

Research Article

Clinical and Ultrasonographic Parameters Associated with Poor Perinatal Outcomes in Fetuses with Fetal Growth Restriction

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Abstract

Objectives: to investigate the association between various clinical and ultrasonographic parameters and perinatal outcomes in cases of FGR, thereby enabling the assessment of FGR severity during the prenatal period and providing prognostic information regarding perinatal outcomes.

Method: This retrospective cohort study was conducted at Dr. Cipto Mangunkusumo General Hospital (RSCM), a tertiary referral hospital in Indonesia. Retrospective data were collected from January 2021 to December 2024 through medical record review. The study population consisted of pregnant women diagnosed with FGR, with a minimum gestational age of 28 weeks at delivery, who met the inclusion and exclusion criteria. Independent variables included a range of clinical and ultrasonographic parameters, while the dependent variable was adverse perinatal outcomes.

Results: Four hundred and eight pregnant women diagnosed with FGR were included in the study. Of these, 224 cases resulted in adverse perinatal outcomes. Multivariate analysis identified several factors significantly associated with adverse outcomes. These included preeclampsia with severe features [OR 1.83; 95% CI: 1.05–3.19], estimated fetal weight (EFW) below the 3rd percentile [OR 2.50; 95% CI: 1.40–4.46], absent or reversed end-diastolic flow (AREDF) in the umbilical artery [OR 11.93; 95% CI: 2.62–54.30], abnormal cerebroplacental ratio (CPR) [OR 1.87; 95% CI: 1.06–3.28], oligohydramnios [OR 1.81; 95% CI: 1.05–3.12], gestational age at delivery between 28 and <32 weeks [OR 69.54; 95% CI: 18.46–261.94], and gestational age between 32 and <37 weeks [OR 3.53; 95% CI: 1.92–6.49].

Conclusion: Several clinical and ultrasonographic parameters in FGR cases – which are preeclampsia with severe features, estimated fetal weight below the 3rd percentile, AREDF in umbilical artery, abnormal CPR, oligohydramnios and gestational age at delivery – showed a significant association with poor perinatal outcomes.

Keywords: fetal growth restriction; perinatal outcomes; ultrasonography.

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INTRODUCTION

Fetal Growth Restriction (FGR) is a condition in which the fetus fails to reach its biological growth potential.^{1,2} This failure can occur for various reasons related to maternal, fetal, and placental factors.³ Despite the diverse underlying causes, FGR often converges on a common final pathway characterized by suboptimal fetal nutrition and impaired uteroplacental perfusion.^{3,4} FGR is estimated to affect approximately 7–15% of all pregnancies and represents a significant contributor to perinatal morbidity and mortality. Mortality rates associated with FGR can reach up to 12% during the fetal period and 8% during the neonatal period.⁵

One of the major challenges in the clinical management of FGR is differentiating a constitutionally small fetus from one with pathologically restricted growth and an increased risk of adverse perinatal outcomes.⁶ Infants affected by FGR are more likely to experience unfavorable perinatal outcomes, including neonatal complications associated with hypoxic conditions, such as Hypoxic-Ischemic Encephalopathy (HIE), Necrotizing Enterocolitis (NEC), Periventricular Leukomalacia (PVL), and neonatal mortality.⁷ The severity of FGR plays a crucial role in determining these outcomes, with more severe cases associated with poorer prognoses.^{6,7} Therefore, accurate assessment of FGR severity during the antenatal period using various clinical and ultrasonographic parameters is essential, particularly for informing decisions regarding the optimal timing of delivery.

Various clinical indicators during pregnancy have been associated with FGR and adverse perinatal outcomes. In addition to clinical parameters, numerous studies have explored the utility of ultrasonographic parameters to improve the identification of fetuses with growth restriction who are at greater risk of perinatal morbidity and mortality.⁸ However, international consensus remains variable regarding the most appropriate Doppler indices for monitoring FGR and guiding decisions on the timing of delivery.⁹ FGR is one of the obstetric conditions associated with substantial variability in clinical practice. This variation arises from multiple factors, including limited high-quality evidence, differences in the risks associated with preterm birth across gestational ages, and the complexity of integrating multiple clinical and ultrasonographic indices to assess fetal compromise.¹⁰

