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Update on the Diagnosis and Classification of Fetal Growth Restriction and Proposal of a Stage-Based Management Protocol

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Key Words

Fetal growth restriction update · Stage-based management protocol · Constitutional small-for-gestational age · Early-severe versus late-mild fetal growth restriction

Abstract

Small fetuses are defined as those with an ultrasound estimated weight below a threshold, most commonly the 10th centile. The first clinically relevant step is the distinction of 'true' fetal growth restriction (FGR), associated with signs of abnormal fetoplacental function and poorer perinatal outcome, from constitutional small-for-gestational age, with a near-normal perinatal outcome. Nowadays such a distinction should not be based solely on umbilical artery Doppler, since this index detects only early-onset severe forms. FGR should be diagnosed in the presence of any of the factors associated with a poorer perinatal outcome, including Doppler cerebroplacental ratio, uterine artery Doppler, a growth centile below the 3rd centile, and, possibly in the near future, maternal angiogenic factors. Once the diagnosis is established, differentiating into early- and late-onset FGR is useful mainly for research purposes, because it distinguishes two clear phenotypes with differences in severity, association with preeclampsia, and the natural history of fetal deterioration. As a second clinically relevant step, management of FGR and the decision to deliver aims at an optimal balance between minimizing fetal injury or death versus the risks of iatrogenic preterm delivery. We propose a protocol that integrates current evidence to classify stages of fetal deterioration and establishes follow-up intervals and optimal delivery timings, which may facilitate decisions and reduce practice variability in this complex clinical condition.

Introduction

Fetal growth restriction (FGR) is defined as a failure to achieve the endorsed growth potential. The diagnosis of fetal 'smallness' is currently performed on the basis of an estimated fetal weight (EFW) below a given threshold, most commonly the 10th centile. It is likely that this definition lacks sensitivity, so that it misses cases of growth restriction that do not fall below the 10th centile, but it identifies a subset of pregnancies at high risk of poorer perinatal outcome. Thus, detection of small fetuses is clinically relevant because as a whole this group of fetuses

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is associated with poorer perinatal outcome, and this represents opportunities for preventing cases of intrauterine fetal death, perinatal brain injury and severe intrapartum fetal distress. In addition, evidence accumulating over the last 20 years has consistently demonstrated how being born small has important implications for the quality of health during adulthood.

Population-based series show that prenatal identification of small-for-gestational age (SGA) babies results in a reduction of adverse perinatal outcomes and stillbirth [1, 2]. However, most SGA babies remain unnoticed until birth, even when routine third-trimester ultrasound is performed [3, 4]. Moreover, according to pregnancy audits, most instances of avoidable stillbirth are related with a failure to antenatally detect SGA [5]. In order to define strategies to improve detection, our understanding of the different clinical forms and its risks factors should also be improved. Furthermore, there is a wide variability in the management of FGR in terms of monitoring and recommended gestational age at delivery, mainly in early-onset forms. Clinical practice variability, a marker of poor quality of care, is partially accounted for by the lack of comparability among studies and the lack of clear recommendations in the medical literature, combined with the difficulty of integrating the meaning of the myriad of parameters described for FGR, with the risks of delivery at different gestational age periods.

In this review we analyze current evidence and suggest a systematic approach to FGR, which entails a proper identification of FGR versus SGA, and a stage-based management protocol which may help in reducing clinical variability.

Distinction between 'Fetal Growth Restriction' and '(Constitutional) Small-for-Gestational Age'

While overall fetal smallness is associated with poorer outcome, clinical evidence suggests that there are, at least, two groups of small fetuses. By arbitrary convention, these two groups are normally referred to as FGR versus constitutional SGA, the latter category henceforth referred as SGA.

FGR is normally used to refer to small fetuses with higher risk for fetal in utero deterioration, stillbirth and overall poorer perinatal outcome as compared with normally grown fetuses. These fetuses are thought to have 'true' growth restriction. In general, FGR is associated with Doppler signs suggesting hemodynamic redistribution as a reflection of fetal adaptation to undernutrition/hypoxia, histological and biochemical signs of placental disease and a higher risk of preeclampsia. The term SGA has been used to differentiate a subgroup of small fetuses that do not present the changes described above, so that there appears to be no fetal adaptation to an abnormal environment and with perinatal outcomes similar to those of normally grown fetuses.

Irrespective of whether these diagnostic labels are a proper reflection of the underlying pathophysiology, from a clinical point of view the distinction between FGR versus SGA is relevant because of the correlation with perinatal outcome. There is wide consensus that it is reasonable to deliver electively FGR when lung maturation can be presumed, or earlier if signs of fetal deterioration are observed. On the contrary, SGA fetuses are associated with virtually normal perinatal outcome and it is generally considered that active management or elective delivery before full term offers no benefit. While the concepts of FGR and SGA may be clear, the distinction of 'true FGR' in clinical practice can be challenging. The differentiation of these two forms has long been based on Doppler signs reflecting fetal adaptation to increased placental resistance and/or hypoxia.

Umbilical Artery as a Standalone Standard Is Not Valid Anymore

For almost 20 years, the umbilical artery (UA) has been widely accepted as the standard to identify FGR. During the 1980s and 1990s, a substantial number of studies demonstrated that abnormal UA Doppler indicated a poorer outcome among small fetuses. In addition, meta-analyses have shown that UA Doppler could improve mortality and perinatal outcome in FGR [6]. This led to identify UA as a surrogate of placental disease and consequently to consider small fetuses with normal UA Doppler as SGA with no placental disease [7]. However, this assumption was based on false premises, because it extended observations that are valid in the most severe subset of FGR fetuses to the whole group of FGR. While UA identifies severe placental disease, it fails to pick up instances of mild placental disease which constitute a proportion of early-onset cases and virtually all instances of late-onset FGR [8].

