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THE INTERNATIONAL SOCIETY OF ULTRASOUND in Obstetrics & Gynecology

GUIDELINES

# Diagnosis and management of small for gestational age fetus and fetal growth restriction

ISUOG SGA-FGR Guideline Task Force

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## A. INTRODUCTION:

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

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

This guideline provides definitions of fetal growth restriction (FGR), previously named intrauterine growth restriction (IUGR), and small for gestational age fetus (SGA), and describes the best possible management options based on available data and knowledge. It is assumed for the purposes of the guideline that the pregnancy is singleton, dating has been correctly carried out (preferably in the first trimester by ultrasound) and that there are no fetal pathologies such as aneuploidies, congenital malformations or infections.

## B. GUIDELINES

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

Fetal growth describes a dynamic process implying multiple observations of fetal size over time. Fetal size is evaluated through biometric evaluation of the head circumference [HC], biparietal diameter [BPD], abdominal circumference [AC] and femur length [FL]) and/or derivation of estimated fetal weight (EFW) computed by different formulae. ISUOG Guidelines on Ultrasound assessment of fetal biometry and growth provide description of methodology, references, standards and quality control of fetal biometry assessment and diagnosis of fetal growth disorders[6]. Controversies on which reference/standard ranges should be used, metrics, and other issues related to the assessment of fetal biometry are described in these Guidelines.

The fetus is considered to be small for gestational age (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 10$^{th}$ percentile for given reference ranges. Nevertheless, other thresholds have been described, such as 5$^{th}$ and 3$^{rd}$ (approximating to two standard deviations [SDs]) or z-score deviations.

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

The main concept behind the differentiation between SGA and FGR is that SGA fetus may be small, but not at increased risk of adverse perinatal outcome, while FGR may be present even if fetal size is above the 10$^{th}$ percentile and it is at increased risk of adverse perinatal and long-term outcome[7-11].

Fetuses with birth weight below the 10$^{th}$ percentile are at increased risk of stillbirth[12] and perinatal mortality[13-15], with the highest risk for birth weight below the 3$^{rd}$ percentile[12,13]. For this reason, fetal size at the lower extreme of the growth charts, AC or EFW below the 3$^{rd}$ percentile for given growth charts, is sufficient as an isolated criteria to define FGR at any gestational epoch[16]. However, optimal fetal growth, with lowest perinatal mortality, seems to be substantially higher than the median birth weight of a normal cohort[13]. In fact, population based cohort studies found increased perinatal mortality even within normal growth percentiles, with lowest risk somewhere between the 70$^{th}$ – 90$^{th}$ percentile, and an inverse association between perinatal mortality and birth weight below the 80$^{th}$ percentile[13]. A large Scottish population-based cohort demonstrated a progressive rise from baseline for the risk of FGR-associated stillbirth below the 25$^{th}$ percentile[17].

In order to differentiate between SGA and FGR where the fetal size is below 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 velocimetry evaluation of placental and fetal circulations and the use of biomarkers. Some of these biophysical parameters are also used to monitor and/or as delivery decision criteria (i.e. Doppler of umbilical artery). Biophysical tools such as ductus venosus, biophysical profile, cardiotocography (CTG) and short term variation (STV) are not used as diagnostic criteria for FGR, but for surveillance and management in already diagnosed 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 (longitudinal growth charts[18], growth velocity chart deviation[18], individualized growth assessment[19]). Overall, the objective is to evaluate the fetal growth trajectory, and identify those fetuses that are deviating from their own 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].

*Customized growth charts.* In customization the fetal weight and growth are adjusted for variables that impact on fetal size. These can include maternal height, weight, age, parity and ethnicity and fetal sex. The adjustment for these variables is suggested to allow for better identification of SGA fetuses at risk of perinatal complications. The evaluation of fetal growth velocity and application of customized growth charts is described more in detail in ISUOG Guidelines on "Ultrasound assessment of fetal biometry and growth"[6].

*Doppler velocimetry*. The rationale behind the application of Doppler velocimetry is that it identifies utero-placental function by evaluation of uterine and umbilical arteries. Utero-placental insufficiency is putatively mediated through spiral adaptation and villous vascular tree alteration. On the fetal side, Doppler velocimetry allows the evaluation of the middle cerebral artery and ductus venosus as fetal cardiovascular adaptation progresses from hypoxia to acidemia.

The lack of physiological transformation of 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 mean pulsatility index (above the 95th percentile) is associated with placental insufficiency and maternal vascular malperfusion of the placenta[21].

Progressively increasing pulsatility index in umbilical artery corresponds to a progressive reduction of placental surface area available for gas and nutrients exchange and increased fetal afterload resistance, until placental vascular insufficiency reflected by absent and, in the end stage phase, reverse end diastolic flow in umbilical artery[22].

The reduced pulsatility index of the fetal middle cerebral artery 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 preferentially to the coronary arteries and adrenal glands[23].

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

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

*Biophysical profile scoring*. The biophysical score consists of the combined evaluation of fetal tone, gross body movement, breathing movement, amniotic fluid volume, and heart rate reactivity. Low biophysical score predicts both fetal pH and outcome[26,27]. The relationship between altered biophysical score and fetal pH seems to be consistent across gestational age[26]. A scoring of ≤4 is associated with a fetal pH ≤7.20, while a score <2 has a 100% sensitivity for acidemia[27]. This correlation remains highly significant with the simplified biophysical profile that is based only on the two variables, fetal heart rate and amniotic fluid assessment[28].

*Cardiotocography and short term variation*. A reactive CTG virtually excludes fetal hypoxemia. The fetal heart rate variability (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. This is not present in SGA where, by definition, fetal hypoxia is not present.

The 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. It has been shown that cCTG predicts accurately fetal acidemia[29]. Visual inspection of conventional CTG does not provide the same information as cCTG and as it is a purely qualitative assessment with a low intra and inter-observer reproducibility.