Neonates with birth weights below the 10th percentile are at increased risk of severe acidosis at birth, low 5-minute Apgar scores, and admission to the Neonatal Intensive Care Unit (NICU).⁷ Prematurity may further exacerbate the risk of adverse outcomes in cases of FGR. Beyond its immediate perinatal consequences, FGR has been implicated in long-term metabolic programming, predisposing affected individuals to metabolic syndrome and cardiovascular and endocrine disorders that may persist into childhood and adolescence.^{11–14} Furthermore, evidence indicates an association between FGR and long-term neurodevelopmental impairments, including a 20–40% reduction in cognitive and learning abilities by school age.^{15–18}

Insufficient maternal nutrition has been shown to adversely affect fetal growth.¹⁹ Maternal dietary patterns are closely linked to the risks of preterm birth and the occurrence of Small-for-Gestational-Age (SGA) infants.²⁰ Research indicates that gestational weight gain below the thresholds recommended by the Institute of Medicine (IOM) is significantly associated with an increased incidence of SGA (OR, 1.53; 95% CI, 1.44–1.64), with the strongest association observed among women who were underweight before pregnancy (OR, 1.89; 95% CI, 1.67–2.14).²¹ Inadequate gestational weight gain has also been associated with increased risks of FGR (OR, 1.61; 95% CI, 1.14–2.27), low birth weight (OR, 2.44; 95% CI, 1.85–3.21), and preterm birth (OR, 2.35; 95% CI, 1.81–3.05), potentially contributing to suboptimal perinatal outcomes.²²

Anemia is a common complication during pregnancy and has been associated with increased maternal and perinatal morbidity. Specifically, third-trimester anemia, defined as a hemoglobin level below 11 g/dL, or anemia diagnosed prior to delivery is associated with increased risks of preterm birth, small-for-gestational-age (SGA) infants, low 5-minute Apgar scores, and neonatal mortality.²³ The likelihood of SGA increases with the severity of anemia.²⁴ Another important clinical factor influencing perinatal outcomes in cases of FGR is the coexistence of severe preeclampsia. Compared with FGR without preeclampsia with severe features, FGR complicated by preeclampsia with severe features is associated with significantly higher risks of preterm delivery, prolonged NICU admission exceeding seven days, and neonatal death.²⁵

Birth weight below the 3rd percentile is widely recognized as an indicator of more severe FGR

and is strongly associated with adverse perinatal outcomes.²⁶ Additionally, abnormal findings on umbilical artery Doppler assessment have been shown to predict poorer perinatal outcomes.²⁷ The Society for Maternal-Fetal Medicine (SMFM) endorses the use of umbilical artery Doppler studies for the surveillance and management of FGR.⁶ However, SMFM does not recommend the routine use of Doppler assessments of the ductus venosus, Middle Cerebral Artery (MCA), or uterine artery in the clinical management of FGR.⁶ In contrast, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) highlights the role of umbilical artery and ductus venosus Doppler evaluations in monitoring early-onset FGR and advocates the use of MCA Doppler and/or the cerebroplacental ratio (CPR) in late-onset FGR to aid in predicting fetal compromise.^{9,10}

Amniotic fluid volume assessment is another standard component of fetal well-being evaluation.²⁸ Evidence from one study suggests that a combination of the umbilicocerebral ratio (UCR) and amniotic fluid volume has greater predictive value for adverse perinatal outcomes in term FGR cases than other ultrasonographic markers.²⁸ However, another study found that reduced amniotic fluid volume alone does not independently increase the risk of adverse outcomes in FGR cases. Nonetheless, oligohydramnios may serve as a significant predictor of clinically relevant perinatal complications when accompanied by severe growth restriction, particularly when fetal weight is below the 3rd percentile.⁷ Despite these findings, evidence remains insufficient regarding the role of amniotic fluid volume assessment in the management of FGR and in determining the timing of delivery.⁶

Determining the severity of FGR and its association with perinatal outcomes is essential for guiding the timing of delivery and predicting neonatal outcomes. However, further evidence is needed, particularly from local populations, which may provide important insights for clinical practice. At Dr. Cipto Mangunkusumo National General Hospital (RSCM), Jakarta, a tertiary referral hospital in Indonesia, no prior study has evaluated the association between clinical and ultrasonographic parameters in FGR cases and subsequent perinatal outcomes. Such data may be useful for parental counseling and clinical decision-making. Therefore, this study was undertaken at our institution to evaluate the association between clinical and ultrasonographic

parameters and perinatal outcomes in FGR cases.