Evidence during the last two decades has demonstrated that SGA, as defined by a normal UA pulsatility index (PI), contains a large proportion of fetuses with worse perinatal outcomes than normally grown fetuses [3, 9–11]. Thus, UA Doppler cannot be used as a standalone criterion to differentiate FGR from SGA.

Improving the Definition of Fetal Growth Restriction: Parameters Identifying the Small Fetus with Poor Outcome

Research over the last 10 years has investigated predictors of poor outcome among mild-late forms of FGR. Current evidence suggests that there is not a single parameter to best differentiate FGR from SGA. The best individual candidate is the Doppler cerebroplacental ratio (CPR). CPR is calculated by dividing the middle cerebral artery (MCA) PI by the UA Doppler PI. This index reflects in a combined fashion mild increases in placental resistance with mild reductions in fetal brain vascular resistance. In animal [12] and clinical [13] models this ratio has been demonstrated to be more sensitive to hypoxia than its individual components and correlates better with adverse outcome [14]. Since the CPR includes the UA, it can replace its use for the detection of FGR at any gestational age.

Aside from CPR, the uterine artery Doppler PI (UtA PI) can be abnormal in the presence of a normal UA Doppler in small fetuses and predicts a poorer outcome in small fetuses. If used in combination with the cerebral or umbilical Doppler, its independent predictive value is reduced, but evidence still suggests that it can marginally improve the identification of poor outcome [11, 15, 16]. Another predictor of poor outcome is a very small EFW. Among fetuses below the 10th centile, those with an EFW <p3 have a much higher risk of adverse perinatal outcome irrespective of the CPR and UtA Doppler indices [17].

Therefore, when either CPR, UtA PI or EFW <p3 is abnormal, the risk of adverse perinatal outcome is increased. In a recent study including 500 small fetuses and 500 normally grown fetuses, the risk of cesarean section for fetal distress or neonatal acidosis was 8% in controls, 11% when all the three parameters were normal and 36% when any was abnormal [18].

Thus, the definition of FGR should include these three parameters. The impact of using such an 'extended' definition in the distinction of small fetuses as FGR or SGA in comparison to a classical UA-based definition is illustrated in figure 1.

It is likely that in future years maternal blood biomarkers are incorporated as a diagnostic criterion of FGR, as a marker of placental involvement. Recent evidence suggests that angiogenic factors predict a poor perinatal outcome among small fetuses, with similar predictive values to those of CPR and UtA PI, but apparently with no additive value [19]. There is a need to conduct more studies confirming this notion and to develop normative gestational age-adjusted values.

SGA Is Not Always Constitutionally Small

As discussed above, the use of the terms FGR and SGA distinguishes two groups with differences in perinatal outcome, and this has important implications for pregnancy management. However, fetuses under this latter diagnostic category have been consistently demonstrated to present signs of brain reorganization in utero and neonatally [20], poor long-term neurological outcome [21], cardiovascular [22] and endocrinological outcome [23]. This evidence demonstrates that such defined SGA fetuses are, in the majority of instances, not just 'constitutionally small'. It remains to be established whether SGA is a category composed by a single problem or a mixture of different causes, which might include among others a subset of fetuses with placental insufficiency of even milder nature, abnormalities in hormonal pathways regulating fetal growth, genetic causes, and true constitutional smallness.

Pathophysiological and Clinical Differences in Early-Severe versus Late-Mild Fetal Growth Restriction

Rationale for Differentiating between Early- and Late-Onset Forms of Fetal Growth Restriction

As far as evidence suggests, FGR is defined by the existence of placental insufficiency [24]. Within this common pathogenesis, FGR presents under two different phenotypes when the onset is early or late in gestation. In general, but not always, there is a correspondence between early-onset and the most severe forms of FGR. Table 1 depicts the main differences between both clinical forms.

Differentiating between early- and late-onset FGR has a clear value for comparability among research studies and to help clinicians in the understanding of the different presentations of the disease. From the point of view of clinical management, it is questionable that this differentiation has added value, as long as a stage-based protocol for management is used, as discussed in later in this article.

Early-Onset Fetal Growth Restriction

Early-onset FGR represents 20–30% of all FGRs [25]. Early FGR presents in association with early PE in up to 50% [25]. Early-onset FGR is highly associated with severe placental insufficiency and with chronic fetal hypoxia. This explains that UA Doppler is abnormal in a high proportion of cases [26]. If left untreated the fetal condition deteriorates with progression to decompensated

