Review articles

Fetal growth restriction – from observation to intervention

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Abstract

Fetal growth restriction (FGR) due to placental dysfunction has important short- and long-term impacts that may reach into adulthood. Early-onset FGR before 34 weeks’ gestation shows a characteristic sequence of responses to placental dysfunction that evolves from the arterial circulation to the venous system and finally to biophysical abnormalities. In this form of FGR safe prolongation of pregnancy is a primary management goal, as gestational age at delivery, birth weight and iatrogenic premature delivery have an important impact on short-term outcome and neurodevelopment. Surveillance intervals should be adjusted based on umbilical artery and venous Doppler studies. Intervention thresholds need to be based on the balance of fetal vs. neonatal risks and therefore critically depend on gestational age. Late-onset FGR presents with subtle Doppler and biophysical abnormalities and therefore poses a diagnostic dilemma. Often unrecognized, term FGR contributes to a large proportion of adverse perinatal outcome. Monitoring intervals should be adjusted based on middle cerebral artery Doppler and fetal heart rate parameters. Delivery timing thresholds can be low. In both forms of FGR neurodevelopmental impacts of placental disease occur before clinical decisions regarding delivery timing arise. This places special emphasis on future preventative studies.

Keywords: Biophysical profile; Doppler; ductus venosus; early-onset fetal growth restriction; late-onset fetal growth restriction; middle cerebral artery; neurodevelopment; umbilical artery.

Introduction

Restriction of normal fetal growth results in slowing of the expected in utero growth velocity leading to the delivery of a neonate below the expected birth weight percentile. Fetal growth restriction (FGR) continues to be a major contributor to perinatal morbidity and mortality increasing the risks of adverse health effects throughout life [4]. The concept of evaluating fetal growth in reference to percentiles has been incorporated into perinatal medicine as early as 1973 [33]. This allows not only prenatal detection of FGR but initiation of diagnostic steps for potential underlying conditions, such as aneuploidy, viral infection and non-aneuploid syndromes prior to birth. With developments in prenatal Doppler ultrasound and evaluation of fetal biophysical parameters [75] a significant amount of information on the prenatal evolution of FGR, fetal responses to placental dysfunction and the short- and long-term impacts of the fetal condition has become available. This information is now becoming highly relevant in defining key issues in the management of FGR due to placental dysfunction.

Critical milestones in placental development

Successful postconceptional blastocyst adherence initiates a coordinated cascade of placental development that can be clinically monitored from the first trimester. Trophoblast invasion into the media of the maternal spiral arteries is responsible for decreasing blood flow impedance in the maternal compartment of the placenta [56]. Villous sprouting and differentiation are fundamental to decrease blood flow resistance in the fetal umbilical circulation, increase the surface area for nutrient and waste exchange and decrease diffusion distance, particularly for O2 [16, 17]. Establishment of sufficient blood supply supports placental synthetic activity of several bioactive substances that are instrumental for maternal pregnancy adaptation to allow preferential nutrition of the placenta and growing fetus [5]. Dedicated transport systems for glucose, amino and fatty acids enhance efficiency of delivery of these essential nutrients to the fetus. With normal development the term placenta receives ~600 mL/min of the maternal cardiac output which is distributed to a villous surface area of 12 m². The fetal compartment is perfused with 200–400 mL/kg/min of fetal blood volume throughout gestation [16, 17, 53].

Early placental vasculogenesis and angiogenesis are controlled by several substances, such as placental growth factor (PLGF), angiopoietins (Ang-2), placental protein 13 (pp-13), pregnancy associated protein A (PAPP-A), endoglinins and VEGF (vascular endothelial growth factor) which increase in the first trimester correlating with placental vascular development [1, 22, 29, 55, 68]. Relative insensitivity of the circulation to vasoactive substances facilitates a significant increase in cardiac output, decreased blood pressure and peripheral resistance in the mother as early as eight weeks’
gestation [19, 23]. Successful trophoblast invasion results in loss of early diastolic notching in the uterine artery Doppler waveform by the end of the first trimester in most women followed by successive decline in the Doppler index throughout gestation [34]. In the umbilical artery (UA) end-diastolic velocity (EDV) is established by the end of the first trimester and Doppler indices continue to fall towards term as umbilical blood flow resistance decreases [34, 59]. The combination of these maternal characteristics, biomarkers of placental vascularization and their Doppler correlates allow first trimester clinical monitoring of key events in placental development. Such integrated evaluation holds promise for first trimester screening for subsequent placental dysfunction [48, 57].