Biomarkers. Placental factors have a potential role in screening, diagnosis and therapy of placental disease linked to hypertensive disorders of pregnancy and/or growth restriction[30]. Several factors have been proposed, including placental proteins, but also microRNA and mRNA, and other factors. Some placental proteins, such as pregnancy-associated plasma protein A (PAPP-A) may be useful biomarker in the first trimester[31,32], while placental growth factor (PLGF) used singly[33] or in combination with soluble Fms-like tyrosine kinase-1 (sFlt-1)[34], are novel strategies to increase test precision for FGR in the 3rd trimester. The rapidly-evolving research-based discussion of the use of biomarkers in screening for SGA/FGR is beyond the scope of these guidelines.

A ratio of sFlt-1/PLGF has been proposed as a short-term predictor to rule out preeclampsia in women in whom it is suspected clinically[35]. Although there are reports that suggest that the use of sFlt-1/PLGF ratio in differentiation and management of SGA/FGR might be helpful[33,34,36-38], a lack of interventional trial data precludes the recommendation of these tests presently as an adjunct to ultrasound imaging.

Recommendations

- Fetal size alone is not sufficient to identify FGR, unless AC or EFW are below the 3rd percentile (Grade of recommendation: C);
- Growth velocity drop (AC or EFW crossing 50 centiles or 2 quartiles) should alert the physician about possible growth restriction (i.e. a drop from 70th percentile to 20th percentile or below) (Grade of recommendation: C);
- Doppler velocimetry of the utero-placental and the feto-placental circulations may be used to distinguish SGA from FGR (Good practice point);
- Multi-modal assessment is recommended for the evaluation of pregnancies with suspected FGR. A cCTG or biophysical profile scoring should be used in combination with Doppler velocimetry (Grade of recommendation: A).

**Definition of early and late FGR**

There are two main phenotypes of FGR that differ significantly in many aspects such as prevalence, prediction from first trimester scan, gestational age at onset, placental histopathological findings, Doppler velocimetry profile, maternal associated disease, severity and perinatal outcome. Table 1 defines the main characteristics of the two phenotypes, defined as early and late FGR based on the observation that one phenotype is more frequent early in gestation and the second near term[39-42]. There is as yet no evidence that customization of fetal size or biomarkers allow differentiation between SGA and early or late FGR.

The distinction between early and late phenotypes is usually based on diagnosis before or after 32-34 weeks. Although the umbilical artery Doppler evaluation seems to discriminate better the two phenotypes of FGR in association with preeclampsia and poorer perinatal outcome[39,40], the gestational age at diagnosis at 32 weeks of gestation seems to be the optimal cut-off[40] and has been introduced and agreed upon as major criteria to differentiate between early and late FGR[16]. Hence we have taken 32 weeks as the 'cut off' between early and late FGR in this guideline.

The definition of FGR changes among different guidelines or author groups[43]. An international Delphi survey consensus on definition of FGR represents, at present, the most recognized criteria[16] and is shown in Table 2. A study sought to validate the Delphi criteria by comparing them to a Hadlock EFW below 10$^{th}$ percentile in predicting adverse neonatal outcome. The study spanned a wide gestation range and the two methodologies were broadly comparable though Delphi criteria were associated with an improved in prediction of adverse neonatal outcome[44].

Recommendations

- The two main phenotypes of FGR, early and late, are characterized by different clinical, ultrasound and pathological characteristics (Grade of recommendation: D);
- The ISUOG working group recommends the Delphi consensus criteria[16] for FGR definition (Good practice point).

**Doppler velocimetry**

*Which indices and cut-offs to use?*

Despite the fact that Doppler velocimetry has been used in obstetric practice for nearly four decades, there is no universal agreement over which indices, thresholds and/or reference ranges to use. These considerations are not applicable when qualitative assessment is performed such as assessing absent/reverse ductus venosus a-wave or absent/reverse end diastolic flow in umbilical artery, but

they affect Doppler velocimetry quantitative evaluation. There is however now international guidance on how to perform utero-placental and fetal Doppler velocimetry[45].

The first issue refers to a considerable methodological heterogeneity in studies reporting reference ranges for Doppler indices in umbilical artery, middle cerebral artery and their ratio, that may at least partly explain the differences among studies that reported reference ranges[46]. Even among studies with highest methodological and quality score, there are significant differences in the definition of "normality" and normal ranges[46]. A recent study that evaluated ten most cited reference ranges articles for umbilical artery, middle cerebral artery and their ratio, found wide discrepancies among Doppler reference values that accounted up to 50% of variability for middle cerebral artery pulsatility index below the 5$^{th}$ percentile cut-off value at term[47]. Similarly, there are significant differences for umbilical artery pulsatility index above the 95$^{th}$ percentile cut-off (20-40%) and cerebro-placental ratio below the 5$^{th}$ percentile (15-35%)[47]. Wide discrepancies have been reported in reference ranges used for biometry evaluation, Doppler parameters and birth weight even at national level in centers with high expertise in management of FGR, that might significantly impact the diagnosis and management of FGR[48].

Secondly, often there is no uniformity in Doppler indices that are used, especially in research studies. So for example, cerebral blood flow redistribution can be defined as middle cerebral artery pulsatility index below different percentile thresholds (5$^{th}$ or 10$^{th}$), z-scores or multiples of median (MoMs), or it can be defined as umbilico-cerebral or cerebro-placental ratio above or below different percentile thresholds, z-scores or MoMs, respectively[49]. The Delphi consensus criteria identified cerebro-placental ratio below the 5$^{th}$ percentile and umbilical artery pulsatility index above the 95$^{th}$ percentile as Doppler criteria to define FGR[16]. The rationale behind the application of middle cerebral to umbilical artery ratio (CPR or UCR), instead of individual components, is that it has been shown to be more sensitive to fetal hypoxia[50] and more associated with adverse perinatal outcome[49,51]. The CPR is more frequently reported than UCR. However, it appears that in the abnormal range the UCR allows for a better differentiation of cases than the CPR[52] as the more abnormal it becomes, the index tends towards an asymptote that approaches infinity. However, it has to be highlighted that there is no strong evidence for any particular threshold. These definitions are based in the main on expert opinion.

