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GUIDELINES

ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction

Clinical Standards Committee

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INTRODUCTION

The evaluation of fetal growth is one of the key objectives of prenatal care. Fetal growth depends on several factors, including uteroplacental function, maternal disease, maternal cardiovascular function or cardiac disease, maternal nutrition, altitude, smoking and illicit drug use, and presence of pathological conditions, such as infection, aneuploidy and some genetic conditions. However, uteroplacental insufficiency or dysfunction represents one of the most frequent causes of abnormal growth in an otherwise normal fetus.

Impaired fetal growth is associated with an increased risk of perinatal mortality and morbidity, and long-term adverse infant outcome[1]. Overall, growth-restricted fetuses have a higher rate of conditions associated with prematurity[2], experience worse neurodevelopmental outcome and are at increased risk of non-communicable diseases in adulthood, such as hypertension, metabolic syndrome, insulin resistance, Type-2 diabetes mellitus, coronary heart disease and stroke[3]. Prenatal recognition of fetal growth restriction (FGR) is a major factor identified in strategies aimed at preventing stillbirth, in which up to 30% of cases are associated with FGR or small-for-gestational age (SGA) in the late third trimester[4,5].

This Guideline provides definitions of FGR, previously referred to as intrauterine growth restriction, and SGA, and describes the best possible management options based on current data and knowledge. For the purposes of this Guideline, we assume that the pregnancy is singleton, pregnancy dating has been carried out correctly (preferably in the first trimester by ultrasound) and that there are no fetal pathologies, such as aneuploidy, congenital malformation or infection. Details of the grades of recommendation used in this Guideline are provided in Appendix 1. Reporting of levels of evidence is not applicable to this Guideline.

GUIDELINE

Definition of and distinction between small-for-gestational age and fetal growth restriction

Fetal growth is a dynamic process and its assessment requires multiple observations of fetal size over time. Fetal size is determined through biometric evaluation of the head circumference, biparietal diameter, abdominal circumference (AC) and femur length and/or derivation of estimated fetal weight (EFW) computed by different formulae. The ISUOG Guidelines on ultrasound assessment of fetal biometry and growth describe methodology, reference ranges, growth standards and quality-control processes for appropriate assessment of fetal biometry and diagnosis of fetal growth disorders[6]. Controversies in relation to reference ranges and other issues related to the assessment of fetal biometry are described in this Guideline.

A fetus is considered to be SGA when its size (biometric evaluation) falls below a predefined threshold for its gestational age. The most common definition of SGA is EFW or AC below the 10th percentile of given

reference ranges. Nevertheless, other thresholds have been described, such as the 5th and 3rd percentiles (the latter approximating to 2 SD) or a *Z*-score of −2.

FGR is a condition that is frequently, but unhelpfully, defined as the fetus failing to reach its genetically predetermined growth potential. The identification of FGR is often not straightforward as fetal growth cannot be assessed through a single biometric evaluation of the fetal size, and growth potential is hypothetical.

The main distinction between SGA and FGR is that a SGA fetus may be small but not at increased risk of adverse perinatal outcome, while a fetus with size above the 10th percentile may be FGR and at increased risk of adverse perinatal and long-term outcome[7–11].

Fetuses with birth weight below the 10th percentile are at increased risk of stillbirth[12] and perinatal mortality[13–15], with those with birth weight below the 3rd percentile being at the highest risk[12,13]. For this reason, fetal size at the lower extreme of the growth charts, for example AC or EFW below the 3rd percentile for given growth charts, can be used as an isolated criterion to define FGR at any gestational epoch[16]. However, the optimal size at birth that is associated with the lowest perinatal mortality seems to be substantially higher than the median birth weight of a normal cohort[13]. In fact, a population-based cohort study found increased perinatal mortality even in fetuses with birth weight within the normal range, with those with birth weight between the 70th and 90th percentiles being at the lowest risk, and an inverse association between perinatal mortality and birth weight below the 80th percentile[13]. A large Scottish population-based cohort study demonstrated a progressive increase in the risk of stillbirth in pregnancies with a predicted birth weight below the 25th percentile[17].

In order to differentiate between SGA and FGR in cases in which the fetal size is below the 10th percentile, additional biophysical parameters are required. Many methods have been proposed for this purpose, such as evaluation of fetal growth velocity, use of customized growth charts, Doppler velocimetric evaluation of placental and fetal circulations and use of biomarkers. Some of these biophysical parameters are also used to monitor fetal status and/or as delivery decision criteria (e.g. umbilical artery (UA) Doppler). Biophysical tools, such as ductus venosus velocimetry, biophysical profile (BPP) scoring and cardiotocographic (CTG) assessment of fetal heart rate short-term variation (STV), are not used as diagnostic criteria for FGR but for the surveillance and management of pregnancies already diagnosed as FGR, and are discussed below.

Tools for diagnosis, surveillance and management of fetal growth restriction

Fetal growth velocity

There are several methods to evaluate fetal growth velocity, including use of longitudinal growth charts[18], assessment of deviation from growth-velocity charts[18] and individualized growth assessment[19]. Overall, the objective is to evaluate the fetal growth trajectory and identify those fetuses that are deviating from their individual trajectory, indicating a failure to reach their growth potential. There is evidence to suggest that reduced fetal growth velocity in the third trimester is associated with increased risk of adverse outcome[11,20]. Reduced growth velocity is normally taken to be a fall between consecutive ultrasound scans of > 50 percentiles for AC or, more commonly, EFW[6].

Customized growth charts

In customized charts, the fetal weight and growth are adjusted for variables known to impact fetal size. These can include maternal height, weight, age, parity and ethnicity and fetal sex. Adjustment for these variables is suggested to allow for better identification of SGA fetuses at risk of perinatal complications[6]. Methods to evaluate fetal growth velocity and application of customized growth charts for this purpose are described in more detail in the ISUOG Guidelines on ultrasound assessment of fetal biometry and growth[6].

Doppler velocimetry

The rationale behind the application of Doppler velocimetry in fetal growth assessment is that it can identify uteroplacental function through evaluation of the uterine and umbilical arteries. Uteroplacental insufficiency is putatively mediated through spiral artery maladaptation and alterations in the villous vascular tree. On the fetal side, Doppler velocimetry allows evaluation of the middle cerebral artery (MCA) and ductus venosus as fetal cardiovascular adaptation progresses from hypoxia to acidemia.

A lack of physiological transformation of the uterine arteries from high- to low-resistance vessels is thought to reflect inadequate trophoblastic invasion of the spiral arteries, leaving a high-resistance circulation. The persistence of high uterine artery mean pulsatility index (PI) (above the 95th percentile) is associated with placental insufficiency and maternal vascular malperfusion of the placenta[21].

Progressively increasing PI in the UA corresponds to a progressive reduction in the placental surface area available for gas and nutrient exchange and increased fetal afterload resistance, and is associated with placental vascular insufficiency reflected by absent and, in the end-stage phase, reversed end-diastolic flow (EDF) in the UA[22].

Reduced fetal MCA-PI is a consequence of vasodilatation, the so called 'brain-sparing' effect. This represents a hemodynamic response to fetal hypoxemia, via direct vascular sensing of oxygen tension in the cerebral circuit, and in other vascular beds a consequent redistribution of fetal cardiac output occurs preferentially to the coronary arteries and adrenal glands[23].

Alterations in the ductus venosus flow velocity waveform, especially absent or reversed a-wave, are

caused by progressive dilatation of the ductus venosus isthmus in order to increase the blood flow toward the heart, in an attempt to compensate for extreme oxygen deprivation[24]. Others consider that absent or reversed a-wave in the ductus venosus is a consequence of increased intra-atrial pressure due to high cardiac afterload (increased vascular placental resistance) and/or a direct effect of fetal acidemia on myocardial cell function[25].

Doppler velocimetry plays a central role in identification, surveillance and management of FGR, because it allows for the identification of uteroplacental insufficiency and/or fetal cardiovascular adaptation to hypoxemia. Importantly, the two phenotypes of FGR, early-onset and late-onset, are characterized by different Doppler velocimetry patterns, as discussed below.

Biophysical profile scoring

The BPP score consists of the combined evaluation of fetal tone, gross body movement, breathing movement, amniotic fluid volume and heart-rate reactivity. BPP score can predict both fetal pH and outcome[26,27]. The relationship between altered BPP score and fetal pH seems to be consistent across gestational ages[26]. A score of ≤ 4 is associated with a fetal pH ≤ 7.20, while a score of < 2 has a sensitivity of 100% for acidemia[27]. This correlation remains highly significant even when using a simplified BPP that is based on assessment of only fetal heart rate and amniotic fluid volume[28].

Cardiotocography and short-term variation

A reactive CTG virtually excludes fetal hypoxemia. The fetal heart rate STV is a biophysical parameter obtained by computerized CTG (cCTG) that reflects autonomic nervous system function. In the context of FGR and the accompanying presence of severe hypoxemia or hypoxia, the fetal sympathetic and parasympathetic activity is altered, resulting in reduced fetal heart rate variation, and, thus, reduced STV.

cCTG and evaluation of STV have been validated against invasive testing in fetal hypoxemia and acidemia and represent the only objective measure of fetal heart rate[29]. Visual inspection of conventional CTG does not provide the same information as cCTG, as CTG represents a largely subjective assessment with low intra- and interobserver reproducibility.

Biomarkers

Placental biomarkers have a potential role in screening, diagnosis and therapy of placental disease linked to hypertensive disorders of pregnancy and/or FGR[30]. Several placental factors have been investigated, including placental proteins as well as microRNA and mRNA. Some placental proteins, such as pregnancy-associated plasma protein-A, are biomarkers of placental function in the first trimester, though its predictive ability is limited[31,32].

The soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio has been proposed as a short-term predictor to rule out pre-eclampsia in women in whom this condition is suspected clinically[33]. Although some reports suggest that use of the sFlt-1/PlGF ratio might be helpful in the management of and differentiation between SGA and FGR[34–38], the lack of interventional trial data precludes the recommendation of these tests as an adjunct to ultrasound imaging. The rapidly evolving research-based discussion of the use of biomarkers in screening for SGA and FGR is beyond the scope of this Guideline.

Recommendations

- Fetal size alone is not sufficient to identify FGR, unless AC or EFW is below the 3rd percentile (**GRADE OF RECOMMENDATION: C**).
- A drop in fetal growth velocity, i.e. drop in AC or EFW of > 2 quartiles or > 50 percentiles (e.g. from 70th percentile to or below 20th percentile), should alert the physician to possible FGR (**GRADE OF RECOMMENDATION: C**).
- Doppler velocimetry of the uteroplacental and fetoplacental circulations may be used to distinguish between SGA and FGR (**GOOD PRACTICE POINT**).
- Multimodal assessment is recommended for the evaluation of pregnancies with suspected FGR. cCTG or BPP scoring should be used in combination with Doppler velocimetry (**GRADE OF RECOMMENDATION: A**).

Definition of early-onset and late-onset fetal growth restriction

There are two main phenotypes of FGR which differ significantly in many aspects, such as prevalence, prediction by first-trimester ultrasound, gestational age at onset, placental histopathological findings, Doppler velocimetric profile, maternal associated disease, severity and perinatal outcome. Table 1 presents the main characteristics of the two phenotypes, which are defined as early-onset and late-onset FGR based on the observation that one phenotype is more frequent in early gestation and the second near term[39–42].

The distinction between early and late FGR is usually based on diagnosis before or after 32–34 weeks' gestation. Although UA Doppler evaluation seems to discriminate better than gestational age between the two phenotypes of FGR with regards to their association with pre-eclampsia and adverse perinatal outcome[39,40], 32 weeks seems to be the optimal gestational-age cut-off at diagnosis and provides a reasonable classification of the two FGR phenotypes[40]. This gestational-age threshold, therefore, is largely agreed upon as the main criterion to differentiate between early and late FGR[16] and is used to distinguish between early- and late-onset FGR in this Guideline.

The definition of FGR varies between different guidelines and author groups[43]. The criteria proposed

Table 1 Main clinical characteristics of early- and late-onset fetal growth restriction (FGR)

Characteristic	*Early-onset FGR*	*Late-onset FGR*
Main clinical challenge	Management	Detection
Prevalence	30%	70%
Gestational age at manifestation	< 32 weeks	≥ 32 weeks
Ultrasound findings	Fetus may be very small	Fetus not necessarily very small
Doppler velocimetry	Spectrum of Doppler alterations that involves umbilical artery, middle cerebral artery and ductus venosus	Cerebral blood-flow redistribution
Biophysical profile	May be abnormal	May be abnormal
Hypertensive disorders of pregnancy	Frequent	Not frequent
Placental histopathological findings	Poor placental implantation, spiral artery abnormalities, maternal vascular malperfusion	Less specific placental findings, mainly altered diffusion
Perinatal mortality	High	Low
Maternal cardiovascular hemodynamic status	Low cardiac output, high peripheral vascular resistance	Less marked maternal cardiovascular findings

Table 2 Definitions for early- and late-onset fetal growth restriction (FGR) in absence of congenital anomalies, based on international Delphi consensus

Early FGR: *GA < 32 weeks, in absence of congenital anomalies*	*Late FGR:* *GA ≥ 32 weeks, in absence of congenital anomalies*
AC/EFW < 3rd centile *or* UA-AEDF *Or* 1. AC/EFW < 10th centile *combined with* 2. UtA-PI > 95th centile *and/or* 3. UA-PI > 95th centile	AC/EFW < 3rd centile *Or at least two out of three of the following* 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles > 2 quartiles on growth centiles* 3. CPR < 5th centile *or* UA-PI > 95th centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery. Reproduced from Gordijn *et al.*[16].

by an international Delphi consensus represent the most recognized definition of FGR (Table 2)[16]. In a recent validation study, the performance of these criteria was compared to that of a FGR definition of EFW < 10th percentile using the Hadlock growth standard, in predicting adverse neonatal outcome[44]. The study cohort spanned a wide gestational-age range and the two definitions had comparable performance, though the Delphi criteria were associated with an improved prediction of adverse neonatal outcome.

Recommendations

- The two main phenotypes of FGR, early and late, are characterized by different clinical, ultrasound and pathological characteristics (**GRADE OF RECOMMENDATION: D**).
- The authors of this ISUOG guideline recommend the Delphi consensus criteria[16] for definition of FGR (**GOOD PRACTICE POINT**).

Doppler velocimetry

Despite the fact that Doppler velocimetry has been used in obstetric practice for nearly four decades, there is no universal agreement on which indices, thresholds and/or reference ranges to use. These considerations are not applicable when qualitative assessment is performed, such as evaluation of absent/reversed ductus venosus a-wave or absent/reversed EDF in the UA, but they affect Doppler velocimetry quantitative evaluation. International guidance on how to perform uteroplacental and fetal Doppler velocimetry is provided by ISUOG[45].

There is considerable methodological heterogeneity in studies reporting reference ranges for MCA and UA Doppler indices and their ratio, which may, at least partly, explain the differences in reported reference ranges[46]. Even among studies with a high methodological quality score, there are significant differences in the definition of 'normality' and normal ranges[46]. A recent study evaluating the 10 most-cited articles providing reference ranges for MCA-PI, UA-PI and cerebroplacental ratio (CPR), found wide discrepancies in Doppler reference values that accounted for a variability of up to 50% in the 5th percentile cut-off value of MCA-PI at term[47]. Similarly, the study found significant differences in the cut-off for UA-PI above the 95th percentile (20–40%) and CPR below the 5th percentile (15–35%)[47]. Wide discrepancies have been reported in reference ranges used for biometry, Doppler parameters and birth weight, even at national level in centers with high expertise in the management of FGR, that might significantly impact the diagnosis and management of FGR[48].

Another reason for the lack of standardization of quantitative Doppler velocimetry is that there is no uniformity in Doppler indices that are used, especially in research studies. For example, cerebral blood-flow redistribution can be defined as MCA-PI below different percentile thresholds (5th or 10th percentile), *Z*-scores or multiples of the median (MoM), or it can be defined as umbilicocerebral ratio (UCR) or CPR above or below different percentile thresholds, *Z*-scores or MoM, respectively[49]. The Delphi consensus procedure identified CPR below the 5th percentile and UA-PI above the 95th percentile as Doppler criteria to define FGR[16]. The rationale behind the application of the ratios of MCA-PI and UA-PI (CPR and UCR), instead of the individual components, is that they have been shown to be more sensitive to fetal hypoxia[50] and to be associated more strongly with adverse perinatal outcome[49,51]. CPR is reported in studies more frequently than is UCR. A recent study suggested that UCR may allow for better differentiation of cases in the abnormal range in early FGR, as compared with CPR[52]. However, it should be highlighted that there is no strong evidence in favor of either ratio.

The high variability in Doppler reference ranges and indices used has a major clinical impact on prenatal diagnosis, monitoring, timing of delivery decision, reproducibility and comparison of findings between research studies, efficacy of clinical policies and protocols, and many other aspects[46]. The discussion about which reference ranges to use for the diagnosis and management of FGR is beyond the scope of this Guideline. However, these differences should be acknowledged and action is needed to homogenize the adoption of Doppler indices, thresholds and reference ranges in clinical and research practice. Table S1 summarizes the most relevant studies reporting reference charts for MCA and its ratios.

Early-onset fetal growth restriction

Early FGR is particularly associated with maternal vascular malperfusion of the placenta, characterized by abnormal transformation of the spiral arteries, pathologic features of the placental villi and multifocal infarction; these disease components result in so-called 'placental insufficiency' and form the most common basis for placenta-mediated FGR[53,54]. Chronic ischemia of the placental villi impairs PlGF secretion and leads to excessive sFlt-1 release by syncytial knots, thus resulting in elevated sFlt-1/PlGF ratio which typifies early FGR and the associated hypertensive disorders of pregnancy[34–38]. Elevated Doppler UA-PI typically precedes a cascade of Doppler alterations, fetal heart rate changes and BPP modifications, with end-stage cardiovascular deterioration caused by severe hypoxemia followed by acidosis[55–57]. Uterine artery, UA and MCA Doppler abnormalities represent early changes in early FGR and may be present for many weeks before severe cardiovascular and metabolic deterioration occurs. Although absent UA-EDF represents a progressive deterioration of uteroplacental function, it still precedes critical fetal deterioration, and the progression to reversed UA-EDF might be slow. However, the rate and rapidity of alteration in UA Doppler, from increased blood-flow resistance to absent EDF, determines the rate of fetal deterioration[56,58]. The late deterioration in early FGR characterized by severe placental insufficiency is reflected by reversal of the EDF in the UA, and worsening generalized cardiovascular and metabolic failure reflected by alterations in the ductus venosus (absent or reversed a-wave)[57,59]. This cardiovascular deterioration might precede or occur in parallel with the alteration of the STV, eventually manifesting as abnormal BPP score, spontaneous repetitive decelerations on CTG and stillbirth[39,60].

At present, there is no effective therapy for early FGR, though efficient recognition and management of severe pre-eclampsia may prolong some pregnancies with early FGR. The timely use of steroids, followed by magnesium sulfate, transfer to a tertiary care center and consideration of the safest mode of delivery, are the key concepts in early-FGR management[61]. Ultimately, delivery represents the only therapeutic option in early FGR, in order to prevent severe consequences from hypoxia and acidosis that can lead to perinatal morbidity and mortality. On the other hand, the decision to deliver has to be balanced against the possible harm caused by prematurity[62,63]. This is further complicated by the fact that the fetus is suffering from growth restriction, which is an independent risk factor for adverse outcomes associated with prematurity, thus making the outcome even more unfavorable[64,65]. This is highlighted by the fact that, in fetuses with early FGR, neonatal survival first exceeds 50% after 26 weeks' gestation, which is 2 weeks later than in their appropriate-for-gestational-age (AGA) counterparts[55]. In this view, optimal monitoring and timing of delivery are of crucial importance when managing early FGR.