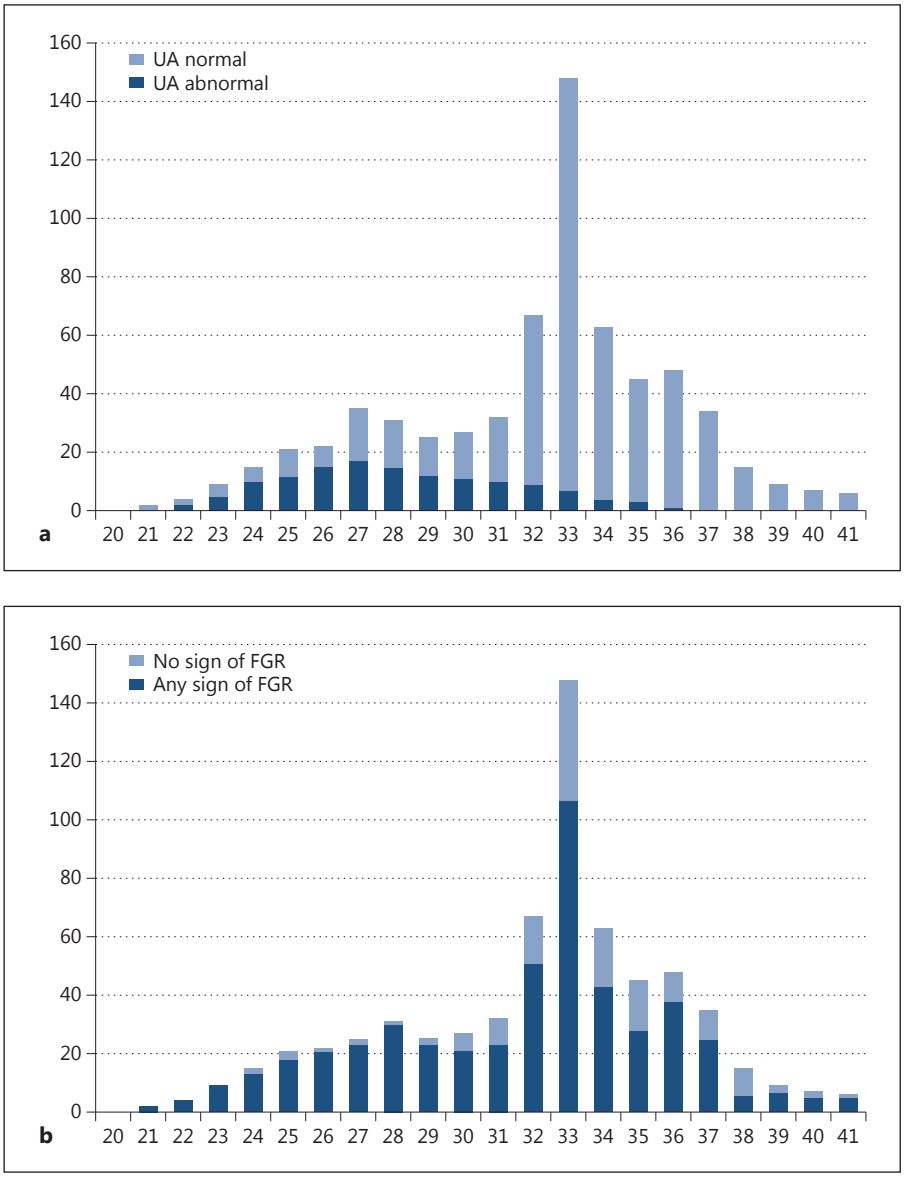

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Fig. 1. Distribution of a large population of small fetuses (n = 656) in FGR or SGA. **a** FGR is defined by an UA PI >95th centile only. **b** FGR is defined using a combination of CPR <5th centile, UtA PI >95th centile and an EFW <3rd centile. Note how a remarkable proportion of 'SGA' defined by UA PI are reclassified as true FGR when the combined definition is used, particularly among late-onset FGR fetuses.

Table 1. Summary of the main differences between early- and late-onset forms of FGR

Early-onset FGR (1–2%)	Late-onset FGR (3–5%)
Problem: management	Problem: diagnosis
Placental disease: severe (UA Doppler abnormal, high association with preeclampsia)	Placental disease: mild (UA Doppler normal, low association with preeclampsia)
Hypoxia ++: systemic cardiovascular adaptation	Hypoxia +/–: central cardiovascular adaptation
Immature fetus = higher tolerance to hypoxia = natural history	Mature fetus = lower tolerance to hypoxia = no (or very short) natural history
High mortality and morbidity; lower prevalence	Lower mortality (but common cause of late stillbirth); poor long-term outcome; affects large fraction of pregnancies

hypoxia and acidosis, which is reflected by escalating abnormalities in the UA and increased PIs in the precordial veins, mainly the ductus venosus (DV). The latency of severe fetal deterioration can vary in individual cases, but it normally lasts weeks [27] and it often follows a cascade of changes which are reflected in a pattern of Doppler changes that allows to monitor the progression of fetal deterioration and tailor elective delivery (fig. 1).

Early severe FGR is associated with severe injury and/or fetal death before term in many cases [28]. Management is challenging and aims at achieving the best balance between the risks of leaving the fetus in utero versus the complications of prematurity.

Late-Onset Fetal Growth Restriction

Late-onset FGR represents 70–80% of FGR [25]. A first distinction with early-onset forms is that the association with late PE is low, roughly 10% [25]. The degree of placental disease is mild, thus UA Doppler is normal in virtually all cases [8]. Despite normal UA PI Doppler, there is a high association with abnormal CPR values [8]. In addition, advanced brain vasodilation suggesting chronic hypoxia, as reflected by an MCA PI <p5, may occur in 25% of late FGR [8]. Advanced signs of fetal deterioration with changes in the DV are virtually never observed [8, 29]. Thus, the cascade of sequential fetal deterioration described above does not occur in late FGR.

Despite a more benign nature as compared with early FGR, there is a risk of acute fetal deterioration before labor, as suggested by the high contribution to late-pregnancy mortality [30], and a high association with intrapartum fetal distress and neonatal acidosis [31]. Thus, late FGR lacks a 'natural history' and may undergo rapid deterioration leading to severe injury or death without observable late-stage signs as in early FGR (cf. fig. 3). This might be explained by a combination of causes, which could include the very low tolerance of term fetuses to hypoxia in comparison with preterm, the more frequent presence of uterine contractions in a term pregnancy, and some instances of rapid placental function failure.