METHODS

This observational analytic study used a retrospective cohort design to examine the association between various clinical and ultrasonographic parameters and perinatal outcomes in cases of fetal growth restriction (FGR). The study was conducted at Dr. Cipto Mangunkusumo General Hospital (RSCM) through a retrospective review of medical records over a four-year period, from January 2021 to December 2024. The accessible population consisted of pregnant women diagnosed with FGR who received antenatal care and delivered at RSCM during the study period, along with their newborns. The inclusion criteria were singleton, live intrauterine pregnancies with intact amniotic membranes; Estimated Fetal Weight (EFW) or Abdominal Circumference (AC) below the 10th percentile according to the Hadlock criteria on ultrasonographic assessment²⁹; gestational age at delivery of at least 28 weeks, determined based on the last menstrual period and/or first-trimester crown-rump length measurement; and at least one ultrasonographic evaluation conducted at the RSCM Maternal-Fetal Medicine (MFM) Clinic, with delivery occurring within 7 days of the last ultrasound examination. Fetuses with congenital anomalies or confirmed chromosomal abnormalities, pregnancies complicated by intrauterine infections, and pregnancies with maternal uterine malformations were excluded. Based on the sample size calculation, assuming a 5% type I error and 80% statistical power, a minimum of 386 subjects was required for the study.

Maternal data were extracted from medical records and included maternal age, parity, pre-pregnancy body mass index (BMI), gestational weight gain, available hematological and urinalysis results, maternal comorbidities, gestational age at the first antenatal visit, gestational age at FGR diagnosis, gestational age at delivery, mode of delivery, indication for cesarean section, cardiotocography (CTG) findings, administration of corticosteroids for fetal lung maturation, and findings from ultrasound examinations conducted at the RSCM MFM Clinic. Ultrasound data included fetal biometry, EFW, Doppler studies, and amniotic fluid volume. These ultrasound assessments were performed between January 2021 and December

2024 by either board-certified obstetricians and gynecologists with an MFM subspecialty or obstetricians and gynecologists undergoing MFM subspecialty training, using GE Voluson E8® or GE Voluson E10® ultrasound machines. Neonatal data were obtained from neonatal medical records and included gestational age at birth, birth weight, sex, Apgar scores, neonatal unit admission, neonatal diagnoses and morbidities, including respiratory distress, HIE, NEC, PVL, IVH, and early-onset neonatal sepsis (EONS), with corresponding culture results, as well as mortality data, when applicable.

The independent variables consisted of clinical parameters, including maternal gestational weight gain, the presence of anemia, and preeclampsia with severe features, and ultrasonographic parameters, including EFW, fetal AC, Doppler indices of the Umbilical Artery (UA), Middle Cerebral Artery (MCA), and ductus venosus, Cerebroplacental Ratio (CPR), and amniotic fluid volume. The dependent variable was adverse perinatal outcome. FGR was defined as an EFW or fetal AC below the 10th percentile for gestational age based on ultrasonographic assessment.⁶ Adverse perinatal outcome was defined as the presence of at least one of the following adverse neonatal events: severe respiratory distress, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), hypoxic-ischemic encephalopathy (HIE), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), early-onset neonatal sepsis, or neonatal death. Maternal gestational weight gain was classified according to the Institute of Medicine (IOM) guidelines based on pre-pregnancy BMI.³⁰ Anemia was defined as a maternal hemoglobin level <11 g/dL in the third trimester or before delivery. Preeclampsia with severe features was diagnosed according to the Indonesian National Guidelines for Medical Services on the Diagnosis and Management of Preeclampsia.³¹ Abnormal umbilical artery (UA) Doppler findings were defined as a pulsatility index (PI) >95th percentile, absent end-diastolic flow (AEDF), or reversed end-diastolic flow (REDF).³² Abnormal middle cerebral artery (MCA) Doppler was defined as a PI <5th percentile.³³ An abnormal CPR was defined as a CPR value (MCA PI/UA PI) <1.³⁴ Ductus venosus Doppler was considered abnormal in the presence of an absent or reversed a-wave. Oligohydramnios was defined as an amniotic fluid index (AFI) below the 5th percentile.³⁵

The administration of corticosteroids for fetal

lung maturation, timing of delivery, and mode of delivery were determined according to local guidelines at RSCM, which were developed with reference to various leading international guidelines.^{6,9} However, because most patients at this hospital were referred from other healthcare facilities throughout Indonesia, the timing of delivery may not have been consistent with these guidelines.

