Early Fetal Growth Restriction

Subjects: Reproductive Biology

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Early fetal growth restriction (FGR) is a complex and multifactorial disorder affecting fetal development. Most cases are related to uteroplacental dysfunction, while non-placental etiologies include chromosomal/genetic anomalies, congenital infections and inborn errors of metabolism.

Keywords: maternal–fetal Doppler ; perinatal complications ; antenatal monitoring ; preterm delivery

1. Introduction

Fetal growth restriction (FGR) complicates approximately 10% of all pregnancies and is among the leading causes of perinatal morbidity and mortality [1][2][3].

It is conventionally differentiated in early or late FGR. These two entities differ not only on the basis of the gestational age at diagnosis, which has been conventionally established at 32 weeks, but also in terms of clinical features, severity of placental dysfunction and maternal morbidity [4][5][6]. Severe placental dysfunction and up to 70% association with hypertensive disorders of the pregnancy (HDP) are among the features characterizing early FGR, which accounts for approximately 20–30% of all cases of FGR [4][7].

FGR often results in multiple perinatal complications [8][9][10] and is an acknowledged risk factor for poor neurological outcome and cardiovascular disease [11][12].

To date, the only treatment option is represented by timed delivery, i.e., required when the risk of intrauterine compromise outweighs that of prematurity. However, there still is a great variation in clinical practice when it comes to FGR monitoring and timing of delivery.

2. Definition and Diagnosis

The Delphi Consensus criteria proposed by a panel of European Fetal Medicine experts for the definition of FGR fetuses include biometric cut-off and Doppler indices of feto-placental function and is currently endorsed by most fetal medicine specialists as well as by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [4][7][13][14][15]. Such definition summarizes the current understanding of the pathogenesis of non-anomalous FGR, which consists of pathological smallness caused by an underlying functional problem.

The evaluation of the fetal anatomy and of the amniotic fluid volume can assist in the differential diagnosis of the underlying etiology of the fetal smallness (e.g., uteroplacental cause, viral infection, karyotype abnormality or genetic syndromes). In accordance with recent data, the latest SMFM guidelines (REF TO BE ADDED) recommend invasive testing with chromosomal microarray analysis in the event of unexplained isolated FGR diagnosed before 32 weeks.

3. Monitoring Tools in Early-Onset Fetal Growth Restriction

Early-onset FGR of utero-placental origin epitomizes a clinical phenotype characterized by increased resistance of the utero-placental circulation, which in turn leads abnormally elevated umbilical artery blood flow resistance [16]. Differently from late-onset FGR, early FGR usually shows a pattern of Doppler deterioration which is related to the degree of the placental dysfunction, starting from abnormalities in the UA Doppler and then involving sequentially the middle cerebral artery (MCA) and the ductus venosus (DV) [17].

On this basis, routine evaluation of the UA Doppler has been proven to reduce perinatal morbidity and mortality [18], and the Royal College of Obstetrician and Gynecologists recommends its use as a primary surveillance tool in fetuses with confirmed or suspected FGR [18]. Different degrees of impaired placental function can be identified by means of the assessment of the pulsatility index (PI) and the UA end-diastolic flow (EDF).

A decrease in MCA resistance, which usually follows the changes in the UA Doppler, is an indirect parameter for the so-called brain sparing effect, which consists of vasodilatation of the brain circulation and represents an adaptive mechanism to chronic hypoxia secondary to uteroplacental insufficiency.

The DV is responsible for the shunting of the oxygenated blood from the umbilical vein to the right atrium during fetal life. In normal conditions approximately 15–30% of the umbilical blood is shunted, while this percentage increases in FGR fetuses in order to improve cerebral and cardiac perfusion.

Computerized cardiotocography (cCTG) is the only tool which allows the quantitative analysis of the STV of the fetal heart rate, which represents an important indicator of fetal wellbeing [19]. cCTG is acknowledged to play a major role in the management of early FGR [4][20][21]. In such cases, STV < 2.6 milliseconds has been related to fetal acidemia and intrauterine death [20][19], while STV > 3.0 milliseconds has been rarely associated with poor fetal outcome [19][21].

Absent end-diastolic flow (AEDF) in the umbilical artery and vasodilatation in the middle cerebral arteries are identified as early changes, while reversed end-diastolic flow (REDF), pathologic short term variability at cCTG and abnormalities in the DV Doppler are depicted as late changes associated with an increased risk of adverse perinatal events [3].

4. Management and Delivery in Early-Onset Fetal Growth Restriction

At present, the TRUFFLE is the only randomized controlled study which has evaluated a standardized monitoring and delivery protocol for FGR fetuses and has demonstrated its effectiveness in optimizing the short- and long-term outcome of non-anomalous FGR fetuses diagnosed between 26 and 32 weeks.

