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Early- Versus Late-Onset Fetal Growth Restriction: Clinical Features, Placental Histopathology, and Risk Factor Analysis

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Abstract

Background

Fetal growth restriction (FGR) is a critical adverse pregnancy complication that significantly contributes to adverse perinatal prognosis, and its clinical manifestations, pathological mechanisms and prognostic impacts vary greatly according to the gestational age of onset. Early-onset and late-onset FGR differ substantially in disease severity and underlying etiologies, to date, few studies have systematically compared the clinical characteristics and placental histopathological lesions of early- and late-onset FGR. Therefore, this study aimed to compare the clinical profiles and placental pathological changes between the two FGR subtypes and further screen key risk factors for early-onset FGR, so as to provide pathological and clinical evidence for the early identification and stratified clinical management of early-onset FGR.

Methods

Our cohort investigation encompassed 461 singleton pregnancies, including FGR, stratified by gestational age at diagnosis into early- and late-onset groups. Maternal demographics, pregnancy complications, delivery outcomes, Doppler parameters, and placental pathology were contrasted across groups. Multivariate regression characterized risk factors for early-onset FGR was constructed.

Results

Early-onset FGR was associated with significantly lower birth weight, higher preterm birth (PB) rates, worse perinatal outcomes, and more severe maternal vascular malperfusion (MVM) in placental lesions compared to late-onset FGR ($p < 0.05$). Relevant risk factors associated with early-onset FGR included autoimmune disease, thyroid disorder, intrahepatic cholestasis of pregnancy (ICP), hypertensive disorders of pregnancy (HDP), and abnormal umbilical artery Doppler, with a particularly strong association with preeclampsia.

Conclusion

Early-onset FGR is characterized by greater disease severity and is strongly linked to maternal systemic conditions, placental vascular insufficiency, and aberrant Doppler hemodynamics. Early-onset FGR is fundamentally a placenta-mediated vascular disorder, compounded by secondary inflammatory activation and maternal systemic dysfunction. Targeted management of these risk factors may improve perinatal outcomes.

Background

Fetal growth restriction (FGR) is a complication affecting around 10% of pregnancies, causing both perinatal morbidity [1, 2] and medically indicated preterm birth (PB) [3]. In 2020, the Society for Maternal-Fetal Medicine (SMFM) defined FGR as an ultrasonographically abdominal circumference (AC) or estimated fetal weight (EFW) under the 10th percentile for gestational age[4].

The etiology is multifactorial, encompassing maternal, placental, and fetal contributions. Relevant maternal conditions include pregestational diabetes, autoimmune disease, preeclampsia (PE), thyroid dysfunction, malnutrition, and chronic renal insufficiency, while fetal genetic syndromes and intrauterine infections also play

recognized roles [1, 5]. Collectively, these factors converge on placental insufficiency and impaired uteroplacental perfusion, which together govern both the severity and gestational timing of FGR onset [6, 7].

FGR is defined based on timing as early (≤ 32 weeks) or late (> 32 weeks) [8], and mounting evidence indicates that these subtypes are pathophysiologically and clinically distinct [9, 10]. Early-onset FGR, comprising roughly 30% of cases, is predominantly driven by placental insufficiency, frequently co-occurs with PE, and characteristically produces abnormal umbilical artery Doppler waveforms [11, 12]. Late-onset FGR, accounting for the remaining 70%, typically presents with milder growth restriction and subtler placental dysfunction, yet remains associated with clinically significant adverse perinatal outcomes [13, 14].

To delineate these differences and identify relevant risk factors specific to early-onset disease, we conducted a retrospective comparison of maternal characteristics, perinatal outcomes, Doppler parameters, and placental pathological lesions across early- and late-onset FGR cohorts.

Methods

Participants

This retrospective cohort study enrolled 461 singleton pregnancies complicated by FGR and delivered at Beijing Obstetrics and Gynecology Hospital, Capital Medical University, during 2023 Jan to Dec. Inclusion required the absence of fetal aneuploidy, major structural anomalies, known genetic disorders, and confirmed maternal–fetal infections. Gestational age was validated via fetal crown–rump length (CRL) measurement. Following the 2019 “Expert Consensus on Fetal Growth Restriction” issued by the Chinese Medical Association, fetal weight percentiles in this study were determined using the National Institute of Child Health and Human Development (NICHD) fetal growth standards for Asian populations, incorporating both AC and EFW parameters. All included neonates had birth weights below the 10th percentile for gestational age. Exclusions comprised multiple gestations, congenital fetal anomalies, and pregnancies with confirmed chromosomal or genetic abnormalities on prenatal testing.

Pregnancies were categorized per established FGR diagnostic criteria [12] as early-onset (≤ 32 weeks; *n* = 187, 40.6%) or late-onset (> 32 weeks; *n* = 274, 59.4%).

Study Design and Data Collection

Maternal baseline variables included age, pre-pregnancy BMI, gravidity, parity, education level, conception mode, family history of diabetes or hypertension, autoimmune disease, and prior adverse pregnancy outcomes. Pregnancy complications recorded were PB, premature rupture of membranes (PROM), placental abruption (PA), anemia, gestational hyperglycemia, HDP, thyroid disease, ICP, and postpartum hemorrhage (PPH). HDP was subclassified as pregnancy-induced hypertension(PIH), PE, or chronic hypertension per American College of Obstetricians and Gynecologists (ACOG) criteria [15]. Pre-pregnancy BMI was classified based on Chinese standards: underweight (< 18 kg/m²), normal (18–24 kg/m²), overweight (24–28 kg/m²), or obese (≥ 28 kg/m²).

Doppler assessments included amniotic fluid volume, pulsatility index (UA-PI), and umbilical artery systolic-to-diastolic (S/D) ratio. Middle cerebral artery flow, ductus venosus a-wave, and cerebroplacental ratio were also monitored; as no significant abnormalities were identified in these parameters, those data are not reported here.

Neonatal outcomes comprised gestational age at birth, sex, birth weight, ponderal index (PI; birth weight [g] × 100 / crown–heel length [cm]^3), delivery mode, fetal distress, one-minute Apgar score, and NICU admission.

