

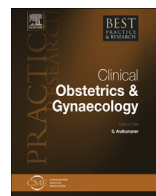


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An integrated approach to fetal growth restriction



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Fetal growth restriction (FGR) is among the most common complications of pregnancy. FGR is associated with placental insufficiency and poor perinatal outcomes. Clinical management is challenging because of variability in clinical presentation. Fetal smallness (estimated fetal weight <10th centile for gestational age) remains the best clinical surrogate for FGR. However, it is commonly accepted that not all forms of fetal smallness represent true FGR. In a significant subset of small fetuses, there is no evidence of placental involvement, perinatal outcomes are nearly normal, and they are clinically referred to as “only” small for gestational age (SGA). Doppler may improve the clinical management of FGR; however, the need to use several parameters sometimes results in a number of combinations that may render interpretation challenging when translating into clinical decisions. We propose that the management of FGR can be simplified using a sequential approach based on three steps: (1) identification of the “small fetus,” (2) differentiation between FGR and SGA, and (3) timing of delivery according to a protocol based on stages of fetal deterioration.

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Introduction

Fetal growth restriction (FGR) is one of the most common causes of poor perinatal and long-term outcomes. The definition of true FGR remains elusive, and its clinical management is challenging

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because of variability in clinical presentation. The best way to identify FGR is yet to be determined. Fetal smallness remains the best surrogate for clinical practice, and the 10th weight centile cutoff is the most universally used standard. However, fetal smallness can be produced by a variety of causes. In a substantial proportion of instances, fetal smallness is caused by placental insufficiency; however, in another important subset of small fetuses, there is no evidence of placental involvement. Clinical evidence suggests that small fetuses with placental insufficiency are associated with poorer perinatal outcomes, whereas the nonplacental group has near-normal perinatal outcomes. By arbitrary convention, the placental insufficiency cases are usually defined as (true) FGR, whereas the remaining “nonplacental” cases are referred to as small for gestational age (SGA), although both the names are not very appropriate. By definition, both groups are “small,” and we do not know whether the nonplacental group also suffers growth restriction or a milder form of placental disease, even if perinatal outcomes are normal. In fact, both SGA and FGR show an increased prevalence of long-term neurodevelopmental, cardiovascular, and endocrinological consequences. However, from a purely obstetrical point of view, in FGR, the “respiratory” function of the placenta is impaired to an extent that it may cause hypoxia and acidosis at baseline conditions (in early/severe forms) or under the stress of uterine contractions (in late/mild forms), whereas in SGA, this is not the case.

In this review, we focus on the obstetrical management of FGR. Ultrasound (US) and Doppler are the mainstay for the management. The distinction between SGA and FGR is extremely relevant, and Doppler is critical to achieve this goal. In addition, Doppler reflects the pathophysiological sequence of fetal deterioration that occurs in earlier and more severe forms of FGR with reasonable accuracy. Although Doppler may improve the clinical management of FGR, the need to use several parameters results in a number of possible combinations that may render interpretation and translation into clinical decisions challenging. We propose that the management of FGR can be simplified using a sequential approach based on three steps: (i) identification of the “small fetus,” (ii) differentiation between FGR and SGA, and (iii) timing of delivery according to a protocol based on stages of fetal deterioration.

Identification of the “small fetus”

Antenatal detection of babies with defective growth often falls short, missing up to 75% of babies at a risk of SGA before delivery [1]. In low-risk pregnancies, the detection rate is worse (approximately 15%) [2]. Such poor performance negatively affects the birth rate as most instances of avoidable still-birth are linked to failures in antenatal SGA detection [3].

First- or second-trimester screening with uterine Doppler and maternal characteristics may detect early-onset growth restriction in up to 90% cases [4]. In addition, up to 60% of the latter are detected because of preeclampsia (PE) [5]. Unfortunately, late-onset growth restriction remains largely overlooked [6,7] when accounting for a large fraction of adverse outcomes [8,9]. Detecting late-onset growth restriction, particularly severe states [10–12], is thus central to third-trimester screening. The diagnosis is universally established by an estimated fetal weight (EFW) below the 10th centile. Widely accepted alternative definitions include an abdominal circumference <10th centile or a declining fetal growth (defined as when the growth trajectory crosses two quartile).

Fundal height determination detects only 16% of SGA infants in low-risk populations [13]. Third-trimester US monitoring of fetal growth is routinely performed in some countries, thus boosting the detection rates to 40–80% [14,15]. However, a recent study reported that universal screening tripled the detection rate of SGA compared with selective screening [16], but another study found similar detection rates when universal and contingent screening were compared [17].

