Difficulties in the Diagnosis and Management of Fetal Growth Restriction

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Abstract

Fetal growth restriction (FGR) is an important topic in perinatal medicine that results from impaired placental function and has poor perinatal outcomes. However, there is a lack of consensus on diagnostic criteria and management strategies worldwide. While some clinicians consider only fetal size in the diagnosis, others disagree and recommend adding fetal growth velocity Doppler indices to the diagnostic criteria. Different strategies are followed for pregnancy follow-up and delivery decision-making. There are different opinions on which Doppler measurements of vessels such as the umbilical artery, middle cerebral artery, and ductus venosus should be performed during follow-up. To assess fetal well-being and to decide on delivery, methods such as cardiotocography, computed cardiotocography, biophysical profile scoring, and biophysical profile scoring are used or not used. The Society of Maternal-Fetal Medicine (SMFM) and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) published guidelines in the same year. However, their perspectives on fetal growth restriction were quite different. We basically analyzed the differences between these two guidelines and the reasons for the differences. As a result, we presented our own practice.

Keywords: Fetal growth restriction (FGR), Fetal size, Maternal-Fetal Medicine, ISUOG.
fetal size and associated poor fetal outcomes. However, the vast majority of these infants are constitutionally small and do not have adverse perinatal outcomes. In addition, Doppler anomalies in Umbilical Artery (UA), Uterine Artery (UtA), Ductus Venosus (DV), and/or Middle Cerebral Artery (MCA) occur as a result of decreased uteroplacental perfusion and increased fetal systemic vascular resistance. In follow-up, tests such as cardiotocography (CTG), computerized cardiotocography (cCTG), or biophysical profile (BPP) that evaluate fetal well-being are also used. Utilizing these tools within a system in the management of FGR improves perinatal and neurodevelopmental outcomes. Still, there is no worldwide consensus on which to use and how often.

FGR is divided into two main classes as early-onset (<32 weeks) and late-onset (≥32 weeks) according to the time of diagnosis. The reason for this classification is based on the differences in severity, natural history, Doppler findings, association with hypertensive complications, placental findings, and treatment between these two FGR phenotypes. Early FGR is often associated with preeclampsia, abnormal umbilical artery Doppler findings, and poor perinatal outcomes. In late FGR, however, there is milder placental dysfunction and consequently less likely to be associated with preeclampsia and changes in umbilical artery Doppler. A consensus statement based on the Delphi procedure proposed separate definitions for early-onset and late-onset FGR. Both guidelines classify FGR as early and late FGR. However, in diagnostic criteria and follow-up tools, SFMF takes a more traditional approach, while ISUOG takes an approach that considers the Delphi procedure in diagnostic criteria and the time of occurrence of FGR in follow-up. In this review, we will evaluate the perspectives of the SFMF and ISUOG guidelines to FGR and describe our own practice.

Etiology and Risk Factors
FGR is caused by maternal, fetal, or placental causes. However, in at least 40% of FGR cases, the etiologic cause may not be identified. In infants with an underlying cause, FGR results from genetic disease in about one-third of infants and the remainder due to poor fetal environment, which is the result of placental and maternal causes. Maternal causes are also considered risk factors and regardless of the cause, the underlying mechanism is placental insufficiency and dysfunction.

Maternal Factors
The risk of FGR is increased in individuals with diseases such as cardiovascular diseases, preeclampsia, and gestational diabetes. The risk also increases in the presence of factors such as anemia, autoimmune diseases, drug use (antiepileptics, chemotherapy drugs, etc.), tobacco and alcohol use.

Fetal Factors
Fetal structural and chromosomal abnormalities are present in 20% of cases, especially in early-onset FGR (<32 GW). Chromosomal anomalies include trisomies (most commonly trisomy 13 and trisomy 18), triploidy (in the diandric type, the extra chromosome comes from the father, and in the digynic type, the extra chromosome comes from the mother and asymmetric FGR is observed). The presence of genetic syndromes and congenital infections can be considered among other causes.

Placental Factors
The most common placental cause that increases the risk of FGR is placental vascular insufficiency. Also, umbilical cord abnormalities and advanced placental maturation increase the risk.

Diagnosis and Management
FGR is defined as infants who fail to reach their predetermined genetic growth potential. The aim of prenatal care is to prevent FGR-related perinatal morbidity and mortality, poor neurodevelopmental outcomes, and long-term adult diseases. Ultrasonographic fetal weight measurement and Doppler examinations (UA, UtA, MCA, DV) are used to detect infants who do not reach their growth potential. In addition, tests including CTG, cCTG, amniotic fluid index (AFI), and biophysical scoring can be performed to determine fetal well-being and timing of delivery.