Contrary to early FGR, late FGR should not represent a management challenge once the diagnosis is established. However, low diagnostic rates still influence that (undiagnosed) FGR contributes to a large share of late pregnancy stillbirths [2].

Common Issues between Early and Late Fetal Growth Restriction

Despite remarkable differences in the severity of the fetal disease, early- and late-onset FGRs are both associated with poor long-term outcome from neurodevelopmental, cardiovascular and metabolic standpoints [21–23, 32, 33]. This supports the notion that regardless of the severity, chronic exposure to adverse intrauterine environment is critical to determine adverse fetal programming. Additionally, it is likely that different fetal maturational stages determine different adaptive programming responses.

As far as evidence suggests, early and late FGRs are both caused by placental disease, but it is unknown whether they are associated with the same type of placental disease. Placental insufficiency in early-onset FGR is associated with histological signs of abnormal early implantation [34]. It is unclear whether late FGR is a mild form of abnormal placental implantation at early pregnancy or a superimposed placental damage occurring during the second half of the pregnancy. Furthermore, there is evidence supporting that placental disease in late-onset FGR might develop late in pregnancy, as suggested by a proportion of these patients developing abnormal UtA Doppler in the third trimester, after previously normal values [35].

Gestational Age Cut-Off to Define Early versus Late

By definition, any cut-off used to classify according to the gestational age at onset of FGR will be arbitrary and determined by the use and timing of third-trimester ultrasound in each setting, and by the protocol determining management and timing of delivery. In addition, since this is not an etiologic classification it will be hampered by a huge degree of overlapping in clinical features.

The cut-off to define early- versus late-onset FGR has commonly been set in an arbitrary fashion at about 32–34 weeks at diagnosis or 37 weeks at delivery. A prospective study using decision tree analysis in >700 cases determined that 32 weeks at diagnosis and 37 weeks at delivery best classified two groups where the differences in terms of adverse perinatal outcome are maximized [36].

Clinical Management of Fetal Growth Restriction and Small-for-Gestational Age Fetuses

Over the following sections we first briefly review existing evidence on the correlation between methods for assessing fetal well-being in FGR and the risk of fetal injury or death. Subsequently, we propose a unique managing guideline for FGR as a whole, which integrates existing evidence to define stages of fetal deterioration, and proposes follow-up intervals, and ideal gestational age at and mode of delivery for each stage.

Brief Description of Methods and Indices for Fetal Assessment and Their Correlation with Perinatal Outcomes

Fetal well-being tests and indices could be roughly classified as chronic or acute. Whilst the former become progressively abnormal due to increasing hypoxemia and/or hypoxia, the latter correlate with acute changes occurring in advanced stages of fetal compromise, characterized by severe hypoxia and metabolic acidosis, and usually precedes fetal death in a few days. Some of the measures and indices discussed below are essentially used for the diagnosis/identification of FGR from SGA, and consequently they are relevant for the decision as to whether delivery is indicated when pregnancy term is reached. Another set of indices have a prognostic value, since they are useful to determine that there is a high risk of deterioration, and consequently they are used to indicate delivery before term is reached.

Umbilical Artery Doppler

UA Doppler is the only measure that provides both diagnostic and prognostic information for the management of FGR. On the one hand, increased UA Doppler PI has a great clinical value for the identification of FGR, alone or combined in the CPR ratio. On the other hand, the progression of UA Doppler patterns to absent or reverse end-diastolic flow correlates with the risks of injury or death.

There is compelling evidence that using UA Doppler in high-risk pregnancies (most of them SGA fetuses) improves perinatal outcomes, with a 29% reduction (2–48%) in perinatal deaths [6]. Absent or reversed end-diastolic velocities, the end of the spectrum of the abnormalities of the UA Doppler, have been reported to be present on average 1 week before the acute deterioration [37]. Up to 40% of fetuses with acidosis show this umbilical flow pattern [37]. There is an association between reversed end-diastolic flow in the UA and adverse perinatal outcome (with a sensitivity and specificity of about 60%), which seems to be independent of prematurity [38]. 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 [39–41], and therefore delivery seems justified.

Middle Cerebral Artery Doppler

MCA informs about the existence of brain vasodilation, a surrogate marker of hypoxia. MCA is considered a rather late manifestation, with acceptable specificity but low sensitivity, which is improved by the use of CPR, as discussed below. There is an association between abnormal MCA PI and adverse perinatal and neurological outcome, but it is unclear whether delivering before term could add any benefit. MCA is particularly valuable for the identification [8] and prediction [42, 43] of adverse outcome among late-onset FGR, independently of the UA Doppler, which is often normal in these fetuses. Fetuses with abnormal MCA PI had a sixfold risk of emergency cesarean section for fetal distress when compared with SGA fetuses with normal MCA PI [44], which is particularly relevant because labor induction at term is the current standard of care of late-onset FGR [45, 46]. Late FGRs with abnormal MCA PI have poorer neurobehavioral competence at birth and at 2 years of age [42, 47].

