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REVIEW ARTICLE

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Clinical practice guidance for the management of fetal growth restriction: an expert review

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ABSTRACT

Background: Fetal growth restriction (FGR) is associated to increased perinatal morbidity and mortality. Prenatal identification and subsequent intervention can improve outcomes. Our aim was to provide recommendations of the management of FGR reaching all possible scenarios (high-income and low-middle-income countries, referral as well as referring centers) but not to stablish a universal standard of care.

Methods: an organizational committee assigned a panel of experts' different topics regarding clinical practice management of FGR. Evidence was prioritized according to the GRADE classification system, with the highest levels of evidence given the greatest weight and organized in practical approach. Although most diagnostic, screening and management options are described, our aim is not to recommend all but to highlight the evidence for each one and give our recommendations for their use understanding that not all settings will have every option available.

Results: We provide a practical approach to allow optimization of timing and mode of delivery in order to avoid unnecessary or excessive interventions and improve perinatal outcomes.

Conclusion: This document aims to provide guidance for the clinical management of pregnancies with suspected FGR.

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Fetal growth restriction; diagnosis; management; prenatal; ultrasound

Introduction

Fetal growth restriction (FGR) is thought to affect 3–7% of pregnancies [1], making it a relatively common pregnancy complication. However, there are many discrepancies among international societies, national guidelines and therefore, within healthcare professionals when considering the diagnosis and clinical management of these pregnancies. The following expert review aims to comprehensively address the most relevant issues and propose an updated management strategy for any healthcare practitioner who may face a pregnancy affected by FGR. Although most diagnostic, screening and management options are described, our aim is not to recommend all but to highlight the evidence for each one and give our recommendations for their use understanding that not all settings will have every option available. Given our intent to reach all possible scenarios (high-income and low-middle-income countries, referral as well as referring centers) this is not intended to establish a universal standard of care.

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Clinical approach in suspected fetal growth restriction

Stepwise approach to the diagnosis of fetal growth restriction

The approach to a small fetus should be systematic to avoid misdiagnosis and offer the best possible counseling and management of the pregnancy. A stepwise approach to the diagnosis is proposed as follows:

1. First, accurate pregnancy dating should be ensured as referenced in our document regarding screening and diagnosis of fetal growth restriction.
2. A complete and detailed maternal history must be recorded to identify possible risk factors for FGR of placental as well as non-placental origin.
3. A detailed anatomy scan is recommended to identify possible malformations that may justify abnormal growth, ultrasound signs that may suggest congenital infection (i.e. microcephaly, ventriculomegaly, calcifications on the liver or the brain), or genetic syndromes (i.e. polyhydramnios, abnormal facies, short long bones, etc).
4. Angiogenesis biomarkers can be used to evaluate if there is an underlying placental disease as well as to tailor follow-up as proposed in subsequent sections.
5. Genetic testing should be considered in particular cases as described below.
6. Congenital infections should be ruled out, particularly in early-onset cases or in the presence of additional ultrasound signs that may suggest them.
7. The severity of FGR should be assessed taking into account Doppler velocimetry and cardiotocography parameters.

Genetic testing

FGR, particularly in its more severe forms is associated with chromosomal abnormalities in up to 19% of cases [1]. Although it is generally accepted that karyotyping is not warranted in all FGR cases and invasive testing should be withheld for specific situations, there is controversy regarding which benefit most from this intervention with some advocating for performing it in all early onset cases [2] (aiming to be more sensitive) whereas others are more restrictive (increasing their specificity) [3].

Considering that the more severe forms of FGR have an increased risk of genetic anomalies, we argue for offering invasive testing at least in the following cases:

- FGR with congenital anomalies (other than hypospadias) or polyhydramnios
- Diagnosis <24 weeks (particularly if there are no maternal or fetal Doppler alterations)
- Diagnosis <28 weeks and:
  - HC <3 standard deviations (SD) [4]
  - Short long bones <3 SD(4) or skeletal anomalies (where it should be considered to add skeletal dysplasia panel)

The recommended genetic test would be QF-PCR and array-CGH [5,6]. Acknowledging the current yield of the different techniques, amniocentesis should be of choice. Considering that FGR is usually diagnosed in the second half of pregnancy and therefore amniocentesis technically feasible, it is preferred over chorionic villous sampling or noninvasive prenatal testing (NIPT) in order to avoid misdiagnosis with placental mosaicism. Furthermore, it allows a more detailed analysis (arrayCGH) when compared to NIPT. The role of NIPT is limited at the moment but evolving. Although results are conditioned by the placental origin of cell-free DNA, it may capture confined placental mosaicism, another cause of FGR. However, if performed, results must be taken cautiously as they may reflect placental mosaicism and not fetal chromosomal anomalies and should be confirmed with invasive testing [1]. On the other hand, if a confined placental mosaicisms involving chromosomes 2, 3, 7, 13, 15, 16 or 22 is demonstrated, close monitoring of fetal growth should be performed [7].

Skeletal dysplasia panels can be included in cases with short long bones <3SD, mineralization anomalies or additional findings suggestive of skeletal dysplasia. Methylation disorders, including Silver Russell can be included when the HC/AC ratio >90th centile [8].

Infection testing

The value of infection testing in isolated FGR seems limited [9,10]. However, it must be taken into account that fetal infections (mainly by cytomegalovirus (CMV), malaria and syphilis) are responsible for up to 5% of small for gestational age (SGA) fetuses [11]. The value of infection testing in isolated FGR seems limited [9,10]. However, it must be taken into account that fetal infections (mainly by cytomegalovirus (CMV), malaria and syphilis) are responsible for up to 5% of small for gestational age (SGA) fetuses [11]. Therefore, in early-onset FGR, maternal serological evaluation of CMV, is recommended (in accordance to many

scientific societies) [2,3,12], especially if it is associated with additional findings suggestive of congenital infections. Other congenital infections are also related to FGR such as toxoplasma, rubella, malaria, syphilis, and Zika virus. We recommend including their testing in high-risk populations to avoid disparities in prenatal care in immigrant population, tropical or low-middle income countries. When serological suggest congenital infection, amniocentesis confirmation is warranted, recommending its performance at least 6 weeks from the onset of the suspected maternal infection [3].Regarding CMV, the study can be performed by:

- Maternal serological status: CMV IgG and IgM and CMV on blood, urine, and saliva, where indicated.
- Amniotic fluid CMV PCR (recommended in very early onset cases, or cases with additional suggestive findings of congenital infection, or cases with positive IgM maternal serology, or if amniocentesis is performed for other reasons).

The interpretation of the serological tests in the second and third trimesters can be challenging and, in cases with suggestive sonographic signs of congenital infection and IgG positivity, the possibility of invasive testing should be discussed with parents to reduce the risk of overlooking congenital infections [13].

Classification of the severity of FGR

The natural history of placental insufficiency escalates from early signs of defective trophoblastic invasion to late signs of overt fetal metabolic acidosis. This progression can be noninvasively captured by maternal and fetal Doppler velocimetry. To obtain a reliable measurement, Doppler recordings should be obtained in a state of rest, with appropriate sonographic adjustments. As with any other reference chart, caution must be undertaken as different nomograms will lead to different diagnostic assignments of risk [14,15]. There are no randomized studies comparing the results of the different developed charts for Doppler evaluation. Different Doppler charts will result in different proportions of fetuses defined as SGA, however the impact on perinatal outcome seems modest while the impact on intervention rate seems significant [15]. Therefore, it is difficult to recommend one over another Doppler chart, and *a priori* evaluation, possibly at the national level, should be performed in terms or evaluation of methodological quality, risk of bias, sensitivity and specificity of given Doppler charts [16].

Uterine arteries

A pulstatility index (PI) >95th centile in the uterine arteries (UtA) [17] is considered a criterion for FGR in small for gestational age (SGA) fetuses <32 weeks as it may reflect uteroplacental insufficiency [18]. by most, including the authors of this review, but not all [2]. Some controversy exists about its use to identify late-onset SGA at high risk of adverse perinatal outcomes, but a recent meta-analysis [19] has shown a moderate predictive capacity for adverse outcomes in late onset-SGA.

