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Minerva Obstetrics and Gynecology 2021 August;73(4):435-41
DOI: 10.23736/S2724-606X.21.04809-7

REVIEW

UPDATE IN LATE FETAL GROWTH RESTRICTION

Preeclampsia and late fetal growth restriction

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ABSTRACT

There is a strong but complex relationship between fetal growth restriction and preeclampsia. According to the International Society for the Study of Hypertension in Pregnancy the coexistence of gestational hypertension and fetal growth restriction identifies preeclampsia with no need for other signs of maternal organ impairment. While early-onset fetal growth restriction and preeclampsia are often strictly associated, such association becomes looser in the late preterm and term periods. The incidence of preeclampsia decreases dramatically from early preterm fetal growth restriction (39-43%) to late preterm fetal growth restriction (9-32%) and finally to term fetal growth restriction (4-7%). Different placental and cardiovascular mechanism underlie this trend: isolated fetal growth restriction has less frequent placental vascular lesions than fetal growth restriction associated with preeclampsia; moreover, late preterm and term fetal growth restriction show different patterns of maternal cardiac output and peripheral vascular resistance in comparison with preeclampsia. Consequently, current strategies for first trimester screening of placental dysfunction, originally implemented for preeclampsia, do not perform well for late-onset fetal growth restriction: the sensitivity of first trimester combined screening for small-for-gestational age newborns delivered at less than 32 weeks is 56-63%, and progressively decreases for those delivered at 32-36 weeks (43-48%) or at term (21-26%). Moreover, while the test is more sensitive for small-for-gestational age associated with preeclampsia at any gestational age, its sensitivity is much lower for small-for-gestational age without preeclampsia at 32-36 weeks (31-37%) or at term (19-23%).

(*Cite this article as:* Marasciulo F, Orabona R, Fratelli N, Fichera A, Valcamonico A, Ferrari F, *et al.* Preeclampsia and late fetal growth restriction. Minerva Obstet Gynecol 2021;73:435-41. DOI: 10.23736/S2724-606X.21.04809-7)

KEY WORDS: Pre-eclampsia; Fetal growth retardation; Placental insufficiency; Ultrasonography, Doppler; Incidence.

Definition of preeclampsia

There is a close link between fetal growth restriction and preeclampsia. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP),[1] preeclampsia is defined as a form of gestational hypertension arising at or after 20 weeks and accompanied by at least one of the following conditions: proteinuria, acute kidney injury, liver dysfunction, neurological complications, hematological complications, or uteroplacental dysfunction – including fetal growth restriction, abnormal umbilical artery Doppler and placenta-related stillbirth. Thus, the coexistence of gestational hypertension and fetal growth restriction identifies preeclampsia with no need for other signs of maternal organ impairment.

Epidemiology of preeclampsia

Preeclampsia is one of the most frequent pregnancy syndromes, affecting 2.7% to 8.2% of pregnancies worldwide.[2] The morbidity and the mortality of this condition are still relevant all

over the world, with 10-15% of direct maternal mortality being associated with preeclampsia.[3] Although preeclampsia can lead to severe maternal and fetal complications at any gestational age, two different subgroups of disease are often identified: early onset (before 34 weeks) and late-onset (after 34 weeks) preeclampsia.[1, 4] Early-onset preeclampsia constitutes about 25% of all cases, while the late-onset population represent the 75% of all preeclamptic women. This dichotomy has a clear association with neonatal morbidity: early-onset preeclampsia carries a substantially higher risk of adverse birth outcomes, such as small-for-gestational age and neonatal Intensive Care Unit admission, than late-onset preeclampsia.[5]

Pathogenesis and pathology

The pathogenesis of preeclampsia has not been fully understood, but some mechanisms are generally considered to be involved in its development:[6, 7] failure of physiological transformation of the maternal spiral arteries due to poor trophoblastic invasion; abnormal maternal immunological tolerance of placental and fetal tissues; imbalance of angiogenic and antiangiogenic factors (often measured as the ratio between soluble FMS-like tyrosine kinase-1 [sFlt-1] and placental growth factor [PlGF] concentrations in maternal plasma); abnormal maternal cardiovascular adaptation to pregnancy.