How to monitor

Once early FGR is suspected/diagnosed, the pregnancy should be monitored and managed in tertiary-level fetal medicine and neonatal units according to a uniform management protocol[66]. Multidisciplinary counseling by neonatology and maternal–fetal medicine specialists is important. Evidence from a randomized trial (Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE)) shows that monitoring and delivery timing according to a specific protocol including ductus venosus Doppler and cCTG provides better-than-expected outcomes[66]. It should be taken into account that cCTG is not available or used universally. In that case, in addition to Doppler evaluation, assessment of conventional CTG and, where undertaken, BPP scoring should be performed[27]. The loss of fetal gross body movement in association with ductus venosus Doppler index alterations can predict fetal cord pH < 7.20, while loss of fetal tone is associated with pH < 7.00 or a base excess < −12 mEq/L[27].

The surveillance frequency should be based on the severity of FGR and UA abnormalities. Progressive deterioration of UA Doppler velocimetry warrants more intensive monitoring every 2–3 days when absent or reversed UA-EDF is present. There is no consensus on monitoring frequency, however, suggested management strategies have been described elsewhere[29,42,67].

MCA Doppler is one of the first parameters that becomes abnormal in early FGR. There seems to be a weak association between low MCA-PI and adverse short-term neonatal outcome and between low MCA-PI and high UCR and 2-year adverse neurodevelopmental outcome[52]. However, gestational age at delivery and birth weight have the most pronounced impact on these outcomes[52]. Thus, MCA Doppler seems to guide monitoring before 32 weeks of gestation but there is no evidence that it should be used to determine delivery timing.

Around 70% of women with early FGR will develop hypertensive disorders of pregnancy, mainly pre-eclampsia[68]. Thus, regular blood-pressure assessment, and monitoring of urinary protein/creatinine ratio and baseline renal–hepatic function in asymptomatic women with early FGR are recommended. Although maternal PlGF testing might be useful[69], the value of biomarkers in the diagnosis and management of FGR in the absence of maternal hypertension remains undefined.

Corticosteroid prophylaxis

All available guidelines on early FGR recommend corticosteroid prophylaxis to prevent neonatal respiratory distress syndrome if the birth is likely to occur before 34 + 0 weeks[43,67,70–74]. However, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends corticosteroid prophylaxis up to 35 + 6 weeks[67]. Despite this recommendation, it is worth noting that no randomized trial has been performed in order to establish whether the benefits of corticosteroids in premature fetuses also apply to premature growth-restricted fetuses, in whom the reduced metabolism of corticosteroids by a smaller placenta and the already high level of endogenous adrenal corticosteroids might further damage the white matter of the brain and myelination[75]. In fetuses with absent or reversed UA-EDF, enhanced daily surveillance is warranted during steroid administration[76].

Magnesium sulfate prophylaxis

There is good evidence for the efficacy of magnesium sulfate for fetal neuroprotection in the context of preterm delivery, however, the exact gestational-age threshold at which this attenuates remains unclear[77]. Many guidelines and studies recommend magnesium sulfate prophylaxis for neuroprotection in growth-restricted fetuses, though the suggested time of commencement varies, being < 32–33 weeks[73], < 32 weeks[70,72], < 30 weeks[78] or < 29 weeks' gestation[79]. In the absence of strong evidence regarding the optimum gestational age of magnesium sulfate prophylaxis that would allow for uniform application among countries, we recommend to refer to local or national guidelines.

When and how to deliver

A large prospective international multicenter study provided evidence that early gestational age at delivery and low birth weight are the primary quantifying parameters that adversely impact on the neonatal outcome of fetuses with early-onset FGR[55]. Indeed, for extreme prematurity (< 27 weeks) and extremely low birth weight (< 600 g), each day of prolongation of the pregnancy improves neonatal survival by 2%. After 27 weeks, ductus venosus Doppler parameters emerged as the primary predictor of neonatal outcome[55].

The first randomized controlled trial on timing of delivery in FGR was the Growth Restriction Intervention Trial (GRIT)[80,81]. The study evaluated the effect of immediate delivery *vs* expectant management when the clinicians were uncertain about the optimal timing of delivery of a compromised fetus. The median time to delivery was 4.9 days in the expectant-management group compared with 0.9 days in the immediate-delivery arm, and there was no significant difference in neurodevelopmental outcome at 2 years or at school age between the two groups[82].

The TRUFFLE study is the largest randomized trial on timing of delivery in early FGR and was based on three randomization arms: early ductus venosus Doppler changes (PI > 95th percentile), late ductus venosus Doppler changes (a-wave at or below baseline) and reduced fetal heart rate STV on cCTG (< 3.5 ms before 29 weeks and < 4.0 ms thereafter)[83]. In addition, in all three arms, safety-net criteria were applied as an absolute indication for delivery, and were represented by spontaneous repeated persistent unprovoked fetal heart rate decelerations in all three arms or by STV < 2.6 ms at 26 + 0 to 28 + 6 weeks and < 3.0 ms at 29 + 0 to 31 + 6 weeks in the ductus venosus arms. The protocol recommended delivery if reversed UA-EDF occurred after 30 weeks or if there was absent UA-EDF after 32 weeks. Overall, the TRUFFLE study provided evidence that timing of delivery based on ductus venosus Doppler measurement in conjunction with cCTG safety-net criteria improves long-term (2-year) neurodevelopmental outcome in surviving infants. The cCTG STV 'safety net' was deliberately set at a level below that of the two ductus venosus randomized groups. Figure 1 presents the protocol recommended by the TRUFFLE study for monitoring and managing pregnancies with early FGR[66]. Despite the fact that data from the TRUFFLE study showed better-than-expected results in terms of infant survival without neurological impairment (82% of children), the gestational age at study entry and at delivery and birth weight were strongly related to adverse outcome. It is important to highlight that outcomes similar to that of the TRUFFLE trial can be replicated only by using the monitoring strategy and delivery-decision criteria based on ductus venosus Doppler and cCTG in conjunction.

If cCTG is not available or not used, delivery timing should be based on combination of Doppler velocimetry indices (mainly ductus venosus before 30 weeks) and conventional CTG, or BPP where this is undertaken. The

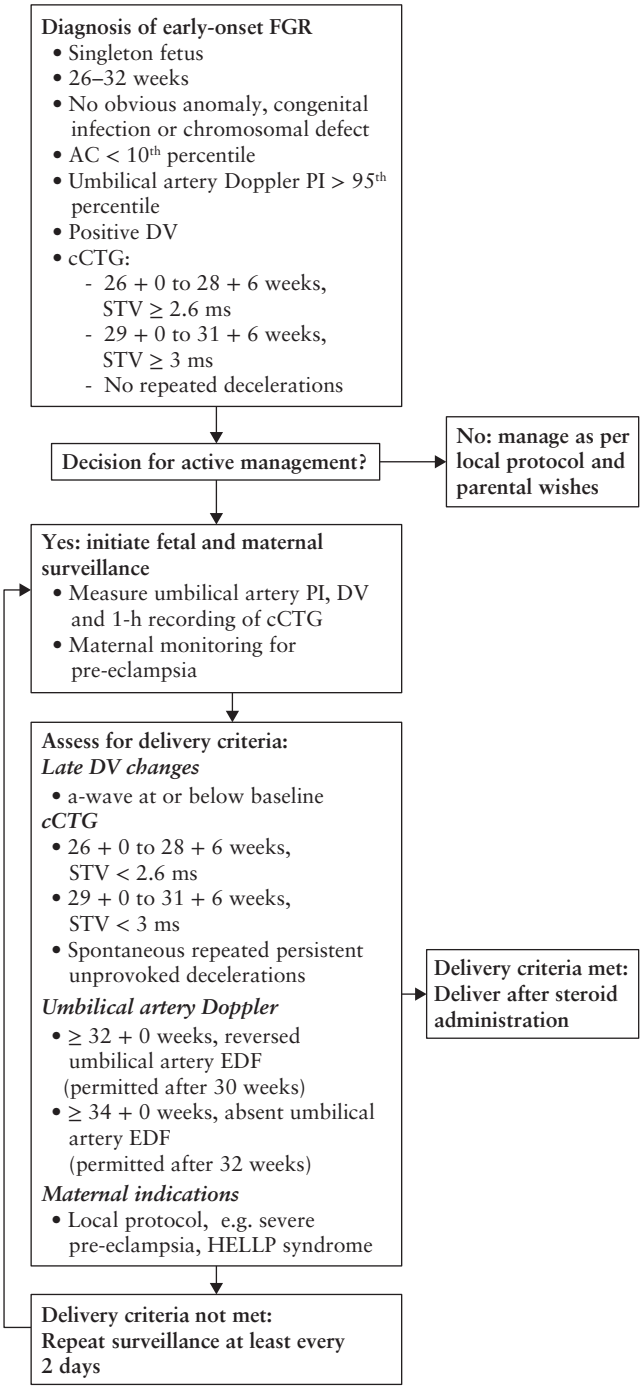

Figure 1 Flowchart explaining protocol recommended by TRUFFLE study for monitoring and management of pregnancies with early diagnosis of fetal growth restriction (FGR). AC, abdominal circumference; cCTG, computerized cardiotocography; DV, ductus venosus; EDF, end-diastolic flow; PI, pulsatility index; STV, short-term variation. Reproduced from Bilardo *et al.*[66].

presence of repeated spontaneous unprovoked decelerations is an indication for delivery. However, when visually interpreting the fetal heart reactivity on conventional CTG, the gestational age and corresponding fetal maturity should be taken into account. Similarly, an absolute indication for delivery is maternal condition (e.g. severe pre-eclampsia, eclampsia, HELLP syndrome) or obstetric emergency conditions, such as placental abruption.