All these differences have a major clinical impact on crucial points such as diagnosis, monitoring, timing of delivery decision, reproducibility and comparison between research studies and efficacy of clinical policies and protocols, and many other aspects[46]. The discussion over which reference ranges to use is beyond the scope of these guidelines. However, these differences have to be acknowledged and urgent action is needed to homogenize the adoption of Doppler indices, thresholds and reference

ranges in clinical and research practice. In the Appendix the summary of the most relevant studies reporting reference charts for middle cerebral artery and its ratios is presented (adapted from Ruiz-Martinez et al.[47]).

**Early fetal growth restriction**

Early FGR is more strongly associated with maternal-vascular malperfusion of the placenta characterized by abnormal transformation of the spiral arteries, pathologic features of the placental villi and multi-focal infarction; all these disease components result in so-called "placental insufficiency" and form the most common basis for placenta-mediated FGR[53,54]. The chronic ischemia of the placental villi both impairs PlGF secretion, and leads to excessive sFLt-1 release by syncytial knots, resulting in the elevated sFlt-1/PlGf ratio, which typifies early FGR and the associated hypertensive disorders of pregnancy. Elevated umbilical artery Doppler pulsatility index, therefore precedes a cascade of Doppler alterations, fetal heart rate changes and biophysical profile modifications, with end-stage cardiovascular deterioration caused by severe hypoxemia and hypoxia till acidosis[55-57]. Uterine, umbilical and middle cerebral artery Doppler abnormalities represent the early changes and may be present for many weeks in the progression of early FGR hemodynamic changes before severe cardiovascular and metabolic deterioration occurs. Although the absent end diastolic flow in umbilical artery represents a progressive deterioration of utero-placental function, it still precedes critical fetal deterioration and the progression to reverse end diastolic flow might be slow. However, the rate and rapidity of alteration in umbilical artery Doppler, from increased blood flow resistance to absent end diastolic flow, 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 end diastolic flow in umbilical artery, and worsening generalized cardio-vascular and metabolic failure reflected by alterations in ductus venosus (absent or reverse a-wave)[57,59]. This cardio-vascular deterioration might precede or occur in parallel to the alteration of the STV, finally manifesting as abnormal biophysical profile score, spontaneous repetitive decelerations on CTG and stillbirth[39,60].

At present, there is no effective therapy in early FGR, though efficient recognition and management of severe preeclampsia 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 in terms of perinatal morbidity and mortality. On the other hand, decision to deliver has to be balanced with possible harm caused by prematurity[62,63], complicated by the fact that the fetus is

suffering from growth restriction, making the outcome even more unfavorable as the FGR is an independent risk factor for these adverse outcomes[64,65]. This is highlighted by the fact that neonatal survival exceeds 50% after 26 weeks, which is 2 weeks later than in appropriately grown for gestational age (AGA) counterparts[55]. In this view, optimal monitoring and timing of delivery decision are of crucial importance when managing early FGR.

*How to monitor?*

Once early FGR is suspected/diagnosed it should be monitored and managed in tertiary-level fetal medicine and neonatal units according to a uniform management protocol[66]. Multidisciplinary counseling between neonatology and maternal-fetal medicine specialists is indicated. There is a developing international consensus on the optimal modality and frequency of monitoring of early FGR, and monitoring by Doppler velocimetry, cCTG or CTG and biophysical profile. In early FGR arterial and venous Doppler assessments are recommended. There is evidence from a randomized trial (TRial of Umbilical Fetal FLow velocities in Europe - TRUFFLE) that monitoring and delivery timing according to a specific protocol with ductus venosus Doppler and cCTG provides better-than-expected outcomes[66]. Thus, in units where cCTG is available, early FGR should be monitored by both ductus venosus Doppler and cCTG-STV assessments. It has to be taken into account that the cCTG is not universally available or used. In that case, in addition to Doppler evaluation, assessment of conventional CTG and, where undertaken, biophysical profile 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 less than 7.20[27], while loss of fetal tone is associated with pH less than 7.00 or a base excess below -12.

The surveillance frequency should be based on the severity of FGR and umbilical artery abnormalities. Progressive deterioration of umbilical artery Doppler velocimetry warrants progressively more intensive monitoring every 2-3 days when absent or reverse end diastolic flow in umbilical artery are present. There is no consensus over monitoring frequency, however the management strategies that might be used are usefully described elsewhere[29,42,67].

The middle cerebral artery Doppler is one of the first parameters that becomes abnormal in early FGR. There seems to be a weak association between middle cerebral artery low pulsatility index and adverse short-term neonatal outcome and between middle cerebral artery low pulsatility index and high umbilico-cerebral ratio with 2-year adverse neurodevelopmental outcome[52]. However, the impact of gestational age at delivery and birth weight have the most pronounced impact on these outcomes[52]. Thus, middle cerebral artery 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 preeclampsia[68]. Thus, regular blood pressure assessment, 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 place 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 RCOG recommends corticosteroid prophylaxis up to $35^{+6}$ weeks[67]. Despite this recommendation, it is worth noting that no randomized trial had been performed in order to establish whether the benefits of corticosteroid in premature fetuses also applies 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]. Where the fetus has absent/reversed end diastolic flow in umbilical artery, enhanced daily surveillance is warranted during steroid administration[76].

Magnesium sulphate prophylaxis

Many guidelines recommend magnesium sulphate prophylaxis for neuroprotection ranging from gestational age <30 weeks[77], <32 weeks[70,72] to 32-33 weeks[73]. The most recent population-based data is strongly supportive of this intervention <32 weeks[78]. However, in the absence of strong evidence regarding the optimum gestational age of magnesium sulphate prophylaxis that would allow for uniform application among countries, we recommend to refer to local or national guidelines.