**Nutrient distribution and the fetal circulation**

The design of the fetal circulation is unique, because it achieves nutrient partitioning by preferential blood streaming across three major shunts. The ductus venosus (DV) is the first active shunt receiving nutrient rich blood from the umbilical vein (UV). Under normal circumstances 70–80% of this blood continues to the liver while the remainder is accelerated towards the foramen ovale [46]. Within the liver, the majority of UV blood reaches the left lobe (60%) with the left portal vein acting as the watershed between the right and left hepatic circulations [40, 42]. The proportions of UV blood shunted to the liver vs. the heart and intrahepatic distribution of the right vs. left lobes can vary in response to changes in the magnitude of umbilical venous volume flow, maternal diet and abnormalities in the arterial placental circulation [36, 41].

Shunting at the level of the foramen ovale regulates the proportion of nutrient rich blood reaching left and right ventricles. Normally, the majority of nutrient rich blood reaches the left ventricle and therefore the coronary and cerebral circulations. In contrast, nutrient depleted blood from the venous cava reaches the right ventricle and therefore the pulmonary circulations and descending aorta. The proportional distribution at this level is influenced by the dimensions of the foramen ovale and the placental (right ventricular) and cerebral (left ventricular) accommodation. At the ductus arteriosus blood streams originating from both ventricles coalesce and shunting between these bloodstreams occurs at the aortic isthmus. Here, decreased left ventricular input pressure into the aorta and/or increased placental afterload promote recirculation of nutrient depleted descending aortic blood towards the cerebral circulation. In addition, several organs have the capability to adjust perfusion by autoregulation [5, 44].

**Fetal response to placental dysfunction**

Fetal response to placental dysfunction evolves from early compensatory reactions to late decompensation in multiple organ systems [5]. This response contributes to the short- and long-term morbidity and the fetal programming that increases the risk for subsequent adult disease in FGR. From a clinical perspective cardiovascular and central nervous system responses are currently most relevant because they can be utilized for clinical management.

**Preclinical signs of placental dysfunction – “venous redistribution”**

Early placental dysfunction has several potential vascular effects before UA Doppler becomes abnormal. Decrease in umbilical venous (UV) volume flow and reduction of the proportion of fetal cardiac output that is distributed to the placenta are vascular signs that precede development of clinical growth delay [45, 58, 60]. Reduced UV volume flow leads to increased DV-shunting away from the liver towards the heart [46]. In addition, there is intrahepatic redistribution of umbilical venous flow away from the right lobe of the liver which is detectable by flow changes at the watershed left portal vein [40, 41]. This venous redistribution is associated with downregulation of the glucose-insulin-IgF growth axis and decreased glycogen store in the liver [72, 73]. Therefore, liver size is decreased and produces the first clinical sign of lagging fetal abdominal circumference growth before the composite estimated fetal weight falls below the 10th percentile.

**Early signs of FGR – “arterial redistribution and delayed behavioral development”**

Early subclinical elevation of placental blood flow resistance and decreasing blood flow resistance in the cerebral circulation produce a decrease in the cerebroplacental Doppler ratio (CPR) [31, 35]. When villous obliteration affects approximately one-third of the villous vasculature the UA Doppler index becomes consistently increased, fetal blood pressure may increase and oxygen transfer may decrease [5, 28, 54]. A significant relative decrease in oxygen and/or an increase in fetal blood pressure produce a consistent decrease of the middle cerebral artery Doppler index. The decrease in the CPR is also described as “redistribution” because it suggests a relative decrease in left ventricular afterload favoring intracardiac redistribution across the foramen ovale towards the left side of the heart. Similarly, decrease in middle cerebral artery pulsatility index suggests preferential perfusion of the brain by autoregulation and accordingly has been termed “brain sparing” [79].