Considering the strong association with severe placental insufficiency and fetal hypoxemia/hypoxia, planned Cesarean section is indicated in the majority of early-onset cases of FGR. Importantly, delivery is indicated based on maternal indications, mainly hypertensive disorders of pregnancy, that could adversely impact the perinatal and maternal outcome[68].

Recommendations

- Pregnancies with early FGR should be monitored and managed in tertiary-level units with the highest level neonatal care (**GOOD PRACTICE POINT**).
- Multidisciplinary management by neonatology and maternal–fetal medicine specialists is indicated (**GOOD PRACTICE POINT**).
- Multimodality assessment, including CTG and UA, MCA and ductus venosus Doppler evaluation, is recommended (**GRADE OF RECOMMENDATION: A**).
- When cCTG is available, STV should be the main parameter assessed (**GRADE OF RECOMMENDATION: A**).
- Monitoring should be scheduled based on the severity of FGR and alterations in UA Doppler (**GOOD PRACTICE POINT**).
- Delivery should be based on biophysical assessments or maternal indication, as follows:
  - At any gestational age: presence of maternal indication (e.g. severe pre-eclampsia, HELLP syndrome) or obstetric emergency requiring delivery (**GOOD PRACTICE POINT**);
  - 24 + 0 to 25 + 6 weeks: personalized management (**GOOD PRACTICE POINT**);
  - ≥ 26 + 0 weeks, deliver if any of the following is present:
    - Spontaneous repeated persistent unprovoked fetal heart rate decelerations (**GRADE OF RECOMMENDATION: A**);
    - Altered BPP (score ≤ 4) (**GOOD PRACTICE POINT**);
  - 26 + 0 to 28 + 6 weeks: deliver if ductus venosus a-wave is at or below baseline or STV < 2.6 ms (**GRADE OF RECOMMENDATION: A**);
  - 29 + 0 to 31 + 6 weeks: deliver if ductus venosus a-wave is at or below baseline or STV < 3.0 ms (**GRADE OF RECOMMENDATION: A**);
  - 32 + 0 to 33 + 6 weeks (permitted after 30 + 0 weeks): deliver if UA-EDF is reversed or STV < 3.5 ms (**GOOD PRACTICE POINT**);
  - ≥ 34 + 0 weeks (permitted after 32 + 0 weeks): deliver if UA-EDF is absent or STV < 4.5 ms (**GOOD PRACTICE POINT**).
- Corticosteroid prophylaxis is recommended if delivery is planned before 34 + 0 weeks of gestation (**GRADE OF RECOMMENDATION: B**).

- Elective Cesarean delivery is recommended if one or more of the following is present: abnormal cCTG STV, ductus venosus Doppler alteration, absent or reversed UA-EDF, altered BPP, maternal indication (**GOOD PRACTICE POINT**).

Late-onset fetal growth restriction

The pathophysiology of late FGR differs from that of early FGR. Late FGR is characterized by milder and more aspecific placental lesions and/or alteration in oxygen and nutrient diffusion[84,85]. Consequently, alterations in UA Doppler and venous districts are rare and fail to identify the vast majority of late-FGR cases or to predict adverse outcome in these fetuses[40]. Several studies have found an association between MCA vasodilatation (i.e. reduction in MCA-PI) or the alteration of its ratio with UA-PI and poorer perinatal outcome[86], including stillbirth[39], higher risk of Cesarean delivery[87–89], and increased risk of abnormal neurodevelopment at birth[90] and at 2 years of age[91]. The rationale for using the ratios of MCA-PI and UA-PI (CPR and UCR) is that they can identify subtle changes between placental and cerebral blood-flow perfusion that may not be appreciated by evaluation of a single parameter. Furthermore, it has been suggested that evaluation of the CPR may improve the prediction of adverse perinatal outcome in growth-restricted fetuses[92–94].

The biophysical abnormalities that characterize late FGR include alteration of fetal breathing, decreased amniotic fluid volume and loss of fetal heart rate reactivity on conventional CTG. However, in fetuses with late FGR, it seems that BPP becomes abnormal only shortly before stillbirth, and therefore, it is not useful in the determination of monitoring intervals[39].

Despite presenting with milder clinical form than early FGR, late FGR is still associated with poor perinatal outcome[87,95] and longer-term educational attainment[91,96,97]. In the TRUFFLE study, the risk of poor neurodevelopmental outcome in babies that were delivered after 32 weeks' gestation remained static until term[98]. This may be due to several factors. The pathophysiology of late FGR is still not completely understood and this may determine a lower identification rate of fetuses exposed to growth restriction near term[99]. Moreover, fetuses near term seem to have reduced tolerance to hypoxemia[100], possibly because of their relatively high metabolic rate, compared with fetuses at an earlier gestation. Thus, frequent monitoring of pregnancies with late FGR is warranted in the same way as for those with early FGR.

How to monitor

At present, MCA-PI and its ratios to UA-PI are the most important Doppler parameters in the surveillance of late FGR. In the presence of UA-PI > 95th percentile, monitoring at least once or twice a week is indicated. A large retrospective study showed that, in FGR pregnancies after 34 + 0 weeks of gestation, the median interval between a low MCA-PI and stillbirth was ≤ 5 days, suggesting that, if delivery has not been indicated by that time, twice-weekly Doppler surveillance may be required after 34 weeks[39]. Moreover, in the same study, almost 90% of stillbirths occurred within 1 week of a normal BPP score in the presence of cerebral vasodilatation, suggesting that BPP may have poor value in determining the frequency of fetal monitoring[39].

Considering the fact that some concerns have been raised regarding the interobserver reliability of MCA-PI measurement, when alteration in MCA-PI, CPR or UCR is encountered, the measurement should be confirmed within 24 h to avoid false-positive results, especially when timing of delivery is based on this finding[101].

Corticosteroid prophylaxis

There is a lack of consensus between guidelines with respect to corticosteroid prophylaxis between 34 and 36 weeks' gestation. Most guidelines on FGR recommend corticosteroid prophylaxis if the birth is likely to occur before 34 + 0 weeks[70–74], however, the RCOG recommends corticosteroid prophylaxis up to 35 + 6 weeks[67].

When and how to deliver

There is no international consensus on the timing of delivery in late FGR, due to the lack of interventional management randomized trials based on Doppler indices in these pregnancies. In fact, national guidelines for the management of FGR are highly variable[43].

The only randomized interventional trial on FGR at or close to term is the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT) study[102]. The study compared the effect of induction of labor *vs* expectant monitoring in singleton pregnancies beyond 36 + 0 weeks of gestation with suspected FGR. The study did not take into account any Doppler assessment and the only Doppler parameter reported was absent EDF in the UA (present in 14/650 pregnancies). The induction-of-labor policy, compared with expectant management, did not affect the rate of adverse neonatal outcome or neurodevelopmental and behavioral outcome at 2 years of age, except for in children with birth weight below the 2.3rd percentile[103]. Moreover, it did not affect the rates of instrumental vaginal delivery and Cesarean section. In the induction-of-labor group, more neonates were admitted to intermediate-level care, but this outcome was reduced when considering only induction after 38 weeks of gestation[104]. Importantly, the proportion of neonates with birth weight below the 3rd percentile was greater in the expectant-monitoring arm, as was the proportion of women who developed pre-eclampsia. Based on these findings, it would appear that induction of labor for suspected FGR after 38 weeks' gestation is not associated with increased incidence of instrumental vaginal delivery or Cesarean section, or

adverse neonatal or 2-year child outcome, while it seems to be associated with decreased incidence of neonates with extremely low birth weight and of progression to pre-eclampsia. Of note, fetuses at term with birth weight below the 3rd percentile have the highest risk of stillbirth, approximately 1:100[12], hence these pregnancies should not exceed 37 + 6 weeks of gestation, independent of Doppler findings. All cases of stillbirth in the DIGITAT trial occurred among women who, despite meeting the inclusion criteria, declined to participate (approximately 1%, pers. comm.). This stresses the importance of monitoring growth-restricted fetuses at or near term, and timely delivery.

In pregnancies with late FGR and UA-PI above the 95th percentile, expert opinion is that delivery should be considered when the gestation is beyond 36 + 0 weeks and not later than 37 + 6 weeks[105].

Though cerebral redistribution is associated with adverse short- and long-term perinatal outcome[49,106–108], there is currently no evidence as to how cerebral Doppler should be utilized in the delivery timing of FGR. However, it seems reasonable that, in pregnancies with late FGR and signs of cerebral blood-flow redistribution, delivery should be considered at around 38 + 0 weeks and not later than 38 + 6 weeks. It is important that each unit predisposes and follows a precise dedicated monitoring protocol, based also on local experience and resources.

Depending on the clinical situation (parity, EFW, cervical findings), induction of labor may be undertaken, but this is not recommended in the context of critical UA Doppler findings (i.e. absent or reversed EDF)[43,105]. Continuous fetal heart rate monitoring during labor should be undertaken. Figure 2 summarizes the proposed management of FGR pregnancies based on cCTG and Doppler findings.