Umbilical arteries

The sequence from normal umbilical artery (UA) to increased PI-UA, absent end-diastolic flow, and, in the end-stage, reversed end-diastolic flow is the classical deterioration spectrum that reflexes the progression of worsening placental insufficiency. Abnormal UA Doppler [20] and its deterioration are commonly seen in early onset FGR. There is a sound basis [21] for the use of this parameter as a prognostic criterion in FGR. Furthermore, there is compelling evidence that using UA Doppler in high-risk pregnancies improves perinatal outcomes, with a 29% reduction in perinatal deaths [22]. A not-so-uncommon situation is to find different values in each of the arteries and in up to 10% of the cases they could be of significance. Thus, the number of arteries sampled, and the sampling method used may alter clinical decision-making, including frequency of surveillance and timing of delivery [23,24]. We advocate for the consideration of the best of the arteries for clinical purposes although evidence is limited in this context.

Middle cerebral artery

Middle cerebral artery (MCA) indicates the presence of fetal brain vasodilation, a surrogate marker of hypoxemia. This assessment is especially important for the identification of those SGA fetuses at higher risk of adverse perinatal outcome, for the detection of late-onset FGR, with frequently normal UA flow. Fetuses with abnormal MCA-PI present a 6-fold risk of emergency cesarean section for fetal distress when compared to SGA fetuses with normal MCA-PI [25]. We suggest that an abnormal MCA Doppler should be considered when facing an MCA-PI <5th centile [16].

Cerebro-placental and umbilico-cerebral ratio

The cerebro-placental ratio (CPR) is calculated by the ratio of MCA to UA Doppler and therefore it has been described to be more accurate and more sensitive than its components on their own [26]. Similarly, the

umbilical-cerebral ratio (UCR) is calculated as the ratio of the UA and the MCA Doppler, which also translates as the relationship between fetal and placental resistances. Therefore, abnormal CPR (considered as <5th centile) [27] or UCR (>95th centile) should alert of a progression to blood flow distribution. The biggest body of literature is reported on CPR. Nevertheless, there is a debate about whether UCR is superior to CPR [28,29].

In a meta-analysis [30], the predictive accuracy of CPR was moderate to high for perinatal death and low for a composite of adverse perinatal outcome including cesarean section for non-reassuring fetal status, 5-min Apgar score < 7, admission to the neonatal intensive care unit, neonatal acidosis and neonatal morbidity. In another meta-analysis [31], the CPR predicted a composite adverse perinatal outcome and an emergent delivery for fetal distress significantly better than the UA and the MCA Doppler. However, the prediction capacity of CPR and UA were similar for perinatal death, low Apgar score, and neonatal intensive care unit (NICU) admission.

Ductus venosus

Ductus venosus (DV) originates from the umbilical vein before it turns to join the portal vein. It allows diverting high-oxygenated blood from the umbilical vein into the right atria working as a shunt that bypasses the liver to the inferior vena cava. The DV exhibits abnormal patterns when there is an increased right intra-atrial pressure because of high cardiac afterload due to an increased vascular placental resistance and/or to the effect of fetal acidemia on myocardial cell function. DV is the strongest single Doppler parameter to predict the short-term risk of fetal death. The risk of fetal death ranges from 40 to 100% in the next 2 to 5 days after the appearance of severe abnormal flow in the DV, that is absent or reverse "a" wave [32]. In addition, milder abnormalities of DV defined as PI> 95th centile [33] has been described, even though less consistently, as an earlier sign of metabolic acidosis. Although SMFM recommendations argue against is use in routine in clinical practice [2], we believe that the results from the TRUFFLE trial should be acknowledged and that, even if late changes are rarely found, more than 10% of early onset cases may benefit from its measurement and probably even more so in settings in which cCTG is not available [34].

Umbilical vein

The measurement of umbilical vein blood flow (UVBF) has been suggested as a tool for the prediction of the development of FGR [35]. Indeed, there is evidence already in the first trimester of early modifications in fetuses that will later develop FGR. Further, it has been applied in the prediction of an unfavorable outcome of late FGR and their monitoring [36–38]. Moreover, the evaluation of UVBF showed potential in differentiating between true SGA and those that present stunted fetal growth (SGA with normal Doppler parameters) [38], and in identifying appropriate for gestational age fetuses that have slowed their growth and present an adverse outcome at birth [39,40]. The main concerns regarding UVBF regards its measuring reproducibility. A recent systematic review showed that when adhering to the same methodology the UVBF is accurate and reproducible [41]. Despite these promising findings, validation data are still missing to support its application in clinical settings and multicenter trials might help to refine the appropriate applications UVBF together with other Doppler and biochemical variables.

Cardiotocography

In hypoxic conditions and fetal metabolic acidosis, there is a decrease in fetal heart rate variability, better captured by the computerized analysis of the short-term variability. With progressive gasometrical deterioration, spontaneous decelerations appear. The loss of the short-term variability occurs at a similar time in the deterioration sequence to the DV abnormalities.

Severity stage-based classification

According to the natural history and the sequence of abnormalities occurring secondary to placental insufficiency, a staging classification has been proposed [42], that can accommodate other parameters into a comprehensive classification and can help clinicians tailor counseling follow-up and management strategies according to the severity of FGR:

- Stage I FGR [mild-moderate placental insufficiency]: defined as those cases that meet the Delphi consensus definition [18] and have an antegrade flow in the UA. *
- Stage II FGR [severe placental insufficiency]: defined by absent end-diastolic flow in UA.
- Stage III FGR [advanced fetal deterioration, low-suspicion signs of fetal acidosis]: defined by reversed diastolic flow in the UA or DV-PI > 95th centile.
- Stage IV FGR [high suspicion of fetal acidosis and elevated risk of fetal death]: There are spontaneous fetal heart rate decelerations, reduced short-term variability at the computerized CTG, or absent/reversed atrial flow (a wave) in the DV Doppler.

*As described in our prior document regarding the definition of FGR and in light of scientific evidence [19,43] obtained after the Delphi consensus definition in 2016, two additional features can be considered for the diagnosis of stage I late-onset FGR:

- EFW <10th centile and sFlt-1/PlGF ratio >38
- EFW <10th centile and UtA PI > 95th centile.

The main key points regarding the diagnosis and classification of the severity of FGR are presented in Table 1 and a summary of our proposed approach to diagnosis in Figure 1.

Prediction of perinatal survival and morbidity at diagnosis of fetal growth restriction

Once a diagnosis of FGR is made, the risks of perinatal morbidity and mortality need to be assessed. FGR fetuses are at an increased risk of perinatal mortality and morbidity, compared to appropriate for gestational (AGA) fetuses. Similarly to models that screen for FGR usually resort to SGA, those targeting complications also use SGA as a proxy. Among SGA-related complications, we find fetal risks such as stillbirth, increased risk of cesarean section for fetal distress and intrapartum stillbirth whereas in the neonatal period, these fetuses have an increased risk of admission to NICU, intracranial hemorrhage, hypoxic ischemic encephalopathy (HIE), convulsions, hypoglycemia, hypothermia, and neonatal death [44–46]. There is evidence suggesting that there is a 10-fold increase in risk of stillbirth and a 5-fold increase in risk of neonatal death in pregnancies with SGA compared to AGA fetuses [44]. Similarly, SGA fetuses compared to those that are AGA are associated with a 2-4-fold increase in risk of neonatal convulsions, intracranial hemorrhage and HIE. Results may vary within centers and parents should be counseled about the risks using local data.

Regarding prediction of perinatal survival and morbidity, the most accurate methods are based on accurate identification of SGA and subsequently considering biophysical and biochemical markers.

Prediction based on fetal size

There is considerable evidence suggesting that the risk of adverse outcomes is inversely related to fetal size with an increasing chance of complications with smaller centiles. In a large study examining the association of birth weight centiles with adverse perinatal outcomes, the authors demonstrated that the risk of adverse perinatal outcome is almost double in the SGA neonates with birthweight (BW) below the 10th centile compared to those with higher BW centiles [102]. Furthermore, results from the PORTO [47] and the DIGITAT [48] trials show that the highest risk of perinatal death and adverse neurodevelopmental outcome is highest when the EFW is <3rd centile. However, it is important to note that >80% of adverse outcomes occur in babies that are not SGA, indicating that even fetuses that are above the 10th centile may still have failed to reach a normal growth potential [102,104]. Current evidence also supports the use of abdominal circumference (AC) as an alternative to EFW for the prediction of adverse outcome [49].