Fetal development in a chronic state of relative nutrient and oxygen deprivation produces a measurable delay in the achievement of behavioral milestones. Relative increase in fetal heart rate baseline, lower heart rate variability and variation, delayed achievement of heart rate reactivity and a delay in the establishment of distinct behavioral states have been documented [5]. These abnormalities are frequently subclinical apparent and therefore are of diagnostic use.

**Late signs of FGR – “critical Doppler and biophysical abnormalities”**

When villous obliteration affects over half of the placenta UA EDV may be absent – or reversed (UA A/REDV) with
a proportionally increased risk for fetal hypoxemia and/or acidemia [5, 54]. This marked increase of placental blood flow resistance and therefore right ventricular afterload might have several central circulatory effects. If foramen ovale blood flow is unrestricted, shunting towards the left ventricle can increase and therefore the left ventricle can contribute a greater proportion to the combined cardiac output [2]. If foramen ovale blood flow is restricted due to a smaller aperture this change may not be observed [44]. At the aortic isthmus, decreasing diastolic forward flow progression to reversal in diastole can be observed proportional to the increase in fetoplacental blood flow resistance [15, 49]. Accordingly, these central changes can increase the distribution of blood with a higher nutritional content to the myocardium and cerebral circulation. However, the contribution of blood with lower nutritional content that is recirculated through the aortic isthmus towards the cerebral circulation can also increase [26, 49].

Once UA A/REDV defines progression to late cardiovascular manifestations abnormalities in venous flow patterns can be the result of several central and peripheral circulatory changes [25]. Marked DV dilatation to facilitate cardiac diversion of UV blood also allows increased retrograde transmission of the atrial pressure-volume changes [12]. A decline in cardiac performance contributes to an elevation of central venous pressure and decreasing forward cardiac function [21, 50]. This is further exacerbated by marked elevation of placental blood flow resistance. An escalation of venous Doppler index elevation is typical in preterminal decompensation of the fetus as several of these vascular factors exert their combined impact in the venous flow velocity waveform [9, 14]. Under these circumstances a-wave reversal in the DV and progressive pulsatility in the UV is observed. Several observations confirm critical vascular deterioration. Coronary blood flow augmentation enhances the visibility of these vessels [8, 61]. Hepatic artery dilatation provides evidence for an attempt to counteract the hepatic steal from excessive venous shunting by increasing the arterial contribution to liver blood supply [43].

As progressive arterial and venous Doppler abnormalities document the acceleration of fetal effects of placental dysfunction biophysical parameters are lost in a sequential manner which is determined by the relative sensitivity of the central regulatory centers to a decline in pH [9, 51, 52, 78]. Accordingly, loss of fetal heart rate reactivity precedes loss of breathing, gross body movements and tone. Decreasing amniotic fluid volume is independent of biophysical progression and more closely related to cardiovascular deterioration [53, 79].

**Impact of gestational age on diagnosis and management**

Gestational age at onset has important impacts on the clinical presentation and therefore diagnosis and management of FGR.

In early onset FGR prior to 34 weeks’ gestation neonates have significantly lower expected survival rates than appropriately grown counterparts [13]. Gestational age and birth-weight are the primary determinants of outcome [7, 14]. The GRIT study further emphasizes that iatrogenic early delivery carries a higher rate of neonatal complications, whereas delayed delivery carries the risk of inadvertent stillbirth [32]. Each day gained in utero increase survival and intact survival by 1–2% with the highest gain below 28 weeks’ gestation [7]. The majority of these pregnancies with early-onset FGR show significant UA Doppler abnormalities documenting the severity of their placental disease.

Late-onset FGR presenting after 34 weeks does not typically pose a dilemma for delivery timing given the lower neonatal risks. However, late-onset FGR is a significant clinical problem that contributes to over 50% of unanticipated stillbirths at term [27]. This form or FGR often is undetected and offers few Doppler abnormalities and subtle biophysical findings suggesting fetal jeopardy. Isolated brain sparing in the absence of UA index elevation and loss of fetal heart rate reactivity are characteristic abnormalities in these patients [3, 6, 38].