Recommendations

- In pregnancies with late FGR, delivery should be based on biophysical assessments or maternal indication as follows:
  - At any gestational age, deliver if one of the following is present:
    - Spontaneous repeated persistent unprovoked fetal heart rate decelerations (**GOOD PRACTICE POINT**);
    - Altered BPP (score ≤ 4) (**GOOD PRACTICE POINT**);
    - Maternal indication (e.g. severe pre-eclampsia, HELLP syndrome) or obstetric emergency requiring delivery (**GOOD PRACTICE POINT**);
    - cCTG STV < 3.5 ms at 32 + 0 to 33 + 6 weeks and < 4.5 ms at ≥ 34 + 0 weeks (**GOOD PRACTICE POINT**);
    - Absent or reversed UA-EDF (**GOOD PRACTICE POINT**);
  - 36 + 0 to 37 + 6 weeks: deliver if UA-PI > 95th percentile or AC/EFW < 3rd percentile (**GOOD PRACTICE POINT**);
  - 38 + 0 to 39 + 0 weeks: deliver if there is evidence of cerebral blood-flow redistribution or any other feature of FGR (**GOOD PRACTICE POINT**).
- In the absence of contraindications, induction of labor is indicated (**GOOD PRACTICE POINT**).
- During labor, continuous fetal heart rate monitoring is recommended (**GOOD PRACTICE POINT**).

Small-for-gestational age

SGA is often considered as a constitutionally small fetus that is otherwise healthy; it is frequently the case that

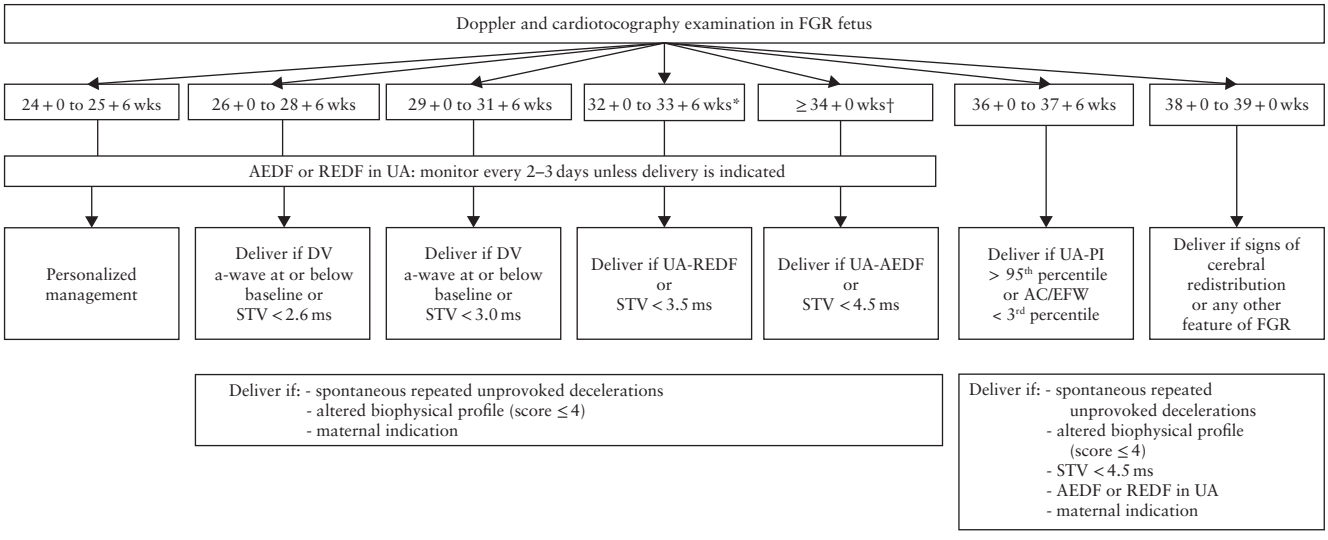

Figure 2 Recommended management of pregnancies with fetal growth restriction (FGR), based on computerized cardiotocography and Doppler findings. *Permitted after 30 + 0 weeks. †Permitted after 32 + 0 weeks. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; DV, ductus venosus; EFW, estimated fetal weight; PI, pulsatility index; REDF, reversed end-diastolic flow; STV, short-term variation; UA, umbilical artery; wks, gestational weeks.

the SGA categorization is applied to a small baby that is structurally normal and has normal Doppler findings. In these cases, the adoption of customized growth charts has been suggested to reduce the proportion of SGA[109]. However, there is evidence suggesting that SGA with normal fetoplacental Doppler can be associated with accelerated placental aging[110], signs of placental underperfusion[111], lower umbilical vein blood flow volume[112], altered maternal hemodynamics[113] and greater incidence of Cesarean section for fetal distress[87] compared with AGA fetuses. Such evidence poses the question as to whether there might be a subgroup of SGA fetuses that do in fact suffer from 'stunted' fetal growth, which adapt to a poor nutritional environment and are not identified by standard biophysical diagnostic tools. Further research is needed to better understand this hypothesis.

How to monitor

At the diagnosis of SGA, fetal Doppler indices (UA-PI, MCA-PI and their ratios) and uterine artery Doppler should be evaluated.

In the case of late SGA (after 32 weeks), once uterine artery Doppler has been assessed at diagnosis, there is no need for uterine artery Doppler to be re-evaluated at each visit as, usually, it remains unchanged from diagnosis of SGA to delivery[114]. Fortnightly assessment of fetal growth is recommended[115]. Late-SGA fetuses with abnormal uterine artery PI at diagnosis, compared to those without, are more likely to progress to brain sparing, in other words 'cross over' to FGR, and this usually occurs at earlier gestational-age epochs. Even late-SGA fetuses with normal uterine artery PI can progress to brain sparing, albeit less frequently and 1–2 weeks later than fetuses with abnormal uterine artery PI[114].

When and how to deliver

Reports suggest that universal induction of labor at term may be more beneficial than expectant management in terms of reduced perinatal mortality[116,117], without increasing the rate of Cesarean section or operative vaginal delivery[118–120]. This is true for both nulliparous women aged ≥ 35 years[116,118] and unselected populations[117,119,120].

Considering that the major cause of perinatal death at term is stillbirth and that some SGA fetuses might suffer some degree of stunted growth that is not adequately identified by current biophysical tools, it is reasonable to consider delivery after $38+0$ weeks of gestation, and the pregnancy should not exceed $39+0$ weeks, in order to reduce the risk of severe growth restriction or stillbirth in fetuses identified as SGA. This recommendation is also supported by the findings of the DIGITAT study[102,104]. Induction of labor is appropriate depending on the clinical situation, and continuous fetal heart rate monitoring in labor should be performed in these cases.

Recommendations

- Fetal Doppler velocimetry should be performed both at the diagnosis of SGA and during follow-up (**GOOD PRACTICE POINT**).
- In case of late SGA, fortnightly assessment of fetal growth and weekly assessment of UA-PI, MCA-PI, CPR and UCR is recommended (**GOOD PRACTICE POINT**).
- When SGA has been identified, delivery should be planned from $38+0$ weeks and the pregnancy should not exceed $39+0$ weeks of gestation (**GRADE OF RECOMMENDATION: A**).
- Continuous fetal heart rate monitoring during labor is indicated (**GOOD PRACTICE POINT**).

What is not known and implications for research

The Delphi consensus on the criteria for FGR diagnosis[16] is of importance as it has established a uniform definition of early and late FGR. However, it is still not clear whether a proportion of fetuses with AC or EFW below the 10th percentile (namely SGA) with normal umbilical and cerebral Doppler indices might suffer from stunted fetal growth as suggested by recent findings[110,121]. This question warrants further exploration. It is hypothesized that even before the signs of hypoxemia establish, there is a 'preclinical' phase during which the fetus is exposed to a reduced supply of nutrients and oxygen to which it responds by reduced growth and oxidative metabolism. There are several hypotheses regarding the underlying pathophysiological processes of fetal growth impairment, such as inadequate maternal perfusion of the uterus due to overrun of the maternal hemodynamic adaptation potential, overrun of the placental potential in response to increasing fetal needs, or placental senescence due to oxidative stress. It may be that UA Doppler alterations and signs of cerebral blood-flow redistribution are not sophisticated enough to capture and discriminate these imbalances between fetal needs and maternal and/or placental potential before hypoxemia establishes. In this respect, more efforts should be made to identify potential predictors of the subgroup of SGA fetuses that is at increased risk of perinatal and long-term adverse outcomes. New emerging biophysical and biochemical tools, such as alternative analysis of fetal heart rate acceleration and deceleration parameters[122], evaluation of maternal hemodynamics[113], evaluation of umbilical vein blood-flow volume[85,112,123] and even assessment of uterine blood-flow volume[124,125] could help to disentangle the different aspects of SGA and FGR.

The finding that sFlt-1/PlGF ratio can predict the short-term presence or absence of pre-eclampsia[33] opens the possibility that placental protein markers can offer considerably enhanced screening test precision to distinguish the healthy SGA fetus from the fetus with placenta-mediated FGR that is at risk of stillbirth and asphyxia-related morbidity. In women with hypertensive disorders, the sFlt-1/PlGF ratio has been shown to be able to differentiate cases with pre-eclampsia and SGA from

those with pre-eclampsia and AGA fetuses[126], and this should be explored further in pregnant patients monitored for SGA and/or FGR[34].

Early FGR is associated with complications related to prematurity, as preterm birth is often necessitated to prevent stillbirth. There is a strong desire to delay progression of the condition once the diagnosis is made. Attempts have been made by several research groups (STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset intrauterine growth Restriction) consortium) to evaluate the role of sildenafil, a phosphodiesterase Type-5 inhibitor, in improving the outcome of fetuses with early FGR. It is believed that its potential vasodilatory effect on the uterine vessels might improve fetal growth *in utero*. The UK-based randomized placebo-controlled trial demonstrated that administration of sildenafil at a dose of 25 mg three times daily ($n = 70$) *vs* placebo ($n = 65$) does not prolong the pregnancy or improve outcomes in severe early-onset FGR diagnosed between $22 + 0$ and $29 + 6$ weeks of gestation[127]. A similar trial from New Zealand and Australia, including 122 cases of early FGR, demonstrated that maternal use of sildenafil has no effect on fetal growth velocity[128]. Significant concerns regarding the safety of sildenafil during pregnancy were raised following an excess of neonatal deaths due to pulmonary hypertension in one trial based in The Netherlands, and it is currently recommended that sildenafil should not be used in FGR outside the setting of high-quality randomized clinical trials[129].