Prediction based on biophysical and biochemical markers

The biophysical markers investigated in the prediction of adverse perinatal outcomes include UtA PI, UA PI, and MCA PI whereas the biochemical markers include PlGF and sFlt-1.

Biophysical parameters: Doppler. The perinatal outcome in early-onset FGR and late-onset FGR have different determinants. With regards to early-onset FGR <32 weeks' gestation, the results from the TRUFFLE-1 RCT reported a perinatal death rate of 8%, while 70% fetuses survived without severe neonatal morbidity

Table 1. Key points regarding the diagnosis and classification of the severity of FGR.

Recommendation
Accurate pregnancy dating is essential for the diagnosis of FGR
A complete medical history should be recorded in order to identify possible risk factors for placental and non-placental FGR
A detailed anatomy scan should be undertaken in order to rule out major congenital anomalies, signs of congenital infection or markers suggestive of genetic syndromes
Angiogenesis biomarkers (sFlt-1/PlGF or PlGF alone) can be determined to evaluate the underlying placental disease
Genetic testing should be withheld for very early cases (<24 weeks), <28 weeks with additional anomalies (femur or head circumference <3SD; polyhydramnios) or FGR with congenital anomalies
Congenital infection by CMV should be ruled out in all early onset cases and others with suggestive findings. Additional testing including toxoplasmosis, rubella, herpes, syphilis, malaria, and Zika virus depending on sonographic findings and the region should be performed.
The severity of FGR can be evaluated through EFW, Doppler velocimetry and cCTG / CTG evaluation
Selection of the Doppler chart may affect the diagnosis of FGR, and care should be taken when selecting one
A stage-based classification of FGR based on Doppler and CTG study can aid in guiding clinicians in establishing a prognosis and management

CMV, cytomegalovirus; CTG, cardiotocography; cCTG, computerized CTG; EFW, estimated fetal weight; FGR, fetal growth restriction; SD, standard deviation.

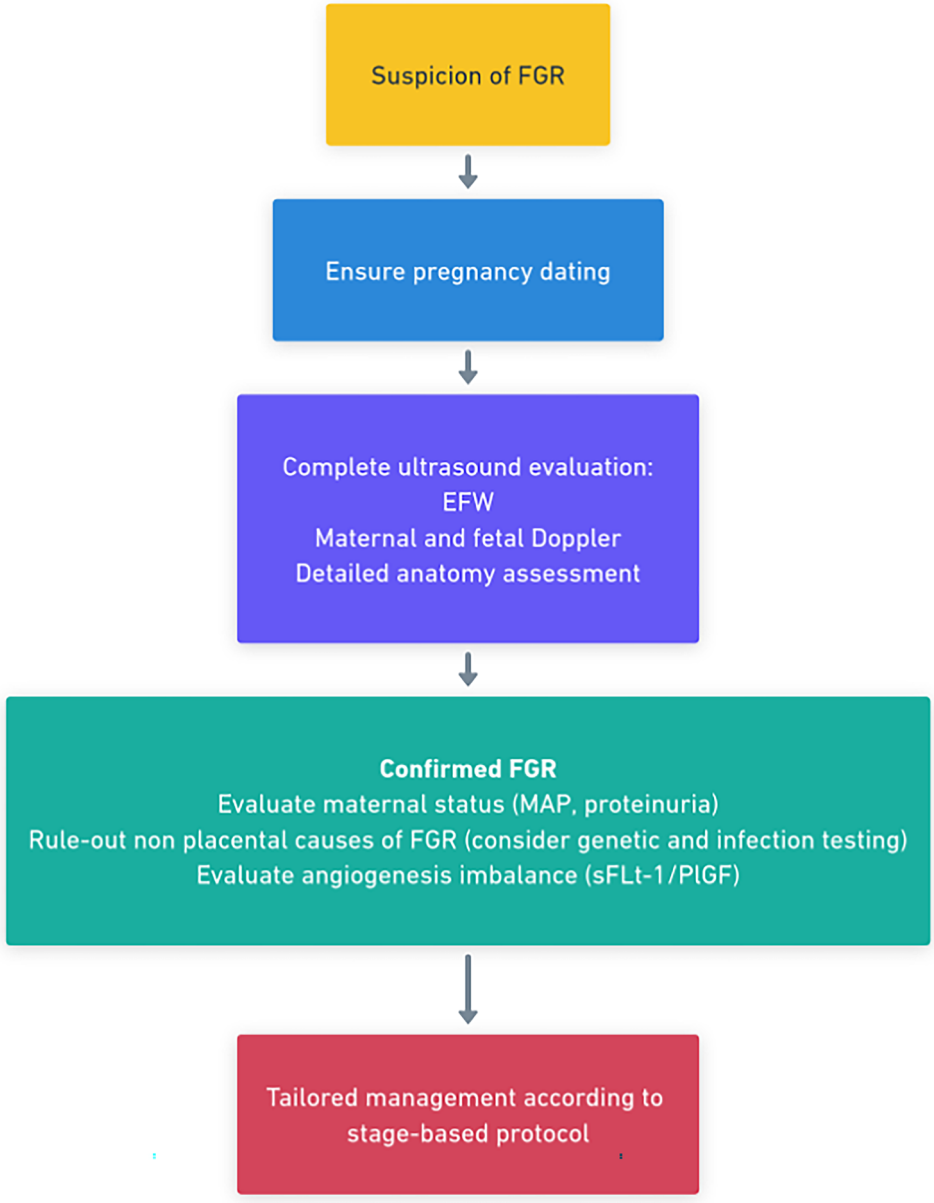

Figure 1. Stepwise approach to the diagnosis of fetal growth restriction (FGR).
EFW, estimated fetal weight, FGR, fetal growth restriction; MAP, mean arterial pressure

when managed with cCTG-STV or Doppler including DV assessment. The proportion without any neurological impairment at 2 years of age was 85% in the cCTG-STV group, 91% in the early-DV group, and 95% in the late-DV group [50].

UA PI and MCA PI are poor predictors of adverse perinatal outcome by themselves in early-onset FGR but they are important in late-onset FGR [25,51–54]. The CPR has been reported to be a predictor of adverse perinatal outcomes such as perinatal death, cesarean section for fetal compromise and admission to NICU [31]. Several studies have investigated the value of CPR in prediction of adverse outcomes, and the majority have been carried out in high-risk pregnancies [55–58]. However, even if there is a strong association, the results suggest that CPR on its own is a poor predictor of adverse perinatal outcomes with low DR and high FPR. In a recent multicenter randomized controlled study (RATIO37) including 11,214 women, the authors reported that planned delivery at term based on ultrasound fetal growth assessment and CPR at term did not reduce perinatal mortality, but there was a reduction in severe neonatal morbidity, compared with fetal growth assessment alone [59]. Finally, in the setting of late-onset FGR, the TRUFFLE-2 RCT is currently assessing whether management based on the UCR z-score and cCTG improves perinatal outcomes [50].

Therefore, there is sufficient evidence (particularly in the early-onset cases) to tailor delivery of FGR fetuses according to fetal Doppler and cCTG-STV (where available) in order to minimize morbidity and mortality.

Biochemical parameters: angiogenesis biomarkers

PlGF and sFlt-1 have been reported to identify pregnancies at risk of developing PE but there is increasing evidence from studies that these biochemical markers are biomarkers of placental dysfunction and may also be effective in predicting adverse perinatal outcomes in pregnancies with SGA neonates [60–62]. In a study of 175 singleton pregnancies with EFW < 10th centile, the authors reported that sFlt-1/PlGF ratio may be useful in distinguishing between FGR and SGA by predicting the need for elective delivery to prevent adverse perinatal outcome [60]. In a study with 120 early-onset FGR fetuses with antegrade UA flow a sFlt-1/PlGF ratio < 85 at diagnosis identified a group of pregnancies in which the need to deliver within 1 week was very low and the interval to delivery was expected to be prolonged for ≥ 4 weeks in > 70% of cases. However, in those with values ≥85, around 30% required delivery within 7 days [63].