The effect of detecting SGA remains unclear. A meta-analysis of randomized trials failed to demonstrate benefit from routine third-trimester scan [18,19]; however, most studies included were relatively old. The most recent study [20] was dated 2003, and it claimed a 30% reduction in FGR. Most studies in the meta-analysis involved no change in management if FGR was diagnosed, and only three studies [20–22] (representing 12% of the patients included) performed US examination after 34 weeks. A recent randomized study [23] showed that routine 36-week scans doubled the rate of detection of SGA compared with 32-week scans.

Detecting SGA has potential benefits. Detection prompts Doppler studies, which reduce stillbirth without increasing neonatal mortality [24]. A large study in the USA reported a significantly increased risk of stillbirth in SGA delivered at term [25]. A study including 92,218 singletons found stillbirth rates of 9.7 versus 18.9 per 1000 birth with antenatally detected versus nondetected FGR [26]. Gestational age in both groups differed by only 10 days (270 vs. 280 days), which underscores the relevance of detection and delivery at term. Another large study [14] reported that undetected severe FGR (<3rd centile) resulted in a four-fold increase in adverse fetal outcomes.

Distinction between FGR and SGA

As previously mentioned, small fetuses in a normally nourished population represent a heterogeneous population with the following main phenotypes: (i) those caused by placental insufficiency and considered true FGR cases; (ii) those in which no signs of placental insufficiency are detected, which may be “constitutionally small” or represent other causes to be elucidated; and (iii) those with congenital malformations (including chromosomopathies) or infections. The last group represents a small proportion. If presenting as severe early cases, a genetic array may improve detection [27,28]. Similarly, cytomegalovirus or malaria (in endemic areas) testing may be appropriate. Thus, most isolated small fetuses will fall within the clinical categories of either FGR or SGA. The clinical distinction between late FGR versus SGA is relevant because it correlates with perinatal outcomes; however, this may be challenging in late pregnancy.

FGR versus SGA in early pregnancy

Umbilical artery (UA) Doppler adequately captures early-onset placental insufficiency. A survey of 45 experts found good agreement that before 32 weeks, abnormal UA Doppler (either increased pulsatility index >95th centile or absent/reversed end diastolic flow) is a criterion for FGR [29]. The use of UA Doppler in high-risk pregnancies has been associated with a reduction in adverse outcomes and a 30% mortality reduction [30]. In addition to the UA, uterine artery (UtA) Doppler reflects placental insufficiency from the maternal side and may capture placental insufficiency that is secondary to other pathophysiologic mechanisms other than early defective trophoblastic invasion [31]. Thus, there is agreement to include this parameter in the definition of early FGR [29]. Finally, we believe that it is reasonable to systematically measure the cerebroplacental ratio (see the following sections).

FGR versus SGA in late pregnancy

In late-onset FGR, the UA Doppler does not reliably reflect placental insufficiency and does not predict adverse outcomes [32,33]. Although late-onset SGA cases are associated with histological signs of placental underperfusion [34], this is not reflected in the UA Doppler. As suggested by animal [35] and mathematical [36] models, the UA Doppler becomes abnormal only if an extensive part of the placenta is involved. On the contrary, middle cerebral artery (MCA) Doppler is abnormal (<5th centile) in 15–20% of term SGA fetuses and is associated with poorer perinatal and neurological outcomes [37–40]. Furthermore, the cerebroplacental ratio (CPR), which combines the pulsatility index of the MCA and UA, is affected in about 25% of term SGA fetuses. The CPR is more sensitive to hypoxia than its individual components [41], and it correlates better with adverse outcomes [42,43]. Abnormal UtA Doppler is also associated with intrapartum fetal distress, emergency cesarean delivery, and admission to intensive care unit [38,44,45]. Finally, a very low EFW centile (<3rd centile) predicts adverse perinatal outcomes irrespective of Doppler findings [11,46].

Observational studies suggest that growth velocity is a good predictor of adverse outcomes in SGA [32]; however, there is a lack of prospective studies evaluating the feasibility and performance in large populations. In future, maternal blood biomarkers such as some angiogenic factors may be used as a diagnostic criterion for FGR in composite algorithms [48–51]. Angiogenic factors that are commonly evaluated in FGR are soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF). These biomarkers are strongly associated with changes in the CPR, UtA [48], and histological signs of

placental underperfusion [51]. Similarly, among small fetuses, PIGF and sFlt-1 measured at diagnosis predict adverse outcomes with a similar performance to that of Doppler US [48].