Ultrasoundographic Fetal Weight Measurement
First, the gestational age should be confirmed. The gestational week is confirmed by comparing the gestational week obtained from the crown-rump length (CRL) measurement in the first-trimester ultrasonography. If there is a difference of more than 7 days between the two measurements, the week of gestation is based on the CRL measurement. On ultrasonography, estimated fetal weight (EFW) is calculated by measuring BPD, HC, AC, and FL, and then the measurement is standardized using different fetal growth nomograms. The most commonly used method is based on the Hadlock formula, which includes standards that are not adjusted for race and gender. We use the Hadlock formula in our clinic.

According to the SFMF guidelines, FGR is an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile. ACOG also accepts this definition and this...
definition is widely used by clinicians in the USA. Fetuses with a birth weight below the 10th percentile have an increased risk of stillbirth and perinatal mortality. Perinatal outcomes are poorer in fetuses with a birth weight below the 3rd percentile. Therefore, worldwide, fetuses with EFW<3rd percentile are considered FGR. It was also found that the diagnostic accuracy of fetuses with AC<10th percentile was similar to that of fetuses with EFW<10th percentile. However, 18%-22% of fetuses considered FGR because EFW<10th percentile or AC<10th percentile are constitutionally small at birth with normal perinatal outcomes. Conversely, there are infants who are not considered FGR by this definition, but who do not reach their true growth potential and consequently have poor perinatal outcomes. In one study, the lowest perinatal mortality was found in infants with birth weight between the 70th and 90th percentile and there was an inverse relationship between birth weight below the 80th percentile and perinatal mortality.

Fetal Growth Rate

There are several methods for monitoring fetal growth rate: longitudinal growth charts and customized growth charts, which assess deviation from growth rate charts. There are studies suggesting that slowing of fetal growth rate in the third trimester is associated with poor perinatal outcomes. Decreased growth velocity is normally taken as a drop of more than 50 percent for AC or, more commonly, EFW between consecutive ultrasound scans.

Doppler Velocity Measurements

The rationale for Doppler velocity measurements in FGR: It shows uteroplacental function on the maternal side. In uteroplacental insufficiency, there is maladaptation of the spiral arteries and abnormality of the villous vascular tree. The uterine artery (UTA) and umbilical artery (UA) are evaluated by Doppler velocity measurements. On the fetal side, the progression of cardiovascular adaptation from hypoxia to acidemia is demonstrated. middle cerebral artery (MCA) and ductus venosus (DV) are evaluated with Doppler.

Uterine artery pulsatility index (PI) >95th percentile is associated with placental insufficiency and impaired maternal vascular perfusion.

A progressive increase in UA PI indicates impaired gas and nutrient exchange at the placental surface and increased fetal afterload resistance. Loss of UA end-diastolic flow (UA-EDF) and, most recently, UA reverse end-diastolic flow (UA-REDF) are signs of increasing severity of residual placental insufficiency. UA Doppler has a key role in the monitoring of FGR and the timing of delivery.

Absent or inverted a-wave in the ductus venosus (DV) indicates increased intraatrial pressure and myocardial ischemia due to increased placental vascular resistance. It is an important tool in terms of timing of delivery, especially in the management of early-onset FGR. Because in early FGR, the clinician is in a decision process between the risk of stillbirth and premature FGR delivery.

ISUOG recommends the international Delphi consensus decisions for the diagnostic criteria of FGR. Accordingly, the diagnostic criteria for FGR are different in early-onset (before 32 weeks of gestation) and late-onset (after 32 weeks of gestation) FGR, provided that congenital anomalies are absent:

Delphi diagnostic criteria in early-onset FGR:
- AC/EFW <3rd percentile or UA-AEDF alone is a diagnostic criterion alone or
- AC/EFW between the 3rd and 10th percentile: accompanied by UtA-PI>95th percentile and/or UA-PI>95th percentile.

Delphi diagnostic criteria in late-onset FGR:
- AC/EFW<3rd percentile is the diagnostic criterion alone or
- Two of the following 3 findings: AC/EFW between the 3rd and 10th percentile, slowing of the AC/EFW follow-up growth rate by more than 2 quartiles (50th percentile), CPR<5th percentile or UA PI>95th percentile.