Postdelivery placental and umbilical cord data included cord length, insertion site, entanglement, torsion, and placental weight and volume. Placental tissue underwent histopathological examination for inflammatory lesions and maternal–fetal vascular malperfusion.

Statistical analysis

Categorical data were summarized as counts and percentages, and group comparisons were performed using the chi-square and Fisher's exact tests. Normally distributed data were displayed as means with standard deviations, assessed using independent-samples *t*-tests, whereas non-normally distributed data (median [M] with interquartile range [P25, P75]) were assessed using the Wilcoxon rank-sum test. To identify relevant risk factors associated with early-onset FGR, multivariate logistic regression was employed, reporting adjusted ORs and 95% CI. Statistics were performed using SPSS (v22.0, IBM, USA); all tests were two-sided and $p < 0.05$ represents significance.

Results

Comparison of the maternal baseline characteristics and complications in E-FGR and L-FGR

The prevalence of autoimmune disease was significantly increased in the early-onset FGR group compared to the late-onset group ($p < 0.05$). Early-onset FGR was associated with significantly higher rates of PB, thyroid disease, HDP, and ICP than late-onset FGR ($p < 0.05$).

We further analyzed the HDP subtype distribution in FGR, HDP exhibited markedly greater prevalent in early-onset than late-onset FGR ($p < 0.001$). Consistent with prior literature, PE occurred nearly twice as frequently in the early-onset group (38.5% vs. 18.6%; $p < 0.001$), while the rates of PIH and chronic hypertension did not differ significantly between subtypes (Table 1).

Table 1
Basement characteristics and maternal complications in E-FGR and L-FGR

Basement characteristics		**E- FGR** **187**	**L- FGR** **274**	**T score/ χ^2**	***p***
Advanced age (N, %)		54(28.9%)	86(31.4%)	0.331	0.565
Pre-pregnancy BMI	< 18 (N, %)	18 (9.6%)	37 (13.5%)	4.566	0.206
	18 ~ 24 (N, %)	129 (69.0%)	197 (71.9%)		
	24 ~ 28 (N, %)	32 (17.1%)	31 (11.3%)		
	≥ 28 (N, %)	8 (4.3%)	9 (3.3%)		
Family history of diabetes (N, %)		23 (12.3%)	24 (8.8%)	1.522	0.217
Family history of hypertension (N, %)		41 (21.9%)	48 (17.5%)	1.386	0.239
Unfavorable pregnancy (N, %)		15 (8.0%)	13 (4.7%)	2.092	0.148
Autoimmune disease (N, %)		15 (8.0%)	6 (2.2%)	8.694	0.003
Education level	Post-secondary education or higher (N, %)	172 (92.0%)	262 (95.6%)	2.673	0.102
	Senior High School or lower (N, %)	15 (8.0%)	12 (4.4%)		
Mode of conception	Spontaneous pregnancy (N, %)	175 (93.6%)	257 (93.8%)	0.009	0.926
	ART (N,%)	12 (6.4%)	17 (6.2%)		
Gravidity	1	107 (57.2%)	177 (64.6%)	2.559	0.11
*Fisher's exact test					

Basement characteristics		E- FGR 187	L- FGR 274	T score/ χ^2	*p*
	(N, %)				
	≥ 2 (N, %)	80 (42.8%)	97 (35.4%)		
Parity	≤ 1 (N, %)	153 (81.8%)	234 (85.4%)	1.059	0.303
	≥ 2 (N, %)	34 (18.2%)	40 (14.6%)		
Pregnancy complications					
PB (N, %)		58 (34.7%)	32 (11.7%)	33.944	0.000
PA (N, %)		7 (3.7%)	13 (4.7%)	0.268	0.604
Pre-anemia (N, %)		47 (25.1%)	79 (28.8%)	0.765	0.382
Thyroid Disease (N, %)		34 (18.2%)	24 (8.8%)	8.972	0.003
PROM (N, %)		41 (21.9%)	88 (32.1%)	5.729	0.017
Gestational Hyperglycemia (N, %)		46 (24.6%)	51 (18.6%)	2.397	0.122
HDP (N, %)		76 (40.6%)	65 (23.7%)	14.986	0.000
PIH (N, %)		3 (1.6%)	8 (2.9%)	-	0.537*
PE (N, %)		72 (38.5%)	51 (18.6%)	22.476	0.000
Chronic hypertension (N, %)		1 (0.5%)	6 (2.2%)	-	0.250*
ICP (N, %)		12 (6.4%)	3 (1.1%)	10.001	0.002
PPH (N, %)		24 (12.8%)	36 (13.1%)	0.009	0.924
*Fisher's exact test					

Neonatal and perinatal outcomes

Regardless of HDP status, early-onset FGR pregnancies exhibited significantly earlier delivery gestational ages, as well as reduced PI, 1- and 5-minute Apgar scores, in comparison with late-onset FGR ($p < 0.001$). Cesarean delivery and NICU admission rates were both significantly elevated in the early-onset group ($p < 0.05$), most markedly among HDP-affected pregnancies. Following adjustment for gestational age at delivery, birth weight remained significantly reduced in the early-onset group, though PI and the number of neonates < 2500 g had no significant difference (Table 2).