A combined model for distinction between SGA and FGR

We proposed a combined model to distinguish FGR from SGA with detection rates of 83% for adverse outcomes [47], which integrates the estimation of fetal weight with Doppler of the UA, MCA, and UtA. FGR is defined when SGA is combined with an abnormal CPR, abnormal UtA, or EFW <3rd centile. These criteria include all the other criteria (i.e., an abnormal UA by definition results in an abnormal CPR). The algorithm is most useful in late-onset FGR, although in early-onset cases, the use of UA might suffice for the diagnosis. A combined model may facilitate detection in most clinical settings, and it can be updated with further research clarifying the contribution of other parameters (discussed earlier).

Clinical implications for management

Although SGA fetuses with moderate growth restriction (>3rd centile) and normal placental function on both the fetal (normal CPR) and maternal (normal uterine Doppler) sides could be considered low risk and managed as constitutionally small babies, those with either severe growth restriction or evidence of placental dysfunction should be considered high risk. In our series [47], “nonplacental” smallness, as defined by the combined algorithm above, accounted for 40% of the population, in which only 17% of the instances of adverse outcomes occurred (cesarean section for fetal distress or neonatal acidosis), whereas late FGR represented the remaining 60% of the population, in which 83% of the instances of adverse outcomes occurred.

The distinction between early and late FGR

As discussed above, FGR presents under two clinical patterns, as determined by the gestational age at onset [33,52,53]. In early-onset FGR, the typical pattern of deterioration progresses from escalating abnormalities in UA and venous Doppler parameters to abnormal biophysical parameters, often necessitating preterm delivery. In addition, there is a high association with PE and perinatal mortality [5,54,55]. In contrast, late-onset FGR is normally associated with less severe placental disease and normal or minimally elevated UA Doppler indices but abnormal CPR and no obvious cardiovascular adaptation beyond the cerebral circulation. The association with PE is minimal [5]. A previous study [56] showed that a cut-off of 32 weeks at diagnosis or 34 weeks at delivery maximized the differences between early- and late-onset FGR (Table 1), although resulting in substantial overlapping of cases with similar characteristics. In an experts' survey, there was good agreement (89%) in defining early FGR as that diagnosed before 32 weeks [29]. In our opinion, the distinction between early and late FGR has great pathophysiological implications, and it is mandatory in any research study performed today. However, as with anything in biology, the transition from the “typical” early to the late FGR case is extremely progressive; therefore, individual cases may show a huge overlapping of features. We

Table 1

Summary of the main differences between early- and late-onset forms of FGR.

Early-onset FGR	Late-onset FGR
CHALLENGE: MANAGEMENT	CHALLENGE: DIAGNOSIS
Prevalence: ~1%	Prevalence: 3–5%
Severe placental disease: UA Doppler abnormal, high association with PE	Mild placental disease: UA Doppler normal, low association with PE
Severe hypoxia ++: systemic CV adaptation	Mild hypoxia: central CV adaptation
High mortality and morbidity.	Lower mortality (but common cause of late stillbirth).

Abbreviations: PE: preeclampsia, CV: cardiovascular.

therefore propose that a single protocol for the management of FGR simplifies the application of the steps required for clinical management.

Timing of delivery in SGA and FGR

We first briefly introduce the most widely proposed and/or used parameters for follow-up and then briefly discuss a proposal for a stage-based management.

Evidence on the parameters for fetal monitoring

There is evidence from a randomized trial [57] that twice-a-week monitoring results in more inductions without any improvement in the perinatal outcomes than monitoring every 2 weeks. Thus, the standard of care for low-risk SGA would be to monitor every 2 weeks. However, in late-onset FGR, such a definition of “low-risk SGA” cannot be trusted on the basis of the umbilical Doppler, and therefore, some other markers are needed.

Amniotic fluid

In a large study on late SGA [58], one-third of the cases had oligohydramnios, as defined by an amniotic fluid index of <5 cm. However, the amniotic fluid index results in more inductions and cesarean sections than the single deepest vertical pocket without improving perinatal outcomes [59]. A meta-analysis [60] of 18 trials showed an association between SGA and abnormal 5-min Apgar but not acidosis or perinatal death [RR 1.6 (95% CI 0.9–2.6)]. Because of the limited evidence, the inclusion of oligohydramnios in the management protocols of SGA/FGR is doubtful.