FGR is a challenging subject of obstetrics that should be managed by maternal-fetal medicine specialists in adequately equipped centers. Detailed fetal ultrasonography should be performed at the time of diagnosis and amniocentesis and microarray examination should be recommended to the family, especially in early-onset FGR, in the presence of polyhydramnios or fetal structural anomalies. Doppler velocity measurements and fetal well-being should be evaluated and the resulting data should be carefully analyzed.

Management Strategies in Early-Onset FGR

It is less frequent (30%) than late-onset FGR. However, it represents more severe placental insufficiency. Therefore, the fetus may be very small, Doppler abnormalities are prominent, the perinatal mortality rate is high and it is associated with maternal comorbidities including hypertension and preeclampsia. In early-onset FGR, increased resistance in UAA, UA, and MCA Doppler are early changes and occur weeks before severe cardiovascular and metabolic deterioration. With increasing severity, UA-AEDF and UA-REDF occur. The rate of transition from UA-AEDF to UA-REDF indicates the severity of placental insufficiency.

In early-onset FGR, late deterioration is the absence or inversion of the a-wave in DV. This cardiovascular and metabolic deterioration occurs before or simultaneously with STV abnormalities. This is followed by abnormal BPP
scoring, spontaneous recurrent decelerations on CTG, and finally stillbirth.\textsuperscript{[33]} Especially in early-onset FGR, maternal factors such as exacerbation of maternal hypertension also influence the decision to deliver.\textsuperscript{[6, 7]} The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study\textsuperscript{[31]} showed that multidisciplinary counseling (by neonatology and maternal-fetal medicine specialists), follow-up in a tertiary center under a specific protocol, and timing of delivery reduce poor perinatal outcomes.\textsuperscript{[10]}

In the TRUFFLE study, the decision to deliver in early-onset FGR was based on late ductus venosus abnormalities and/or decreased short-time variability (STV) on cCTG or repetitive decelerations in fetal heart rate. ISUOG\textsuperscript{[7]} adopts the recommendations of this study for the decision to deliver. However, cCTG is not a tool used worldwide. According to ISUOG, when cCTG is not available, if the biophysical profile score is 4 or less, delivery should be decided in echoing FGR. We also use biophysical profile scoring in our center. The SFMF\textsuperscript{[6, 7]} on the other hand, does not recommend any of the tools of ductus venosus, cCTG, or biophysical profile scoring in early-onset FGR. In both early and late-onset FGR, CTG is used in addition to UA Doppler, which is used worldwide (also recommended by ISUOG). False positivity of CTG alone for fetal distress is common. This necessitates the need for additional methods in the decision-making process, especially when prematurity is taken into account. For these reasons, we use UA, DV Doppler, and biophysical profile scoring in early-onset FGR. Different intervals such as 1-2 weeks have been proposed as follow-up intervals.\textsuperscript{[6, 7]}

In the absence of Doppler abnormalities, we apply Doppler and biophysical profile scoring to FGR at 1-week intervals. As recommended by other guidelines,\textsuperscript{[6, 7]} we measure fetal weight at 2-3-week intervals. In early-onset FGR, we hospitalize the patient in case of UA-AEDF or UA-REDF. Both ISUOG and SFMF\textsuperscript{[6, 7]} recommend UA Doppler at 2-3 days in this situation. Similarly, we hospitalize the patient and perform Doppler examination 2 days apart and CTG 3 times a day. If the CTG is nonreactive, we do biophysical profile scoring. We also administer betamethasone to the mother for lung maturation, similar to the recommendations of the other two guidelines.\textsuperscript{[6, 7]} If preterm delivery is highly probable and has not been used previously. Apart from fetal indications, maternal obstetric emergencies such as placental abruption, severe pre-eclampsia, eclampsia, and HELLP syndrome are indications for emergency delivery even at the limit of viability (24-26 weeks of gestation).\textsuperscript{[6, 7]}

In addition, recurrent decelerations on CTG are indications of labor after 26 weeks of gestation.\textsuperscript{[6, 7]} As recommended by ISUOG,\textsuperscript{[7]} we recommend delivery when the biophysical score is 4 or less and this finding is recurrent. In early-onset FGR, our labor indication protocol according to gestational week is as follows:

- 26-30 weeks of gestation: Absence of a wave or inverted a-wave on DV\textsuperscript{[7]}
- 30-32 weeks of gestation: UA-REDF\textsuperscript{[6, 7]}
- 32-34 weeks of gestation: UA-AEDF. SFMF\textsuperscript{[6]} and ISUOG\textsuperscript{[7]} recommend delivery between
- 33-34 weeks of gestation in case of UA-AEDF.