Table 2
Comparison of neonatal and perinatal outcomes

		E-FGR		L-FGR		T-score/χ^2, *p*		Adjusted OR (95% CI)*, *p* (Total)	
		Total (187)	HDP (76)	Total (274)	HDP (65)	Total	HDP	Adjusted OR/β-score	*p*
Birth gestational age (wk)		34.75 ± 5.260	32.62 ± 4.836	38.26 ± 1.532	37.34 ± 1.670	t = -10.407 *p* = 0.000	t = -7.493 *p* = 0.000	-	-
Fetal gender (N. of birth)	Male	71 (38.0%)	32 (42.1%)	113 (41.2%)	33 (50.8%)	χ^2 = 0.496 *p* = 0.481	χ^2 = 1.058 *p* = 0.304	-	-
	Female	116 (62.0%)	44 (57.9%)	161 (58.8%)	32 (49.2%)			-	-
Birth weight (g)		1925.94 ± 789.724	1538.62 ± 708.032	2513.36 ± 261.806	2357.31 ± 337.132	t = -11.431 *p* = 0.000	t = -8.529 *p* = 0.000	-0.862*	*p* = 0.003
Low Birth Weight* (N.%)		131 (70.1%)	67 (88.2%)	106 (38.7%)	39 (60.0%)	χ^2 = 43.778 *p* = 0.000	χ^2 = 14.886 *p* = 0.000	1.222 (0.734–2.037)	*p* = 0.441
PI*		43.01 ± 13.81	36.77 ± 12.32	52.85 ± 4.21	50.33 ± 5.33	t = -11.065 *p* = 0.000	t = -8.234 *p* = 0.000	0.193*	*p* = 0.493
Mode of delivery	Cesarean section (N.%)	99 (52.9%)	50 (65.8%)	115 (42.0%)	36 (55.4%)	χ^2 = 7.100 *p* = 0.029	χ^2 = 1.711 *p* = 0.425	1.131 (0.905–1.412)	*p* = 0.279
	Operative vaginal delivery (N. %)	8 (4.3%)	2 (2.6%)	24 (8.8%)	3 (4.6%)				
	Vaginal delivery (N.%)	80 (42.8%)	24 (31.6%)	135 (49.3%)	26 (40.0%)				
Fetal distress (N.%)		55 (29.4%)	16 (8.6%)	106 (38.7%)	17 (6.2%)	χ^2 = 4.206 *p* = 0.04	χ^2 = 0.925 *p* = 0.336	0.969 (0.624–1.506)	*p* = 0.890
Apgar score	0 ~ 3 (N.%)	31 (16.6%)	18 (23.7%)	-	-	χ^2 = 48.719	χ^2 = 17.661	0.568	*p* = 0.264

* Low Birth Weight:<2500g, PI: birth weight (g)/height (cm), adjusted OR: adjusting for the impact of gestational weeks at delivery; birth weight and PI are continuous data, adjusted by linear regression and β-score

		E-FGR		L-FGR		T-score/χ^2, *p*		Adjusted OR (95% CI)*, *p* (Total)	
		Total (187)	**HDP (76)**	**Total (274)**	**HDP (65)**	**Total**	**HDP**	**Adjusted OR/β-score**	***p***
(1 min)	4 ~ 7 (N.%)	2 (1.1%)	2 (2.6%)	4 (1.5%)	2 (3.1%)	*p* = 0.000	*p* = 0.000	(0.211–1.533)	
	≥ 8 (N.%)	154 (82.4%)	56 (73.7%)	270 (98.5%)	63 (96.9%)				
Apgar score	0 ~ 7 (N.%)	31(16.6%)	18 (23.7%)	0 (0.0%)	0 (0.0%)	χ^2 = 48.697	χ^2 = 17.648	-	*p* = 0.997
(5 min)	≥ 8 (N.%)	156 (83.4%)	58 (76.3%)	274 (100.0%)	65 (100.0%)	*p* = 0.000	*p* = 0.000		
Admission of NICU (N. %)		97 (51.9%)	51 (67.1%)	105 (38.3%)	36 (55.4%)	χ^2 = 8.290 *p* = 0.004	χ^2 = 2.037 *p* = 0.154	1.078 (0.681–1.704)	*p* = 0.749

* Low Birth Weight:<2500g, PI: birth weight (g)/height (cm), adjusted OR: adjusting for the impact of gestational weeks at delivery; birth weight and PI are continuous data, adjusted by linear regression and β-score

Doppler, umbilical cord, and placental findings

Abnormal umbilical artery Doppler, comprising elevated S/D ratio and absent or reversed end-diastolic flow (AEDF/REDF), were substantially more common in pregnancies with early-onset FGR ($p < 0.001$). UA-PI, amniotic fluid volume, umbilical cord entanglement, cord torsion, and placental morphology classified by umbilical cord insertion did not differ significantly between groups. The early-onset group demonstrated significantly lower placental volume, placental weight, umbilical cord length, and fetal-to-placental weight ratio ($p < 0.001$) (Table 3).

Table 3
Comparison of ultrasound, umbilical cord, and placental conditions in E-FGR and L-FGR

		E-FGR		L-FGR		T-score/Z-score/χ^2, *p*	
		Total(140)	**HDP(66)**	**Total(180)**	**HDP(39)**	**Total**	**HDP**
		Ultrasound parameters					
UA S/D	Nor (No. %)	147 (78.6)	48 (63.2)	263 (96.0)	60 (92.3)	χ^2 = 39.26	χ^2 = 19.15
	Increased (No. %)	18 (9.6)	13 (17.1)	10 (3.6)	5 (7.7)	*p* = 0.000	*p* = 0.000
	AEDF/REDF (No. %)	22 (11.8)	15 (19.7)	1 (0.4)	-		
*UA-PI[1]		0.87 (0.76, 1.02)	0.96 (0.83, 1.16)	0.88 (0.75, 0.97)	0.92 (0.82, 0.99)	Z = -0.507 *p* = 0.612	Z = -1.443 *p* = 0.149
AF	Nor (No. %)	154 (83.2%)	66 (88.0%)	229 (83.9%)	56 (86.2%)	χ^2 = 0.033	χ^2 = 0.106
	Low (No. %)	31 (16.8%)	9 (12.0%)	44 (16.1%)	9 (13.8%)	*p* = 0.856	*p* = 0.745
		Umbilical cord parameters					
Umbilical cord length (cm)		47.03 ± 12.47	43.79 ± 13.99	53.60 ± 10.63	53.43 ± 10.16	T = − 6.08 *p* = 0.000	T = − 4.73 *p* = 0.000
Umbilical cord entanglement (No. %)		55 (29.4)	17 (22.4)	89 (32.5)	21 (32.3)	T = 0.49 *p* = 0.485	T = 1.76 *p* = 0.185
Umbilical cord torsion (No. %)		18 (9.6)	9 (11.8)	29 (10.6)	4 (6.2)	χ^2 = 0.11 *p* = 0.738	χ^2 = 1.35 *p* = 0.245
Placental morphology	Nor (No. %)	141 (75.4)	56 (73.7)	197 (71.9)	49 (75.4)	χ^2 = 1.87	χ^2 = 1.45
	Battledore placenta (No. %)	38 (20.3)	18 (23.7)	67 (24.5)	14 (21.5)	*p* = 0.600	*p* = 0.694