Doppler parameters

UA Doppler. UA Doppler in high-risk pregnancies improves perinatal outcomes, with a 29% reduction in perinatal deaths [61]. Absent or reversed end-diastolic velocities are present on average 1 week before the acute deterioration [62] and are associated with adverse perinatal outcomes [63]. After 30 weeks, the risk of stillbirth of a fetus with isolated reversed end-diastolic velocities in the UA Doppler overcomes the risks of prematurity [64–66], and therefore, delivery seems justified.

MCA Doppler and CPR. MCA Doppler indicates brain vasodilation, a surrogate marker of hypoxia, and is associated with adverse perinatal and neurological outcomes [67–71]; however, it is unclear whether delivering before term could add any benefit. MCA is particularly valuable for the identification of [33] and prediction of adverse outcomes in [37,67] late-onset FGR, independent of the UA Doppler, which is often normal in these fetuses. However, MCA is a rather late manifestation, with acceptable specificity but low sensitivity, which is improved by the use of the CPR.

The CPR improves the sensitivity of UA and MCA alone because it is already decreased when its individual components are still within normal ranges [41,43]. In late-onset SGA fetuses, abnormal CPR is present in 25% of the cases [72], and it is associated with abnormal perinatal outcomes [68].

Ductus venosus Doppler. Ductus venosus (DV) is the strongest single parameter to predict the short-term risk of fetal death in early-onset FGR. DV becomes abnormal only in advanced stages of fetal compromise [52,62,63,73], and absent/reversed velocities during atrial contraction are associated with perinatal mortality [74], with a 40–100% risk in early-onset FGR [66,75]. Thus, this parameter is considered sufficient to recommend delivery at any gestational age after the completion of steroids. In 50% of the cases, abnormal DV precedes the loss of short-term variability in computerized cardiotocography (cCTG) [52], and in 90% of the cases, it precedes the biophysical profile (BPP) by 48–72 h [73].

Aortic isthmus Doppler. Aortic isthmus (AoI) reflects the balance between the impedance of the brain and systemic vascular systems [76,77], and it represents the next step in the sequence starting with the UA and MCA Doppler. It is associated with both adverse perinatal [78] and neurological outcomes [79]

but precedes DV abnormalities by 1 week [80,81], and thus, its predictive accuracy is not superior to that of DV for short-term mortality [66].

Fetal heart rate (FHR) analysis by conventional CTG and cCTG

Although highly sensitive, cardiotocography has a 50% rate of false positives for predicting adverse outcomes [82]. A meta-analysis [83] of high-risk pregnancies failed to demonstrate a reduction in perinatal mortality. Therefore, there is no evidence to support traditional FHR monitoring in FGR fetuses. An additional limitation is the subjective and challenging interpretation in preterm fetuses.

cCGT is a step forward in the management of FGR. It evaluates short-term variability of the FHR, and it is sensitive enough to detect advanced fetal deterioration, with a value similar to that of DV reverse atrial flow. Although in approximately half the cases abnormal DV precedes the loss of short-term FHR variability, the latter is the first to become abnormal in the remaining cases [52].

BPP

Recent studies on early-onset very preterm FGR fetuses have raised concerns on the false-positive rate, with up to 23% of instances of intrauterine fetal death occurring in cases with BPP of >6 and 11% in those with BPP of >8 [84]. A meta-analysis [85] showed no significant benefit of BPP in high-risk pregnancies. Consequently, whenever Doppler expertise and/or cCTG are available, the use of BPP is questionable.

Evidences on the timing of delivery

No treatment has been demonstrated to benefit growth restriction [86–90]. Thus, assessment of fetal well-being and timely delivery remain as the main management strategies. The GRIT trial [65] compared premature delivery with delivery delayed for as long as possible. Immediate versus delayed delivery resulted in an almost equal number of additional deaths; however, at 2 years of age, there was a trend toward more disability in the immediate delivery group [64]. The TRUFFLE trial [91] compared three strategies in early onset FGR (<32 weeks): short-term variation < 3.5–4 ms, early changes in the DV (pulsatility index > 95th centile), and late DV changes (absent/reversed atrial flow). Overall, perinatal and neonatal outcomes were better than those previous series (70% intact survival) [54], reinforcing that when a protocol is established, there is an improvement in care. Overall, neurodevelopmental impairment was less likely in survivors of the DV groups compared to those in the cCTG group; however, there was some overlapping in the actual use of the tests used in each study group. The main message was that cCTG and DV could be combined in the management of early FGR babies. Finally, the DIGITAT trial reported similar perinatal, neonatal, and 2-year outcomes when induction of labor and expectant monitoring were compared in term SGA pregnancies [12,58,69]; however, the study did not differentiate SGA from true FGR.