The research data were tabulated using Microsoft Excel® 365 and analyzed using SPSS for Windows version 25.0. The distribution and normality of continuous variables were assessed using the Kolmogorov-Smirnov test because the number of subjects exceeded 50. Normally distributed data were presented as means and standard deviations, whereas non-normally distributed data were presented as medians with minimum and maximum values. Categorical variables were presented as frequencies and percentages. The chi-square or Fisher's exact test was used to compare categorical variables, as appropriate. Logistic regression analysis was performed to assess the association between the independent variables and adverse perinatal outcomes. A p-value <0.05 was considered statistically significant. Variables identified in the bivariate analysis were subsequently included in a multivariate analysis using a backward logistic regression model. The effect of each variable was expressed as an odds ratio (OR) with a 95% confidence interval (CI). The quality of the logistic regression model was assessed using calibration parameters based on the Hosmer-Lemeshow test and discrimination parameters based on the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

ETHICAL CLEARANCE

This study received ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Dr. Cipto Mangunkusumo Hospital, with approval number KET-122/UN2.F1/ETIK/PPM.00.02/2025, dated February 10, 2025.

RESULTS

A total of 408 subjects met the inclusion and exclusion criteria and were included in the final analysis. Among them, 224 subjects (54.9%) experienced adverse perinatal outcomes.

The baseline characteristics of the study

population are presented in Table 1. The median maternal age was 30 years, and anemia was identified in 20.8% of subjects. Preeclampsia with severe features was present in 55.6% of cases, while early-onset FGR was observed in 65.7%. Preterm birth before 37 weeks of gestation occurred in 70.3% of cases, and cesarean delivery

was performed in 83.8%. The median birth weight was 1,625 g. Severe respiratory distress requiring mechanical ventilation occurred in 25.2% of newborns, while neonatal mortality was observed in 15.2% of cases. Among subjects with adverse perinatal outcomes, 201 (89.7%) were born preterm.

Table 1. Characteristics of the Subjects

Characteristics ^a	Outcome Groups		
	Adverse perinatal outcome ^b (n = 224)	Favorable perinatal outcome (n = 184)	Total (n = 408)
Maternal			
Age (year)	30 (18-45)	29 (16-45)	30 (16-45)
Gravidum	2 (1-12)	2 (1-7)	2 (1-12)
Parity	1 (0-5)	1 (0-4)	1 (0-5)
Pre-pregnancy BMI (kg/m ²)	25.4 ± 5.9	23.9 ± 5.7	24.7 ± 5.8
Weight gain (kg/week)	0.41 ± 0.32	0.37 ± 0.27	0.39 ± 0.29
Hemoglobin (g/dl)	12.4 ± 1.8	11.9 ± 1.5	12.2 ± 1.7
Anemia incidence (n, %)	45 (20.1)	40 (21.7)	85 (20.8)
Preeclampsia with severe features incidence (n, %)	161 (71.9)	66 (35.9)	227 (55.6)
Gestational age when FGR was diagnosed (week)	30 (26-35)	32 (28-37)	31 (26-37)
Gestational age when last examined by US (week)	32 (28-40)	37 (30-40)	34 (28-40)
Gestational age at delivery (week)	32 (28-40)	37 (30-40)	34 (28-40)
The interval from gestational age at FGR diagnosis to delivery (weeks)	2 (0 – 9)	4 (0 – 11)	3 (0-11)
Gestational age group at birth (n, %)			
28 s.d < 32 weeks	94 (42.0)	3 (1.6)	97 (23.8)
32 s.d < 37 weeks	107 (47.8)	83 (45.1)	190 (46.6)
37 s.d 40 weeks	23 (10.3)	98 (53.3)	121 (29.7)
Early onset FGR (n, %)	184 (82.1)	84 (45.7)	268 (65.7)
Delivery by cesarean section (n, %)	204 (91.1)	138 (75.0)	342 (83.8)
Administration of corticosteroids for fetal lung maturation (n, %)	184 (82.1)	74 (40.2)	258 (63.2)
Normal cardiotocograph (n, %)	104 (46.4)	142 (77.2)	246 (60.3)
Umbilical artery PI (n, %)			
Normal	68 (30.4)	124 (67.4)	192 (47.1)
> 95th percentile	64 (28.6)	58 (31.5)	122 (29.9)
AEDF	70 (31.3)	2 (1.1)	72 (17.6)
REDF	22 (9.8)	0	22 (5.4)
CPR	0.87 ± 0.44	1.30 ± 0.50	1.07 ± 0.51
AFI (cm)	6.5 (0.2 – 27.0)	8.6 (0.6 – 24.0)	7.6 (0.2 – 27.0)
EFW (gram)	1229 (518 – 2810)	2115 (959 – 3000)	1653 (518 – 3000)
Fetal			
Birth weight (gram)	1250 (550 – 2850)	2110 (1090 – 2880)	1625 (550 – 2880)
Male gender at birth (n,%)	120 (53.6)	97 (52.7)	217 (53.2)
Apgar score minute 1	6 (1 – 8)	8 (3 – 9)	7 (1 – 9)
Apgar score minute 5	8 (0 – 9)	9 (7 – 10)	8 (0 – 10)
Admission to neonatal unit (n, %)	220 (98.2)	58 (31.5)	278 (68.1)
Severe respiratory distress (n, %)	103 (46.0)	0	103 (25.2)
Bronchopulmonary dysplasia (n, %)	43 (19.2)	0	43 (10.5)
HIE (n, %)	20 (8.9)	0	20 (4.9)
NEC (n, %)	45 (20.1)	0	45 (11.0)
PVL (n, %)	33 (14.7)	0	33 (8.1)
IVH (n, %)	49 (21.9)	0	49 (12.0)
EONS with positive culture (n, %)	38 (17)	0	38 (9.3)
Neonatal mortality (n, %)	62 (27.7)	0	62 (15.2)