		E-FGR	L-FGR			T-score/Z-score/χ^2, *p*	
		Total(140)	**HDP(66)**	**Total(180)**	**HDP(39)**	**Total**	**HDP**
	velamentous placenta (No. %)	6 (3.2)	1 (1.3)	9 (3.3)	2 (3.1)		
	Others (No. %)	2 (1.1)	1 (1.3)	1 (0.4)	-		
Placental parameters							
*PV (cm^3)[2]		208.6 ± 114.2	174.2 ± 98.9	258.3 ± 114.1	259.3 ± 101.3	T = − 4.59 *p* = 0.000	T = − 5.03 *p* = 0.000
Placental weight (g)		407.9 ± 137.0	366.4 ± 133.4	475.1 ± 87.6	482.0 ± 73.6	T = − 6.42 *p* = 0.000	T = − 6.49 *p* = 0.000
Fetoplacental weight ratio[2]		4.6 ± 1.3	4.1 ± 1.1	5.5 ± 1.1	5.0 ± 1.0	T = − 6.12 *p* = 0.000	T = − 5.034 *p* = 0.000

*[1] non-normal distribution data ([M] with [P25, P75]) were analyzed using Wilcoxon rank-sum test); *[1] 47 missing cases in E-FGR, 91 missing cases in L-FGR; (early-onset FGR/late-onset FGR: 140/180 cases respectively, early-onset FGR with HDP/late-onset FGR with HDP: 66/39cases respectively).

[2] PV: = (4/3) × π × (length/2) cm× (width/2) cm× (thickness/2) cm, fetoplacental weight ratio: neonatal birthweight (g) /placental weight (g)

Placental pathology

Placental lesions were grouped based on the 2014 Amsterdam Placental Workshop Group Consensus into vascular processes, comprising maternal and fetal stromal-vascular lesions and inflammatory-immune processes [16, 17]. Overall severity of inflammatory lesions was comparable between early- and late-onset FGR. Nevertheless, among pregnancies complicated by HDP, mild placental inflammation was significantly more severe in the early-onset group($p < 0.001$). Immune/idiopathic lesions, mainly villitis of unknown etiology (VUE) and chronic histiocytic intervillositis-conditions previously linked to FGR and fetal mortality [17]-were distributed similarly across groups in the present study.

Among MVM lesions, retroplacental hemorrhage ($p < 0.05$) and distal villous hypoplasia (DVH) ($p < 0.001$) were higher in early-onset FGR, while decidual vasculopathy and placental infarction did not reach significance. Fetal vascular malperfusion lesions, including stem vessel obliteration, intramural fibrin deposition, thrombosis, and avascular villi, were comparable between groups (Table 4).

Table 4
Comparison of individual placental lesions in E-FGR and L-FGR

		E-FGR		L-FGR		T-score/χ^2, *p*	
		Total (143)	**HDP (67)**	**Total (187)**	**HDP (43)**	**Total**	**HDP**
Infectious inflammatory lesions (No. %)	Mild	119 (83.2%)	58 (40.6%)	162 (86.6%)	40 (21.4%)	χ^2 = 0.518 *p* = 0.472	χ^2 = 14.262 *p* = 0.000
	Moderate-severe	23 (16.1%)	8 (5.6%)	25 (13.4%)	3 (1.6%)		- *p* = 0.062*
Immune/idiopathic inflammatory lesions (No. %)		31 (21.7%)	17 (25.4%)	30 (16.0%)	8 (18.6%)	χ^2 = 1.708 *p* = 0.191	χ^2 = 0.683 *p* = 0.408
		Maternal vascular malperfusion					
Retroplacental hemorrhage		5 (3.5%)	1 (0.07%)	-	-	- *p* = 0.015*	- *p* = 1.000*
Placental infarcts		26 (18.2%)	11 (7.7%)	25 (13.4%)	10 (5.3%)	χ^2 = 1.437 *p* = 0.231	χ^2 = 0.748 *p* = 0.387
Mural hypertrophy		2 (1.4%)	1 (0.7%)	3 (1.6%)	-	- *p* = 1.000*	- *p* = 0.433*
Decidual vascular lesion		7 (4.9%)	5 (3.5%)	3 (1.6%)	2 (1.1%)	- *p* = 0.108*	- *p* = 0.246*
Distal villous hypoplasia		68 (47.6%)	38 (26.6%)	52 (27.8%)	18 (9.6%)	χ^2 = 13.652 *p* = 0.000	χ^2 = 16.519 *p* = 0.000
Fetal vascular malperfusion							
Thrombosis		3 (2.1%)	1 (0.7%)	2 (1.1%)	2 (1.1%)	χ^2 = 0.574 *p* = 0.449	χ^2 = 0.123 *p* = 0.725

*44 missing cases in E-FGR (143/187), 87 missing cases in L-FGR (187/274).*Fisher's exact test

	E-FGR		L-FGR		T-score/χ^2, *p*	
	Total (143)	**HDP (67)**	**Total (187)**	**HDP (43)**	**Total**	**HDP**
Intramural fibrin deposition	4 (2.8%)	-	5 (2.7%)	3 (1.6%)	χ^2 = 0.005 *p* = 0.946	χ^2 = 2.315 *p* = 0.128
Stem vessel obliteration	2 (1.4%)	1 (0.7%)	-	-	χ^2 = 2.631 *p* = 0.105	χ^2 = 1.312 *p* = 0.252
Avascular villi	1 (0.7%)	1 (0.7%)	-	-	χ^2 = 1.312 *p* = 0.252	χ^2 = 1.312 *p* = 0.252
*44 missing cases in E-FGR (143/187), 87 missing cases in L-FGR (187/274).*Fisher's exact test						

Relevant risk Factor Analysis

Multivariate logistic regression (Table 5) identified five relevant risk factors for early-onset FGR: autoimmune disease (adjusted OR 3.559; 95% CI 1.284–9.862), ICP (adjusted OR 4.258; 95% CI 1.109–16.344), abnormal umbilical artery Doppler (adjusted OR 5.299; 95% CI 2.567–10.940), thyroid disease (adjusted OR 2.214; 95% CI 1.230–3.983), and HDP (adjusted OR 1.620; 95% CI 1.045–2.512). And in HDP, the association between PE and early-onset FGR is stronger (adjusted OR 1.983; 95% CI 1.248–3.152, *p* = 0.004).