Impairment of physiological transformation of spiral arteries is characterized by abnormal extravillous trophoblast invasion, persistence of endothelial cells, arterial endothelial activation, and often acute atherosis leading to utero-placental hypoperfusion, oxidative stress, intravascular inflammation, and angiogenic imbalance.[8-10] The association between fetal growth restriction and preeclampsia is complex and not fully understood but finds a common ground in placental vascular dysfunction.[11]

The features of placentas associated with fetal growth restriction and preeclampsia are not universally defined and classified, but there are a number of morphological and molecular features involved in the pathophysiology of both preeclampsia and fetal growth restriction.[11-15] However, while this association is strong for the earlier and more severe forms of preeclampsia and fetal growth restriction, it becomes less evident with advancing gestational age:[15] while isolated early-onset preeclampsia often presents a reduction in the volume of terminal and surface area, late-onset preeclampsia has a minor impact on placental features.[16] Isolated fetal growth restriction has less frequent placental vascular lesions than fetal growth restriction associated with preeclampsia.[17] Isolated late-onset fetal growth restriction compared to isolated late-onset preeclampsia shows a reduced total placental volume, and reduced vascular and villous subcomponents in the intermediate and terminal villi.[16]

Incidence of preeclampsia in pregnancies with fetal growth restriction

The aforementioned differences in the placental pathology of pregnancy complicated by early- and late-onset forms of disease are a likely explanation for the variations in the incidence of preeclampsia in pregnancies complicated by fetal growth restriction. Table I[18-25] summarizes the prevalence of preeclampsia in early preterm, late preterm and term fetal growth restriction as reported by some of the most relevant studies on the subject.[18-25] It is evident that the incidence of preeclampsia decreases dramatically from early preterm fetal growth restriction (39-43%) to late preterm fetal growth restriction (9-32%) and finally to term fetal growth restriction (4-7%). Even in term fetal growth restriction, a milder phenotype (fetal biometry between the 3rd and 10th centile and normal Doppler) is less frequently associated with preeclampsia (3.7%) than a more severe phenotype (fetal biometry <3rd centile or abnormal Doppler; 7.3%).[25]

A population-based observational study conducted using 2007-2010 data from the Norwegian Medical Birth Registry investigated the association between birth weight, preeclampsia and gestational age at birth.[21] Using data derived from this study, Figure 1[21] shows that in pregnancies delivered at 34-36 weeks, newborns from pre-eclamptic mothers had a distribution shifted towards a lower

TABLE I.—*Incidence of preeclampsia in pregnancies complicated by fetal growth restriction (FGR).*

Article	Years	Country	FGR definition	Incidence of preeclampsia		
				Early preterm FGR	Late preterm FGR	Term FGR
Boers *et al.* 2010[18]	2004-2008	the Netherlands	EFW/AC<10th centile OR flattening of growth curve			72/1102 (6.5%)
Lees *et al.* 2015[19, 20]	2005-2010	Europe	EFW/AC<10th centile AND abnormal Doppler	195/503 (38.8%)		
Rasmussen *et al.* 2014[21]	2007-2010	Norway	BW<10th centile	40/94 (42.6%)	96/299 (32.1%)	349/7407 (4.7%)
Spinillo *et al.* 2019[22]	2010-2016	Italy	EFW/AC<10th centile for at least 2 ultrasound examinations	69/164 (42%)	59/276 (21.4%)	
Tan *et al.* 2018[23]	2014-2016	Europe, Israel	BW<10th centile	28/71 (39%)	72/344 (20.9%)	64/1761 (3.6%)
Stampalija *et al.* 2020[24]	2017-2018	Europe	EFW/AC<10th centile AND abnormal Doppler		79/856 (9.2%)	
Meler *et al.* 2021[25]	2010-2020	Spain	EFW between 3rd and 10th centile AND normal Doppler			20/544 (3.7%)
			EFW<3rd centile OR EFW<10th centile AND abnormal Doppler			36/493 (7.3%)

EFW: estimated fetal weight; AC: fetal abdominal circumference.

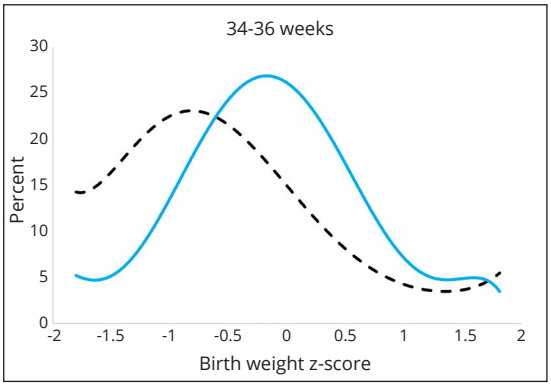

Figure 1.—Distribution of z-scores of birth weight in pregnancies with preeclampsia (dashed line) and without preeclampsia (continuous line) delivering at 34-36 weeks. Modified from Rasmussen *et al.*[21]