^a) Numeric data with normal distribution are presented as mean ± standard deviation. Numeric data with non-normal distribution are presented as median (minimum–maximum). Categorical data are presented as frequency (percentage of total cases per column/outcome)

^b) Adverse perinatal outcome is a composite variable if any of severe respiratory distress, bronchopulmonary dysplasia, HIE, NEC, PVL, IVH, early neonatal sepsis, or neonatal mortality is present.

The bivariate analysis of clinical and ultrasonographic parameters associated with adverse perinatal outcomes. Significant associations were observed for pre-pregnancy BMI, preeclampsia with severe features, early-onset FGR, EFW below the 3rd and 5th percentiles, umbilical artery Doppler abnormalities, MCA

PI below the 5th percentile, abnormal CPR, oligohydramnios, abnormal CTG findings, and gestational age at birth. No significant associations were observed for inadequate or excessive gestational weight gain, anemia, or AC below the 3rd percentile.

Table 2. Bivariate Analysis between Clinical and US Parameters and Perinatal Outcomes

Variable	Adverse Perinatal Outcome n (%)	Favorable Perinatal Outcome n (%)	P-value*	OR (CI 95%)
Total weight gain during pregnancy				
Inadequate	75 (50.3)	74 (49.7)	0.670	0.89 (0.53 – 1.49)
Excessive	98 (60.1)	65 (39.9)	0.272	1.33 (0.80 – 2.21)
Adequate	51 (53.1)	45 (46.9)	-	Ref
BMI pre-pregnancy				
Underweight	25 (43.1)	33 (56.9)	0.307	0.73 (0.40 – 1.33)
Overweight	74 (64.3)	41 (35.7)	0.025	1.74 (1.07 – 2.83)
Obese	39 (59.1)	27 (40.9)	0.258	1.39 (0.78 – 2.48)
Normal	86 (50.9)	83 (49.1)	-	Ref
Anemia				
Yes	45 (52.9)	40 (47.1)	0.683	0.91 (0.56 – 1.46)
No	179 (55.4)	144 (44.6)	-	Ref
Preeclampsia with severe features				
Yes	161 (70.9)	66 (29.1)	<0.001	4.57 (3.01–6.95)
No	63 (34.8)	118 (65.2)	-	Ref
FGR onset				
Early	184 (6.87)	84 (31.3)	<0.001	5.47 (3.49–8.57)
Late	40 (28.6)	100 (71.4)	-	Ref
EFW Percentile < 3				
Yes	183 (65.6)	96 (34.4)	<0.001	4.09 (2.62–6.39)
No	41 (31.8)	88 (68.2)	-	Ref
EFW Percentile < 5				
Yes	200 (59.7)	135 (40.3)	<0.001	3.02 (1.77 – 5.16)
No	24 (32.9)	49 (67.1)	-	Ref
AC Percentile < 3				
Yes	186 (56.7)	142 (43.3)	0.138	1.45 (0.88 – 2.36)
No	38 (47.5)	42 (52.5)	-	Ref
AC Percentile < 5				
Yes	203 (56.7)	155 (43.3)	0.050	1.81 (0.99 – 3.29)
No	21 (42.0)	29 (58.0)	-	Ref
Umbilical artery Doppler				
PI >95 th percentile	64 (52.5)	58 (47.5)	0.003	2.01 (1.26–3.19)
AEDF	92 (97.9)	2 (2.1)	<0.001	83.88 (20.04 – 351.14)
Normal	68 (35.4)	124 (64.6)	-	Ref
AEDF or REDF in umbilical artery				
Yes	92 (97.9)	2 (2.1)	<0.001	63.42 (15.35 – 262.05)
No	132 (42.0)	182 (58.0)	-	Ref
MCA PI <5th percentile				
Yes	139 (65.6)	73 (34.4)	<0.001	2.48 (1.66 – 3.71)
No	85 (43.4)	111 (56.6)	-	Ref
Abnormal CPR (<1)				
Yes	154 (74.4)	53 (25.6)	<0.001	5.44 (3.55 – 8.32)
No	70 (34.8)	131 (65.2)	-	Ref
Oligohydramnios (AFI < percentile 5)				
Yes	136 (63.8)	77 (36.2)	<0.001	2.15 (1.44 – 3.19)
No	88 (45.1)	107 (54.9)	-	Ref
Normal CTG				
Yes	120 (74.1)	42 (25.9)	<0.001	3.90 (2.53 – 6.01)
No	104 (42.3)	142 (57.7)	-	Ref
Gestational age group at birth weeks)				
28 to <32	94 (96.9)	3 (3.1)	<0.001	133.51 (38.79 – 459.48)
32 to <37	107 (56.3)	83 (43.7)	<0.001	5.49 (3.21 – 9.39)
37 to 40	23 (19.0)	98 (81.0)	-	Ref
Total	224 (54.9)	184 (45.1)		