Table 5
Multivariate regression analysis of risk factors for early-onset FGR

Predictor	**B Coefficient**	**Std. Error**	**Wald**	***p*-value**	**Adjust OR [Exp(B)]**	**95% CI**
autoimmune diseases	1.269	0.520	5.960	0.015	3.559	1.284–9.862
Hypertensive Disorders in pregnancy(HDP)	0.482	0.224	4.645	0.031	1.620	1.045–2.512
PE	0.685	0.236	8.393	0.004	1.983	1.248–3.152
Thyroid Disease	0.795	0.300	7.032	0.008	2.214	1.230–3.983
Abnormal Doppler of umbilical artery	1.668	0.370	20.328	0.000	5.299	2.567–10.940
ICP	1.449	0.686	4.456	0.035	4.258	1.109–16.344
Constant	-0.912	0.132	47.920	0.000	0.402	—

Discussion

FGR complicates approximately 10% of pregnancies and confers substantial risks of perinatal mortality and morbidity [18, 19]. When stratified by gestational diagnosis age, early-onset FGR (≤ 32 weeks) [20] generally presnts a more severe clinical course than late-onset FGR (≥ 32 weeks) and accounts for a disproportionate burden of adverse perinatal outcomes [21]. We characterized the clinical and placental histopathological differences between these subtypes and defined the relevant risk factors driving early-onset disease.

Early-onset FGR, which constitutes around 30% of all FGR cases, is generally considered a placental-origin disease. [12, 22]. In our cohort, autoimmune disease, thyroid disorder, and ICP were all significantly more prevalent in the early-onset group. Heightened autoimmune activity in pregnancy may impair trophoblastic invasion and precipitate placental insufficiency [23]. Experimental evidence also indicates that maternal hypothyroidism downregulates placental nutrient transporters, thereby limiting fetal substrate delivery [24]. ICP, characterized by maternal pruritus and elevated total bile acid levels, further impairs trophoblastic invasion and placental development, thereby providing a mechanistic basis for its established association with FGR [25]. By collectively disruping placental formation and function, these conditions jointly compromise fetal oxygen and nutrients supply.

HDP and PE are strongly associated with early-onset FGR, with reported co-occurrence rates approaching 70% in the literature [26]. Our data are consistent with this: the incidence of HDP was significantly higher in the early-onset group (40.6% *vs*. 23.7%, $p < 0.001$), and PE occurred nearly twice as frequently (38.5% *vs*. 18.6%, $p < 0.001$). Both conditions share impaired spiral artery remodeling as a central pathophysiological mechanism, which reduces intervillous perfusion and exacerbates uteroplacental insufficiency [27, 28]. Regardless of HDP status, the fetal-placental weight ratio was significantly lower in early-onset FGR pregnancies ($p < 0.001$), indicating diminished nutrient transport capacity per unit of placental mass. This finding that implicates placental insufficiency as the central pathological mechanism underlying FGR in pregnancies complicated by HDP. Associated histological alterations-including increased syncytial knots, villous edema, and fibrinoid necrosis-further underscore the broad structural and functional consequences of HDP-associated placental dysfunction.

The placental pathological profiles of early- and late-onset FGR reflect their distinct pathophysiological mechanisms. Inadequate decidual trophoblastic invasion and impaired spiral artery remodeling reduce maternal blood flow to the intervillous space [17, 29], and the consequent chronic ischemia-reperfusion injury drives MVM [16, 30], a lesion pattern strongly associated with early-onset FGR [31, 32]. Fetal vascular malperfusion(FVM), by contrast, did not differ between groups, suggesting that it is not subtype-specific [19].

Consistent with prior reports [32, 33], MVM lesions classified according to the Amsterdam Placental Workshop Group Consensus, including retroplacental hemorrhage, decidual vasculopathy, placental infarction, and DVH, were significantly more prevalent in early-onset FGR, corroborating the central role of maternal malperfusion in this subtype [20]. Specifically, DVH was significantly elevated in early-onset FGR ($p < 0.001$), whereas decidual vasculopathy and placental infarction showed no significant intergroup differences. DVH is regarded as an early manifestation of aberrant placental development and angiogenesis, arising secondary to intervillous underperfusion and, in particular, oscillations in intraplacental oxygen tension [29]. As pregnancy progresses, cumulative insults and evolving maternal systemic changes progressively compromise materno-feto-placental perfusion, driving the subsequent development of placental infarction and decidual vasculopathy and thereby impairing placental nutrient transfer and fetal oxygenation [34]. DVH therefore represents an upstream pathological event relative to infarction and decidual vasculopathy, accounting for its disproportionate high prevalence in the early-onset phenotype.

A further notable finding was the significantly higher incidence of mild infectious-inflammatory lesions in early-onset FGR complicated by HDP compared with late-onset cases (40.6% *vs*. 21.4%, $p < 0.001$). Both early-onset FGR and PE are prototypical placenta-mediated conditions in which dysregulated immune responses at the maternal–fetal interface converge with defective placental vascular development [35]; the superimposition of HDP appears to amplify this inflammatory activation specifically in the early-onset setting. Collectively, these findings-including MVM lesions and infectious-inflammatory lesions-support early-onset FGR as a placenta-mediated syndrome characterized by placental maldevelopment, impaired maternal vascular perfusion, and secondary immune-inflammatory dysregulation. These findings highlight the importance of early identification and management of maternal conditions associated with compromised uteroplacental perfusion.

