Diagnosis and surveillance of late-onset fetal growth restriction

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By consensus, late fetal growth restriction is that diagnosed >32 weeks. This condition is mildly associated with a higher risk of perinatal hypoxic events and suboptimal neurodevelopment. Histologically, it is characterized by the presence of uteroplacental vascular lesions (especially infarcts), although the incidence of such lesions is lower than in preterm fetal growth restriction. Screening procedures for fetal growth restriction need to identify small babies and then differentiate between those who are healthy and those who are pathologically small. First- or second-trimester screening strategies provide detection rates for late smallness for gestational age <50% for 10% of false positives. Compared to clinically indicated ultrasonography in the third trimester, universal screening triples the detection rate of late smallness for gestational age. As opposed to early third-trimester ultrasound, scanning late in pregnancy (around 37 weeks) increases the detection rate for birthweight <3rd centile. Contrary to early fetal growth restriction, umbilical artery Doppler velocimetry alone does not provide good differentiation between late smallness for gestational age and fetal growth restriction. A combination of biometric parameters (with severe smallness usually defined as estimated fetal weight or abdominal circumference <3rd centile) with Doppler criteria of placental insufficiency (either in the maternal [uterine Doppler] or fetal [cerebroplacental ratio] compartments) offers a classification tool that correlates with the risk for adverse perinatal outcome. There is no evidence that induction of late fetal growth restriction at term improves perinatal outcomes nor is it a cost-effective strategy, and it may increase neonatal admission when performed <38 weeks.

Key words: fetal growth restriction, infant, late-onset disorders, newborn, small-for-gestational age, term birth

Definition of "late-onset" fetal growth restriction

Late fetal growth restriction (FGR) is usually defined as that diagnosed >32 weeks of pregnancy. One study[1] showed that a cut-off of 32 weeks at diagnosis or 34 weeks at delivery maximized the clinical differences between early- and late-onset FGR, in terms of perinatal mortality (7.1% vs 0%; $P < .001$), adverse perinatal outcome (13.4% and 4.6%; $P < .001$), and association with preeclampsia (35.1% vs 12.1%; $P < .001$). More recently, a survey was conducted on 45 experts aiming at reaching consensus on the definition of late vs early FGR.[2] There was good agreement (89%) in defining late FGR as that diagnosed >32 weeks.

While in early-onset FGR the typical pattern of deterioration progresses from escalating abnormalities in Doppler parameters to abnormal biophysical parameters,[3,4] in late-onset FGR there is a common pattern of normal or minimally elevated umbilical Doppler indices with mildly abnormal cerebral Doppler, but without obvious cardiovascular changes beyond these findings.[5,6] Contrary to early-onset FGR, in late-onset FGR the association with preeclampsia is weak.[7] The Table shows the main differential features between both clinical subtypes.

Another major source of terminological confusion is the distinction between pathologically and constitutionally small fetuses. By convention, both clinical forms have been termed as "fetal growth restriction" and constitutional "smallness for gestational age" (SGA), respectively. Whereas FGR represents a pathological condition (mainly associated with placental insufficiency[8]) associated with adverse perinatal outcome, constitutional smallness is associated with near-normal perinatal outcomes as it represents the lowest end of the size spectrum of normal fetuses.

Short- and long-term consequences of late FGR

Neonatal and infant consequences

Approximately one third of the medically indicated late preterm births are complicated with FGR.[9] Late FGR is associated with cesarean delivery for fetal distress, neonatal acidosis, and admission to the neonatal unit.[10] The association with harder hypoxic events emerges when large cohorts are analyzed. Mendez-Figueroa et al,[11] in a cohort of 5416 term, uncomplicated pregnancies with SGA (birthweight [BW] <10th centile) found a higher incidence of neonatal death (1.1 vs 0.4/1000 births; adjusted odds ratio [OR], 2.56; 95% confidence interval [CI], 1.83−3.57). In another recent study, Chauhan et al[12] evaluated in a cohort of 115,502 uncomplicated pregnancies of nonanomalous singletons born at term the association between SGA (<10th centile of BW: n = 4983) and hypoxic composite neonatal morbidity including 5-minute Apgar score <5 (prevalence among SGA 0.4%), hypoxic

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Received Oct. 3, 2017; revised Nov. 16, 2017; accepted Dec. 1, 2017.

The authors report no conflict of interest.

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0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2017.12.003

ischemic encephalopathy (prevalence 0.4%), seizures (prevalence 0.1%), and neonatal death (prevalence 0.1%). After adjusting for potential confounders, hypoxic composite neonatal morbidity was significantly higher in SGA (1.1%) compared with normally grown babies (0.7%; adjusted relative risk [RR], 1.44; 95% CI, 1.07−1.93). A large case-control study[13] including 493 babies with cerebral palsy born ≥35 weeks found severe smallness (BW <2 SD) to be associated with an OR of 4.81 (95% CI, 2.7−8.5).