*When and how to deliver?*

The data from a large prospective international multicenter study provided evidence that early gestational age and birth weight are the primary quantifying parameters that impact the neonatal outcome[55]. Indeed, for extreme prematurity (<27 weeks) and extremely low birth weight (<600 grams), each day of prolongation of gestation improves neonatal survival by 2%. Afterwards, ductus venosus Doppler parameters emerged as the primary factor in predicting neonatal outcome[55].

The first randomized controlled trial on timing of delivery in FGR was the Growth Restriction Intervention Trial (GRIT)[79,80]. The study evaluated the effect of immediate delivery versus expectant management in case of clinician's uncertainty on optimal management of FGR. The time to delivery in expectant management was 4.9 days, versus 0.9 days in the immediate delivery arm, and seemed to

be associated with more favorable neurodevelopmental outcome. However, there were no significant differences in outcome at school age[81].

The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) is the largest randomized trial on timing of delivery management in early FGR based on 3 randomization arms: early and late ductus venosus changes and cCTG-STV, including the safety net for all three arms[82]. The safety net represented an absolute indication for delivery and was represented by spontaneous repeated persistent unprovoked decelerations in all three arms and STV below 2.6 ms at $26^{+0}$-$28^{+6}$ weeks and below 3 ms at $29^{+0}$-$31^{+6}$ weeks in ductus venosus arms, respectively. The protocol recommended delivery if reversed umbilical artery end diastolic flow occurred after 30 weeks or if there was absent umbilical artery end diastolic flow 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' improves long-term (2 years neurodevelopmental) infant outcome in survivors. In TRUFFLE, the cCTG STV 'safety net' was deliberately set at a level below that of the two ductus venosus randomized groups. The Figure 1 represents the flow chart of the protocol recommended by TRUFFLE study[66]. Despite the fact that data from TRUFFLE study showed better than assumed results in terms of survival without neurological impairment (82% of children), the gestational age at study entry and delivery, and birth weight were strongly related with 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 making 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 below 30 weeks) and conventional CTG, or biophysical profile where this is undertaken. The presence of repeated spontaneous unprovoked decelerations is an indication for delivery. However, when visually interpreting the fetal heart reactivity at conventional CTG, the gestational age and corresponding fetal maturity should be taken into account. Similarly, an absolute indication for delivery is maternal conditions (severe preeclampsia, eclampsia, HELLP) or obstetric emergency conditions such as abruption.

Considering the strong association with severe placental insufficiency and fetal hypoxemia/hypoxia a planned Cesarean section is indicated in the high 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

- Early FGR should be monitored and managed in tertiary level units with highest level neonatal

care (Good practice point);

- Multidisciplinary management by neonatology and maternal-fetal medicine specialists is indicated (Good practice point);
- Multi-modality assessment is recommended including: CTG, umbilical artery, middle cerebral artery and ductus venosus Doppler evaluation (Grade of recommendation: A);
- Where cCTG is available, STV is the main parameter that is assessed (Grade of recommendation: A);
- Monitoring should be programmed based on the severity of FGR and alteration in umbilical artery (Good practice point);
- Delivery should be based on biophysical assessments or maternal indication, as follows:
    - Deliver at any gestation if maternal indications (e.g. severe preeclampsia, HELLP syndrome) or obstetric emergencies requiring delivery (Good practice point);
    - $24^{+0}$-$25^{+6}$ weeks: personalized management (consensus based) (Good practice point);
    - ≥$26^{+0}$-$28^{+6}$ weeks: deliver if ductus venosus A-wave at or below baseline or STV below 2.6 ms (Grade of recommendation: A);
    - ≥$29^{+0}$-$31^{+6}$ weeks: deliver if ductus venosus A-wave at or below baseline or STV below 3.0 ms (Grade of recommendation: A);
    - ≥$32^{+0}$ weeks (permitted after $30^{+0}$ weeks): deliver if umbilical artery end diastolic flow is reversed or STV below 3.5 ms (Good practice point);
    - ≥$34^{+0}$ weeks (permitted after $32^{+0}$ weeks): deliver if umbilical artery end diastolic flow is absent or STV below 4.5 ms (Good practice point);
    - ≥$26^{+0}$ weeks of gestation deliver if any of the following is present:
        - Spontaneous repeated persistent unprovoked decelerations (Grade of recommendation: A);
        - Altered biophysical profile (score ≤4) (Good practice point);
- Corticosteroid prophylaxis is recommended if delivery is planned at before $34^{+0}$ weeks of gestation (Grade of recommendation: B);
- Elective Cesarean delivery is recommended if one or more of the following are present: abnormal cCTG-STV, ductus venosus alteration, umbilical artery absent or reverse end diastolic flow, altered biophysical profile, maternal indication (Good practice point).

**Late fetal growth restriction**

The pathophysiology of late FGR is different from early FGR. Late FGR is characterized by milder and more aspecific placental lesions and/or alteration of oxygen and nutrient diffusion[83,84]. Consequently, alterations of umbilical artery Doppler and venous districts are rare and fail to identify the vast majority of late FGR and predict an adverse outcome in these fetuses[40]. Several studies found an association between vasodilatation in middle cerebral artery (in other words, reduction in pulsatility index), the so called brain sparing effect, or alteration of its ratio to umbilical artery with poorer perinatal outcome, including stillbirth[39], higher risk of Cesarean delivery[85-87], increased risk of abnormal neurodevelopment at birth[88] and at 2 years of age[89]. The rationale of using a ratio between middle cerebral artery and umbilical artery, the so called cerebro-placental ratio (CPR) or umbilical-cerebral ratio (UCR), is that they enhance subtle changes between placental and cerebral blood flow perfusion that may not be appreciated by evaluation of only single parameter. Further, it has been suggested that ratios may improve the prediction of adverse perinatal outcomes[90-92].