Elevated uteroplacental resistance in early-onset FGR underlies the abnormal Doppler profiles that characterize this subtype [8]. Defective trophoblastic invasion increases resistance within placental arteries and produces the spectral alterations observed in the UA [13]. Specifically, AEDF or REDF indicates obliteration of approximately 60% of the placental villous vasculature [36–38]. In our cohort, the early-onset group showed significantly higher rate of abnormal Doppler findings than the late-onset group ($p < 0.001$). Beyond Doppler surveillance, placental biomarkers provide a valuable complementary window into disease severity. Disrupted villous development promotes syncytial knot formation, which suppresses placental growth factor (PlGF) secretion while upregulating soluble fms-like tyrosine kinase-1 (sFlt-1), thereby elevating the sFlt-1/PlGF ratio [33, 39–42]. This ratio correlates closely with the degree of placental dysfunction and the severity of histological abnormalities across PE, FGR, PB and related disorders[43]. Moreover, both decreased PlGF and an elevated sFlt-1/PlGF ratio have been independently associated with adverse outcomes in early-onset FGR [44, 45]. Serial measurement of these markers, therefore, represents a practical strategy for monitoring placental function and anticipating clinical deterioration in high-risk pregnancies.

No effective intrauterine treatment currently exists for placenta-mediated FGR [46], making timely delivery the primary determinant of prognosis. Early-onset FGR almost invariably necessitates iatrogenic PB, which itself confers substantial neonatal morbidity and mortality [13]. PB was nearly three times more frequent in the early-onset group in our cohort (34.7% *vs*. 11.7%, $p < 0.001$), and gestational age at delivery was significantly earlier regardless of HDP status (34.75 ± 5.26 *vs*. 38.26 ± 1.53 weeks without HDP; 32.62 ± 4.84 *vs.* 37.34 ± 1.67 weeks with HDP; $p < 0.001$). Cesarean delivery was more prevalent in the early-onset class (52.9% *vs*. 42.0%, $p < 0.001$) and increased further in both groups when HDP was present (65.8% *vs*. 55.4%), driven by the compounding effects of placental insufficiency, abnormal Doppler findings, fetal hypoxia, and HDP-related complications. Early-onset FGR was also associated with lower birth weight, lower PI, lower 1- and 5-minute Apgar scores, and higher NICU admission rates (51.9% *vs*. 38.3%, all $p < 0.05$). After adjustment for gestational age at delivery, birth weight remained significantly reduced in the early-onset class, whereas differences in low birth weight rates, PI, Apgar scores, and NICU admission were attenuated to non-significance, identifying gestational age as a key confounder of these outcome disparities.

Multivariate logistic regression identified autoimmune disease, thyroid disorder, HDP, ICP, and abnormal UA Doppler as independent risk factors for early-onset FGR, providing clinicians with a multivariable framework for individualized risk stratification and timely intervention. Maternal serum PlGF or expressed as the sFlt-1/PlGF ratio and combined with ultrasound biometry, has emerged as a reliable indicator of placental function and a validated predictor of adverse outcomes in early-onset FGR [47–49]. These biomarkers will be incorporated into our subsequent predictive modeling.

Our study has several limitations. First, as a single-center retrospective cohort study, it relies on clinical information collected from electronic medical records, which may introduce potential bias. Second, partial missing data existed for placental pathological parameters, which may potentially bias the interpretation of histopathological findings.

Third, as reported in previous literature, reduced PlGF and an elevated sFlt-1/PlGF ratio show an independent association with adverse pregnancy outcomes among women with early-onset FGR, in this study we did not investigate circulating placental biomarkers such as PlGF and sFlt-1/PlGF ratio; therefore, we could not evaluate their predictive value for early-onset FGR. Further prospective studies collecting complete placental pathological specimens and placental biomarker data are needed to validate our findings and we will incorporate these factors to develop a predictive model for early-onset FGR.

Conclusions

Early-onset FGR may be reasonably regarded not as a discrete disease but as a syndrome arising from the combined effects of placental ischemia, and dysregulated immune responses at the maternal-fetal interface. Late-onset FGR, by contrast, may represent a comparatively limited ischemic process confined to the final stages of pregnancy-a pathophysiological distinction that may partly account for the differences between the two phenotypes. Early-onset FGR is associated with a substantially higher risk of PB, adverse neonatal outcomes, and placental vascular pathology than its late-onset counterpart. Integrating maternal risk factor profiling, serial Doppler ultrasonography, and angiogenic biomarkers-particularly PlGF and the sFlt-1/PlGF ratio-may provide a promising preliminary strategy for early identification and optimized surveillance of at-risk pregnancies. Until effective intrauterine therapies become available, comprehensive monitoring-guided management remains a key approach to reducing perinatal morbidity and mortality in early-onset FGR.

Abbreviations

FGR fetal growth restriction

HDP hypertensive disorders of pregnancy

ICP intrahepatic cholestasis of pregnancy

EFW estimated fetal weight

AC abdominal circumference

CRL crown–rump length

PB preterm birth

PROM premature rupture of membranes

PA placental abruption

PPH postpartum hemorrhage

ACOG American College of Obstetricians and Gynecologists

S/D systolic-to-diastolic

UA-PI umbilical artery pulsatility index

VUE villitis of unknown etiology

NICU Neonatal Intensive Care Unit

AEDF absent end-diastolic flow

REDF reversed end-diastolic flow

BMI body mass index

MVM maternal vascular malperfusion

PIGF placental growth factor

sFlt-1 soluble fms-like tyrosine kinase-1

Declarations

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Authors' contributions

Ying Li: conceptualized the study, collected data, wrote the initial paper, analyzed and interpreted the data, revised the paper according to other authors' comments.**Yi Chen:** made critical revisions of the manuscript for important intellectual content and contributed to the study concept, design and implementation and acquired funding. **Xiaokui Yang:** supervised data quality and data analysis, performed research and project administration, review & editing of the manuscript. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Data availability

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

Ethics approval and consent to participate

This study was approved by the Human Ethics Committees of Beijing Obstetrics and Gynecology Hospital, Capital Medical University. Because this study involves a retrospective review of existing data from the medical record system, and no patient identifiable information is disclosed, the informed consent to participate was waived by the Human Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University.

Consent for publication

Not applicable

Competing interests

No competing interests declared.