Based on these important clinical differences emphasis in early-onset FGR is safe pregnancy-prolongation whereas in late-onset FGR accurate diagnosis still demands all the attention. A diagnostic approach to the small fetus with a decreased abdominal circumference is displayed in Figure 1 [76].

**Fetal Surveillance**

The goal of fetal surveillance is to prevent stillbirth and irreversible compromise. In pregnancies complicated by FGR this requires adjustment of monitoring intervals based on signs of disease acceleration and the appropriate choice of intervention thresholds. The latter require balance between fetal and neonatal risks specific to gestational age and specifics of the fetal presentation. In early-onset FGR safe prolongation of pregnancy is a primary goal, whereas recognizing the subtle features of progressive compromise appears the major challenge of term FGR.

**Selection of monitoring intervals**

In early-onset FGR the typical longitudinal progression of arterial to venous Doppler abnormalities and finally the deterioration of biophysical variables has been described by several groups [9, 14, 20, 25, 37, 67, 77]. This information is useful for the determination of monitoring intervals. Early-onset FGR appears to progress to abnormal venous Dopplers in two forms that have a latency of 4 and 6 weeks between diagnosis and delivery [77]. Clinical progression can be predicted by UA and DV Doppler. When UA EDV is present and there are no additional obstetric factors requiring consideration, weekly surveillance is likely appropriate. Loss or reversal of EDV, increasing DV Doppler indices, and decreasing amniotic fluid volume indicate disease acceleration and require shortening of the monitoring intervals up to
Figure 1 This figure displays a decision tree following the evaluation of fetal anatomy, amniotic fluid volume, umbilical and middle cerebral artery Doppler. The most likely clinical diagnosis based on the test results is presented on the right-hand side. A high index of suspicion for aneuploidy, viral and non-aneuploid syndrome needs to be maintained at all times. AFI = amniotic fluid index, A/REDV = absent/reversed end-diastolic velocity.

daily monitoring if delivery cannot be justified because of severe prematurity. Such an integrated monitoring approach as shown in Figure 2 can safely delay delivery for up to 2 weeks compared to traditional monitoring – an interval that has significant survival impacts in pregnancies presenting before 28 weeks’ gestation [10].

In late-onset FGR, the typical sequence of umbilical to venous Doppler abnormalities is lacking and latency between diagnosis and delivery may be up to 9 weeks [6, 77]. However, isolated new onset brain sparing, decreasing amniotic fluid, loss of heart rate reactivity and absent fetal breathing movements have all been described more frequently as preceding unexpected stillbirth (Figure 3) [6, 38]. Accordingly, weekly surveillance may be insufficient when these abnormalities occur and twice, or even three times, weekly monitoring may be required. Therefore, adjustment of monitoring intervals more likely relies on middle cerebral artery Doppler than in the preterm FGR fetus. Unfortunately, monitoring protocols have not been evaluated with these important clinically different early- and late-onset FGR.

Delivery timing – selecting intervention thresholds

Delivery thresholds are determined by the balance of fetal and neonatal risks and are therefore particularly challenging in early-onset FGR. In these pregnancies, the importance of safe pregnancy prolongation is counterbalanced by the challenge to select appropriate surveillance intervals to avoid inadvertent stillbirth. In preterm FGR, it is clear that progression to venous Doppler abnormalities significantly increases the risk of fetal acidemia, and additional deterioration of the biophysical profile score (BPS) and/or the computerized CTG can be considered as prelabor evidence of acidemia [14, 62, 76, 78]. In addition, the risk of stillbirth increases if these abnormalities persist [6, 14, 37]. The discussion on the optimal delivery trigger is based on the assumption that fetal deterioration has independent adverse impacts on neonatal outcome.