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

Late FGR, despite presenting in milder form than early FGR, is still associated with poor perinatal outcome[85,93] and longer term educational attainment[89,94,95]. In TRUFFLE, the risk of poor neurodevelopmental outcome in babies that delivered after 32 weeks was static week-by week until term[96]. This may be due to several factors. The pathophysiology behind late FGR is still not completely understood and this may determine a lower identification rate of fetuses exposed to growth restriction near the term[96]. Next, fetuses near term seem to have a reduced tolerance to hypoxemia[98] possibly because of their relatively high metabolic rate compared to early FGR. Thus, frequent monitoring of late FGR is warranted in the same way as for early FGR.

*Corticosteroid prophylaxis*

Between 34-36 weeks there is a lack of consensus between guidelines. 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].

*How to monitor?*

At present, the assessment of middle cerebral artery and its ratios to umbilical artery seems to be the most important Doppler parameters in the surveillance of late FGR. A large retrospective study showed that in case of FGR after $34^{+0}$ weeks of gestation the median interval between a low middle

cerebral artery pulsatility index and stillbirth was ≤ 5 days, suggesting that, if delivery was still not indicated, twice weekly surveillance may be required[39]. In the presence of umbilical artery pulsatility index above the 95$^{th}$ percentile at least once to twice weekly monitoring is indicated. Moreover, almost 90% of stillbirths in this cohort occurred within 1 week of a normal biophysical profile in the presence of cerebral vasodilatation, suggesting that biophysical profile might be poor in determining the frequency of fetal monitoring[39].

Considering the fact that some concerns have been raised regarding the inter-observer reliability of middle cerebral artery pulsatility index measurement, when alteration of middle cerebral artery, cerebro-placental or umbilico-cerebral ratios are encountered the measurement should be confirmed within 24 hours to avoid false positive results, especially when timing of delivery is based on this finding[99].

*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 late FGR. In fact, national guidelines for the management of FGR are highly variable[43].

The only randomized interventional trial for FGR at or close to term was the DIGITAT study, Disproportionate Intrauterine Growth Intervention Trial At Term[100]. The study compared the effect of induction of labor versus expectant monitoring management in singleton pregnancies beyond 36$^{+0}$ weeks of gestation with suspected FGR. The study did not take into account any Doppler assessment; the only umbilical Doppler parameter reported was absent end diastolic flow (14/650). The induction of labor policy did not affect the rate of adverse neonatal outcome or neurodevelopmental and behavioral outcome at 2 years of age, except for children with birth weight below 2.3$^{rd}$ percentile[101]. Moreover, it did not affect either the rates of instrumental vaginal delivery or Cesarean section. In the induction group more neonates were admitted to intermediate levels of care, but this outcome was reduced when the induction was limited after 38 weeks of gestation[102]. Importantly, the proportion of neonates with birth weight below the 3$^{rd}$ percentile was greater in the expectant monitoring arm, as was the proportion of women that developed preeclampsia. Based on these findings it would appear that induction for suspected FGR after 38 weeks is not associated with increased rate of instrumental vaginal delivery or Cesarean section or adverse neonatal or 2-year child outcome, while decreasing the rate of extremely low birth weight neonates and the rate of progression to preeclampsia. Of note that fetuses at term with birth weight below the 3$^{rd}$ percentile have the highest risk of stillbirth, approximately 1:100[12]. Based on these results it is appropriate not to exceed 38$^{+0}$ weeks of gestation in the case of late FGR independent of Doppler findings. All cases of

stillbirth in the DIGITAT trial occurred among those women that despite meeting inclusion criteria declined to participate (approximately 1%, personal communication). This stresses the importance of monitoring SGA fetuses at or near term, and timely delivery.

In the case of late FGR and umbilical artery pulsatility index above the 95$^{th}$ percentile, expert opinion is that delivery should be considered when the gestation is beyond 36$^{+0}$ weeks and not later than 37$^{+0}$ weeks[103].

There is emerging awareness that there might be an impact of cerebral blood flow redistribution on adverse short and long term outcome[49,104-106]. However, in the absence of randomized interventional trials, it is still not clear whether the assessment and delivery decision based on Doppler evaluation of cerebral blood flow redistribution is beneficial in terms of short and long term neurodevelopmental outcome and which is the optimal gestational age to deliver (beside the optimal Doppler parameter and threshold). A randomized controlled interventional trial (TRUFFLE-2 RCT) is to start in 2020 and aims to answer this question. However, it seems reasonable that in the case of late FGR with signs of cerebral blood flow redistribution it is advisable to consider delivery around 38$^{+0}$ 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, estimated fetal weight, cervical findings), induction of labor may be undertaken but this is not recommended in the context of critical umbilical artery Doppler findings (i.e. absent or reverse end diastolic flow)[43,103]. Continuous fetal heart rate monitoring during labor should however be undertaken.

Recommendations

- In case of late FGR deliver if:
  - One of the following is present at any gestational age (Good practice points):
    - Spontaneous repeated persistent unprovoked decelerations;
    - Altered biophysical profile (score ≤4);
    - Maternal indications (e.g. severe preeclampsia, HELLP syndrome) or obstetric emergencies requiring delivery;
    - cCTG-STV below 3.5 ms at 32$^{+0}$-33$^{+6}$ weeks and below 4.5 ms ≥34$^{+0}$ weeks ;
    - Absent or reverse end diastolic flow in umbilical artery;
  - 36$^{+0}$ and not later than 37$^{+0}$ weeks of gestation (Good practice point):
    - Umbilical artery pulsatility index above the 95$^{th}$ percentile;
  - 38$^{+0}$ weeks of gestation (Good practice point):

- Evidence of cerebral blood flow redistribution;
- In the absence of other 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**

Small for gestational age, as defined by Delphi consensus criteria[16], is to be considered as constitutionally small fetuses-in other words healthy. In these cases the adoption of customized growth charts could reduce the proportion of SGA[107]. However, there is some evidence that suggests that SGA with normal standard Doppler is associated with accelerated placental ageing[108], signs of placental underperfusion[109], lower umbilical vein blood flow volume[110], altered maternal hemodynamics[111], and greater proportion of Cesarean section for fetal distress[85] than appropriate for gestational age fetuses. Such recent evidence poses a question as to whether within SGA fetuses there might be a subgroup of fetuses that do in fact suffer from 'stunted' fetal growth, who adapt to a poor nutritional environment, and that 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 all fetal Doppler indices should be assessed (umbilical artery, middle cerebral artery and their ratio) and uterine artery Doppler evaluation.