Several novel approaches are being investigated for improving the outcome of pregnancies with early-onset FGR. The EVERREST (doEs Vascular endothelial growth factor gene therapy safEly impRove outcome in seveRe Early-onset fetal growth reSTriction?) group[125] is planning an uncontrolled open-label trial in pregnancies affected by early FGR in order to evaluate the efficacy of localized injected maternal vascular endothelial growth factor gene therapy to improve fetal growth. Given that high maternal vascular resistance and low cardiac output are characteristic in early FGR, vasodilator agents and increasing intravascular volume have been suggested to improve fetal growth and prolong gestation[130]. Importantly, therapies for maternal hypertension that reduce cardiac output, such as beta blockers, have been linked to poor perinatal outcome and stillbirth and should be used with caution in these cases.

Besides the need for homogeneous application of Doppler indices, thresholds and reference ranges, the question regarding their clinical utility for monitoring of and timing delivery in FGR pregnancies diagnosed > 32 weeks' gestation is still to be answered. The evidence of association between signs of cerebral blood-flow redistribution and adverse pregnancy outcome is based mainly on retrospective and observational studies, in which the application of Doppler indices might have influenced pregnancy management and outcome, and therefore introduced bias. Currently, there is no randomized interventional trial on the utility of Doppler parameters in timing delivery in late FGR. Thus, the key research question is whether early delivery of fetuses with late FGR and signs of cerebral blood-flow redistribution is beneficial (by removing the fetus from exposure to a hostile environment and hypoxemia) or harmful (by inducing late prematurity). A study of this kind should address the issues of perinatal morbidity and mortality, as well as long-term neurodevelopmental outcomes. Moreover, it is not clear which monitoring policy is most beneficial and which Doppler parameters and thresholds perform best in late FGR. Ongoing randomized controlled trials on this topic will provide answers to these important questions.

CONCLUSION

Early diagnosis, close follow-up and timely delivery of pregnancies with FGR are of crucial importance for perinatal short- and long-term outcome. The identification of FGR is not always straightforward, for several reasons. First, a single biometric measurement of fetal size is not sufficient to evaluate fetal growth, except perhaps in the case of extremely small fetal size. Thus, additional biophysical tools and/or evaluations are needed in order to identify FGR. Second, there are two phenotypes of FGR that differ significantly in many aspects. Knowledge of the clinical manifestation and progress of early-onset and late-onset FGR is of crucial importance for all aspects of management (from diagnosis to delivery). At present, the most recognized criteria to define early and late FGR are those derived from an international Delphi survey consensus[16].

Once the diagnosis of FGR has been made, multimodality assessment (including Doppler velocimetry, cCTG and BPP), which may differ between countries, is recommended. Early FGR is associated more strongly with abnormal trophoblastic invasion and consequent placental insufficiency. The risk of perinatal mortality and morbidity and long-term adverse outcome is very high in these pregnancies, and depends both on the severity of growth restriction and prematurity. For this reason, pregnancies with early FGR should be managed in multidisciplinary tertiary-level units. Despite the severity of early FGR, the cascade of Doppler alterations is quite well-known and randomized controlled trials have provided a robust level of evidence for delivery criteria.

Late FGR has a milder clinical presentation than does early FGR, and hence, it is not associated with severe prematurity but can still be associated with significant morbidity. Despite that, at present, the diagnosis and management of late FGR, especially near term, is complex. The assessment of MCA-PI and its ratios to UA-PI have a central role in the identification of late FGR. However, there is no clear evidence as to whether the decision to deliver based on Doppler evaluation of cerebral blood-flow redistribution might be beneficial in terms of short- and long-term neurodevelopmental outcome and which is the optimal gestational age at which to deliver these pregnancies.

In conclusion, the diagnosis and management of FGR pregnancies still pose some concerns and dilemmas. In

fact, there is some evidence that even SGA fetuses with normal Doppler velocimetry might suffer some degree of growth restriction not identifiable by standard biophysical tools. New technologies and tools might be helpful in differentiating between SGA and FGR, and randomized controlled trials on management that are in progress will hopefully provide clear evidence on some unanswered questions. The real challenge remains to determine whether therapeutic intervention in FGR will ever be feasible.

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APPENDIX 1 Levels of evidence and grades of recommendation used in ISUOG Guidelines

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with low risk of bias
1–	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with very low risk of confounding, bias or chance and high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with low risk of confounding, bias or chance and moderate probability that the relationship is causal
2–	Case–control or cohort studies with high risk of confounding, bias or chance and significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic review or randomized controlled trial rated as 1++ and directly applicable to the target population; or systematic review of randomized controlled trials or body of evidence consisting principally of studies rated as 1+ applicable directly to the target population and demonstrating overall consistency of results
B	Body of evidence including studies rated as 2++ applicable directly to the target population and demonstrating overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1+
C	Body of evidence including studies rated as 2+ applicable directly to the target population and demonstrating overall consistency of results; or evidence extrapolated from studies rated as 2++
D	Evidence of level 3 or 4; or evidence extrapolated from studies rated as 2+
Good practice point	Recommended best practice based on clinical experience of the Guideline Development Group

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Most relevant studies reporting reference ranges for fetal middle cerebral artery (MCA), cerebroplacental ratio (CPR) and umbilicocerebral ratio (UCR). Adapted from Ruiz-Martinez *et al.*[47]

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Opinion

Diagnosis and management of fetal growth restriction: the SMFM guideline and comparison with the ISUOG guideline

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Fetal growth restriction (FGR), broadly defined as a fetus not reaching its growth potential, is caused by maternal, fetal and placental conditions that contribute to suboptimal placental perfusion, fetal nutrition and, in some cases, oxygenation[1,2]. FGR is associated with significant short- and long-term morbidity and mortality[1–3]. The application of a structured guideline for the clinical management of pregnancies with FGR has been shown to enhance standardization of care and improve outcome[4]. The Society for Maternal–Fetal Medicine (SMFM) has recently released a revised and comprehensive guideline on the prenatal diagnosis and management of FGR[5]. This Opinion is intended to highlight important aspects of the SMFM FGR guideline and provide the rationale for discrepant elements when compared with the FGR guideline of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[6].

Terminology and diagnostic criteria

The SMFM defines FGR as an ultrasonographic estimated fetal weight (EFW) or abdominal circumference below the 10th percentile for gestational age[5]. Despite the fact that a significant number of constitutionally small fetuses are included below the 10th percentile threshold for FGR, large population-based studies have consistently shown increased perinatal morbidity and mortality below this weight threshold, with pregnancy risks comparable to, or higher than, those associated with other high-risk pregnancy conditions, with established fetal surveillance patterns. In a retrospective cohort study including all singleton neonates born in the USA in 2005, the risk for intrauterine fetal demise in those with birth weight $< 10^{th}$ percentile was 5-fold higher than in those with birth weight $\geq 10^{th}$ percentile[7]. A meta-analysis of 28 studies found that newborns with weight below the 10th percentile had significantly lower standardized neurodevelopmental scores[8], and a large long-term epidemiologic study found that term newborns with birth weight $< 10^{th}$ percentile had an increased risk for adult-onset diabetes when adjusted for body mass index and parental history of diabetes mellitus[9]. Finally, a study evaluating the placentas of singleton fetuses with EFW $< 10^{th}$ percentile in the third trimester and normal umbilical artery (UA) Doppler, that were delivered after 34 weeks' gestation, found that placental histopathologic signs of underperfusion were present in 66.7% of cases and correlated with a higher incidence of emergency Cesarean section and neonatal acidosis[10]. Interestingly, middle cerebral artery (MCA) and cerebroplacental ratio (CPR) Doppler indices did not predict pathologic markers of underperfusion in that study[10]. In view of these findings, we believe that the 10th percentile EFW threshold seems to be the most suitable cut-off for the diagnosis of FGR and is currently the most commonly applied threshold for FGR diagnosis in several national guidelines[11].

In an attempt to distinguish between FGR and constitutionally small fetuses, consensus-based definitions for both early- and late-onset FGR were established through a Delphi procedure[12] and recently adopted by the ISUOG FGR guideline[6]. The strength of the Delphi procedure is in creating consensus between a panel of experts, through a series of sequential rounds of questions, on topics that cannot be answered by clinical research[13,14]. Since FGR research is evolving, the Delphi approach carries the risk of introducing definition parameters into clinical practice based on opinions, without the benefit of scientific vigor. For instance, uterine artery Doppler was included in the Delphi definition as a contributory parameter for the diagnosis of early FGR despite its low sensitivity (25.8%) in predicting composite adverse pregnancy outcomes[15]. Although there is an association in late FGR between abnormal CPR and short-term adverse outcome, there is no strong evidence to date on whether incorporating CPR in clinical management actually improves outcome[16] and, therefore, we feel that its inclusion in the definition of late FGR should await the results of the planned randomized trial on this subject[16]. Finally, the proposed Delphi definition of FGR will increase testing utilization, as uterine artery or MCA Doppler testing will be required in about 10% of pregnancies.

In this issue of the Journal, Roeckner and colleagues compared the performance of the SMFM and ISUOG criteria for the diagnosis of FGR in predicting a small-for-gestational-age (SGA; birth weight $< 10^{th}$ percentile) neonate and neonatal morbidity[17]. The SMFM criteria had higher sensitivity than the ISUOG criteria for the prediction of neonatal SGA (54.7% *vs* 28.8%) but had a higher false-positive rate (6.7% *vs* 1.6%). The positive predictive value for the prediction of neonatal morbidity was poor for both definitions

(15.3% *vs* 25.5%), which likely reflects, at least in part, the rarity of adverse neonatal outcomes in pregnancies diagnosed with FGR that undergo antenatal surveillance and appropriate management[17]. Based on these data, we believe that the simplicity of the application of the SMFM criteria offers a more straightforward and pragmatic approach to the diagnosis of FGR, that also has the ability to identify more at-risk pregnancies[17].