Based on the assumption that a monitoring strategy including the cCTG STV and the DV Doppler can allow practitioners to safely delay delivery before the occurrence of fetal compromise, the TRUFFLE study has demonstrated that the perinatal outcome of surviving early FGR fetuses is significantly better among those delivered based on late DV changes [4][20][21][22], even though no differences were noted when evaluating the primary outcome of the study, i.e., survival without neurodevelopmental impairment among the three randomization arms of the TRUFFLE. According to the results of the study, the DV Doppler represents the most important parameter in the prediction of intrauterine death in early-onset FGR [23].

“Safety net” criteria for delivery within the TRUFFLE cohort included spontaneous decelerations at CTG, UA REDF between 30 and 32 weeks, UA AEDF between 32 and 34 weeks or UA PI > 95th centile beyond 34 weeks. Therefore, according to the TRUFFLE protocol, the abnormalities of the UA Doppler should not be considered when evaluating the option of delivery prior to 30 weeks of gestation [4][20].

Importantly, the “safety net” criteria accounted for a significant number of indications for delivery, both in the primary [4][20] and in a recently published secondary analysis of the datasets including only the cases delivered < 32 weeks, mostly within the late DV group [21].

The umbilical artery Doppler becomes the most important parameter to assess the timing of delivery beyond 32 weeks of gestation. More specifically, according to the TRUFFLE protocol, delivery is recommended between 32 and 34 weeks of gestation in the case of AEDF occurrence, while, beyond 34 weeks, delivery should be considered in the event of UA PI >95th centile [4][20]

With respect to cerebral redistribution, which represents an adaptive mechanism to fetal hypoxemia and can be identified by means of a reduction in the impedance in the middle cerebral artery (MCA) and in the cerebroplacental ratio (CPR) (or cerebro-umbilical (C-U) ratio), there is no evidence supporting its role in the monitoring strategy of early FGR fetuses.

A recently published secondary analysis of the TRUFFLE cohort dataset regarding the longitudinal changes in the STV has shown that it is not possible to predict the occurrence of abnormal STV or late changes in the DV Doppler, thus concluding that, in the case of advanced fetal compromise, cCTG monitoring should be undertaken at least on a daily basis [24], while monitoring of fetal Doppler can be performed twice a week or on alternate days in the event of advanced fetal compromise.

5. Early-Onset Fetal Growth Restriction in the TRUFFLE Era: Delivery and Fetal Outcomes

The identification of the optimal timing of delivery represents the crucial clinical challenge in the management of early FGR fetuses, as it requires a balance between the risks of prematurity and stillbirth and those of severe intrauterine hypoxia with organ damage due to inadequate tissue perfusion [23][25]. The TRUFFLE group has designed a reliable

protocol for the monitoring and the identification of the optimal timing of delivery in early FGR, unless severe maternal complications supervene [4][26][27]. According to the data from the earlier papers from the group, overall survival and survival without neurodevelopmental morbidity showed remarkably higher than expected percentages [4][20], 92% and 70%, respectively. Intrauterine deaths and overall mortality accounted for only 2% and 8% of the included cases, respectively, while cerebral palsy was reported in only six fetuses (1%) within this cohort of preterm and severely growth-restricted fetuses.

As regards the mode of delivery, there is no recommendation by the TRUFFLE group as to whether to deliver vaginally or by cesarean section, although 97% of the included women underwent cesarean delivery. Of note, the recent guidelines on the diagnosis and management of FGR recommend elective cesarean delivery in the presence of any among abnormal cCTG STV, ductus venosus Doppler alteration, absent or reversed UA-EDF, altered blood pressure or maternal indication [28].

6. Periviable Fetal Growth Restriction

While the perinatal and the 2-year neurodevelopmental outcomes of FGR diagnosed between 26 and 32 weeks has been described in the TRUFFLE randomized trial [4][20][21][29][30], little evidence exists for counseling the prospective parents when a diagnosis of FGR is made at periviable gestation. The recently published ISUOG guidelines [28] recommend personalized management up to 26 weeks of gestation; therefore, active management in terms of monitoring and delivery can be deferred until 26 weeks is reached in order to improve the chance of survival and disease-free survival, particularly in the context of fetuses who have not reached a “viable” EFW.

Within the limitations of the small case-series available on the topic, the reported perinatal survival is not dissimilar between anomalous and non-anomalous FGR paired for gestational age at diagnosis, even though the diagnosis of a genetic abnormality associated with the fetal smallness proved to be invariably lethal [31]. Of note, in a single-center case-series, the anomalous FGR fetuses accounted for almost one third of all the fetuses identified as FGR at periviable gestation, thus highlighting the importance of a thorough assessment of the fetal anatomy when fetal smallness is diagnosed prior to 26 weeks.

7. Conclusion

A standardized protocol integrating Doppler and cCTG parameters for the monitoring of the pregnancies complicated by early FGR has been developed, and available evidence supports its use for the management of FGR between 26 and 32 weeks in order to optimize the perinatal outcome as well as the survival without neurodevelopmental delay of preterm FGR fetuses. Delivery should be undertaken only if either the DV or the STV become abnormal, and available evidence suggests that, once the placental origin of the growth restriction is confirmed, the perinatal and infant outcomes are better than formerly reported.

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