In another study of 60 and 55 FGR and SGA fetuses at 32–36 weeks' gestation, multivariable regression analysis showed that the sFlt-1/PlGF ratio improved the prediction of adverse perinatal outcomes suggesting that the ratio may potentially improve individualization of care in late-onset SGA pregnancies [64]. The value of assessment of sFlt-1 and PlGF routinely at 35–36 weeks was investigated in a prospective observational study of more than 19,000 pregnancies. These biomarkers were associated with increased risk of cesarean section for fetal compromise in labor and admission to NICU but they failed to provide any significant contribution in prediction of adverse perinatal outcome in a multivariate model that included maternal factors, EFW and feto-placental Doppler indices [65].

Finally, a recent RCT(66) demonstrated that tailoring delivery in SGA at term with the sFlt-1/PlGF ratio was non-inferior to the use of Doppler. The study included 1,088 SGA pregnancies at term which were randomized to management with knowledge of Doppler or angiogenesis biomarker. Those with abnormal Doppler, or a sFlt-1/PlGF > 38 were managed as FGR and labor induction recommended from 37 weeks. The results showed that management with angiogenesis biomarkers resulted in similar results of intrapartum cesarean for fetal distress, neonatal acidosis and perinatal outcomes with a reduction in maternal preeclampsia and an increase in gestational age at delivery and birthweight.

Therefore, there is increasing evidence that angiogenesis biomarkers can help assess the time-to-delivery in early onset and tailor delivery in late-onset cases.

Prediction of outcomes at the limit of viability

The diagnosis of FGR at an extremely preterm GA poses a great challenge as there is still great uncertainty regarding the likelihood of survival without major sequelae. It is known that, controlling for GA, extremely preterm infants with early-onset FGR have a 3-fold higher risk of mortality and a 2-week lag in survival compared with normally grown fetuses [67]. A recent meta-analysis on early onset FGR including 2,895 pregnancies found a 12% intrauterine death, 8% neonatal death, and 81% overall survival. The most common morbidity was respiratory distress syndrome affecting 34% of neonates, followed by sepsis (30%) and retinopathy of prematurity (13%). Considering children with follow-up to 12% of surviving children suffered from cognitive impairment and/or cerebral palsy [68].

The prognosis of very early cases will ultimately depend on the underlying etiology, GA, and weight at delivery. Viability should be assessed by perinatal experts and parents should be counseled for an active attitude toward the pregnancy, once a 50% survival chance can be achieved. This usually can be attained when both 26 weeks 'and 500 g are reached. However, there are other factors that should be taken into account such as fetal Doppler status at diagnosis [69], fetal sex, with better outcomes in females, the possibility of optimizing delivery with prior administration of antenatal corticosteroids and magnesium sulfate, the setting in which the pregnancy is managed or the angiogenic imbalance [70]. The most common form of predicting perinatal survival is by combining GA and EFW, although newer approaches have been proposed with promising results including fetal Doppler or GA and PlGF [70–72]. The main key points regarding the prediction of perinatal survival and morbidity are summarized in Table 2.

Management of FGR

In the setting of early-onset FGR, referral to a tertiary care center where evaluation can be performed by maternal-fetal medicine and neonatology experts is warranted.

Longitudinal surveillance should start once viability is considered (at 24–26 weeks) and include feto-maternal Doppler and fetal biometry evaluation together with

Table 2. Key points in the prediction of perinatal survival and morbidity.

Recommendation
Parents should be counseled about the increased risk of perinatal complications in FGR including stillbirth, increased risk of cesarean section for fetal distress and intrapartum stillbirth whereas in the neonatal period, FGR fetuses have an increased risk of admission to neonatal intensive care unit, intracranial hemorrhage, hypoxic ischemic encephalopathy, convulsions, hypoglycemia, hypothermia, and neonatal death.
The key to prevention of adverse perinatal outcome is effective prenatal detection of FGR fetuses as lack of prenatal diagnosis of FGR increases the risk of perinatal death 5-10-fold.
Pregnancies with early-onset FGR should be managed in specialist centers with facilities for carrying out cCTG and fetal Dopplers. If cCTG is unavailable, CTG can be considered as an acceptable safety net combined with DV monitoring. Delivery based on DV prior to 32 weeks improves perinatal survival compared to a strategy based on cCTG alone. A high proportion of FGR pregnancies (80–90%) delivered based on cCTG-STV or DV deliver neonates without major neurological morbidity.
CPR is effective in identifying pregnancies at risk of an adverse perinatal outcome in high-risk pregnancies such as those with known SGA.
sFlt-1/PlGF ratio can help discern high risk SGA that may benefit from intensive monitoring and early intervention
sFlt-1/PlGF >38 can be used to tailor delivery in SGA at term as an alternative to fetal Doppler
The prediction of perinatal survival without major sequelae at the limit of viability poses a great challenged and should be assessed by perinatal experts
Extremely preterm infants with early-onset FGR have a 3-fold higher risk of mortality and a 2-week lag in survival compared with normally grown fetuses. Viability should be considered when a reasonable chance of survival can be attained (~ 50%)

cCTG, computerized cardiotocography; CPR, cerebroplacental ratio; DV, ductus venosus; FGR, fetal growth restriction; SGA, small for gestational age.

cCTG assessment. Furthermore, additional tests can be performed such as biophysical profile scoring, conventional cardiotocography (when cCTG is not available), and angiogenesis biomarker determination.

General recommendations

Cases with early-onset FGR should be referred to tertiary care level centers. Hospital admission is not required if there are no other comorbidities that preclude outpatient management but is recommended when approaching indicated delivery.

Maternal recommendations

Counting fetal movements

Progressive hypoxemia is associated with a reduction in fetal activity and therefore, reduced fetal movements could be considered an adaptation mechanism to placental insufficiency [73]. Furthermore, corticosteroid administration, a common situation in FGR pregnancies, can also decrease them [74]. Most studies evaluating counting fetal movements have focused on low or mixed-risk pregnancies and have not proved beneficial [75,76]. Still, awareness of reduced fetal movements (<10 in 2 h) in the setting of FGR could be used as a safe and inexpensive tool to suspect further fetal deterioration or need for further investigation (for example, biophysical profile scoring, additional CTG monitoring or an additional scan) in between scheduled visits [77].

Nutrition, toxic exposure

Tobacco and any other toxic exposure should be stopped, and stress reduction is warranted. Although a Mediterranean diet and mindfulness/relaxing activities have shown to reduce the incidence of FGR [78], their use once established has not been determined. Other interventions such as bed rest or dietary supplements (proteins, vitamins) have not proved any benefit and should not be routinely offered.

Preeclampsia screening

Placental dysfunction, especially in early-onset cases, can translate into maternal hypertensive disorders, mainly PE. Therefore, regular blood pressure measurement (both at home as well as in-office) and monitoring of proteinuria and renal and hepatic function are warranted.

Fetal follow-up

Fetal follow-up should include regular evaluation of Doppler parameters, fetal biometry, and fetal status through cardiotocography. Additional tests can include biophysical profile or angiogenesis biomarker determination.

Sonographic evaluation

Fetal and maternal Doppler indices should be evaluated at diagnosis and can be used to tailor follow-up. Fetal Doppler evaluation is recommended at every visit, including UA, MCA and CPR. In cases with abnormal UA PI, especially in the setting of early-onset FGR, DV should be assessed as well [34]. The use of UtA PI beyond diagnosis has not proved to add any benefit therefore routine longitudinal measurement is not recommended [79]. The value of the assessment longitudinal changes of the UA, MCA, CPR, DV [80] and fetal size [81] remains controversial when compared to solely the last measurement. However, we argue for longitudinal evaluation of said parameters considering that the "last measurement" could detect fetal deterioration and change clinical indications.

Considering the inherent errors in estimating fetal weight [82] and to minimize their impact, the time interval between EFW estimation should be at least two weeks [83].

Amniotic fluid should be routinely assessed as the deepest vertical pocket and can be made part of the biophysical profile study [84].

Standard and computerized cardiotocography

Antenatal CTG has been unable to show a reduction in perinatal mortality compared to no intervention in high-risk pregnancies, probably due to the low interobserver correlation [85]. However, computerized CTG (cCTG) has shown an improvement in results when compared to no intervention as well as to conventional CTG [86].