* Chi-square test (for variables with two categories); logistic regression with enter method (for variables with more than two categories)

Variables associated with adverse perinatal outcomes in the bivariate analysis were subsequently entered into the multivariate logistic regression analysis. The results are presented in Table 3. After multivariate analysis, six independent factors were significantly

associated with adverse perinatal outcomes: preeclampsia with severe features, EFW below the 3rd percentile, AREDF in the umbilical artery, abnormal CPR, oligohydramnios, and gestational age at birth of 28 to <32 weeks or 32 to <37 weeks.

Table 3. Multivariate Analysis between Clinical and US Parameters and Perinatal Outcomes

Variable	B	S.E.	P-value*	Adjusted OR (CI 95%)
Preeclampsia with severe features	0.604	0.284	0.033	1.83 (1.05 – 3.19)
Percentile EFW < 3	0.918	0.295	0.002	2.50 (1.40 – 4.46)
AREDF umbilical artery	2.479	0.773	0.001	11.93 (2.62 – 54.30)
Abnormal CPR (< 1)	0.625	0.288	0.030	1.87 (1.06 – 3.28)
Oligohydramnios (AFI < percentile 5)	0.592	0.279	0.034	1.81 (1.05 – 3.12)
Gestational group at birth (weeks)				3.53 (1.92 – 6.49)
28 to <32	4.242	0.677	<0.001	69.54 (18.46 – 261.94)
32 to <37	1.261	0.311	<0.001	3.53 (1.92–6.49)
37 to 40	Ref			Ref
Constant	-2.879	0.382	<0.001	-

*) logistic regression with backward method

Abbreviations: B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; EFW, estimated fetal weight; AREDF, absent or reversed end-diastolic flow; CPR, cerebroplacental ratio; AFI, amniotic fluid index.

The logistic regression equation formula was prepared to determine the prognosis of poor perinatal outcomes. The Hosmer and Lemeshow test showed a p-value of 0.803, meaning that a well-calibrated equation was obtained. Furthermore, an AUC of 0.89 (95% CI 0.86 - 0.92) was obtained for this logistic regression equation, which indicates a significant AUC value with a strong discrimination value.

The logistic regression equation was as follows;
 $y = -2.879 + (0.604 \times \text{preeclampsia with severe features}) + (0.918 \times \text{EFW percentile } <3) + (2.479 \times \text{AREDF}) + (0.625 \times \text{abnormal CPR}) + (0.592 \times \text{oligohydramnios}) + (4.242 \times \text{gestational age at birth 28 to } <32 \text{ weeks}) + (1.261 \times \text{gestational age at birth 32 to } <37 \text{ weeks})$

where y represents the logit (log-odds) of the probability of an adverse perinatal outcome. For each binary variable, a score of 1 was assigned when the condition was present and 0 when it was absent. For gestational age at birth, the 37–40-week group was used as the reference category.