Cerebroplacental Ratio

The CPR is essentially a diagnostic index. The CPR improves remarkably the sensitivity of UA and MCA alone, because increased placental impedance (UA) is often combined with reduced cerebral resistance (MCA). Thus, the CPR is already decreased when its individual components suffer mild changes but are still within normal ranges [13, 48]. In late SGA fetuses, abnormal CPR is present before delivery in 20–25% of the cases [49], and it is associated with a higher risk of adverse outcome at induction, although to a lesser degree than MCA [44]. There are no long-term studies evaluating the neurobehavioral or neurodevelopmental consequences of late SGA with abnormal CPR. However, it is remarkable that even in the general population, an abnormal CPR predicts neurobehavioral problems at 18 months of age [50]. Interestingly, the anterior cerebral artery-CPR rather than the MCA-CPR showed the stronger association, demonstrating a differential impact of regional alterations in cerebral blood flow impedance on development, which is consistent with findings in early FGR [51, 52].

Ductus Venosus Doppler

DV is the strongest single Doppler parameter to predict the short-term risk of fetal death in early-onset FGR. Longitudinal studies have demonstrated that DV flow waveforms become abnormal only in advanced stages of fetal compromise [27, 37, 38, 53]. Consistently, there is a good correlation of abnormal DV waveform with late-stage acidemia at cordocentesis [54]. Absent or reversed velocities during atrial contraction are associated with perinatal mortality independently of the gestational age at delivery [55], with a risk ranging from 40 to 100% in early-onset FGR [41, 56]. Thus, this sign is normally considered sufficient to recommend delivery at any gestational age, after completion of steroids. A DV above the

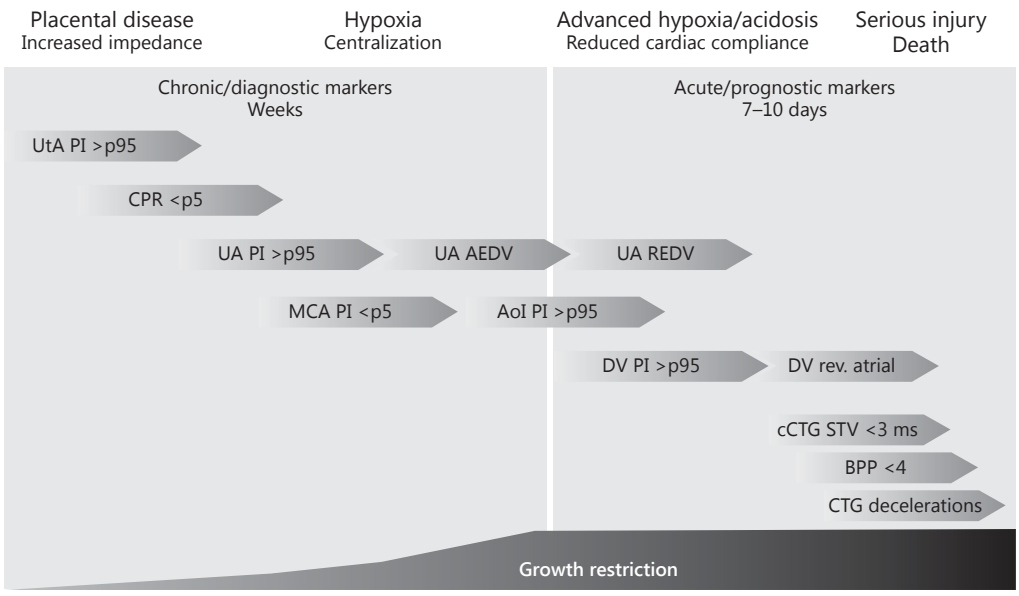

Fig. 2. Fetal deterioration and monitoring in early-severe FGR. Placental disease affects a large proportion of the placenta, and this is reflected in changes in the UA Doppler in a high proportion of cases. The figure depicts in a schematic and simplified fashion the pathophysiologic progression with the main adaptation/consequence in placental-fetal physiology, and the accompanying cascade of changes in Doppler parameters. The sequence illustrates the average temporal relation among changes in parameters, but the actual duration of deterioration is influenced by severity. Regardless of the velocity of progression, in the absence of accompanying PE this sequence is relatively constant, particularly as regards end-stage signs and the likelihood of serious injury/death. However, severe PE may distort the natural history and fetal deterioration may occur unexpectedly at any time (see text for abbreviations).

95% centile is associated with higher risks but not as consistently as when atrial flow is reverse. Overall, the sensitivity for perinatal death is still 40–70% [28, 55, 57]. A systematic review of 18 observational studies (including 2,267 fetuses) found that DV Doppler has predictive capacity for perinatal mortality [58]. In about 50% of cases, abnormal DV precedes the loss of short-term variability (STV) in computerized cardiotocography (cCTG) [27], and in about 90% of cases it is abnormal 48–72 h before the biophysical profile (BPP) [53]. Hence, it is considered to provide a better window of opportunity for delivering fetuses in critical conditions at very early gestational ages.

Aortic Isthmus Doppler

The aortic isthmus (AoI) Doppler is associated with increased fetal mortality and neurological morbidity in early-onset FGR [59]. This vessel reflects the balance between the impedance of the brain and systemic vascular systems [60, 61]. Reverse AoI flow is a sign of advanced deterioration and a further step in the sequence starting with the UA and MCA Dopplers (fig. 2, 3). Remarkably, the AoI can be found abnormal also in a small proportion of late-onset FGRs [29].