In the case of late SGA (after 32 weeks), once the uterine artery Doppler has been assessed there is no need to repeat this at each visit while, usually, they remain unchanged from diagnosis of SGA to delivery[112]. Fortnightly assessment of fetal growth is recommended[113]. Some late SGA fetuses with abnormal uterine artery pulsatility index at diagnosis are more likely and earlier progress to brain sparing, in other words 'cross over' to FGR. Even late SGA fetuses with normal uterine artery pulsatility index can progress to brain sparing albeit less frequently and 1-2 weeks later[112] and many experts suggest weekly Doppler monitoring.

*How and when to deliver?*

Reports suggest that universal induction of labor at term may be more beneficial than expectant management in terms of reduced perinatal mortality[114,115], without increasing the rate of Cesarean section or operative vaginal delivery[116-118]. This is true for both nulliparous women ≥35 years[114,116] and unselected population[115,117,118].

Considering that the major cause of perinatal death at term is stillbirth and that some SGA might suffer some degree of 'stunted' growth not adequately identified by current biophysical tools, it is reasonable to consider the induction of labor after $38^{+0}$ weeks of gestation to reduce the risk of severe growth restriction or stillbirth and not to exceed $39^{+6}$ weeks of gestation where SGA has been identified. This recommendation is also supported by the results from DIGITAT study[100,102]. 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

- Both at the diagnosis of SGA and during the follow-up, fetal Doppler velocimetry should be performed (Good practice point);
- In case of late SGA, fortnightly assessment of fetal growth and weekly assessment of umbilical artery, middle cerebral artery and their ratios (CPR or UCR) is recommended (Good practice point);
- When SGA has been identified, induction of labor should be planned from $38^{+0}$ weeks of gestation, and not exceeding $39^{+6}$ weeks of gestation (Grade of recommendation: A);
- Continuous fetal heart rate monitoring during labor is indicated (Good practice point).

Flowchart for management of FGR

**What is not known and implications for research**

The application of the Delphi consensus criteria[16] on FGR diagnosis 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 below the $10^{th}$ percentile (namely SGA) with normal umbilical and cerebral Doppler indices might however suffer from stunted fetal growth as suggested by recent findings[108,119]. This question warrants further exploration. It is hypothesized that even before the signs of hypoxemia establish, there might be a "preclinical" phase during which the fetus is exposed to reduced supply of nutrients and oxygen balanced by reduced growth and oxidative metabolism. There are several hypotheses regarding the underlying pathophysiological processes, such as inadequate maternal perfusion of the uterus due to an overrun of the maternal hemodynamic adaptation potential, an

overrun of the placental potential in response to an increasing fetal needs, or placental senescence due to oxidative stress. It might be that alterations of the umbilical artery Doppler 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 for a subgroup of SGA fetuses that is at an increased risk of perinatal and long-term adverse outcomes. New emerging biophysical and biochemical tools such as alternative analysis of fetal ECG[120], evaluation of maternal hemodynamics[111], evaluation of umbilical vein blood flow volume[84,110,121]; and even assessment of uterine blood flow volume[122,123] could help to disentangle the different aspects of SGA and FGR.

The impressive results obtained by placental protein biomarkers in pregnant patients with hypertensive disorders of pregnancy[35] offers 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 morbidity. In women with hypertensive disorders, the sFlt-1/PLGF ratio has been able to differentiate the severity of cases with preeclampsia and SGA from cases with preeclampsia and appropriate for gestational age fetuses[124] and this should be explored further in pregnant patients monitored for SGA and/or FGR fetuses[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 consortium) to evaluate the role of Sildenafil, a phosphodiesterase type 5 inhibitor, in improving the outcomes of 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 has demonstrated that Sildenafil at 25 mg three times daily (n=70) vs. placebo (n=65) does not prolong pregnancy or improve outcomes in severe early FGR diagnosed between $22^{+0}$ and $29^{+6}$ weeks of gestation[125]. A similar trial from New Zealand and Australia including 122 cases of early FGR has demonstrated that maternal Sildenafil use has no effect on fetal growth velocity[126]. Significant concerns regarding the safety of Sildenafil during pregnancy have been raised with an excess of neonatal deaths due to pulmonary hypertension identified in one trial based in the Netherlands, and it is recommended that it should not be used in FGR outside the setting of high quality randomized clinical trials.

Several novel approaches are being investigated for improving the outcome of early FGR. The EVERREST group[123] is planning an uncontrolled open-label trial in pregnancies affected by early FGR in order to evaluate the efficacy of localized injected maternal VEGF 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[127]. Certainly, therapies for maternal hypertension that reduce cardiac output such as beta blockers have been linked to poor perinatal outcome and stillbirth and must be used in caution in these cases.

Besides the need of homogeneous application of Doppler indices, thresholds and reference ranges, the question regarding their clinical utility for monitoring and timing delivery in FGR diagnosed >32 weeks of gestation is still to be answered. The evidence of association between signs of cerebral blood flow redistribution is based mainly on retrospective and observational studies, where the application of Doppler indices might have influenced the management, and outcome and therefore introduced bias. Currently, no randomized interventional trial evidence exists based on Doppler parameters in timing delivery decision in late FGR. Thus, the key research question is whether early delivery in fetuses with late FGR and with signs of cerebral blood flow redistribution is beneficial (by removing the fetus from the 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 would be most beneficial and which Doppler parameters and thresholds would perform best. Ongoing randomized controlled trials on this topic will provide answers to these important questions.