References

1. Srirambhatla A, Mittal S, Vedantham H. Efficacy of Pulsatility Index of Fetal Vessels in Predicting Adverse Perinatal Outcomes in Fetuses with Growth Restriction - Differences in Early- and Late-Onset Fetal Growth Restriction. Maedica. 2022;17(1):107–15.
2. Stone J. Fetal Growth Restriction Prevention: Is There a Role for Aspirin, Heparin, Statins, and Others? CLIN OBSTET GYNECOL. 2025;68(4):550–7.
3. Anselem O, Goffinet FO, Jarreau P, Zeitlin J, Monier I. Perinatal survival among very preterm singletons born after detection of early-onset fetal growth restriction with or without maternal hypertensive disorders: A population-based study in France. Eur J Obstet Gynecol Reprod Biol. 2023;282:43–9.
4. Society FMMS, Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal?growth restriction: (Replaces Clinical Guideline Number 3, April 2012). AM J OBSTET GYNECOL. 2020;223(4):B2–17.
5. Alves P, Malheiro MF, Gomes JC, Ferraz T, Montenegro N. Risks of Maternal Obesity in Pregnancy: A Case-control Study in a Portuguese Obstetrical Population. Revista brasileira de Ginecol e obstetricia: revista da Federacao Brasileira das Sociedades de Ginecol e Obstet. 2019;41(12):682–7.
6. Beksac MS, Fadiloglu E, Tanacan A, Mamopoulos A, Basol M, Muresan D, Athanasiadis A. A Cut-off Value for Gestational Week at Birth for Better Perinatal Outcomes in Early- and Late-Onset Fetal Growth Restriction. Z GEBURTSH NEONATOL. 2019;223(5):289–96.
7. Silver RM. Examining the link between placental pathology, growth restriction, and stillbirth. Best Pract Res Clin Obstet Gynecol. 2018;49:89–102.
8. Muniz CS, Dias BF, Motoyama PVP, Almeida CTC, Feitosa FEDL, Araujo Júnior E, Alves JAG. Doppler abnormalities and perinatal outcomes in pregnant women with early-onset fetal growth restriction. J maternal-fetal neonatal medicine: official J Eur Association Perinat Med Federation Asia Ocean Perinat Soc Int Soc Perinat Obstetricians. 2022;35(25):7276–9.
9. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. ULTRASOUND OBST GYN. 2016;48(3):333–9.
10. Inácio QAS, Araujo Júnior E, Nardozza LMM, Petrini CG, Campos VP, Peixoto AB. Perinatal Outcomes of Fetuses with Early Growth Restriction, Late Growth Restriction, Small for Gestational Age, and Adequate for Gestational Age. Revista brasileira de Ginecol e obstetricia: revista da Federacao Brasileira das Sociedades de Ginecol e Obstet. 2019;41(12):688–96.
11. Su EJ. Scaling the EVERREST of severe, early-onset fetal growth restriction. J Clin Investig. 2023;133(18):e173563.
12. Lees CC, Stampalija T, Baschat A, Da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet gynecology: official J Int Soc Ultrasound Obstet Gynecol. 2020;56(2):298–312.

13. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. FETAL DIAGN THER. 2014;36(2):86–98.
14. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. AM J OBSTET GYNECOL. 2018;218(2S):S790–802.
15. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. OBSTET GYNECOL. 2013;122(5):1122–31.
16. Khong TY, Mooney EE, Ariel I, Balmus NCM, Boyd TK, Brundler M, Derricott H, Evans MJ, Faye-Petersen OM, Gillan JE, et al. Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. ARCH PATHOL LAB MED. 2016;140(7):698–713.
17. Redline RW. Classification of placental lesions. AM J OBSTET GYNECOL. 2015;213(4 Suppl):S21–8.
18. Giouleka S, Tsakiridis I, Mamopoulos A, Kalogiannidis I, Athanasiadis A, Dagklis T. Fetal Growth Restriction: A Comprehensive Review of Major Guidelines. OBSTET GYNECOL SURV. 2023;78(11):690–708.
19. Spinillo A, Gardella B, Adamo L, Muscettola G, Fiandrino G, Cesari S. Pathologic placental lesions in early and late fetal growth restriction. ACTA OBSTET GYN SCAN. 2019;98(12):1585–94.
20. Bujorescu DL, Ra Iu AC, Motoc AGM, Tu C, Sas IC, Gorun I, Gorun IF, Folescu OM, Gurgu R. Placental pathology in early-onset fetal growth restriction: insights into fetal growth restriction mechanisms. Romanian J morphology Embryol = Revue roumaine de morphologie et embryologie. 2023;64(2):215–24.
21. González A, Peguero A, Meler E, Camprubí-Camprubí M, Rovira C, Gomez-Roig MD, Oros D, Ibáñez-Burillo P, Schoorlemmer J, Masoller N, et al. Treatment of early-onset fetal growth restriction with low molecular weight heparin does not prolong gestation: a randomized clinical trial. AM J OBSTET GYNECOL. 2025;232(6):551–2.
22. Shen H, Zhao X, Li J, Chen Y, Liu Y, Wang Y, Liu X, Cheng W. Severe early-onset PE with or without FGR in Chinese women. Placenta. 2020;101:108–14.
23. Tincani A, Nalli C, Khizroeva J, Bitsadze V, Lojacono A, Andreoli L, Shoenfeld Y, Makatsariya A. Autoimmune diseases and pregnancy. Best Pract Res Clin Endocrinol Metab. 2019;33(6):101322.
24. Kent NL, Atluri SC, Moritz KM, Cuffe JSM. Maternal hypothyroidism in rats impairs placental nutrient transporter expression, increases labyrinth zone size, and impairs fetal growth. Placenta. 2023;139:148–58.
25. Aksan Desteli G, Sahin-Uysal N, Cok T, Gulumser C, Kalayci H, Yanik FF. First trimester maternal serum PAPP-A levels and associated pregnancy complications in intrahepatic cholestasis of pregnancy. CLIN EXP OBSTET GYN. 2016;43(5):673–7.
26. Dall'Asta A, Brunelli V, Prefumo F, Frusca T, Lees CC. Early onset fetal growth restriction. Maternal health neonatology Perinatol. 2017;3:2.
27. Zur RL, Kingdom JC, Parks WT, Hobson SR. The Placental Basis of Fetal Growth Restriction. OBSTET GYN CLIN N AM. 2020;47(1):81–98.
28. Feenstra ME, Bourgonje MF, Bourgonje AR, Schoots MH, Hillebrands J, Muller Kobold AC, Prins JR, van Goor H, Ganzevoort W, Gordijn SJ. Systemic Oxidative Stress in Severe Early-Onset Fetal Growth Restriction Associates with Concomitant Pre-Eclampsia, Not with Severity of Fetal Growth Restriction. Antioxid (Basel Switzerland). 2023;13(1):46.
29. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth?restriction. AM J OBSTET GYNECOL. 2018;218(2S):S745–61.
30. Ernst LM. Maternal vascular malperfusion of the placental bed. *APMIS: acta pathologica, microbiologica, et immunologica Scandinavica* 2018, 126(7):551–560.