Although management protocols and delivery triggers were not standardized, the GRIT study has been very important for clarifying the effect of delivery timing on infant outcomes. This study confirmed prior results from observational studies that earlier delivery is associated with higher neonatal mortality and an increased neurodevelopmental delay secondary to prematurity-related complications [32, 74]. FGR neonates delivered before 26 weeks and/or with a birthweight <500 g have survival chances below 50%. Therefore, individualization of care in these pregnancies needs to be discussed with the patient including the option of non-intervention [7]. Between 26 and 29 weeks each day in utero improves survival up to 2% and delaying delivery until biophysical parameters become abnormal can potentially prolong pregnancy up to 10 days with an estimated 20% increased survival [10, 20]. Only after 28 weeks does venous Doppler deterioration have an additional impact on neonatal complications [7, 14] and delivery timing may be improved by considering venous Doppler parameters. This approach is currently being evaluated in the trial of umbilical and fetal flow in Europe [47].

Intervention thresholds are far less challenging in late-onset FGR where the emphasis should be on detection and determination of surveillance intervals because gestational age plays a minor role in determining outcome.
Figure 2  The management algorithm for pregnancies complicated by fetal growth restriction is based on the ability to perform arterial and venous Doppler as well as a full five component biophysical profile score. This is the typical management approach we practice at the University of Maryland, Baltimore for preterm growth restricted fetuses (unless otherwise indicated). Max = maximum, A/REDV = absent/reversed end-diastolic velocity, BPS = biophysical profile score, DV = ductus venosus, MCA = middle cerebral artery, NICU = neonatal intensive care unit, tid = three times daily, UA = umbilical artery.

Neurodevelopment in FGR – a major concern

Prior studies suggested that fetal acidemia has a stronger adverse impact on neurodevelopment than hypoxemia alone [71]. Accordingly, it has been assumed that clinical deterioration up to the point of fetal acidemia is justifiable in early-onset FGR because the prematurity related neonatal risks and impact on neurodevelopment are much higher [10, 14, 32, 47, 74]. Follow-up studies that suggested a stronger impact of UA-AREDV on neurodevelopment had the disadvantage that venous Doppler and BPP were not concurrently evaluated [60]. More recently, it has been confirmed that gestational age and birthweight are significant determinants of neurodevelopment in FGR [11, 39, 74]. Moreover, UA-AREDV (i.e., the severity of placental dysfunction), before the onset of further fetal deterioration was identified as the only prenatal variable with an independent impact on neurodevelopment [11]. Even in mild FGR evidence of redistribution is associated with abnormalities in neurodevelopment [24, 63, 65].

These findings are significant because they suggest that placental dysfunction can impact neurodevelopment before fetal manifestations become clinically apparent and especially before clinical management decisions on delivery timing become relevant in early-onset FGR. This underscores the importance of research into early screening and prevention strategies especially for early-onset FGR. In this respect, recent studies suggest that the combination of maternal risk factors, biomarkers of placentalation and uterine artery Doppler studies can identify patients at high risk in the first trimester. This is a critical observation, since first trimester therapeutic intervention in high-risk groups appears to offer the greatest impact on reducing the risk of subsequent placental disease.

Summary

The underlying mechanisms and clinical deterioration of growth-restricted fetuses due to placental dysfunction has been better clarified over the last few years. Changes in the cardiovascular system allow monitoring of disease acceleration, whereas deterioration of biophysical variables occurs later and confirms increasing risk for acidemia and stillbirth. Early- and late-onset FGR is associated with strikingly different responses to placental dysfunction. Early-onset typically progress to venous Doppler abnormalities whereas late-onset FGR has very subtle vascular and biophysical features of deterioration that may escape detection. In early-onset FGR, the high prematurity related impact on neonatal outcome and neurodevelopment forces a management approach that is currently focused on safe pregnancy prolongation. The substantial contribution of late-onset FGR to unanticipated stillbirths highlights the importance of screen-
ment strategies. Prevention and/or the development of intrauterine treatment strategies as delivery thresholds are no longer an issue. Risk for adverse neurodevelopment precedes the clinical deterioration and therefore requires a shift of research focus on prevention and/or the development of intrauterine treatment strategies.

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