## CONCLUSION

Diagnosis, follow-up and timely delivery of 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 measure of fetal size is not sufficient to evaluate fetal growth, except perhaps for 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. The knowledge of clinical manifestation and progress of early and late 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 international Delphi survey consensus[16].

Once the diagnosis of FGR has been made, multi-modality assessment is recommended which may differ between countries (beside Doppler velocimetry, cCTG or biophysical profile). Early FGR is more strongly associated with abnormal trophoblastic invasion and consequent placental insufficiency. The risk of perinatal mortality and morbidity and long-term adverse outcome is very high and depends both on the severity of growth restriction and prematurity. For this reason, early FGR should be

managed in multidisciplinary tertiary level units. Despite the severity of FGR, the cascade of Doppler alterations is quite well known and randomized controlled trials provided good level of evidence for delivery criteria.

Late FGR clinically presents in milder form than early FGR and hence is not associated with severe prematurity but can be associated with significant morbidity. Despite that, at present, the diagnosis and management of late FGR, especially near term, is complex. The assessment of middle cerebral artery and its ratio to umbilical artery seems to have a central role for identification of late FGR. However, there is no clear evidence that delivery decision 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 to deliver.

In conclusion, diagnosis and management of FGR still poses some concerns and dilemmas. In fact, there is some evidence that SGA fetus with normal Doppler velocimetry might however 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 management randomized controlled trials that are in progress, will hopefully provide clear evidence on some unanswered questions. The real challenge remains whether therapeutic intervention in FGR will ever be feasible.

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***TABLES***

*Table 1. Main clinical characteristics of early and late fetal growth restriction.*

| | **Early FGR (<32 weeks)** | **Late FGR (≥32 weeks)** |
|---|---|---|
| Main clinical challenge | Management | Detection |
| Prevalence | 30% | 70% |
| Gestational age at manifestation | Early in gestation | Late in gestation |
| Ultrasound characteristics | May be very small | Not necessary very small |
| Doppler velocimetry characteristics | 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 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. Definition of fetal growth restriction based on a Delphi consensus procedure. From *Gordijn SJ et al*[16].

| **Definition of fetal growth restriction based on Delphi consensus criteria**[16] | |
|---|---|
| **Early FGR (<32 weeks)** | **Late FGR (≥32 weeks)** |
| • AC/EFW below the 3rd percentile or umbilical artery absent or reversed end diastolic flow<br>**OR**<br>• AC/EFW below the 10th percentile combined **with**<br>o Uterine arteries mean pulsatility index above the 95th percentile<br>**AND/OR**<br>o Umbilical artery pulsatility index above the 95th percentile | • AC/EFW below the 3rd percentile<br>**OR at least 2 of following**<br>• AC/EFW below the10th percentile<br>• AC/EFW crossing 50 centiles (2 quartiles)<br>• Cerebro-placental ratio below the 5th percentile or umbilical artery pulsatility index above the 95th percentile |