AoI has a strong association with both adverse perinatal [62] and neurological outcome [59]. However, longitudinal studies show that the AoI precedes DV abnormalities by 1 week [29, 63], and consequently it is not as good to predict the short-term risk of stillbirth [41]. In contrast, AoI seems to improve the prediction of neurological morbidity [59]. Among early-onset FGR with positive DV atrial velocities, a reverse AoI indicated a very high risk of late neonatal neurological injury (57 vs. 9.7%) [41]. In the opinion of the authors, reverse AoI could already be incorporated in clinical protocols as a sign of severe placental insufficiency and could justify considering elective delivery beyond 34 weeks of gestation. If future studies confirm the strong association with neurological morbidity, reverse AoI flow could be used to indicate delivery even earlier, but more data are required.

Fetal Heart Rate Analysis by Conventional and Computerized Cardiotocography

Early studies on high-risk pregnancies showed that, though highly sensitive, CTG has a 50% rate of false positives for the prediction of adverse outcome [64]. In addition, a meta-analysis [65] on high-risk pregnancies failed

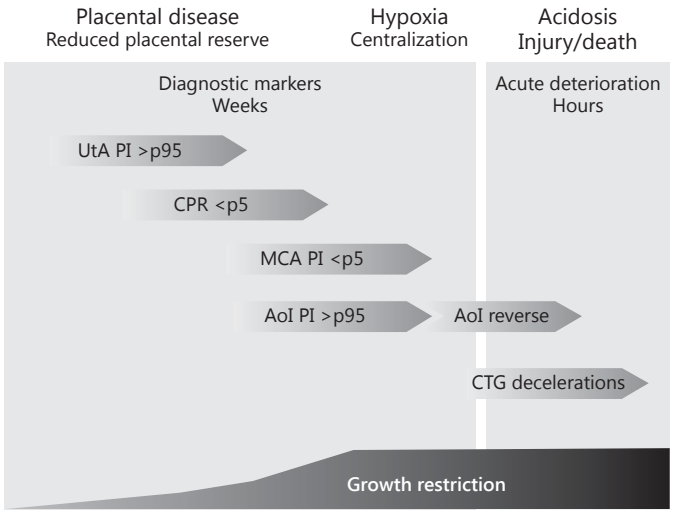

Fig. 3. Fetal deterioration and monitoring in late-mild FGR. Placental disease is mild and UA Doppler values are not elevated above the 95th centile. The effects of fetal adaptation are best detected by the CPR, which can pick up mild changes in the AU and MCA Doppler. An important fraction of cases do not progress to baseline hypoxia so that they remain only with abnormal CPR. Once baseline hypoxia is established, placental reserve is minimal and progression to fetal deterioration may occur quickly, as suggested by the high risk of severe deterioration or intrauterine fetal death after 37 weeks in these cases, possibly due to a combination of a higher susceptibility to hypoxia of the term-mature fetus and the more common presence of contractions at term (see text for abbreviations).

to demonstrate any beneficial effect in reducing perinatal mortality. Hence, there is no evidence to support the use of traditional fetal heart rate (FHR) monitoring or 'nonstress tests' in FGR fetuses. We must acknowledge that these studies were conducted in the early 1980s, and the control group had no fetal well-being assessment or outdated techniques such as biochemical tests. However, in general, a silent FHR pattern or the presence of spontaneous decelerations represent a very late event preceding fetal demise, and consequently measures that allow earlier identification and delivery must be used. A main limitation of conventional CTG is the subjective interpretation of the FHR, which is extremely challenging in very preterm fetuses with a physiologically reduced variability.

cCTG has represented a step forward and has provided new insights into the pathophysiology and management of FGR. cCTG evaluates STV of the FHR, an aspect that subjective evaluation cannot assess. Current evidence suggests that cCTG is sensitive to detect advanced fetal deterioration, and it provides a value similar to DV reverse atrial flow for the short-term prediction of fetal death. STV closely correlates with acidosis and severe hypoxia as demonstrated by cord blood sampling at the time of a cesarean section [66–68]. Recent longitudinal series have pointed to a potential role as an acute marker [27]. STV becomes abnormal, coinciding with the DV, whereas in about half of cases, abnormal DV precedes the loss of short-term FHR variability, the latter is the first to become abnormal in the other cases [27].

Biophysical Profile

BPP is calculated by combining ultrasound assessment of fetal tone, respiratory and body movements, with amniotic fluid index and a conventional CTG. It was designed to improve the performance of FHR. Observational studies show an association between abnormal BPP and perinatal mortality and cerebral palsy [69]. Studies in which a cordocentesis was performed demonstrated a good correlation with acidosis [70], with fetal tone and gross motor movements the best correlated components. However, as with FHR, a high false-positive rate (50%) limits the clinical usefulness of the BPP [71]. Early observational studies reported a very low risk of false positives for acidosis and perinatal death, but more recent studies on early-onset very preterm FGR fetuses raise concerns over the false-positive rate, with up to 23% of instances of intrauterine fetal death in fetuses with BPP >6 and 11% in those with BPP >8 [72]. A meta-analysis [73] showed no significant benefit of BPP in high-risk pregnancies. Consequently, whenever Doppler expertise and/or cCTG are available, the incorporation of BPP in management protocols of FGR is questionable.

Amniotic Fluid Index

Amniotic fluid index (AFI) is used essentially as part of BPP. Amniotic fluid volume is believed to be a chronic parameter. In fact, among the components of BPP, it is the only one that is not considered acute. A meta-analysis [74] of 18 randomized studies demonstrated that a reduced AFI is associated with an abnormal 5-min Apgar score, but there was no association with acidosis or perinatal death in SGA (RR 1.6, 95% CI 0.9–2.6). Longitudinal studies in early-onset FGR fetuses have shown that the AFI fluid index progressively decreases [27, 38]. One week before acute deterioration, 20–30% of cases have oligohydramnios [38, 53]. There is limited evidence on the role of oligohydramnios to predict perinatal complications in FGR fetuses managed with Doppler so that its inclusion in management protocols is questionable.