The cCTG evaluates the fetal heart rate short-term variation (STV), a surrogate of the sympathetic and parasympathetic activity that is altered in cases of severe fetal hypoxemia [87]. Normal ranges of STV have been described for each GA range and cCTG has been validated as the only objective measure of FHR [51,88].

Following the safety-net recommendations from the TRUFFLE-1 RCT study, an abnormal cCTG should be defined as a STV < 2.6 ms between 26 + 0 and 28 + 6 weeks of gestation, <3.0 mm between 29 + 0 and 31 + 6 ms. Additionally, between 32 + 0 and 33 + 6 weeks' gestation a STV <3.5 ms can be considered abnormal and if <4.5 ms beyond 34 weeks [12].

Therefore, we recommend that antenatal follow-up of FGR should include cCTG monitoring with STV assessment once viability is considered. However, in settings where cCTG is not available, the performance of CTG is advised as the detection of spontaneous unprovoked decelerations or fetal bradycardia should warrant expedited delivery [85].

Biophysical profile (BPP)

BPP is a score made of a combination of four fetal parameters (breathing movement, gross body movement, tone, and CTG), and amniotic fluid volume assessment, each assigned a rating of 2 (when normal) or 0 (when abnormal). Lower scores are consistently associated with poorer fetal pH and outcomes across GA [89,90]. Simplified versions that solely use fetal heart rate and amniotic fluid volume have also shown a good correlation to these outcomes. Values <2 have proved a sensitivity of 100% for acidemia. However, equivocal results [6–10] are fairly common (15–20%) in FGR. Furthermore, a normal result has a low negative predictive value. A systematic review found that the use of BPP was not associated with a reduction in perinatal deaths but resulted in an increase in cesarean sections [91]. Therefore, BPP is not routinely recommended for fetal surveillance in the preterm FGR fetus and could be considered in settings with no other forms of fetal follow-up or reduced perception of fetal movements.

Angiogenesis biomarkers

Biomarkers have been proposed both for the prediction of SGA as well as for tailoring of management once a diagnosis is made. Once a diagnosis is made, the most promising biomarkers have shown to be sFlt-1 and PlGF, more particularly, their ratio and PlGF alone. Higher values of sFlt-1/PlGF and lower of PlGF have shown shorter time to delivery, lower weight gain, and higher rates of PE [92]. A large cohort study [93] showed that, when measured at 36 weeks, the combination of fetal biometry <10th centile and abnormal sFlt-1/PlGF ratio had a positive predictive value for FGR around 3 times higher than any other ultrasonographic parameter. Thus, angiogenesis biomarkers might be a useful tool to guide follow-up and a RCT has shown non-inferiority when compared to Doppler parameters in the management of term SGA [66].

We suggest increasing the frequency of scheduled antenatal visits when sFlt-1/PlGF values exceed 85 given the chances of more rapid deterioration [63,94]. Extremely high levels of sFlt-1/PlGF (>655) have shown a short time to delivery (median <7 days) both in cases with PE and FGR alone [95]. Therefore, these values should warrant hospitalization, fetal maturation, and close monitoring.

In SGA at term, the sFlt-1/PlGF ratio can be considered as an alternative to Doppler to tailor gestational age at delivery [66]. This could be of use in settings in which a blood test is more easily accessible than an expert sonographer.

Frequency of follow-up

There is no consensus on the frequency of visits, especially in cases with antegrade end-diastolic flow in the UA, in which evidence comes from expert opinion. We advocate for adapting follow-up to the proposed stage-based classification:

- Stage I FGR: every 7–14 days*
- Stage II FGR: every 2–4 days (~2–3 times/week)
- Stage III FGR: every 24–48 hours (~3–4 times/week)
- Stage IV FGR: every 12–24 hours

*Standard follow-up of Stage I FGR could be every 7 days but in selected cases with a more favorable profile (normal fetal Doppler and sFlt-1/PlGF <38) reassessment can be made up to 14 days. Upon these general recommendations, there may be centers adhered to ISUOG and FIGO recommendations on follow-up that can implement a routine policy of twice weekly reassessment of all pregnancies with FGR stage I and umbilical artery PI > 95th centile.

Special consideration must be taken into account in cases with PE or marked angiogenic imbalance (sFlt-1/PlGF >85) in which the frequency of follow-up initially should be doubled as a more rapid fetal deterioration is expected. In cases with extremely high values of sFlt-1/PlGF (>655), fetal evaluation with careful assessment of the placenta every 1–2 days is warranted.

Medical interventions

Different therapies including statins [96], sildenafil [97] or low-weight molecular heparin [98] have been attempted to prolong pregnancy or improve pregnancy outcomes in FGR. The available evidence is not sufficient to recommend any outside research protocol.

There is some evidence regarding the benefit of using NO donors [97,99] and plasma expansion [99,100] to improve maternal hemodynamics in FGR. Still, further research is needed to confirm these findings and optimize treatment protocols.

Although there are no known medical interventions to alter the course of FGR, the appropriate use of antenatal corticosteroids for fetal maturation and magnesium sulfate for neuroprotection in preterm fetuses have been shown to improve perinatal outcomes.

Corticosteroids

The use of antenatal corticosteroids has proved as a useful to ol in accelerating fetal maturation in preterm neonates. Evidence in FGR is more limited and controversial [101,102] given the high level of endogenous corticosteroids and reduced metabolism from the smaller placenta might affect an already damaged white matter [103]. Nevertheless, administration of a single course of corticosteroids (either betamethasone or dexamethasone) in FGR that requires delivery <34+0 weeks is recommended. Although societies such as SMFM advocate for their use until 37 weeks if no prior course has been given [2], a subanalysis of the currently ongoing trial TRUFFLE 2 (102) did not show a beneficial effect of steroids on short-term outcome of fetuses with late FGR.

As most cases will have a planned scheduled delivery, corticosteroids administration should be withheld until the delivery is expected 24 h to 7 days, to maximize the benefit.

- Stage I: withhold corticosteroids.
- Stage II: corticosteroids from 31+0 weeks.
- Stage III: corticosteroids from 26 weeks, although could be deferred until 28 weeks in cases with DV PI < 95th centile.
- Stage IV: start corticosteroids within one week of considering viability.
- In cases with sFlt-1/PlGF >655 and GA <34+0 weeks antenatal corticosteroid administration is recommended.

Magnesium sulfate

The benefits of magnesium sulfate on preterm birth have been established. However, there is a paucity of data on its effects on FGR as these cases have been traditionally excluded from studies. Nevertheless, all available evidence points to a decrease in the risk of perinatal death and neurodevelopmental impairment and current recommendations vary on the GA limit for its administration [104]. Given the available evidence, we recommend the use of magnesium sulfate in these pregnancies until 32 weeks [105]. Ideally, it should be administered at least four hours before delivery but should not delay the delivery in cases of abnormal CTG or any other emergent indication (abruptio placentae, maternal complications…). The main Key points in the management of fFGR are presented in Table 3.

Timing and mode of delivery

Optimizing time and mode of delivery have shown to improve perinatal outcomes in FGR [106].

Delivery: time and mode

Given that there is no intrauterine treatment to alter the course of FGR, improvement of perinatal outcomes relies on the optimization of time and mode of delivery. There is no universal consensus on the best timing to deliver although most agree that it should be based on Doppler and cCTG findings, not on a fixed value of EFW or GA at diagnosis (early vs late). We propose planning delivery according to the stage based classification as described below, which is largely based on the findings of the TRUFFLE(50) and DIGITAT(48) studies.

Regarding mode of delivery, although FGR is associated with higher rates of low Apgar, arterial pH, or cesarean section for non-reassuring CTG, it should not

Table 3. Key points in the management of fetal growth restriction.