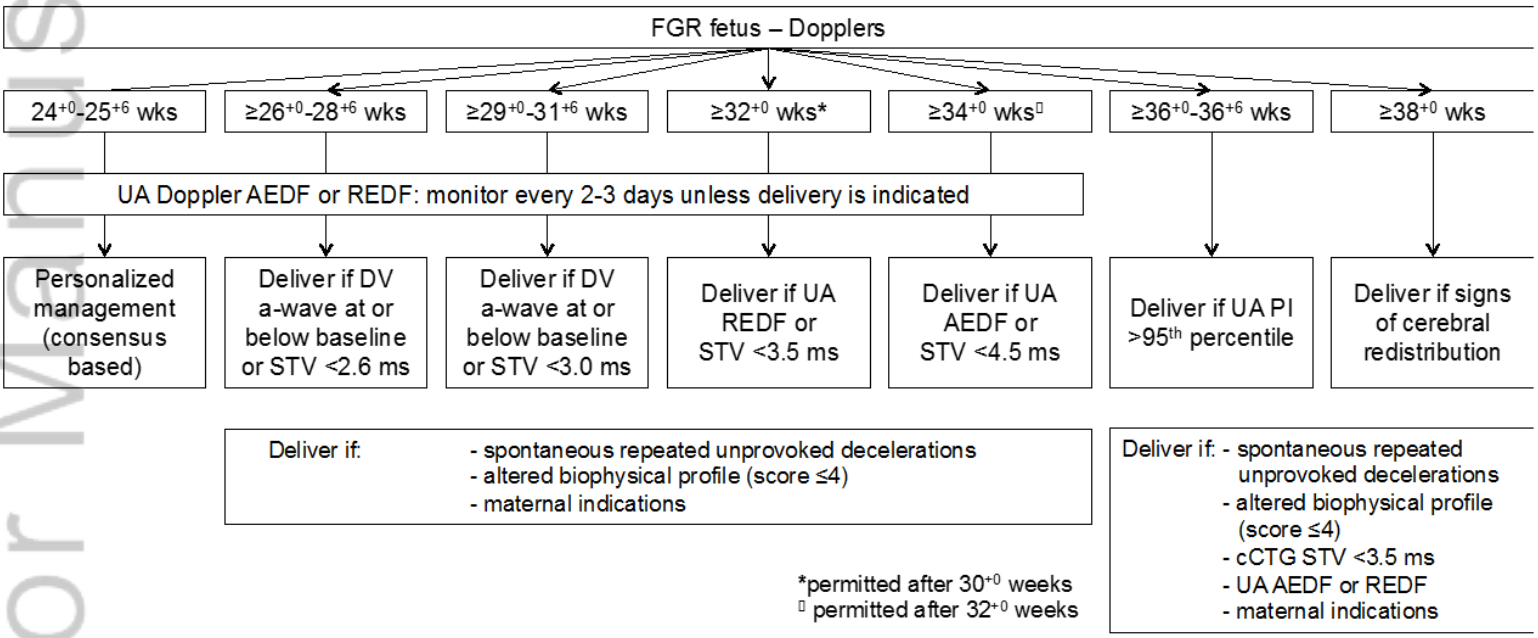
**APPENDIX**

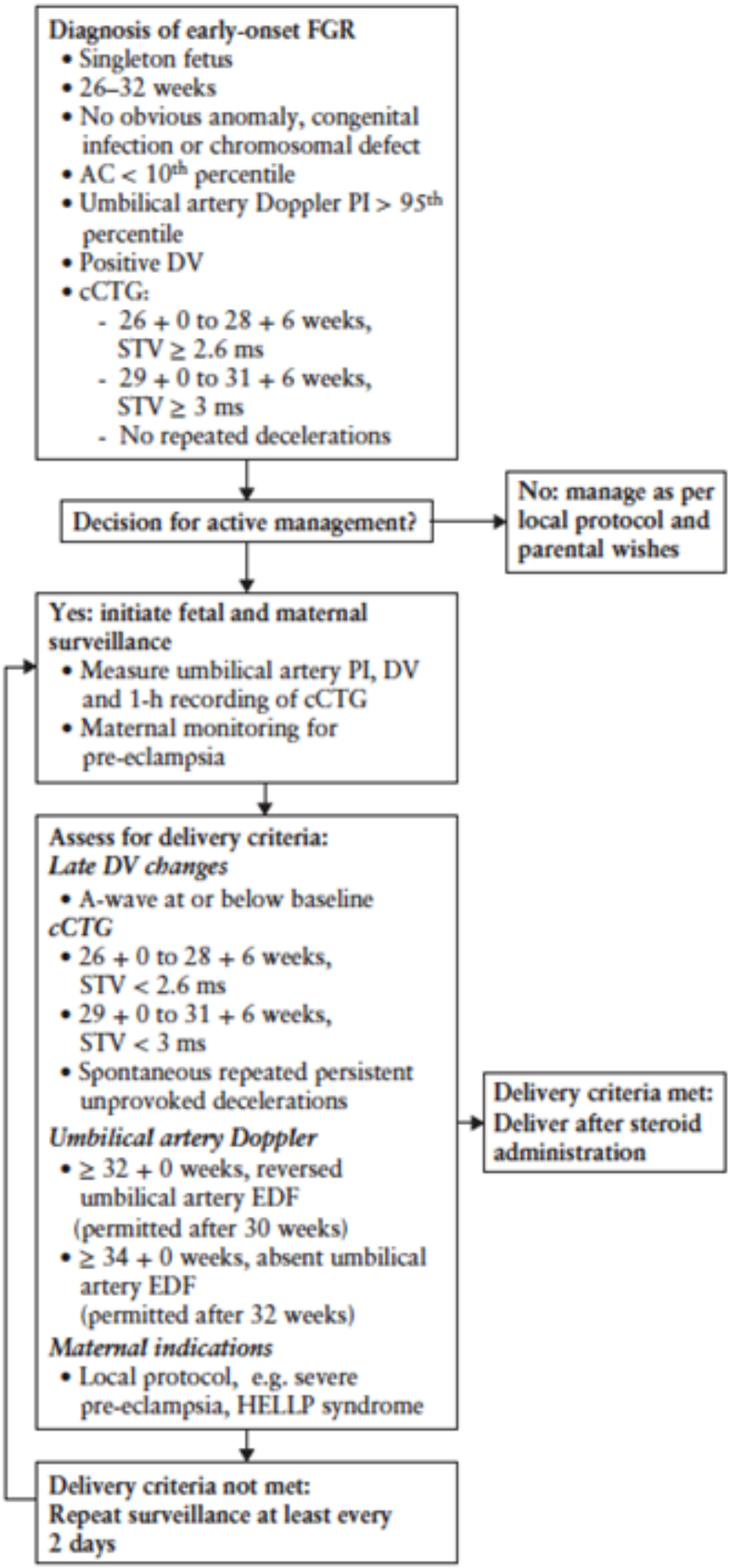
**Table A1.** Table shows the most relevant studies that reported reference ranges for middle cerebral artery (MCA) and its ratios, cerebro-placental (CPR) and umbilico-cerebral ratio (UCR). Adapted from (Ruiz-Martinez et al[47]).

| **Study** | **Arduini** | **Kurmanavicius** | **Baschat** | **Ebbing** | **Morales-Rossello** | **Ciobanu** |
|---|---|---|---|---|---|---|
| **Year** | 1990 | 1997 | 2003 | 2007 | 2014 | 2019 |
| **Country** | Italy | Switzerland | Germany | Norway | Spain | UK |
| **Design** | Cross-sectional | Cross-sectional | Cross-sectional | Longitudinal | Cross-sectional | Cross-sectional |
| **Data Collection** | Prospective | Prospective | Prospective | Prospective | NR | |
| **Number of women** | 1556 | 1675 | 306 | 161; 566 observations | 2323 | 72417 |
| **Weeks** | 20-42 | 24-42 | 20-40 | 19-41 | 19-41 | 20-41 |
| **GA uniformly distributed** | yes | No | no | yes | no | No (4 periods) |
| **Vessels** | UA, MCA, UCR | UA, MCA, CPR | UA, MCA, CPR | UA, MCA, CPR | MCA, CPR | UA, MCA, CPR |
| **Doppler parameter** | PI | RI | PI | PI | PI | PI |

**Table A2.** Levels of evidence and grades of recommendations 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 applicable directly to the target population; or systematic review of randomized controlled trials or a 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 the clinical experience of the Guideline Development Group |



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