Evidence about Timing of Delivery in Fetal Growth Restriction

Since no treatment has been demonstrated to be of benefit in growth restriction [75–79], assessment of fetal well-being and timely delivery remain as the main management strategy. The aim behind a clinical protocol for managing FGR is to combine existing evidence on various methods for monitoring fetal well-being in order to establish the risks of fetal injury or death, and to balance them against the risks of prematurity if the fetus is delivered. Added into the equation is the awareness that leaving pregnancies with FGR to deliver at term may also lead to perinatal morbidity and delayed effects such as cerebral palsy [80].

The Growth Restriction Intervention Trial (GRIT) study [40] was a multicenter randomized controlled trial aimed to compare the effect of delivering early with delaying birth for as long as possible. A total of 588 fetuses between 24 and 36 weeks were randomized to immediate delivery or delayed delivery until the obstetrician was no longer certain. The study observed that when obstetricians were uncertain about timing of delivery based on UA Doppler, they were prepared to vary the timing by about 4 days, and although such delay caused some stillbirths, earlier delivery resulted in an almost equal number of additional deaths. Moreover, at 2 years of age, there was a trend towards more disability in the immediate delivery group [39]. Concerns regarding the external validity of this study exist [81], since only 5% of the eligible population was recruited, which raises doubts about the representativeness of the sample.

One randomized equivalence trial exists comparing the effect of induction of labor or expectant monitoring in women after 37 weeks of gestation with suspected SGA. They found negligible differences in peri- and neonatal outcomes between induction of labor and expectant monitoring [45, 46]. At 2 years of age, about half of the cohort were evaluated for neurodevelopmental and neurobehavioral assessment, with no differences between both strategies [82]. Based on these results, it was concluded that it seems reasonable to offer delivery after 37 weeks in SGA infants. As the authors pointed out in the discussion of this study, further studies differentiating true FGR from other causes of SGA not associated with poor perinatal outcome are required to clarify this question.

Stage-Based Protocol for Managing Fetal Growth Restriction

FGR is probably among the obstetrical entities with the greatest variation in clinical practice. This results from a combination of the lack of strong supportive evidence, the complexity of the variables and indices that need to be integrated for assessing fetal deterioration, and the variable risks associated with prematurity at different gestational ages.

Although when considered as groups there are clear differences between early- and late-onset forms, on an individual basis there is important overlapping of clinical features at borderline gestational ages. In addition, cases with the same gestational age at onset are often detected at different time points during gestation. Figure 1 illustrates how FGR represents a continuum with increasing number of instances as gestational age progresses. Consequently, a management scheme that establishes follow-up intervals and timing of delivery on the basis of fetal risks can include both early- and late-onset forms in an integrated fashion.

The main aims behind clinical management of FGR should be firstly to distinguish FGR from SGA and secondly to ascertain whether there is risk of in utero fetal injury or death. Thus, a first step is to identify within the small fetuses the subset of FGR, because they will have an increased risk of adverse outcome and stillbirth and should be managed actively once term is reached. A second step is to identify the presence of any sign suggesting that there is risk of fetal injury or death that may recommend delivery before term.

While strong evidence is lacking to support firm recommendations on the timing of delivery, a protocol that integrates the best available evidence can help reducing clinical practice variation. One approach is to group in stages those indices or signs that are associated with similar fetal risks, since they should indicate similar follow-up intervals and timing of delivery. Thus, based on the existing evidence extensively discussed above and, where no evidence is available on experts' opinion, we suggest to profile several stages, or prognostic groups, which define different management strategies (table 2; fig. 4).

In a first step, once a small fetus (i.e. EFW <10th centile) has been identified, UtA PI, UA PI, MCA PI and the CPR should be measured in order to classify FGR versus SGA. For FGR fetuses, changes in the UA, DV and AoI Doppler, and cCTG where available, are used to define stages of deterioration.

Small-for-Gestational Age. Excluding infectious and genetic causes, the perinatal results are good. Fortnightly Doppler and growth assessment is a standard practice. Labor induction should be recommended at 40 weeks. Cervical induction with Foley catheter may be recommended to reduce the risk of hyperstimulation [83]. Fortnightly monitoring is safe [84].