Recommendation
Pregnancies affected by FGR should be managed by a multidisciplinary team. Early-onset cases should be referred to tertiary care centers with expertise in the management of these pregnancies, able to assist an extremely preterm newborn
Maternal education in counting fetal movements can be used as an inexpensive tool to monitor fetal wellbeing in between scheduled visits
Women should be counseled about the benefits of cessation of any toxic exposure (tobacco, alcohol, drugs)
Stress reduction including work leave as well as following a healthy diet is recommended. There is no evidence to support a nutritional supplements nor bed rest.
Maternal education about signs and symptoms of hypertensive disorders of pregnancy as well as regular blood pressure, renal ad liver function assessment is recommended given the association of FGR and preeclampsia
Fetal follow-up should include at least regular sonographic evaluations (fetal biometry and Doppler) together with cCTG (or CTG if cCTG not available)
Fetal Doppler should be performed at every visit including UA, MCA and CPR. In early-onset FGR or abnormal UA Doppler DV should be assessed as well
EFW should be assessed at a minimum interval of two weeks to minimize measurement errors
cCTG with STV assessment according to gestational age should be performed for early-onset FGR follow-up. If cCTG is not available, conventional CTG is recommended as unprovoked decelerations or fetal bradycardia should warrant expedite delivery
BPP performance is not routinely recommended in FGR given the high false positive and negative rates
Angiogenesis biomarkers can be a useful tool to tailor follow-up. sFlt-1/PlGF >85 should warrant increased surveillance and >655 hospitalization and fetal maturation
Follow – up visit frequency should be tailored to a stage-based classification
Visit frequency should be increased in cases with concomitant preeclampsia or angiogenic imbalance (sFlt-1/PlGF >85)
A single course of ACS is recommended when delivery is expected <34 weeks
ACS should be withheld until delivery is considered to be scheduled within one week
Magnesium sulfate prophylaxis should be administered ideally for 4 h before delivery in cases <32 weeks
Magnesium sulfate prophylaxis should not delay delivery in cases with abnormal CTG or any other emergent indication

ACS, antenatal corticosteroids; BPP, biophysical profile; cCTG, computerized cardiotocography; CPR, cerebroplacental ratio; CTG, cardiotocography; DV, ductus venosus MCA, middle cerebral artery; UA, umbilical artery.

Table 4. Key points regarding timing and mode of delivery in fetal growth restriction (FGR).

Recommendation
Indication for delivery should not be based on GA at diagnosis or a fixed value of EFW alone
Timing of delivery in early onset FGR can be determined by DV and cCTG-STV evaluation
Timing of delivery should be adapted to the severity of FGR at the last scan according to a stage-based classification
In dichorionic twins, follow-up and delivery can be tailored according to the stage-based classification proposed for singleton gestations We propose an expectant management in stage IV until 28 weeks' gestation in order to reduce neonatal morbidity and mortality of the healthy twin and delivery no later than 37 weeks in stage I
FGR is not an indication for cesarean section per se, and labor induction can be attempted in cases with antegrade umbilical artery flow
Continuous CTG monitoring during labor induction and active labor is recommended given the lower tolerance to uterine contractions
In labor induction that requires cervical ripening, mechanical methods should be considered as a first-line option given their lower rates of uterine hyperstimulation and adverse perinatal outcome
Histo-Pathological examination of the placenta is indicated to assess the risk of FGR recurrence in subsequent pregnancies

ACS, antenatal corticosteroids; cCTG, computerized cardiotocography; CTG, cardiotocography; DV, ductus venosus; GA, gestational age.

be considered as an indication of cesarean delivery "per se." In cases with no or mild Doppler alterations, that is with antegrade end-diastolic umbilical artery flow, labor induction can be considered a safe option. However, cases with further deterioration of placental function (AREDF UA, altered DV, or CTG), are at higher risk of intrapartum cesarean section thus, a planned cesarean section might improve perinatal results.

We advocate for adjusting the timing and mode of delivery to a stage-based classification

- Stage I: 36 – 38+6 weeks of gestation. Offer labor induction
- Stage II: 32 - 34 weeks. Programmed cesarean section
- Stage III: 30 - 32 weeks. Programmed cesarean section
- Stage IV: at any point once potential viability achieved. Programmed cesarean section.

Regarding labor induction, special considerations must be undertaken. First, continuous CTG monitoring is warranted to detect fetal repercussions to labor as they have a lower tolerance to uterine contractions. Second, we suggest the use of mechanical methods in cases that require cervical ripening given their lower rates of uterine hyperstimulation and adverse perinatal outcome. Retrospective studies have shown a potential benefit [107,108].

The histo-pathological examination of the placenta can be useful for the assessment of the recurrence risk in subsequent pregnancies. Therefore, it is suggested to send the placenta for a histo-pathological analysis in cases with FGR [109].

The main key points regarding timing and mode of delivery in FGR are shown in Table 4 and a summary of the proposed management strategy in Figure 2.

Multiple gestation: dichorionic twins

Selective FGR poses a unique management challenge in twin pregnancies, where one twin shows signs of compromise while the other twin grows normally. Balancing

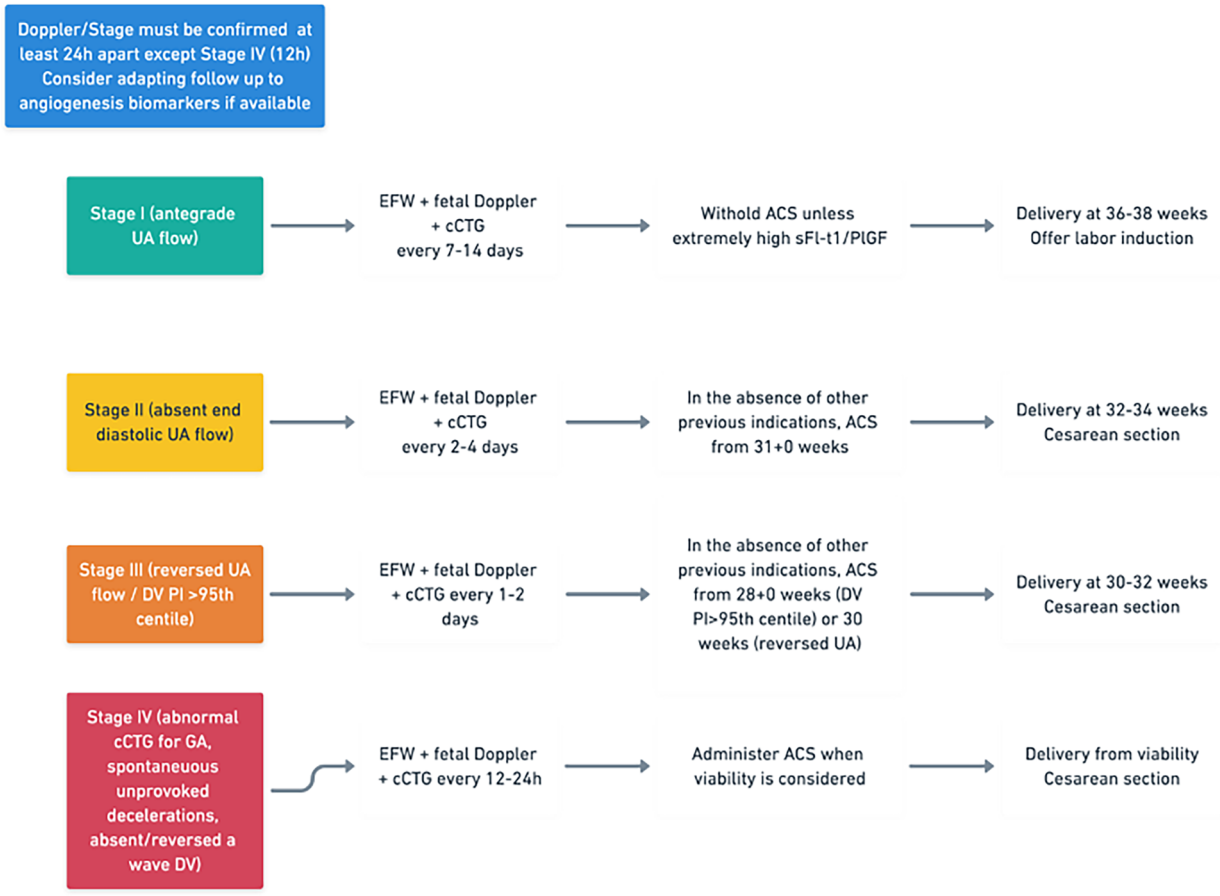

Figure 2. Summary of stage-based management of fetal growth restriction.
ACS, antenatal corticosteroids; cCTG, computerized cardiotocography; DV, ductus venosus; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery

the best interests of both twins is crucial, as management decisions, whether intervention or conservative, impact both. Expectant management may lead to fetal demise in the growth-restricted twin, while elective premature delivery carries the risk of prematurity in the normally grown twin. There is a lack of evidence supporting specific GA cutoffs for determining appropriate management [110]. Nevertheless, expectant management may be preferred in very preterm cases, while delivery of both twins may be recommended in less preterm cases. As a reasonable compromise, delivery should not be based on the FGR twin before 28 weeks and should be discussed with parents considering local data and outcomes between 28 and 32 weeks. Therefore, in the setting of FGR in twins we proposed the following gestational ages for delivery:

- Stage I: 36 - 37 weeks
- Stage II: 32 - 34 weeks
- Stage III: 30 - 32 weeks
- Stage IV: 28 weeks

Breastfeeding for the newborn with fetal growth restriction

Risk-benefit balance

Breastfeeding is currently considered the feeding method of choice for most infants. The World Health Organization (WHO) recommends exclusive breastfeeding during the first 6 months of life [111]. Among other benefits, breast milk reduces the incidence of necrotizing enterocolitis, infectious diseases, sudden infant death, type 2 diabetes, obesity, and hypertension [112], all of them occurring more frequently in FGR infants [113]. Therefore, feeding with human milk seems to have a protective role on FGR and promote a healthy catch-up growth, although there is a lack of studies that confirm it [114,115].

Breastfeeding is a safe practice for FGR infants born at term [116]. However, it is common for preterm and FGR babies not to reach mature breastfeeding skills and achieving the WHO's goal can be singularly challenging. Recently, WHO has released a document to

support breastfeeding in these vulnerable babies [117]. When a very low-birth weight (< 1,500 g) or extremely low-birth weight (< 1,000 g) is expected, parents should be informed that the provision of maternal milk is still the first choice. However, enteral or parenteral feeding is expected, and human milk requires fortifiers such as additional protein, phosphorus, and other nutrients.

Antenatal counseling

The time of FGR diagnosis and follow-up visits can be an excellent opportunity to initiate or reinforce prenatal education about the benefits of breastfeeding, as well as inform about existing resources for breastfeeding advice. Particularly in FGR babies, mothers should receive education on milk expression before birth as it prevents feelings of frustration and depression [118]. Antenatal information also provides mothers time to plan the resources and supports they may need to maintain breastfeeding after delivery.

As in normally grown newborns, promoting early skin-to-skin contact whenever possible, contributes to successful breastfeeding [119]. On the contrary, mothers who smoke or use recreational drugs should know that these habits negatively influence milk supply [120]. The main key points regarding breastfeeding advice are presented in Table 5.

Neonatal and follow-up care

Growth-restricted newborns are usually identified based on charts derived from birthweight [121,122], whereas FGR is based on EFW prenatal charts. FGR infants have a 5–30% increase in mortality and are 2.5 times more likely to be born premature. In addition to increased mortality, FGR infants are at higher risk of being admitted to NICU, to have long-term developmental delay as well as diseases of adulthood.

Table 5. Key points in breastfeeding advice in fetal growth restriction.

Recommendation
Breastfeeding is a safe feeding practice for FGR infants born at term
WHO recommendation of exclusive breastfeeding during the first 6 months of life is extensive to FGR infants. However, those with a birthweight <1500 g commonly require enteral feeding and additional fortifiers
Promote skin-to-skin whenever possible
Consider that vulnerable infants (including FGR and preterm) are more likely to abandon breastfeeding
Promote smoking and drug cessation
Provide antenatal education on milk expression
Initiate or reinforce prenatal education and provide information about existing resources on breastfeeding at the time of FGR diagnosis or follow-up visits

FGR, fetal growth restriction.

Antenatal monitoring, a detailed pregnancy history, and anthropometric measurements as well as postnatal physical exam are essential for the evaluation of FGR infants. The diagnosis based only on the anthropometric measurements is not consistent, because there is no consensus on the definition (prenatal and postnatally). It seems reasonable to use both prenatal and postnatal definitions of FGR as they target different complications. Prenatal ones, particularly those that consider Doppler findings and not solely EFW centile <10th centile, seem more accurate for identifying fetuses at risk of intrauterine adverse events as well as lower tolerance to delivery, separating them from constitutionally small fetuses. On the other hand, postnatal definitions, that consider anthropometric features, serve for the identification of postnatal complications such as hypoglycemia, bronchopulmonary dysplasia or hypoxic-ischemic encephalopathy. Regarding postnatal complications, in preterm cases <34 weeks, a study showed that only prenatal FGR cases in which a birthweight below the 3rd percentile is confirmed in postnatal charts (Olsen or Intergrowth standard) are at higher risk of adverse postnatal outcome [123]. In contrast, in late onset FGR infants with a prenatal or postnatal diagnosis of this condition have an increased risk of neonatal morbidity even if these diagnoses are not coincident [124].

To confirm the diagnosis, considerations of the prenatal history as well as postnatal findings are critical [125].

Based on the possible etiological categories some of the factors that should be investigated as part of the prenatal history are:

- Environmental: exposure to teratogenic agents, alcohol, tobacco, marihuana, or illicit drugs
- Maternal factors: short pregnancy intervals, medical conditions such as diabetes, renal insufficiency, cardiac disease, autoimmune disease, age, ethnicity and poor weight gain.
- Placental: Multiple gestation, placental disorders, umbilical cord abnormalities.
- Fetal: genetic disorders, congenital infections.
- Postnatal physical exam of the infant looking for malformations or other signs of non-placental FGR is critical. Some of the features seen on FGR infants are, scaphoid abdomen, thin umbilical cord, decrease skeletal muscle, loose and dry skin.

In non-placental FGR and depending on the etiology, there may be additional features such as congenital anomalies like microcephaly, cardiac murmurs, hepatosplenomegaly, and others.

Care during the neonatal period

Given that FGR infants are exposed to hyponutrition and/or hypoxemia, they may not tolerate well the labor and have an increased risk of admission to the NIC. Thus, the resuscitation team should always be present at the delivery for prompt evaluation and resuscitation if needed.

Frequent complications shortly after birth are hypothermia and hypoglycemia. Due to the low glycogen stores and increased insulin sensitivity, FGR infants are at risk of hypoglycemia and many of them require a higher glucose infusion rate than normally grown newborns. These infants also have a decrease in brown fat and subcutaneous fat predisposing them to heat loss. Body temperature should be closely monitored as some of these infants may need higher environmental temperatures to prevent hypothermia, particularly those born prematurely.

It is important to avoid additional risk factors for complications that are more common in these growth restricted infants, such as IVH, HIE, respiratory complications as pulmonary hypertension and bronchopulmonary dysplasia, necrotizing enterocolitis and sepsis.

When indicated, screening for early diagnosis of congenital infections and or genetic conditions should be performed as soon as possible.

Research evidence supports breastfeeding or breast milk for nutrition, as it may have a protective effect preventing lack of catch-up growth and necrotizing enterocolitis. The main keypoints in postnatal evaluation and care of FGR neonates are presented in Table 6 and illustrated in Figure 3.

Table 6. Key points in postnatal evaluation and care.

Recommendations for postnatal evaluation and are
The definition of prenatal and postnatal FGR varies as they target different outcomes.
The possible causes of FGR should be investigated at first post-natal evaluation
The resuscitation team should always be present at the delivery for prompt evaluation and resuscitation if needed
Common early complications include hypothermia and hypoglycemia and should be closely monitored
It is important to avoid additional risk factors for complications that are more common in these growth restricted infants, such as intraventricular hemorrhage, hypoxic ischemic encephalopathy, respiratory complications as pulmonary hypertension and bronchopulmonary dysplasia, necrotizing enterocolitis and sepsis.
Breastfeeding should be encouraged
Rapid weight catch up should be discouraged as it promotes central adiposity
Neurodevelopmental outcome, mainly related with motor performance, has been shown to be affected in FGR infants. FGR infants should be followed and monitored closely for early detection of potential complications and if possible, implement preventive strategies

FGR, fetal growth restriction.

Long-term follow-up

FGR has significant long-term consequences, including increased neurodevelopmental abnormalities, metabolic syndrome, and cardiovascular disease.