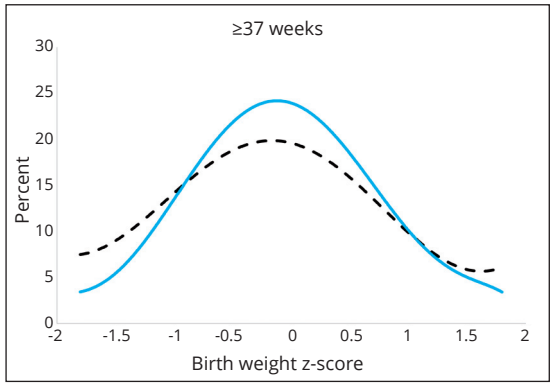

Figure 2.—Distribution of z-scores of birth weight in pregnancies with preeclampsia (dashed line) and without preeclampsia (continuous line) delivering at 37 weeks or beyond. Modified from Rasmussen *et al.*[21]

birth weight. However, at 37 weeks or more, such difference was not evident (Figure 2).[21]

Such observations confirm that the association between fetal growth restriction and preeclampsia loosens with advancing gestation.

Maternal cardiac function

Verlohren *et al.*[26] studied the correlation between birth weight and preeclampsia in a large cohort of unselected pregnancies. They demonstrated a bimodal skewed distribution of birth weight in late-onset preeclampsia, with a higher prevalence of both small-for-gestational age births and large-for-gestational age births. They hypothesized that these findings can be attributed to a dual etiology of late-onset preeclampsia: one shared with early-onset preeclampsia and resulting in fetal growth restriction babies, with placental dysfunction caused by impaired spiral artery remodeling; the other caused by maternal cardiac dysfunction and inability to satisfy the metabolic demands of a larger placenta in large-for-gestational age fetuses.

Tay *et al.* studied the correlation between maternal cardiac output and peripheral vascular resistance in preeclampsia and fetal growth restriction in a prospective cross-sectional study.[27] They assessed maternal cardiovascular parameters in 14 pregnancies with isolated preeclampsia only, 16 with isolated fetal growth restriction and 15 with both preeclampsia and fetal growth restriction. They compared the findings with a control group of 107 healthy person observations. Women with preeclampsia had a higher body mass index at the beginning of pregnancy compared with controls. Preeclampsia was characterized by a higher cardiac output and lower peripheral vascular resistance. On the contrary, women with isolated fetal growth restriction were characterized by higher peripheral vascular resistance than uncomplicated pregnancies. In pregnancies where preeclampsia and fetal growth restriction occurred together, the maternal cardiovascular phenotype was characterized by an even higher peripheral vascular resistance and lower cardiac output than in isolated fetal growth restriction. In complicated pregnancies of all types, increased augmentation index and pulse wave velocity indicated an abnormal arterial function.

Maternal cardiovascular features may however be influenced by the criteria used for defining fetal growth restriction: di Pasquo *et al.*[28] compared pregnancies with properly growth restricted fetuses to those with simple small-for-gestational-age fetuses and controls. They found a lower cardiac output and higher peripheral vascular resistance in proper fetal growth restriction compared to small-for-gestational-age and controls.

Orabona *et al.*[29] extended the assessment of maternal cardiac function at 6 to 48 months postpartum, comparing women with a history of normotensive fetal growth restriction, preeclampsia with fetal growth restriction, and preeclampsia without fetal growth restriction. Women with normotensive fetal growth restriction showed a similar subclinical left ventricular systolic and diastolic function impairment to preeclampsia without fetal growth restriction (manifested as concentric ventricular remodeling, reduced right ventricular systolic function and left atrial strain). Left ventricular hypertrophy was present in about 10% of cases with preeclampsia (with or without fetal growth restriction) but not in those with normotensive fetal growth restriction. Even after elevated liver enzymes and low platelet count (HELLP) syndrome, concurrent fetal growth restriction appears to be an independent risk factor for persistent endothelial dysfunction.[30] These findings highlight the need to consider both preeclampsia and fetal growth restriction as risk factors for cardiovascular complications later in life, and the importance of referring these women to a regular follow-up after pregnancy.[31]

Maternal Body Mass Index

The cohort study by Kovo *et al.*[17] not only demonstrated different placental findings between fetal growth restriction cases with or without preeclampsia, but also analysed pregnancy outcomes, which were generally worse in the group with preeclampsia compared with the group without in terms of birth weight, preterm delivery and cesarean section rate, as well as neonatal complications. They also demonstrated a higher body mass index in the group with fetal growth restriction and preeclampsia.