In these Doppler anomalies, we recommend cesarean delivery as recommended by both guidelines.

**Late-Onset FGR**

It develops after 32 weeks of gestation. It is responsible for 70% of FGRs. The fetus may not be very small as placental insufficiency is milder. Maternal comorbidities such as hypertension and preeclampsia are less frequent. Doppler anomalies are less prominent. Increased resistance is usually not encountered in UA. However, the fetus is less resistant to hypoxia in the later weeks. Fetal pregnancy loss may occur in the UA without increased PI resistance. The decrease in CPR, which is the MCA PI/UA PI ratio, is due to the diversion of blood flow to the brain and is called the brain-protective effect. It is the main characteristic of late-onset FGR. The PORTO study\textsuperscript{[3]} was a large prospective study evaluating the optimal management of FGR infants between 24 GW and 37 GW. They found that CPR and multi-vessel Doppler improved perinatal outcomes. According to their study, CPR had 66% sensitivity and 85% specificity in predicting poor perinatal outcomes and was not always in the same commonly accepted order of Doppler abnormalities. The ISUOG guideline\textsuperscript{[6]} uses CPR in late-onset FGR and accepts the threshold value indicating abnormality as the 5th percentile. However, there is no adequate standardization in this regard, and in a large systematic review, the sensitivity and specificity of CPR in predicting poor perinatal outcomes were found to be lower compared to the PORTO study.\textsuperscript{[3, 18]}

Furthermore, it is not used as a criterion for the timing of delivery. For these reasons, the SFMF\textsuperscript{[6]} does not use CPR. Randomized prospective studies are needed to ensure adequate standardization. However, in late-onset FGR, increased UA resistance is usually not observed and fetal death can occur within a few days even with a CTG reactive and/or biophysical profile score of 10/10. CTG and biophysical profile scoring do not inform the clinician about the frequency of follow-up. CPR should be used to get an idea of when the fetal condition may deteriorate. For these reasons, we use CPR in late-onset FGR. However, we use the CPR threshold value simply as CPR<1 instead of the 5th percentile. Although it is not an ideal threshold, we think it is useful in managing the disease. In late-onset FGR, if CPR<1, poor perinatal outcomes are imminent. Doppler and biophysical profile scoring at 2-3 day intervals should be considered. Hospitalization should be considered if the
The stillbirth rate is less in late-onset FGR. However, stillbirth can occur without obvious signs and is observed more frequently than early-onset FGR (70%). Moreover, according to the TRUFFLE study, the frequency of neurodevelopmental disorders observed in early-onset FGR does not decrease in late-onset FGR. For these reasons, we recommend follow-up at 1-week intervals as in FGR. At each follow-up, we check UA PI, MCA PI, and CPR, and also perform biophysical profile scoring. Our follow-up protocol is similar to the ISUOG guidelines. However, cCTG is not available in our center. SFMF, on the other hand, recommends follow-up with UA Doppler and NST similar to early FGR and fetal weight measurement at 3-4 week intervals.

The Intrauterine Growth Intervention Trial at Term (DIGITAT) study on the timing of delivery in near-term late-onset preterm FGR compared labor induction and expectant management in pregnancies with suspected FGR beyond 36 weeks of gestation. Here, pregnancies with UA-AEDF were excluded and perinatal outcomes were similar between the two groups. Only neonates in the induction group received more intermediate care. In those over 38 weeks of gestation, the results were similar. Therefore, as recommended by both SFMF and ISUOG.

- We recommend induction of labor for 38-39 gestational weeks pregnant women with EFW between 3-10 percentile and without significant Doppler abnormalities. SFMF recommends delivery at 37 weeks of gestation and ISUOG recommends delivery between 36 and 37 weeks for pregnant women with EFW<3 persentiles or UA PI>95 percentiles. Like SFMF, we also recommend induction of labor at 37 weeks gestation.

Conclusion

In conclusion, there is deep disagreement in the management of FGR. The main reason for this is that Doppler indices are not yet standardized. Prospective randomized studies on Doppler indices are needed to reduce stillbirths, poor perinatal outcomes, and poor neurodevelopmental outcomes. Furthermore, FGR should be followed up in tertiary centers with a multidisciplinary approach.

Disclosures

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References

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