The probability of experiencing an adverse perinatal outcome was calculated using the logistic regression formula;

$$p = \frac{1}{1 + \exp(-y)}$$

y = result of the logistic equation

where **p** represents the predicted probability of an adverse perinatal outcome and y represents the result of the logistic regression equation.

Ductus venosus (DV) Doppler assessments were available for only 59 cases, limiting the inclusion of this variable in the multivariate analysis. Among these cases, seven fetuses exhibited abnormal DV waveforms, including four cases with an absent a-wave and three with a reversed a-wave. Notably, all fetuses with abnormal DV waveforms experienced adverse perinatal outcomes.

Among the total study population, 131 subjects underwent two ultrasound examinations at least 2 weeks apart. Therefore, abdominal circumference growth velocity (ACGV) could be calculated for these subjects. The mean ACGV was 3.5 mm/week in the FGR group with adverse perinatal outcomes and 4.6 mm/week in the FGR group with favorable perinatal outcomes. Although the mean ACGV tended to be higher in the favorable perinatal outcome group, the difference was not statistically significant (p = 0.27).

DISCUSSION

Previous studies have demonstrated that women with a pre-pregnancy body mass index

(BMI) classified as underweight ($<18.5 \text{ kg/m}^2$) are at increased risk of delivering infants with fetal growth restriction (FGR), with an odds ratio of 1.50 (95% CI: 1.37–1.63).³⁶ However, in this study, the mean pre-pregnancy BMI of the subjects was 24.7 kg/m^2 , indicating that most subjects were not classified as underweight before pregnancy. This discrepancy may be attributed to the relatively high proportion of overweight and obese pregnant women in this study, a condition that is often associated with metabolic syndrome and may contribute to the development of hypertensive disorders in pregnancy, including preeclampsia with severe features, which was also frequently observed in this study.

This research was conducted at Dr. Cipto Mangunkusumo General Hospital (RSCM), the national referral center in Indonesia, which inherently manages a patient population with a high level of clinical complexity. Consequently, the subjects were characterized by advanced maternal and/or fetal complications, as well as a notably high incidence of preterm deliveries and neonatal mortality.

Several independent variables were found to be significantly associated with adverse perinatal outcomes based on bivariate analysis. These included preeclampsia with severe features, early-onset fetal growth restriction (FGR), EFW below the 3rd and 5th percentile thresholds, abnormal Doppler findings in the umbilical artery (including absent or reversed end-diastolic flow [AREDF]), abnormal Doppler indices in the middle cerebral artery, cerebroplacental ratio (CPR) abnormalities, oligohydramnios, non-reactive cardiotocography (CTG) patterns, and gestational age at delivery.

Maternal weight gain during pregnancy was not significantly associated with perinatal outcomes in this cohort. This finding suggests that while inadequate or excessive weight gain may influence the risk of developing FGR, it does not appear to be predictive of FGR severity or its direct impact on neonatal outcomes.

Similarly, maternal anemia did not demonstrate a statistically significant relationship with adverse perinatal outcomes. This may be attributable to the undifferentiated categorization of anemia in this study, in which specific etiologies such as iron-deficiency anemia, which is most commonly linked to fetal growth restriction, intrauterine fetal demise, preterm delivery, and impaired fetal neurodevelopment—were not investigated.³⁷ Furthermore, anemia was assessed at only a single time point in the third trimester, limiting

the ability to detect anemia occurring during earlier and potentially more critical periods of pregnancy.

Fetal abdominal circumference (AC) measurements below the 5th or 3rd percentile did not show a statistically significant association with adverse perinatal outcomes. In contrast, the Estimated Fetal Weight (EFW) percentile calculated using the Hadlock formula, which incorporates head circumference, abdominal circumference, and femur length demonstrated a significant correlation with perinatal outcomes. This suggests that global fetal growth, as reflected by EFW, provides a more comprehensive assessment of fetal well-being and prognostic value for perinatal outcomes than abdominal circumference alone.

