lung maturity (n = 82). Of the 199 patients included, 60 of the eligible patients (31%) had FGR and 139 (69%) had an ultrasound demonstrating a normal growth profile (Figure 1).

FIGURE 1
Flow chart of patients included/excluded in our analysis



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In the FGR study group, we included 16 patients with an abdominal circumference less than the third percentile and 2 with an abdominal circumference at the fourth percentile, all of which had an abnormal UA Doppler. Demographics, preeclampsia characteristics, delivery outcomes, and neonatal outcomes for eligible patients are described in Table 1. Maternal demographics in regard to age, race, tobacco use, and history of chronic hypertension were similar between the 2 groups but differed in parity and body mass index (BMI). The group of patients without FGR on average had a higher BMI than those with FGR, with an average BMI of 33.1% and 30.1%, respectively ($P = .04$).

Additionally, women with fetal growth restriction were diagnosed with preeclampsia at earlier gestational ages, median (interquartile range [IQR]), 28 (25–31) weeks vs those without fetal growth restriction 32 (29–33) weeks ($P < .001$). No differences in presence of severe disease, major complications, or need for intravenous antihypertensive

TABLE 1
Demographic and medical complications and obstetrical outcomes by study group

Variables	No FGR (n = 139)	FGR (n = 60)	*P* value
Demographic data			
Maternal age, mean (SD)	28.1 ± 6.5	27.0 ± 7.7	.34
Parity, median (IQR)	1 (0–3)	(0–0)	< .001
Race, n, %			.53
White	54 (64.3)	30 (35.7)	
Black	75 (64.3)	27 (26.5)	
Hispanic	4 (66.7)	2 (33.3)	
Other	3 (75.0)	1 (25.0)	
Tobacco use, n, %	27 (19.9)	16 (26.7)	.29
Body mass index, kg/m^2, mean (SD)	33.1 ± 10.0	30.1 ± 7.9	.04
Chronic hypertension, n, %	40 (29.4)	11 (18.3)	.10
Preeclampsia characteristics			
Gestational age at diagnosis, wks, median (IQR)	32 (29–33)	28 (25–31)	< .001
Severe preeclampsia, n, %	116 (85.9)	55 (91.7)	.26
Composite of major complication, n, %	67 (51.1)	24 (42.9)	.30
Need for intravenous antihypertensive medication, n, %	64 (47.1)	28 (46.7)	.96
Delivery outcomes			
Gestational age at delivery, wks, median (IQR)	33 (30–34)	29 (26–32)	< .001
Interval to delivery, d, median (IQR)	5 (2–12)	3 (1–6)	< .001
Indication for delivery, n, %			
Reached scheduled delivery date	21 (15.7)	3 (5.0)	.03
Development of severe preeclampsia	80 (58.8)	29 (48.3)	.17
Neurological symptoms	51 (37.5)	10 (16.7)	.003
HELLP syndrome	21 (15.4)	8 (13.3)	.70
Nonreassuring fetal status	23 (16.9)	35 (58.3)	< .001
Induction, n, %	69 (50.7)	19 (31.7)	.01
Cesarean delivery, n, %	86 (63.2)	48 (80.0)	.02
Neonatal outcomes			
Birth weight, g, mean (SD)	1810 ± 736	992 ± 437	< .001
Small for gestational age, n, %	26 (19.1)	37 (61.7)	< .001
Neonatal mortality, n, %	6 (4.4)	8 (13.3)	.02
Neonatal intensive care unit admission, n, %	106 (78.5)	58 (96.7)	.001
Neonatal length of stay, d, median (IQR)	14 (10–18)	44 (27–64)	< .001

FGR, fetal growth restriction.
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medications were seen between the 2 groups.

Our primary outcome, latency until delivery, was significantly shorter in women with FGR, median (IQR) of 3 (1–6) days vs those with normal EFW, 5 (2–12) days ($P < .001$; Figure 2). Fewer women with FGR were managed until their scheduled date of delivery, 3 (5.0%) vs those without FGR, 21 (15.7%) ($P = .03$). In the presence of FGR, delivery was more likely for nonreassuring fetal status, 35 (58.3%) vs 23 (16.9%). There were no differences in deliveries secondary to development of severe preeclampsia or the HELLP syndrome.