It has been shown by spectroscopy that late SGA fetuses[14] and, to a greater extent, late FGR infants[15] (defined by BW <3rd centile or Doppler abnormalities) have brain metabolite differences vs normally grown babies that are correlated with later neurodevelopment. A meta-analysis[16] on neurodevelopment in term SGA babies including 28 studies (7861 SGA babies) found that SGA-born infants had 0.32 SD poorer (95% CI, 0.25−0.38) standardized neurodevelopmental scores.

TABLE
Main differential features between both clinical phenotypes of fetal growth restriction

	Early FGR	Late FGR
Prevalence[7]	0.5−1%	5−10%
Challenge[10]	Management (gestational age at delivery)	Detection and diagnosis
Evidence of placental disease [1,7,a]	High 70% Abnormal umbilical Doppler 60% Association with preeclampsia Severe angiogenic disbalance	Low <10% Abnormal umbilical Doppler 15% Association with preeclampsia Mild angiogenic disbalance
Pathophysiology and oxygen delivered to brain[6]	Hypoxia +/+ Systemic cardiovascular adaptation	Hypoxia +/− Central cardiovascular adaptation
Clinical impact[10]	High mortality and morbidity	Low mortality/morbidity + high prevalence = large etiological fraction of adverse outcomes

FGR, fetal growth restriction.

[a] Crispi F, Dominguez C, Llurba E, Martin-Gallan P, Cabero L, Gratacos E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol 2006;195:201-7.

Figueras. Late-onset fetal growth restriction. Am J Obstet Gynecol 2018.

Long-term consequences

At long term, the effects of SGA are more difficult to disentangle from other environmental factors. However, a recent cohort[17] (n = 1,100,980) study that adjusted for maternal and paternal educational level found that term SGA was significantly associated with an increased risk of poor school performance at the time of graduation from compulsory school (grades <10th percentile), with adjusted OR and 95% CI ranging from 1.85 (1.65−2.07) for severe SGA (<3 SD of BW) to 1.5 (1.43−1.58) for moderate SGA (BW −2 to −3 SD). In a subanalysis, all BW groups were associated with an increased risk of poor school performance among boys with short stature (10.1% of those individuals born with a BW <2 SD) compared to those with nonshort stature. Finally, it has been suggested that fetal programing also operates in term SGA babies,[18] predisposing them to a higher incidence of metabolic syndrome. Another recent large cohort study[19] on 49,927 female nurses found that term SGA (<10th centile of BW) was associated with an increased risk of adult-onset (diagnosed >30 years) diabetes mellitus (OR, 2.42; 95% CI, 1.44−4.07, adjusted for body mass index and parental history of diabetes).

Placental histopathological findings in late FGR

Placentas from FGR fetuses delivered at term have significantly increased frequencies of uteroplacental vascular lesions (especially infarcts) compared to normal controls, although the incidence of such lesions is much lower than in preterm FGR.[20-22] Furthermore, it has been reported that compared to normal term pregnancies, placentas from FGR at term may have an increased incidence of other villous lesions including fibrosis, hypovascularity, and avascularity, suggestive of fetal thrombotic events.[23] Hence, differences in placental histopathological findings between late and early FGR are more quantitative (in severity and extension) rather than qualitative.[24] A series of 142 placentas from singleton SGA pregnancies born >34 weeks with normal umbilical artery (UA) Doppler velocimetry found that 54.2% had placental weights <3rd percentile (compared to 9.9% of 142 placentas from normally grown babies; $P < .001$). Only 21.8% (31/142) of SGA placentas were free of histological abnormalities, while it was 74.6% (106/142) in the normally grown group ($P < .001$). In the abnormal SGA placentas (111/142) there were a total of 161 lesions (classified according standardized criteria[25]) attributable to maternal underperfusion in 64% (103/161), fetal underperfusion in 15.5% (25/161), and inflammation in 20.5% (33/161). Interestingly, those pregnancies with signs of underperfusion[25] had a significantly higher incidence of emergency cesarean delivery for nonreassuring fetal status (44.1% vs 21.4%, respectively; $P = .013$) and neonatal metabolic acidosis at birth (33.3% vs 14.3%, respectively; $P = .023$) than did those without signs of underperfusion.[26] Furthermore, neonatal morbidity (as assessed by the Morbidity Assessment Index For Newborns score[27]) differed significantly between those with and without placental signs of underperfusion (89 vs 0, respectively; $P = .025$). Finally, 83 infants of the same cohort were followed up for 2-year