A stage-based protocol for managing FGR/SGA

Although strong evidence supporting firm recommendations on the timing of delivery is lacking, a protocol that integrates the best available evidence can help in reducing clinical practice variation. One approach is to group the indices or signs that are associated with similar fetal risks in stages because they should indicate similar follow-up intervals and timing of delivery. Thus, we suggest to manage SGA/FGR in an integrated fashion and profile several stages, or prognostic groups, that define different management strategies. The stages and recommendations are summarized below and in Figure 1. For obvious reasons, when FGR is associated with severe PE, this protocol should be combined with a protocol for the management of PE, which considers the maternal condition and the possibility of rapid fetal deterioration in this disease, and decisions should be adjusted accordingly.

SGA: Fortnightly Doppler and growth assessment is safe [57] and constitutes standard practice. Labor induction is recommended at 40 weeks.

Stage I FGR [severe smallness or mild placental insufficiency]: Either UtA, UA, or MCA Doppler or the CPR is abnormal. Available evidence suggests a low risk of fetal deterioration before term. Labor induction beyond 37 weeks is acceptable, but the risk of intrapartum fetal distress is increased [68]. Weekly monitoring is recommended.

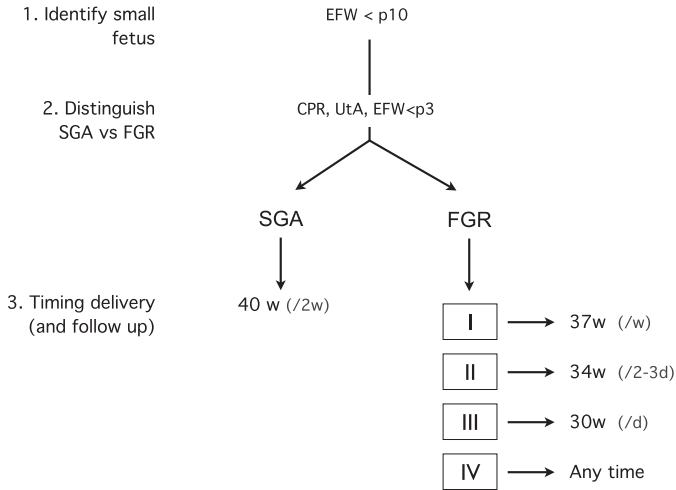


Figure 1. Integrated protocol for the management of FGR.

Stage II FGR [severe placental insufficiency]: This stage is defined by UA AEDV and also probably by reverse Aol. Delivery should be recommended after 34 weeks. The risk of emergent cesarean section at labor induction exceeds 50%; therefore, elective cesarean section is a reasonable option. Monitoring twice a week is recommended.

Stage III FGR [advanced fetal deterioration, low-suspicion signs of fetal acidosis]: The stage is defined by reverse diastolic flow in the UA or a DV-PI of > 95th centile. Stage III is associated with a higher risk of stillbirth and poorer neurological outcomes. However, because signs suggesting a very high risk of stillbirth within days are not present yet, it seems reasonable to delay elective delivery to reduce the effects of severe prematurity as much as possible. We recommend delivery by cesarean section after 30 weeks. Monitoring every 24–48 h is recommended.

Stage IV FGR [high-suspicion of fetal acidosis and high risk of fetal death]: There are spontaneous FHR decelerations, reduced short-term variability (<3 ms) in the cCTG, or reverse atrial flow in the DV Doppler. Delivery after 26 weeks by cesarean section at a tertiary care center under steroid treatment for lung maturation (and prophylaxis of cerebral palsy with magnesium sulfate) is recommended. Intact survival exceeds 50% only after 26–28 weeks, and before this threshold, parents should be counseled by multidisciplinary teams. Monitoring every 12–24 h until delivery is recommended.

Conflict of interest

The authors have no conflict of interest to declare.

Practice points

- US and Doppler are the mainstay for the management of FGR.
- The primary goal is the identification of the small fetus, and for this, the use of EFW and a cut-off of 10th centile remain the most widely used standards.
- The second goal is distinction between FGR and SGA because this has implications for the follow-up intervals and timing of delivery.
- Once FGR is identified, the third goal is to determine monitoring intervals and timing of delivery. This is best achieved with an integrated protocol based on the fetal stage of deterioration.

Research Agenda

- A more precise phenomapping of the “small fetus syndrome” and the variable causes leading to this problem is required.
- Better algorithms to identify the true forms of FGR are required.

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