31. Pinheiro B, Sarmento-Gon Alves I, Ramalho C. Association Between Placental Pathology and Early-Onset Fetal Growth Restriction: A Systematic Review. FETAL PEDIATR PATHOL. 2025;44(1):40–52.
32. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. FETAL DIAGN THER. 2014;36(2):117–28.
33. Audette MC, Kingdom JC. Screening for fetal growth restriction and placental insufficiency. SEMIN FETAL NEONAT M. 2018;23(2):119–25.
34. Dankó I, Tankó A, Kelemen E, Cserni G. Fetal growth restriction and preeclampsia as endpoints of a spectrum from the viewpoint of placental histopathology. MINERVA OBSTET GYNEC. 2026;78(3):205–14.
35. Miranda J, Maestre N, Devia M, Zapata R, Ochoa-Díaz MM, Annicchiarico W. Inflammation at the Maternal-Fetal Interface: Mechanisms Linking Maternal-Fetal Immunity to Preeclampsia and Fetal Growth Restriction. Int J Mol Sci. 2026;27(9):3954.
36. Pedroso MA, Palmer KR, Hodges RJ, Costa FDS, Rolnik DL. Uterine Artery Doppler in Screening for Preeclampsia and Fetal Growth Restriction. Revista brasileira de Ginecol e obstetricia: revista da Federacao Brasileira das Sociedades de Ginecol e Obstet. 2018;40(5):287–93.
37. Tolu LB, Ararso R, Abdulkadir A, Feyissa GT, Worku Y. Perinatal outcome of growth restricted fetuses with abnormal umbilical artery Doppler waveforms compared to growth restricted fetuses with normal umbilical artery Doppler waveforms at a tertiary referral hospital in urban Ethiopia. PLoS ONE. 2020;15(6):e234810.
38. Al Hamayel NA, Baghlaf H, Blakemore K, Crino JP, Burd I. Significance of abnormal umbilical artery Doppler studies in normally grown fetuses. Maternal health neonatology Perinatol. 2020;6:1.
39. Stepan H, Galindo A, Hund M, Schlembach D, Sillman J, Surbek D, Vatish M. Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction. Ultrasound Obstet gynecology: official J Int Soc Ultrasound Obstet Gynecol. 2023;61(2):168–80.
40. Drewlo S, Levytska K, Sobel M, Baczyk D, Lye SJ, Kingdom JCP. Heparin promotes soluble VEGF receptor expression in human placental villi to impair endothelial VEGF signaling. J Thromb haemostasis: JTH. 2011;9(12):2486–97.
41. Gaccioli F, Aye ILMH, Sovio U, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. AM J OBSTET GYNECOL. 2018;218(2S):S725–37.
42. Herraiz I, Llurba E, Verlohren S, Galindo A, Spanish GFTS. Update on the Diagnosis and Prognosis of Preeclampsia with the Aid of the sFlt-1/ PlGF Ratio in Singleton Pregnancies. FETAL DIAGN THER. 2018;43(2):81–9.
43. Hong J, Crawford K, Cavanagh E, Clifton V, Kumar S. Prediction of preterm birth in women with fetal growth restriction - Is the weekly change in sFlt-1/PlGF ratio or PlGF levels useful? ACTA OBSTET GYN SCAN. 2024;103(6):1112–9.
44. Sharp A, Jackson R, Cornforth C, Harrold J, Turner MA, Kenny L, Baker PN, Johnstone ED, Khalil A, von Dadelszen P, et al. A prediction model for short-term neonatal outcomes in severe early-onset fetal growth restriction. Eur J Obstet Gynecol Reprod Biol. 2019;241:109–18.
45. Lobmaier SM, Figueras F, Mercade I, Perello M, Peguero A, Crovetto F, Ortiz JU, Crispi F, Gratacós E. Angiogenic factors vs Doppler surveillance in the prediction of adverse outcome among late-pregnancy small-for-gestational-age fetuses. Ultrasound Obstet gynecology: official J Int Soc Ultrasound Obstet Gynecol. 2014;43(5):533–40.
46. Deepak V, El-Balawi L, Harris LK. Placental Drug Delivery to Treat Pre-Eclampsia and Fetal Growth Restriction. Small. 2024;20(41):e2311165.

47. Bonacina E, Mendoza M, Farràs A, Garcia-Manau P, Serrano B, Hurtado I, Ferrer-Oliveras R, Illan L, Armengol-Alsina M, Carreras E. Angiogenic factors for planning fetal surveillance in fetal growth restriction and small-for-gestational-age fetuses: A prospective observational study. BJOG: Int J Obstet Gynecol. 2022;129(11):1870–7.
48. Spencer R, Maksym K, Hecher K, Mar ÁI K, Figueras F, Ambler G, Whitwell H, Nené NR, Sebire NJ, Hansson SR, et al. Maternal PlGF and umbilical Dopplers predict pregnancy outcomes at diagnosis of early-onset fetal growth restriction. J Clin Investig. 2023;133(18):e169199.
49. Bonacina E, Armengol-Alsina M, Casellas A, Dalmau M, Diaz P, Roldán E, Temprado J, Duaso M, Ampurdanes Q, San José M et al. Angiogenic factors and fetal Doppler for predicting adverse pregnancy outcome in early-onset small fetuses with and without pre-eclampsia. Ultrasound Obstet gynecology: official J Int Soc Ultrasound Obstet Gynecol 2026:10–1002.