Clinical management

There is consensus among FGR guidelines on the importance of UA Doppler in fetal surveillance and timing of delivery[11]. However, data to inform the frequency of UA Doppler evaluation are limited. Based on the SMFM guideline, upon diagnosis of FGR initial evaluation every 1–2 weeks is recommended, with subsequent evaluation every 2–4 weeks if the UA blood flow remains normal[5]. Findings indicative of decreased end-diastolic flow (EDF) in the UA should be evaluated weekly. When absent EDF in the UA is noted, assessment 2–3 times per week is recommended and evidence of deterioration to reversed EDF should warrant further escalation of care and surveillance in preparation for delivery[5].

Cardiotocography (CTG) is well-accepted as a primary surveillance tool in high-risk pregnancies[5]. In many management schemes, CTG has been cited as a standard monitoring tool, despite the lack of rigorous studies proving its efficacy[18]. Abnormal CTG with loss of fetal heart rate variability has been associated with acidosis and hypoxemia, and the presence of spontaneous repetitive decelerations is a trigger for delivery in viable fetuses with FGR[5,6,19,20]. It is important to note that abnormal CTG in FGR may be present in the absence of UA Doppler abnormalities and may represent an alternate pathway of fetal deterioration.

The SMFM does not recommend Doppler assessment of the MCA or ductus venosus (DV) in the clinical management of FGR, which is a significant difference from the ISUOG guidelines[5,6]. Evidence supporting these recommendations is presented in the following sections.

Middle cerebral artery Doppler

In the setting of FGR, MCA Doppler provides information about cerebral vasodilation, an early adaptive mechanism of fetal hypoxemia[21–23]. However, there is currently limited evidence to suggest that its incorporation into clinical decision-making in early FGR actually improves outcome. In a meta-analysis of 35 studies on the subject, abnormal MCA Doppler had limited positive predictive accuracy for perinatal mortality and adverse perinatal outcome[24]. In a secondary analysis of data on early FGR from the TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe) study, MCA Doppler was found to have a modest association with neonatal and 2-year infant outcome and did not add useful information beyond UA and DV Doppler for optimizing the timing of delivery[25]. As such, there is currently no compelling evidence to support the use of MCA Doppler in fetal surveillance or in delivery timing in early FGR[2,24,25].

In late FGR, studies have demonstrated that 15% to 20% of fetuses with normal UA Doppler have MCA Doppler findings of cerebral vasodilation[26]. CPR has also been studied for its utility in predicting adverse outcomes and guiding delivery timing in late FGR[27–31]. Recently, a prospective multicenter observational feasibility study, involving 856 pregnancies with late FGR, was undertaken as part of the design process for the TRUFFLE-2 randomized trial for determining arterial Doppler thresholds that are most strongly associated with adverse outcome and optimal timing for delivery[16]. The study showed that the first Doppler observation of MCA pulsatility index $< 5^{th}$ percentile and umbilicocerebral ratio *Z*-score above gestational-age-specific thresholds had the highest relative risks for composite adverse outcome, although gestational age at delivery and birth-weight *Z*-score showed a stronger association[16]. The authors concluded that it is still unclear whether cerebral redistribution is a marker of severity of FGR or an independent risk factor for adverse outcome, and that its usefulness in clinical management can be answered only in a randomized trial[16]. We therefore believe that the incorporation of cerebral Doppler in the management of late FGR should await further evidence from randomized trials[5].

Ductus venosus Doppler

In the setting of severe early FGR, spectral Doppler abnormalities of the DV reflect an advanced stage of fetal compromise and are associated with significant increase in perinatal morbidity and mortality[32–36]. The role of DV in the clinical management of pregnancies with early FGR was evaluated prospectively in the TRUFFLE trial which compared the efficacy of DV Doppler with that of computer-generated fetal heart rate short-term variation (cSTV) in fetal monitoring and timing of delivery[4]. Infant survival without neurological impairment at 2 years of age was significantly higher in the group delivered according to late DV abnormalities (95%) when compared with the group delivered according to cSTV (85%)[4]. The authors concluded that incorporating DV Doppler in the management of early FGR can guide the decision for delivery and possibly reduce long-term neurological sequelae[4]. The ISUOG guidelines for FGR include DV Doppler abnormalities as a trigger for delivery in pregnancies with early FGR[6]. Despite the evidence that DV Doppler accurately predicts perinatal morbidity and mortality in early FGR, its use in the clinical management of FGR is not recommended in the SMFM FGR guidelines[5]. This deliberate decision was based on the following points.

The TRUFFLE trial was designed to compare delivery triggers between cSTV and DV Doppler abnormalities and, thus, caution should be exercised in extrapolating these findings to clinical settings that do not utilize cSTV, such as in the USA, but rely on visual interpretation

of CTG. The safety-net criteria in the TRUFFLE trial that mandated delivery irrespective of the randomization arm, and which accounted for the delivery of 33% of pregnancies in the late-DV group, included cSTV cut-offs that are difficult, if not impossible, to identify on visual interpretation of CTG[4]. Indeed, in an editorial presenting the key messages from the TRUFFLE trial, the authors recommended against replacing visual interpretation of CTG with cSTV in settings in which cSTV is not available[37]. In addition, they stated that, if the results of the TRUFFLE trial are implemented in guidelines or local protocols, the safety-net criteria (which included cSTV) should be an integral part and that the TRUFFLE trial results are only generalizable in settings in which cSTV is available.

Unlike the UA, DV waveform abnormalities, including absent or reversed a-wave, may result from cardiac or vascular abnormalities in the absence of placental disease or fetal hypoxemia, and, thus, may partake in the inadvertent clinical decision to deliver a premature fetus, especially in settings that lack Doppler expertise. It is also important to note that the contribution of DV Doppler in the clinical management of early FGR is somewhat limited, as absent or reversed a-wave in the DV is encountered quite infrequently in the clinical setting. In a recent retrospective cohort study from two tertiary referral units, including 132 singleton growth-restricted fetuses with absent or reversed EDF in the UA, absent or reversed a-wave velocities in the DV were noted in only 15/132 (11%) of fetuses[38]. Indeed, in the TRUFFLE trial, delivery decision guided by DV Doppler abnormalities accounted for only about 10% of pregnancies allocated to the late-DV group, as most pregnancies were delivered due to safety-net criteria or other fetal or maternal indications[39]. In view of this limited role of DV in clinical decision-making in early FGR and the lack of prospective trials elucidating the role of DV Doppler in the setting of visual interpretation of CTG, there is currently insufficient evidence to recommend DV Doppler as part of a national guideline for clinical management of FGR in the USA[5]. With the understanding of limited generalization of the existing data on this subject, maternal–fetal medicine practices that wish to incorporate DV in the clinical management of early FGR may consider restricting its application to fetuses with absent or reversed EDF in the UA, in order to refine timing of delivery in the gestational-age window between 26 and 30 weeks of gestation.

Conclusions

Rigorously developed guidelines in medicine have the power to simplify the complexity of scientific research and develop recommendations that can potentially enhance health quality and outcome. In particular, the development of a FGR guideline that reflects a critical appraisal of the existing evidence is fundamental to enhancing clinician and patient decision-making and in standardization of care. This is of utmost importance given the vast number of scientific publications on the subject and the impact of FGR on population health.

In developing the SMFM FGR guideline, we have strived to maintain simplicity and clarity in order to enhance compliance and health equity. We have also ensured that the recommendations are applicable and relevant to existing practice patterns and that major decisions, such as delivery triggers, are based on solid evidence that actually impacts perinatal outcome rather than mere associations.

Finally, we commend our colleagues, the authors of the ISUOG FGR guideline, for their massive contribution to the FGR literature and their continued quest for discovery to help answer critical questions on this subject. Indeed, we are all beneficiaries of these scientific discoveries as the FGR guidelines will evolve over time to reflect the current state of science on this subject.

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Opinion

Diagnosis and management of fetal growth restriction: the ISUOG guideline and comparison with the SMFM guideline

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Both published in 2020, the guidelines of the Society for Maternal–Fetal Medicine (SMFM)[1] and those of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[2] on fetal growth restriction (FGR) make recommendations in respect of the diagnosis, monitoring and delivery timing of FGR pregnancies. The SMFM guidance[1], being a document aimed primarily at USA practitioners, is authored by three USA-based authors. As ISUOG is an international society, the authorship of the ISUOG FGR guideline is drawn globally (Europe, the Americas and Asia-Pacific)[2]. There are important differences between the two guidelines, which are in many places contradictory. Thus, instead of achieving a highly desirable unanimity in respect of the three main aspects of FGR management, namely diagnosis, monitoring and delivery timing, it seems that an international consensus still remains elusive. In this Opinion, we debate the relative merits of the conflicting recommendations provided in the ISUOG and SMFM guidelines on FGR, given the major impact these differences might have on the management of FGR pregnancies.

Terminology and diagnostic criteria

The SMFM guideline defines FGR as estimated fetal weight (EFW) or abdominal circumference (AC) $< 10^{th}$ percentile[1]. Though simple to apply, this definition classifies small-for-gestational-age (SGA) fetuses as FGR and would potentially label 10% of all babies as being growth restricted. While there is no doubt that EFW or AC $< 10^{th}$ percentile is associated with increased risk of adverse outcomes[3,4], this definition takes perinatology back to the 1990s, when there was intractable controversy about whether SGA represents a surrogate for FGR and, if not, why.