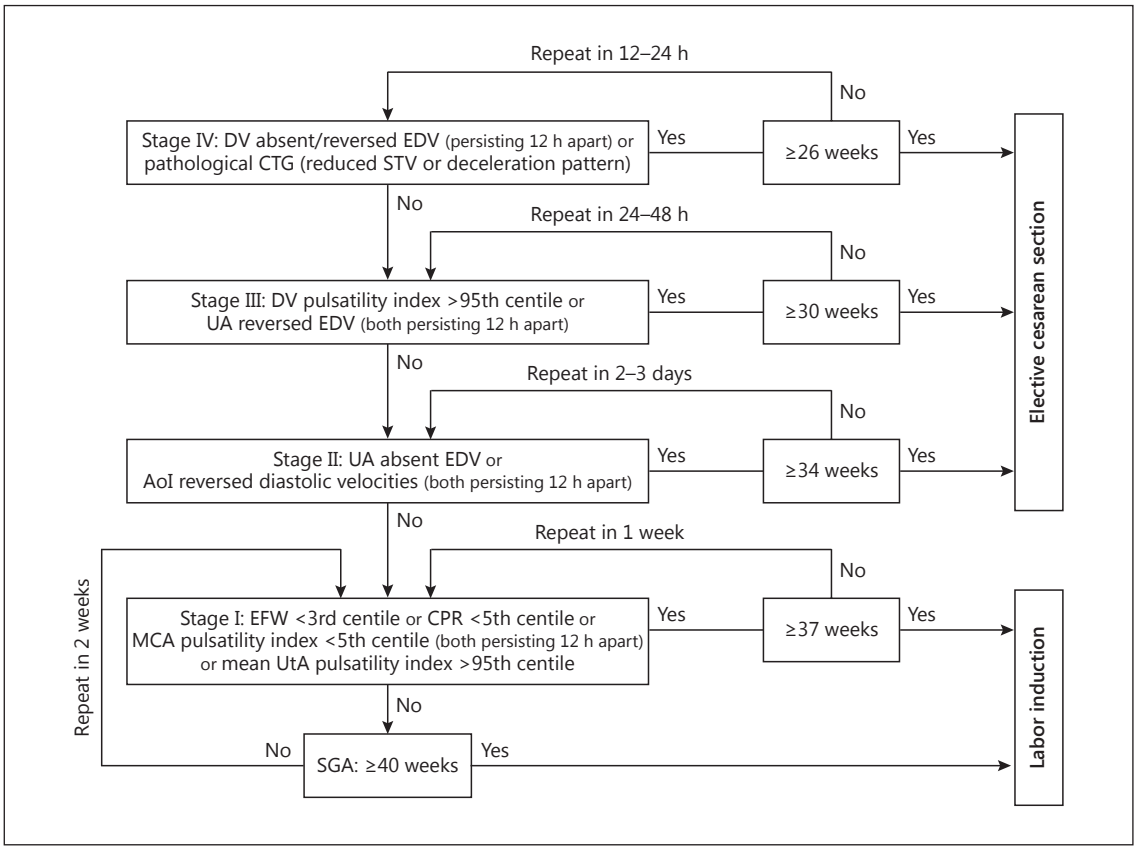

Fig. 4. Stage-based decision algorithm for the management of FGR (see text for abbreviations).

Table 2. Stage-based classification and management of FGR

Stage	Pathophysiological correlate	Criteria (any of)	Monitoring*	GA/mode of delivery
I	Severe smallness or mild placental insufficiency	EFW <3rd centile CPR <p5 UA PI >p95 MCA PI <p5 UtA PI >p95	Weekly	37 weeks LI
II	Severe placental insufficiency	UA AEDV Reverse AoI	Biweekly	34 weeks CS
III	Low-suspicion fetal acidosis	UA REDV DV-PI >p95	1–2 days	30 weeks CS
IV	High-suspicion fetal acidosis	DV reverse a flow cCTG <3 ms FHR decelerations	12 h	26 weeks** CS

All Doppler signs described above should be confirmed at least twice, ideally at least 12 h apart. GA = Gestational age; LI = labor induction; CS = cesarean section. * Recommended intervals in the absence of severe preeclampsia. If FGR is accompanied by this complication, strict fetal monitoring is warranted regardless of the stage. ** Lower GA threshold recommended according to current literature figures reporting at least 50% intact survival. Threshold could be tailored according to parents' wishes or adjusted according to local statistics of intact survival.

Stage I Fetal Growth Restriction (Severe Smallness or Mild Placental Insufficiency). Either UtA, UA or MCA Doppler, or the CPR are abnormal. In the absence of other abnormalities, 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 [44]. Cervical induction with Foley catheter is also recommended. Weekly monitoring seems reasonable.

Stage II Fetal Growth Restriction (Severe Placental Insufficiency). This stage is defined by UA absent-end diastolic velocity (AEDV) or reverse AoI. Although evidence for UA AEDV is stronger than that for AoI, observational evidence suggests an association between the latter to abnormal neurodevelopment, so that both criteria become a single category. Delivery should be recommended after 34 weeks. The risk of emergent cesarean section at labor induction exceeds 50%, and, therefore, elective cesarean section is a reasonable option. Monitoring twice a week is recommended.

Stage III Fetal Growth Restriction (Advanced Fetal Deterioration, Low-Suspicion Signs of Fetal Acidosis). The stage is defined by reverse absent-end diastolic velocity (REDV) or DV PI >95th centile. There is an association with a higher risk of stillbirth and poorer neurological outcome. However, since signs suggesting a very high risk of stillbirth within days are not present yet, it seems reasonable to delay elective delivery to reduce as possible the effects of severe prematurity. We suggest delivery should be recommended by cesarean section after 30 weeks. Monitoring every 24–48 h is recommended.

Stage IV Fetal Growth Restriction (High Suspicion of Fetal Acidosis and High Risk of Fetal Death). There are spontaneous FHR decelerations, reduced STV (<3 ms) in the cCTG, or reverse atrial flow in the DV Doppler. Spontaneous FHR deceleration is an ominous sign, normally preceded by the other two signs, and thus it is rarely observed, but if persistent it may justify emergency cesarean section. cCTG and DV are associated with very high risks of stillbirth within the next 3–7 days and disability. Deliver after 26 weeks by cesarean section at a tertiary care center under steroid treatment for lung maturation. 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.

Particularly at early gestational ages, and at whatever stage, coexistence of severe PE may distort the natural history and strict fetal monitoring is warranted since fetal deterioration may occur unexpectedly at any time.

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