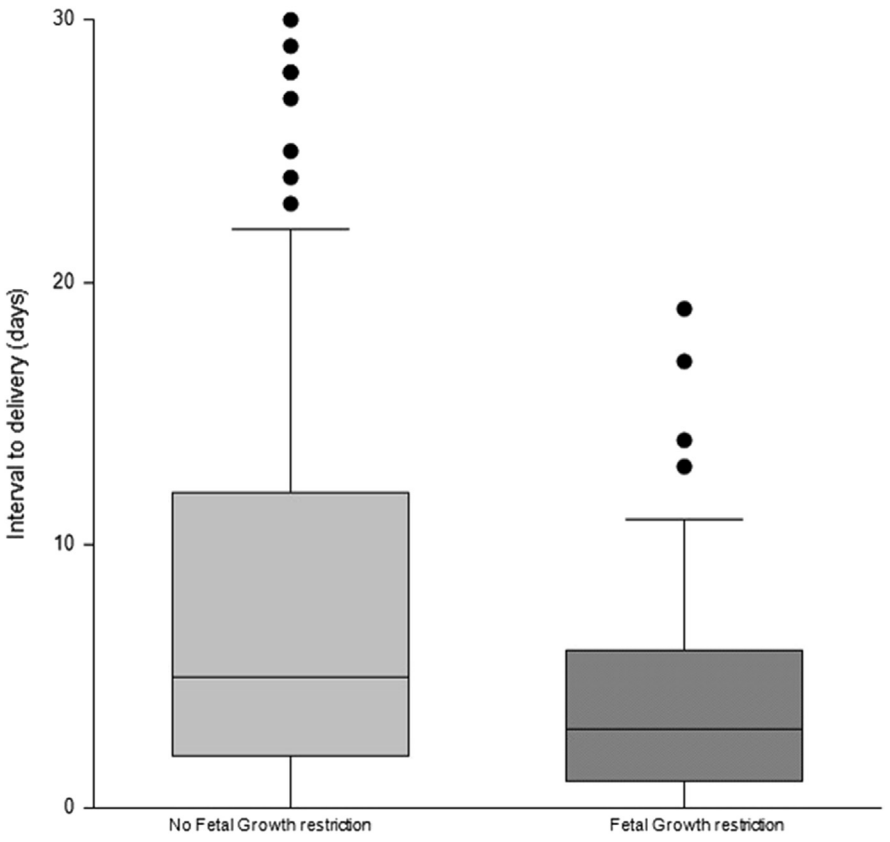
When the decision for delivery was made, patients in the FGR group were less likely to be induced (31.7% vs 50.7%, $P = .01$) and more likely to have a cesarean delivery (80.0% vs 63.2%, $P = .02$). After delivery, growth-restricted fetuses had significantly lower birthweight (992 g ± 437 vs 1810 g ± 736, $P < .001$), a higher percentage of small-for-gestational-age neonates (61.7% vs 19.1%, $P < .001$), higher neonatal mortality (13.3% vs 4.4%, $P < .02$), higher rates of NICU admissions (96.7% vs 78.5%, $P < .001$), and longer median length of stay in the NICU, median (IQR) of 44 (27–64) days vs 14 (10–18) days ($P < .001$).

A post hoc logistic regression analysis controlling for confounding variables including race, tobacco use, chronic hypertension, gestational age at delivery, severe preeclampsia, and fetal sex was performed. The association between fetal growth restriction and latency less than 7 days remained significant, adjusted OR 1.66 (95% CI 1.12–2.47). However, the associations with adverse neonatal outcomes were no longer significant (Table 2).

Comment

In this retrospective cohort over a 5 year period of time at a single academic health center, we have shown that the latency period from diagnosis to delivery in women with concurrent preeclampsia less than 34 weeks and FGR is significantly shorter than in women with preeclampsia with normally grown fetuses.

FIGURE 2
Distribution of interval to delivery (days) in pregnancies with and without FGR



Box plot of distribution of interval to delivery (days) in pregnancies with and without fetal growth restriction. The median is demarcated, the box parameters represent the 25th and 75th percentiles, with tails extending to the 10th and 90th percentiles with outliers demonstrated ($P < .001$).

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This finding could improve counseling with regard to management, for example, lowering the threshold for maternal transfer when indicated.

When FGR was present, the median interval until delivery was only 3 days and 79.3% of patients were delivered within 7 days. It is well established that pregnancies less than 34 weeks' gestation benefit from antenatal corticosteroid administration and maternal transport to a tertiary care center.[23-25]

Additionally, it has been shown that antenatal corticosteroids have maximum benefit when given 1−7 days prior to birth,[26] and therefore, in the setting of concomitant FGR, there should be no delay in administration, even when there is maternal stability or FGR is the heralding sign of disease. Additionally, pregnancies complicated by FGR were less likely to reach a scheduled date of delivery (37 weeks), and they were more likely to be delivered for nonreassuring fetal status as well as to be delivered by cesarean delivery.

These results are likely related to more pronounced underlying placental dysfunction/insufficiency when preeclampsia is complicated by FGR. An initial analysis revealed that the pregnancies complicated by both preeclampsia and FGR had lower birthweights, a higher percentage of small-for-gestational-age infants, a higher rate of NICU admission, and a longer stay in the NICU. However, a post hoc analysis was performed and these outcomes were no longer significant.