The SMFM definition of FGR as fetal size below the 10^{th} percentile does not take into account the fetal growth trajectory or functional indices, such as Doppler of the uteroplacental and fetoplacental circulations[5]. By contrast, the ISUOG guidelines recommend the adoption of the Delphi consensus criteria for the diagnosis of FGR (Table 1)[6], which seek to differentiate FGR from SGA and include both fetal growth trajectory and Doppler findings as additional considerations. The Delphi consensus was based on the opinions of leading world experts in FGR management, some of whom were from the Americas. The risk of a 'catch all' definition based on the 10^{th} percentile is that a proportion of babies whose size is below this cut-off are labeled as growth restricted and undergo enhanced monitoring and potentially intervention when it is not necessary[7]. In this context, if one were to pick an appropriate percentile at which the risk of adverse outcome is significant then this would most likely be the 3^{rd} percentile rather than the 10^{th} percentile[7–10]. Importantly, any size threshold that does not take into account the fetal growth pattern carries the risk of missing fetuses whose growth trajectory slows and who are therefore at risk of adverse outcome, even if their absolute size is greater than the 10^{th} percentile[5,10–16]. Furthermore, using the SMFM definition, only one-third of babies that are stillborn at or near term would be considered to be growth restricted[17]. Indeed, unrecognized FGR represents the single most common risk factor for stillbirth[18].

Table 1 Definitions for early and late fetal growth restriction (FGR) in the absence of congenital anomalies, based on the international Delphi consensus

Early FGR: *GA < 32 weeks, in absence of congenital anomalies*	*Late FGR:* *GA ≥ 32 weeks, in absence of congenital anomalies*
AC/EFW < 3^{rd} centile *or* UA-AEDF *Or* 1. AC/EFW < 10^{th} centile *combined with* 2. UtA-PI > 95^{th} centile *and/or* 3. UA-PI > 95^{th} centile	AC/EFW < 3^{rd} centile *Or at least two out of three of the following* 1. AC/EFW < 10^{th} centile 2. AC/EFW crossing centiles > 2 quartiles on growth centiles* 3. CPR < 5^{th} centile *or* UA-PI > 95^{th} centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery. Reproduced from Gordijn *et al.*[6].

Finally, early-onset (before 32 weeks) and late-onset (after 32 weeks) FGR have different clinical manifestations and characteristics[19–22]. The diagnostic criteria used in term FGR do not apply well at, for example, 26 weeks, as the Doppler profile is quite different[6,19,20,23]. Though it is possible to argue (as the SMFM does) that AC or EFW $< 10^{th}$ percentile *de facto* defines FGR and that Doppler assessment is irrelevant because only the fetal size is important, there is little doubt that Doppler criteria better identify those fetuses that show signs of placental impairment or dysfunction[8,12,19,24,25] and are at higher risk of adverse outcome[26]. A fetal size cut-off defines a different population in early gestation from that in term or late preterm pregnancy. A study comparing the SMFM and ISUOG definitions of FGR in a high-risk cohort, published in this issue of the Journal[27], showed that, although the SMFM definition had greater sensitivity for predicting birth weight $< 10^{th}$ percentile, the ISUOG definition had a higher specificity. It should be borne in mind, however, that the finding of higher sensitivity using the SMFM guideline was inevitable, given the outcome was prediction of birth weight $< 10^{th}$ percentile based on prenatal ultrasound showing AC or EFW $< 10^{th}$ percentile.

Umbilical artery Doppler

Both the ISUOG and the SMFM guidelines make recommendations in respect of monitoring FGR pregnancies and timing delivery using umbilical artery (UA) Doppler. With respect to monitoring frequency, the ISUOG guideline suggests that, in the presence of absent (AEDF) or reversed (REDF) end-diastolic flow in the UA, monitoring before 34 weeks should be performed every 2–3 days[2]. The SMFM recommends hospitalization and surveillance with cardiotocography (CTG) 1–2 times per day when UA-REDF is detected[1]. Given that there is no good evidence underlying this guidance, both SMFM and ISUOG provide appropriately cautious advice.

With respect to delivery timing, both guidelines graduate their recommendations for delivery based on gestational age and the degree of abnormality of the UA Doppler waveform (REDF, AEDF and raised impedance) in broadly similar ways after 30 weeks, with neither suggesting that FGR should be left undelivered beyond 39 weeks. The difference is that the ISUOG guideline recognizes the absence of evidence for basing delivery timing on UA Doppler whereas the SMFM guideline classifies as Grade 1B the recommendation for delivery prior to 37 weeks in the presence of UA Doppler abnormalities (strong recommendation, moderate-quality evidence). This is important as there is no evidence from randomized controlled trials (RCTs) that informs what are usually very carefully balanced decisions and where clinical experience and expertise may be in the mother and fetus' best interest. A meta-analysis of RCTs on the application of UA Doppler *vs* no UA Doppler in high-risk pregnancies showed reduced perinatal mortality in women in whom UA Doppler was performed[28]; however, to our knowledge, no RCT on delivery timing based on UA Doppler is available to date.

Middle cerebral artery Doppler

The SMFM guideline recommends *not* to use middle cerebral artery (MCA) Doppler in the routine management of early- or late-onset FGR (Grade 2B recommendation). It is not clear to what particular aspect of clinical management this recommendation refers. A low MCA impedance indicates redistribution of fetal cardiac output preferentially to crucial fetal organs, such as the brain, heart and adrenal glands, in response to fetal hypoxemia and/or hypercapnia[29–32]. There is abundant evidence showing that cerebral blood-flow redistribution is associated with a spectrum of adverse short- and long-term outcomes[33–44]. Moreover, in late-onset FGR, cerebral blood-flow redistribution may be the only Doppler sign to suggest placental dysfunction[19,36,45]. In view of these data, the ISUOG guideline recommends that signs of cerebral blood-flow redistribution should be considered as a criterion to identify late FGR, in line with the Delphi consensus criteria, and that twice-weekly surveillance might be carried out in its presence based on available data[21]. The association between two phenomena does not imply a causative link, and there is still no strong evidence for the use of MCA in the context of triggering delivery[46]. However, the issues of identifying an 'at-risk' baby and of enhanced monitoring are distinct from determining timing of delivery and, in contemporary practice, the evaluation of cerebral blood-flow redistribution should not in our view be neglected as it is justified in having a role in diagnosis and monitoring, especially in late FGR.

Ductus venosus Doppler and computerized cardiotocography

Apart from the dissimilarities in respect of FGR diagnosis, the greatest and arguably most clinically important difference between the SMFM and ISUOG guidelines is that the SMFM guideline does not differentiate between management of early-onset and late-onset FGR.

In early FGR, the risks of prematurity must be balanced against prolonged intrauterine fetal exposure to hypoxemia and acidemia, both of which are associated with perinatal morbidity and mortality[47]. Therefore, gestational age requires consideration when interpreting test results with a view to decide on elective delivery. Extremely low values of short-term variation (STV) in computerized analysis of CTG (cCTG) is a reliable predictor of metabolic acidemia at delivery or intrauterine death[48–55]. Increased pulsatility in the ductus venosus (DV) reflects myocardial decompensation resulting in increased end-diastolic ventricular pressure and decreased forward flow velocities during atrial contraction (a-wave) as early changes and absent or reversed flow as late changes of its waveform[56]. These changes might also reflect a progressive dilatation of the DV as an adaptive response to worsening hypoxemia[56]. DV abnormalities represent a relatively late biophysical sign in early FGR and are associated with significantly increased risk of stillbirth[23,48,57,58].

The TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe) multicenter study assessed whether changes in the fetal DV could be used as indication for delivery instead of CTG STV alone in pregnancies with early-onset FGR[59]. Pregnancies were allocated randomly to one of three arms in which the timing of delivery was determined based on reduced STV on cCTG, early DV Doppler changes or late DV Doppler changes. The primary outcome of survival without neurodevelopmental impairment at 2 years of age was significantly more common in infants of women who were assigned to delivery according to late DV changes (95%; 95% CI, 90–98%) compared with those assigned to delivery according to cCTG (85%; 95% CI, 78–90%; $P = 0.005$). Importantly, safety-net criteria for delivery applied to all patients irrespective of the randomization group. These comprised cut-off 'rescue' values of STV in the two DV arms and, additionally, spontaneous repeated unprovoked heart rate decelerations on CTG and UA Doppler showing REDF from 30–32 weeks and AEDF from 32–34 weeks onwards in all three arms. The safety-net criteria indicated delivery in 33%, 23% and 15% of cases in the late-DV, early-DV and cCTG groups, respectively[59]. Thus, a key message from the TRUFFLE study is that the best outcome in early FGR is obtained when fetuses are monitored and delivery timing is decided based on both DV and cCTG[60], where only cCTG can allow an objective and reproducible measurement of fetal heart rate STV.

As the cCTG safety-net criteria were an integral part of the TRUFFLE study protocol, they are also central to the recommendations of the ISUOG guidelines for monitoring and timing of delivery of pregnancies with early-onset FGR. Clinical guidelines should justify their recommendations based on data acquired and conclusions drawn from studies providing the highest quality of evidence, i.e. well-performed randomized trials (Grade A evidence). It is therefore surprising that the SMFM guideline on FGR recommends against both Doppler assessment of the DV and use of cCTG STV in the routine clinical management of early-onset FGR, and classifies the recommendation to *not* use Doppler and cCTG as Grade 2B. In this context, it is questionable whether it is appropriate to refer to 'routine' clinical management of early-onset FGR, which is a rare disease requiring specialist input[61]. Early FGR is not a 'routine' condition and should not be managed in a clinical setting lacking expertise in maternal and fetal Doppler investigations.

Conclusions

We appreciate that the SMFM guideline was developed based on many considerations, not least in relation to taking into account training, ultrasound and cCTG resources. However, guidelines should primarily aim to improve clinical care based on the best available evidence and technology rather than by maintaining the '*status quo*' or recommending management that is available in a routine maternity setting.

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