Fetal Growth Restriction: An Update on Recent Trends in Management

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ABSTRACT

Fetal growth restriction (FGR) denotes a pathological process in which a fetus does not attain its biologically determined growth potential. It is an important cause of perinatal mortality and morbidity. Till date there is lack of consensus on the definition and management of FGR amongst different obstetrical bodies. This review aims to explore the available literature on the subject in order to help in defining FGR and discuss the latest management protocols.

KEYWORDS: Fetal growth restriction, Umbilical artery Doppler, Ductus venosus Doppler, Middle cerebral artery Doppler.

INTRODUCTION

The definition of fetal growth restriction (FGR) is difficult. As the name implies, a fetus who does not reach its biological growth potential is growth restricted. Different factors are implicated in causation, the most important being impaired placental function. Small for gestational age (SGA) has been defined by thresholds ranging from 10th, 5th or 3rd centile for gestational age. Although the same reference ranges have often been used by investigators for FGR, it is not synonymous with SGA.1 Some FGR fetuses are SGA while 50–70% of SGA fetuses are simply constitutionally small; the fetal growth being appropriate for maternal size and ethnicity.2

This review aims to consolidate the existing information which would help clinicians to differentiate between FGR and SGA. We will also discuss recent management protocols to help time delivery in women with FGR fetus.

DATA IDENTIFICATION

The Cochrane Library, Medline and PubMed electronic databases were searched for original articles, meta-analysis and standard guidelines issued by maternal and fetal medicine bodies. The search was restricted to articles in English language, from January 1990 to January 2018, and confined to humans. Databases were searched using relevant MeSH terms, including all subheadings and this was combined with a keyword search. Search words included ‘fetal growth restriction’, ‘small for gestational age’, ‘fetal Dopplers’, ‘umbilical artery (UA) Doppler’, ‘middle cerebral artery (MCA) Doppler’ ‘ductus venosus (DV) Doppler’.

BACKGROUND

Small for gestational (SGA) fetuses can be classified into the following:

1. Constitutionally small fetus.
2. Non-placenta mediated growth restricted fetus (e.g. structural or chromosomal anomaly, inborn errors of metabolism and fetal infection).
3. Placenta-mediated FGR.

Traditionally, all SGA fetuses have been considered to be at increased risk of perinatal mortality and morbidity. However, most of the adverse outcomes are concentrated in FGR.2

FGR can have two different presentations; early or late onset FGR. An arbitrary limit of 32–34 weeks has been assigned for this differentiation. The natural history, diagnosis and management differs for both entities.

Early onset FGR represents 1/3rd of the total cases of FGR and in almost half of the cases, has an association with early onset pre-eclampsia and severe placental insufficiency. The umbilical artery Dopplers become abnormal early due to severe hypoxia and systemic
cardiovascular adaptation in these cases and it is associated with high fetal mortality and morbidity.³

Later onset FGR constitutes majority of FGR [almost two-thirds]. The placental disease is usually milder with less than 10% cases associated with late pre-eclampsia. Despite the seemingly innocuous nature, there is risk of acute fetal deterioration especially in association with labor. The natural history is unpredictable and advanced signs of fetal deterioration with ductus venous Doppler changes as seen in early onset FGR are almost never observed in late onset FGR.³,⁴

**PATHOPHYSIOLOGY**

**Fetal Arterial Blood Flow Redistribution**

The sequence of events in FGR secondary to placental insufficiency starts with increased resistance in umbilical artery, progressing on to absent diastolic flow and finally reversal of flow. The increase in impedance in the umbilical artery is followed by increase blood flow to vital fetal body organs, i.e. brain, myocardium, adrenal glands and spleen which is reflected by decreased systolic diastolic ration in the MCA doppler. There also occurs reduction in the perfusion of the kidneys, gastrointestinal tract and the lower extremities. This whole phenomena of change in blood flow at various sites is known as arterial redistribution or ‘centralization of flow’. It is hypothesized that altered partial pressures of oxygen and carbon dioxide stimulate chemoreceptors to allow preferential delivery of nutrients and oxygen to vital organs, thereby compensating for diminished placental resources.⁵

This arterial redistribution is best monitored by MCA Doppler as already discussed above. The compensation by increased fetal cerebral blood flow distribution is, however limited and a plateau in cerebral blood flow reaches in 2 weeks, before development of severe jeopardy to the fetus. Therefore, arterial vessels are considered unsuitable for longitudinal monitoring of FGR fetuses. Cardiac and venous velocity waveforms give more information regarding fetal well-being or compromise.⁵

Pathological fetal heart rate patterns are evident late in the sequence of deterioration. An average time interval between onset of abnormal umbilical artery Dopplers and onset of late fetal heart rate decelerations is around 2 weeks, but this is highly volatile and may be considerably shorter in late onset FGR as compared to early onset FGR. It is seen that the tolerance of fetus to hypoxia decreases with advancing gestation.