To our knowledge, one other study has evaluated whether fetal growth restriction has any impact on duration of expectant management of patients with preeclampsia diagnosed at less than 34 weeks' gestation.[27] This study, published by Chammas et al[27] in 2000, was an observational study looking at the frequency of fetal deterioration

TABLE 2
Logistic regression analysis of study outcomes

Outcome measure	Normal growth (referent) (n = 139)	FGR (n = 60)	OR	95% CI	aOR	95% CI
Interval of < 1 wks, n, %	79 (58.1)	47 (79.3)	1.62	1.14−2.29	1.66	1.12−2.47
Neonatal care unit admission	106 (78.5)	58 (96.7)	2.81	1.35−5.87	1.74	0.80−3.78
Neonatal length of stay > 4 d, n, %	94 (72.9)	45 (93.8)	2.36	1.28−4.37	1.51	0.76−2.97
Neonatal mortality, n, %	6 (4.4)	8 (13.3)	1.82	1.05−3.17	1.06	0.53−2.13

Regression model maternal race, tobacco use, underlying chronic hypertension, gestational age at delivery, severe preeclampsia, fetal sex, odds ratio, adjusted odds ratio, and 95% confidence intervals are presented.

aOR, adjusted odds ratio; *CI*, confidence interval; *FGR*, fetal growth restriction; *OR*, odds ratio.

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during expected management of severe preeclampsia less than 34 weeks and whether the presence of fetal growth restriction altered the admission-to-delivery interval.

In the study by Chammas et al, a total of 65 patients with severe preeclampsia less than 34 weeks were identified. All patients were first admitted for a 24 hour observation period, started on magnesium, given betamethasone, and placed on continuous fetal heart rate monitoring. During the initial 24 hour observation period, 18 patients (28%) were deemed too unstable for further expectant management and delivered and excluded from the analysis. In the remaining 47 patients who were expectantly managed, 14 (29.8%) had FGR and 33 (70.2%) did not have FGR. The presence of FGR was found to have a significantly shorter admission-to-delivery interval (3.1 $\pm$ 2.1 days) than those pregnancies not complicated by FGR (6.6 $\pm$ 6.1 days, $P < .05$) and 87.5% of patients with FGR were delivered within 7 days. No differences in neonatal outcomes were seen between the 2 groups.

The results in the study by Chammas et al[27] are very similar to the findings in our study. Both studies found that patients with preeclampsia and concurrent FGR had shorter latency periods (approximately 3 days in both studies) during attempted expectant management and were likely to be delivered within 1 week of admission. Although these studies are similar in design, there are some differences. The first notable difference is that in our study we included all patients with preeclampsia, not just patients with severe disease. In addition, we included only patients who had a management plan that explicitly stated expectant management beyond a steroid window was going to be attempted, excluding those who had a plan for delivery upon admission or after completion of the steroid window.

The birthweights reported by Chammas et al[27] in both those with FGR and those without were very similar, and this may have contributed to their findings. In addition, our study included 199 patients, including 60 with FGR, compared with 47 women, 14 of which had FGR.

The strengths of this study include a relatively robust sample size for patients with both preeclampsia and FGR, an accurate assessment of EFW performed by registered sonographers in a dedicated obstetrical unit, no loss to follow-up, and a standardized protocol-based diagnosis and management of preeclampsia at a single group academic practice. In addition, we used the medical record to obtain data, thereby increasing the accuracy of the data collected and enabling us to determine original management intentions, etc.

Although our study has many strengths, it also has limitations. The first limitation is that our study is a retrospective cohort study and therefore inherently has selection bias. Although FGR is not a factor considered in delivery algorithms in our preeclampsia protocol, whether managing medical teams lowered their threshold for delivery based on coexistent FGR cannot be determined by our study design and would require blinding of the managing team to the fetal growth profile, which is unlikely to be performed. Second, the interval to delivery was calculated from the day of admission to the day of delivery, and women may have presented at varying stages of disease. However, it would seem women with FGR may have been detected earlier, given the perceivable fetal effect, and therefore, one would expect that this would have lengthened the interval to delivery in these patients, and our data demonstrated a shortening.

This study provides evidence that FGR is associated with a shorter interval to delivery in patients undergoing expectant management of preeclampsia when the disease is diagnosed prior to 34 weeks' gestation. These data could be used to more accurately and effectively counsel families regarding expectations for delaying delivery as well as in decision making regarding betamethasone administration and maternal transport when indicated. ■

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Study data were collected and managed with REDCap software (Research Electronic Data Capture), which is hosted at Cincinnati Children's Hospital Medical Center under the Center for Clinical and Translational Science and Training grant UL1-RR026314-01 NCRR/NIH. REDCap is a secure, web-based application that was designed to support data capture for research studies to provide the following: (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources.

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