Bicocca *et al.* evaluated Body Mass Index at delivery and rates of early- and late-onset hypertensive disorders of pregnancy in a population-based retrospective cohort study. They demonstrated that increasing severity of obesity is associated with a progressive increase in the risk of both early-onset and late-onset preeclampsia, with significant differences becoming apparent from 24 weeks of gestation.[32] However, Rasmussen *et al.*[21] showed that the excess of large-for-gestational age births in preeclampsia at term (confirmed by[26]) is largely mediated by maternal obesity. This adds to the complexity of the relationship between preeclampsia and fetal growth in late gestation.

Screening for late-onset fetal growth restriction and preeclampsia

Late-onset fetal growth restriction is still largely unpredicted in the first or second trimesters of

pregnancy. Early screening to predict the likelihood of a growth restricted fetus includes maternal history, uterine artery Doppler and maternal biophysical or biochemical markers.[33] A systematic review and meta-analysis by Cnossen *et al.* identified uterine artery Doppler as a predictor of fetal growth restriction, with better predictive capabilities when performed in the second trimester than in the first.[34] Following the trend to combine first trimester biophysical and biochemical markers for the prediction of preeclampsia, Crovetto *et al.*[35] demonstrated that an algorithm including maternal characteristics, biophysical markers (blood pressure and uterine artery Doppler) and angiogenic factors (PlGF and sFlt-1 plasma concentrations) at 11-13 weeks of gestation achieved a sensitivity for late-onset fetal growth restriction of 66%, with a 10% false positive rate. The sensitivity for late-onset fetal growth restriction with preeclampsia was only slightly better than for normotensive fetal growth restriction (70.2% *vs.* 63.5%).

Poon *et al.* in the screening program for preeclampsia (SPREE) study[23] applied the Fetal Medicine Foundation algorithm for preterm preeclampsia screening based on a combination of maternal characteristics, mean arterial pressure, uterine artery Doppler and maternal PLGF at 11-13 weeks' gestation in a population of 16,451 singleton pregnancies. The risk cut-off for preterm preeclampsia was set at 1 in 100. They also assessed the effect of first trimester screening for preeclampsia on the prediction of small-for-gestational age newborns. As shown in Table II[23] for two different birth weight cut-offs, the sensitivity of this screening approach was higher for small-for-gestational age babies delivered at less than 32 weeks (56-63%), and progressively decreased for those delivered at 32-36 weeks (43-48%) or at term (21-26%). Moreover, while the test was more sensitive for small-for-gestational age associated with preeclampsia at any gestational age, its sensitivity was much lower for small-for-gestational age without preeclampsia at 32-36 weeks (31-37%) or at term (19-23%). This is relevant since we already reported that, in the same population (Table I)[18-25] only 21% and 4% of small-for-gestational age deliveries were associated with preeclampsia at late preterm and term gestation, respectively. Therefore, while first trimester screening for preeclampsia with the Fetal Medicine Foundation approach may identify a significant proportion of preterm small-for-gestational age, potentially avoidable with aspirin prophylaxis, most small-for-gestational age cases, particularly those delivering at term without preeclampsia, cannot be predicted.

Conclusions

Fetal growth restriction and preeclampsia have a strong but complex relationship. While early-onset fetal growth restriction and preeclampsia are often strictly associated, such association becomes looser in the late preterm and term periods. Different placental and cardiovascular mechanism underlie this trend. Consequently, current strategies for first trimester screening of placental dysfunction, originally implemented for preeclampsia, do not perform well for late-onset fetal growth restriction.

TABLE II.—*Proportion of small-for-gestational-age (SGA) newborns with first-trimester combined risk for preterm preeclampsia >1 in 100 in all SGA pregnancies and in those with or without preeclampsia. Modified from Tan* et al.[23]

	Preeclampsia risk >1 in 100		
	All SGA	SGA with preeclampsia	SGA without preeclampsia
Birth weight <10th percentile			
≥37 weeks	20.7%	59.4%	19.3%
32-36 weeks	43.0%	77.8%	30.5%
<32 weeks	56.3%	89.3%	34.9%
Birth weight <3rd percentile			
≥37 weeks	26.0%	71.1%	23.4%
32-36 weeks	47.9%	72.5%	37.3%
<32 weeks	63.2%	88.9%	40.0%

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors read and approved the final version of the manuscript.

History.—Article first published online: May 5, 2021. - Manuscript accepted: February 8, 2021. - Manuscript received: February 2, 2021.