FGR followed by rapid catch-up weight gain during early life promotes central adiposity and is a risk factor for adult morbidity, like obesity, insulin-resistant type 2 diabetes, and cardiovascular diseases [126]. Furthermore, as stated in prior sections, breastfeeding should be encouraged as it has shown a reduction in the development of obesity as well as other metabolic comorbidities [116].

Growth-restricted fetuses are at higher risk of cardiovascular disease and hypertension, already in childhood and adolescence. Therefore, lifestyle recommendations should be given to minimize the risk of developing hypertension, which can also be more difficult to control once established [127]. Furthermore blood pressure and weight monitoring in these children is warranted for early detection of the disease.

In follow up studies, neurodevelopmental outcome, mainly related with motor performance, has been shown to be affected in FGR infants. Other studies have demonstrated a volumetric decrease in gray matter in limbic regions of the brain and significant lower cognitive and motor scores. Also compared with children with normal fetal growth, FRG is associated with poorer educational attainment [128].46 From a psychological perspective, FGR infants are at increased risk for autism and emotional brain associated with both cognitive and psychiatric risk [129]. Cognitive and psychomotor development should be monitored to identify cases that will benefit from early stimulation therapy referrals [130].

Based on the available information, FGR infants should be followed and monitored closely for early detection of potential complications and if possible, implement preventive strategies. Multidisciplinary research is needed to develop effective preventive strategies and therapies to optimize the long-term outcome of FGR infants.

Counseling for future pregnancies

Knowledge of the recurrence risk of FGR is essential to determine antenatal care in subsequent pregnancies and possible preventive strategies.

Risk of recurrence

It has been established that having had an SGA fetus increases the risk of having one in a subsequent pregnancy [131,132]. Furthermore, delivering an SGA

<table>
<tr><th colspan="5">POSTNATAL EVALUATION AND CARE OF FGR INFANTS</th></tr>
<tr><td></td><td>MEASUREMENTS</td><td colspan="2">MATERNAL HISTORY</td><td>PHYSICAL</td></tr>
<tr><td rowspan="2">Diagnosis</td><td rowspan="2">-Birthweight < 10 centile
or < 3 centile.</td><td>Environmental
-Exposure to teratogenic agents, alcohol, tobacco, marihuana, or illicit drugs etc.</td><td>Maternal
Age, ethnicity, poor weight gain, and short pregnancy intervals,
renal insufficiency, cardiac disease,
diabetes
autoimmune disease.</td><td rowspan="2">Scaphoid abdomen,
thin umbilical cord, decrease skeletal muscle,
loose and dry skin
Hepatomegaly
Cardiac murmur
Malformations
Microcephaly
etc.</td></tr>
<tr><td>Placenta
Multiple gestation, placental disorders, umbilical cord abnormalities</td><td>Fetus
Genetic conditions
Congenital infections</td></tr>
<tr><td>Neonatal care</td><td>AT DELIVERY
Attendance to delivery room by resuscitation team</td><td>AFTER BIRTH
Hypothermia
Hypoglycemia</td><td>LABORATORY
Genetic test
rule out congenital infections</td><td>IN THE NICU
Higher risk of
IVH, Respiratory failure
NEC, Pulmonary hypertension</td></tr>
<tr><td></td><td colspan="4">BREASTFEEDING OR USE BREAST MILK</td></tr>
<tr><td>Follow up</td><td>Neurodevelopmental
-Lower motor scores
-Lower cognitive scores
-Poorer educational attainment</td><td>Psychological
-Risk for autism
- Cognitive and psychiatric risk</td><td>Adult diseases
-Obesity
-Diabetes
-Cardiac diseases</td><td></td></tr>
<tr><td colspan="5">CONTINUE MONITORING AND FOLLOW UP</td></tr>
<tr><td colspan="5">DEVELOPMENT OF STRATEGIES FOR PREVENTION AND OPTIMIZATION OF OUTCOMES</td></tr>
</table>

Figure 3. Proposed postnatal evaluation and care of fetal growth restricted (FGR) infants.
FGR, fetal growth restriction; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis

newborn in the first pregnancy has been reported to be associated not only with a recurrent SGA but also with an increased risk of stillbirth in a second pregnancy [133]. However, the degree to which the risk of subsequent SGA is increased is difficult to determine as it depends on many factors including maternal ones (young maternal age, Asian ethnicity, and smoking [134,135], GA at onset, severity of the SGA, number of previous SGA pregnancies or coexistence with hypertensive disorders of pregnancy.

The overall recurrence risk of having an SGA fetus has been estimated to affect about one-quarter of successive pregnancies. Cohort studies have considered an 8-fold increase in subsequent pregnancies, the highest recurrence risk occurring around the same GA as the first singleton SGA birth, and a higher rate of recurrence in forms of SGA with poorer growth (≤5th centile). Furthermore, the risk of recurrence of SGA also increases with the number of previous pregnancies complicated by SGA. In a recent retrospective analysis of women who had more than one consecutive non-anomalous, singleton, term live birth, the risk of SGA (defined as birthweight <10th centile) in subsequent pregnancies after one SGA newborn ranged from 20.5% in the second to 30.4% in the fourth pregnancy [135]. In this scenario, this study showed that a woman in her fourth pregnancy faces a 5-fold higher risk of SGA if she had one previous SGA, and a 66-fold higher if she had three previous SGA newborns.

Interestingly, hypertensive disorder of pregnancy (HDP) was significantly associated with an increased SGA recurrence risk only when the index delivery had occurred after 32 weeks of gestation [132]. A large Dutch registry showed that early onset PE in the first pregnancy doubled the risk of SGA in the second pregnancy, and SGA in the first pregnancy doubled the risk of PE in the second pregnancy even in the absence of hypertensive disorders in the previous pregnancy [136].

Placental histology has also shown that different entities have different risks of recurrence. The most common form of placental pathology, maternal

vascular malperfusion is associated to a risk of recurrence between 10 and 25% [137]. On the other hand, fetal vascular malperfusion, which is associated to FGR but also stillbirth has a low risk of recurrence. There are two rare entities (chronic histyocitic intervillositis and massive perivillous fibrinoid deposition) that are associated to the most extreme forms of FGR and stillbirth and hold the highest risk of recurrence (>50%) [138].

Preconception counseling

Women whose pregnancy was complicated by a growth disorder should be accurately counseled about the recurrence risk of SGA, as there are some modifiable risk factors in preparation for a subsequent pregnancy they might work on, mostly in terms of voluptuous behaviors (such as smoking or alcohol intake cessation) and lifestyle habits (such as regular physical activity or proper, uptake of Mediterranean diet). Little or no effect was found for supplementation with long-chain polyunsaturated fatty acids, such as omega-3, on pregnancy outcomes and growth [139], even when specifically focusing on the risk of recurrent SGA.

They should also be counseled that a short interpregnancy interval (from less than six to twelve months) is an independent risk factor for SGA in the subsequent pregnancy [140].

Subsequent pregnancy management

History of SGA/FGR should be recorded in the first pregnancy visit and used to help in risk stratification. In very selected cases (antiphospholipid syndrome, massive perivillous fibrinoid deposition in placental histology), LWMH can be considered a prophylactic strategy. Considering the relatively high risk of recurrence, these women should receive closer antenatal surveillance, including uterine artery evaluation at the mid-trimester scan, more frequent monitoring of fetal growth from 24 weeks, and maternal blood pressure. The key points regarding counseling for future pregnancies are presented in Table 7.

Table 7. Key points regarding counseling for future pregnancies.

Recommendation
Women with a history of FGR should be counseled regarding the risk of recurrence based on maternal factors, gestational age at onset and delivery, severity of FGR, coexistence of hypertensive disorders, and placental histopathological findings
Women with a history of FGR should be counseled about modifiable risk factors for future pregnancies including reduction of voluptuous activities and the benefits of regular exercise and Mediterranean diet
Women with a history of FGR should be counseled about the benefits of an interpregnancy interval of at least 12 months
Women with a history of FGR should undergo close surveillance of fetal growth
Women with a history of FGR should undergo close surveillance of maternal blood pressure considering an increased risk of hypertensive disorders of pregnancy

FGR, fetal growth restriction.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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