**Measurement of Fetal Dopplers**

Umbilical artery Doppler is a measure of the resistance to flow in the fetal side of placenta. There are several methods of analyzing umbilical artery waveforms (Fig. 1), viz. systolic to diastolic ratio (S/D), Pulsatility index (PI = systolic – diastolic/mean) and Resistance index (RI = systolic – diastolic/systolic). PI has been accepted as the best method as it is independent of the angle of insonation and can be used even if there is no diastolic flow. The best measurement of umbilical artery doppler is obtained in a free loop of umbilical cord. Measurements closer to fetal insertion will show higher resistance and those closer to placental insertions will show lower resistance. The Dopplers should be obtained when fetus is not moving and particularly in the absence of respiratory movements. Several measurements taken at different places ensure that a correct result is obtained.

Umbilical artery Doppler is the only method that provides both diagnostic and prognostic information for the management of FGR. It is used for identification of FGR and the progression of umbilical artery Dopplers can help in prognostication. Absent end diastolic flow (AEDF) or reversed end diastolic flow (REDF) in the umbilical artery usually appear at an average of 1 week before acute deterioration of fetus.⁶
It is important to understand that umbilical artery shows increased resistance only when at least 60% of the placental vascular bed is obliterated. This diminishes the importance of umbilical artery doppler as a marker in late onset FGR because these fetuses are usually afflicted with only mild placental disease.

Centralization of flow or ‘brain-sparing effect’ is a fetal hemodynamic change characterized by increased oxygen to fetal brain to compensate for a decreased transfer of oxygen across the placenta. This is seen as decreased resistance in fetal MCA which essentially is a marker of brain vasodilatation and hypoxia. Altered MCA Doppler (Fig. 2) is a late manifestation but has reasonable specificity. It is useful in late-onset FGR, independent of umbilical artery doppler which may often be normal.

Assessment of ductus venosus waveforms gives information about venous side of fetal circulation (Fig. 3). The passage of blood through narrow part of ductus venosus shows continuous uninterrupted forward flow during cardiac cycle and gives a unique appearance of turbulence. The maximal velocity in the waveform corresponds to ventricular systole and minimum velocity to the right atrial contraction. The peak systolic velocity in ductus venosus is in the range of 40–80 cm/second. Normal venous flow suggests continuing fetal compensation. In the final stages of fetal compromise, when the fetal cardiac function is affected, there is breakdown of hemodynamic compensatory mechanisms leading to interrupted blood flow in ductus venosus progressing to reversed flow during atrial contraction. A sudden increase in pulsatility of ductus venosus waveform, accompanied with loss of α-wave precedes the onset of pathological fetal heart rate patterns and decreased short-term variation (STV). Reversal of flow in ductus venosus is an ominous sign of impending fetal death. Ductus venosus is therefore considered the strongest single doppler parameter to predict short-term risk of fetal death in early onset FGR. Absent or reversed flow during atrial contraction is associated with perinatal demise independent of gestational age of the fetus, with a sensitivity of 40–70%. The trial of umbilical and fetal flow in Europe (TRUFFLE) trial concluded that timing of delivery based on late changes in the ductus venosus waveform might produce an improved developmental outcome at 2 years of age.

Aortic Isthmus (AoI) Doppler can be used in prediction of fetal mortality and neurological morbidity in early onset FGR. It is a sign of advanced deterioration, which appears after redistribution of flow is observed in MCA. However as it precedes ductus venosus abnormalities by a week, it is not a short-term indicator of stillbirth risk. Its reversal is more important in prediction of late neonatal neurological injury. Gratacos et al. suggested that AoI be incorporated in clinical protocols of Doppler and reverse AoI could be used to time elective delivery beyond 34 weeks.

Amniotic fluid index (AFI) is a parameter for measurement of chronic hypoxia. There is a progressive decrease in the AFI levels and longitudinal studies have
shown 20–30% of fetuses to have oligohydramnios, a week before acute deterioration.21-23 AFI is a component of biophysical profile (BPP). A reduced AFI is associated with abnormal Apgar score at 5 minutes.24

## SGA or FGR? The Vital Question

Diagnosis of a SGA fetus usually relies on ultrasound measurement of fetal abdominal circumference (AC) or estimation of fetal weight (EFW) as the clinical examination in cases of SGA is unreliable. Fetal arterial Doppler studies are useful to differentiate between SGA fetuses and FGR fetuses. In the hypoxemic group, due to impaired placental perfusion, the cerebroplacental ratio is low.