Multivariate logistic regression analysis identified six independent variables that were significantly associated with poor perinatal outcomes: the presence of preeclampsia with severe features, EFW less than the 3rd percentile, abnormal umbilical artery Doppler with absent or reversed end-diastolic flow (AREDF), abnormal cerebroplacental ratio (CPR), oligohydramnios, and gestational age groups at birth.

Early-onset severe preeclampsia and chronic hypertension with superimposed preeclampsia are known to exert profound negative effects on fetal growth trajectories.³⁸ Compared with isolated FGR, FGR cases complicated by preeclampsia with severe features are associated with significantly higher rates of preterm delivery, prolonged neonatal intensive care unit (NICU) admission exceeding 7 days, and increased neonatal mortality.²⁵ The findings from this study reinforce the clinical importance of preeclampsia with severe features as a critical determinant in the management and risk stratification of pregnancies complicated by FGR.

An EFW below the 3rd percentile is recognized as indicative of a more severe phenotype of fetal growth restriction (FGR) and is significantly correlated with adverse perinatal outcomes. Evidence from a large-scale retrospective cohort study involving over three million singleton pregnancies demonstrated that fetuses within the $<3^{\text{rd}}$ percentile birth weight category had approximately a threefold increased risk of intrauterine fetal demise compared with those in the 3rd–5th percentile group, and a four- to sevenfold increased risk compared with those in the 5th–10th percentile group.²⁶ Moreover, this study identified an EFW below the 3rd percentile

as the most critical biometric threshold for predicting poor perinatal outcomes.

An abnormal cerebroplacental ratio (CPR) is indicative of fetal hypoxemia, characterized by preferential redistribution of blood flow toward vital organs namely, the brain, heart, and adrenal glands at the expense of peripheral circulation, a physiological adaptation referred to as the "brain-sparing reflex."³⁹ Meanwhile, the presence of absent or reversed end-diastolic flow (AEDF/REDF) in the umbilical artery reflects advanced placental pathology and is strongly associated with higher perinatal mortality rates.⁶ This study supports these associations, showing that 92 out of 94 fetuses with AREDF experienced adverse perinatal outcomes, and all cases with REDF resulted in poor outcomes.

The prognostic relevance of oligohydramnios is also substantiated by this study, in which it was shown to significantly elevate the risk of adverse perinatal outcomes. In the context of worsening placental insufficiency, fetal blood flow is preferentially redistributed to ensure cerebral perfusion, compromising renal blood flow in the process. This results in diminished fetal urine output and subsequently reduced amniotic fluid volume.⁴⁰

Regarding Ductus Venosus (DV) Doppler, the available data were limited to only 59 subjects. The technical complexity of DV Doppler assessment, especially in larger fetuses or in cases of oligohydramnios, makes this modality more challenging than umbilical artery or middle cerebral artery Doppler. Furthermore, this study showed that AREDF in the umbilical artery and abnormal CPR were independent variables significantly associated with poor perinatal outcomes. Thus, with or without DV Doppler evaluation, Doppler assessments of the umbilical artery and middle cerebral artery are mandatory in the evaluation of FGR cases.

Abdominal Circumference Growth Velocity (ACGV) is an important parameter for assessing fetal growth. Prior studies have demonstrated that small-for-gestational-age (SGA) fetuses with reduced growth velocity are at substantially higher risk for adverse perinatal outcomes.^{41,42} In this study, although the mean ACGV tended to be higher in the group with favourable perinatal outcomes, the difference was not statistically significant. This might be due to measurement variability or an insufficient sample size to detect a meaningful difference. To our knowledge, this was the first study at our institution to evaluate

the clinical and ultrasonographic parameters of FGR cases in relation to perinatal outcomes in a considerable number of subjects. However, there were some limitations to this study. First, FGR fetuses who showed decelerated growth but maintained estimated fetal weight and abdominal circumference above the 10th percentile would not be included in this study because of the FGR definition criteria used. In addition, anemia was assessed only through hemoglobin levels measured at the end of pregnancy, which may not reflect earlier deficits. Finally, the analysis did not include maternal comorbidities beyond preeclampsia with severe features that could potentially influence perinatal outcomes..

CONCLUSION

This study concludes that several clinical and ultrasonographic parameters in FGR cases—including preeclampsia with severe features, estimated fetal weight below the 3rd percentile, AREDF in the umbilical artery, abnormal cerebroplacental ratio (CPR), oligohydramnios, and gestational age at delivery were significantly associated with poor perinatal outcomes.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT of INTEREST

The authors declare no conflict of interest.

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The authors have nothing to report.

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