## Defining FGR

Till recently, there was no gold standard to define FGR. A Delphi consensus was conducted in 2016 to agree to a definition of FGR and the designation between early and late onset FGR.25 Early FGR was defined till 31 weeks 6 days while at 32 weeks or later was termed late FGR.

### Criteria for definition of early FGR:
- AC/EFW < 3rd centile or UA-AEDF
  - Or
- AC/EFW < 10th centile combined with
  - Uterine artery PI > 95th centile and/or
  - Umbilical artery PI > 95th centile

### Criteria for definition of late FGR:
- AC/EFW < 3rd centile
  - Or
- At least 2 out of following 3 criteria should be present
  1. AC/EFW < 10th centile
  2. AC/EFW crossing centiles > 2 quartiles on growth centiles
  3. Cerebroplacental ratio < 5th centile or umbilical artery PI > 95th centile

## Management

The first aim of management should be differentiation between SGA and FGR. The second aim is to identify fetuses at risk of fetal injury or death. The most important decision in FGR management is the timing of delivery. While in a fetus near term this decision is easy, the dilemma remains as to when to deliver a very preterm fetus [<33 weeks]. In general, a balance should be made between iatrogenic preterm delivery and its profound consequences with the intrauterine hostile environment because of prolonged exposure to hypoxia and malnutrition. Despite a number of surveillance tests available the controversy remains regarding the best combination of tests to time delivery. Gratacos et al.17 proposed a stage-wise management of FGR which can be adapted to suit the low-resource settings of developing countries.

With the identification of a small fetus, fetal Dopplers should be measured in order to ascertain whether a fetus is SGA or FGR. As SGA fetuses also have risk of higher adverse outcome, they should be monitored two weekly with growth scans and fetal Dopplers, and should be considered for delivery at 40 weeks.26

### Stage-wise Protocol for an FGR Fetus (Table 1)17

<table>
<thead>
<tr>
<th>Stage of FGR</th>
<th>Doppler frequency recommended</th>
<th>Steroid cover</th>
<th>Magnesium sulphate cover</th>
<th>Vaginal delivery/cesarean section (CS)</th>
<th>Earliest gestation at which termination advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Weekly</td>
<td>–</td>
<td>–</td>
<td>Vaginal delivery may be tried</td>
<td>37 weeks</td>
</tr>
<tr>
<td>II</td>
<td>Biweekly</td>
<td>+/-</td>
<td>–</td>
<td>Cesarean Section</td>
<td>34 weeks</td>
</tr>
<tr>
<td>III</td>
<td>1–2 days</td>
<td>+</td>
<td>+</td>
<td>Cesarean Section</td>
<td>30 weeks</td>
</tr>
<tr>
<td>IV</td>
<td>12 hours</td>
<td>+</td>
<td>+</td>
<td>Cesarean Section</td>
<td>26–28 weeks</td>
</tr>
</tbody>
</table>
Stage II FGR (Severe Placental Insufficiency): This is defined by umbilical artery absent diastolic velocity or reverse AoI doppler. These babies should be recommended to be delivered beyond 34 weeks. Monitoring twice a week is deemed appropriate, and elective cesarean section should be planned.

Stage III FGR (Advanced Fetal Deterioration, Low Suspicion of Fetal Acidosis): The hallmark is reverse umbilical artery flow or ductus venosus PI > 95th centile. There is a high risk of stillbirth and poor neurological outcome. However, as signs of impending fetal demise are still not present, efforts should be made to prolong pregnancy till atleast 30 weeks. Monitoring every 24–48 hours depending on clinical picture should be done. An elective cesarean section after steroid cover is recommended. Magnesium sulphate is recommended for neurological protection.

Stage IV FGR (High Suspicion of Fetal Acidosis and High-risk of Fetal Death): The most important feature is reverse atrial flow in ductus venosus. This is followed closely by reduced STV [<3 ms] in computerized cardiotocography and spontaneous fetal heart rate decelerations. The latter is an ominous sign and if present, is indicative of impending fetal death. The baby should be delivered, if more than 26 weeks, by cesarean section. Steroid and magnesium sulphate cover is recommended. The infant survival may approach 50% at 26–28 weeks and parents should be counseled to this end.

CONCLUSION
Fetal growth restriction is a major cause of perinatal mortality and morbidity and its proper management is an essential quality indicator of antenatal care. The accurate and timely detection remains a significant challenge in obstetrics. The key points of care include the following:
1. Differentiation between SGA and FGR.
2. Antenatal monitoring by serial biometry and fetal Dopplers on USG.
3. Timing of delivery according to abnormal blood flows in ductus venosus Doppler.

REFERENCES

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