



Current Trends in Management of Fetal Growth Restriction

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Abstract Fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) are the terms used for a fetus which has not attained its full growth potential. FGR fetus is associated with high perinatal and neonatal morbidity and mortality, besides long term neurological handicap because of in utero hypoxia. Three decades of research has indicated that almost all treatment strategies are ineffective in treating FGR. Panorama of management includes identifying women at risk, correct dating, distinguishing between a constitutionally small and a true FGR, monitoring for fetal hypoxia, growth, and a timely intervention to avoid death or damage.

Keyword Fetal Growth Restriction · Intrauterine Fetal Growth Restriction · Intrauterine Growth Retardation

Introduction

Fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) are the terms used for a fetus which has not attained its full growth potential, usually less than 10 centile at a frequency of 10 % of all pregnancies [1]. FGR is associated with high perinatal and neonatal mortality and morbidity, besides long term neurological handicap. These babies also suffer from metabolic syndrome in adult life, a disease with its origin in utero.

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Disappointingly, treatment strategies are largely ineffective, therefore, the crux of the management is monitoring for fetal hypoxia and a timely intervention to deliver.

Etiology

Etiology may be due to maternal, fetal, or placental disorders [2]. These are set in Table 1.

Nomenclature

There is a change in thinking on the nomenclature of FGR. Symmetrical and asymmetrical terms are no longer used because majority of asymmetrical FGRs become symmetrical later and asymmetrical ones do not do better than symmetrical ones, unlike what was thought earlier. Currently, FGR is classified as early onset (onset < 34 weeks gestation, usually starting in mid-trimester) and late onset (onset \geq 34 weeks gestation). Early onset FGR differs from late onset one in its response to hypoxia. Early onset FGR fetus responds to hypoxia/chronic deprivation in a hierarchical manner from compensatory to a decompensatory phase. These changes are depicted in Fig. 1 [3].

Usually, early onset FGR shows the above mentioned changes from arterial to venous circulation but at times, cardiovascular (Doppler) and behavioral response of fetus (BPP) can occur independent of each other resulting in discordant Doppler and BPP changes. Therefore, an integrated approach using multivessel Dopplers and BPP is the recommended management practice.

In late onset FGR, sequential changes from arterial to venous circulation are absent. Umbilical artery Doppler is usually normal in up to 20 % of cases. Cerebral

Table 1 Etiology of FGR

Conditions	Causes
Maternal	Chronic hypertension, pregestational diabetes, cardiovascular disease, substance abuse, autoimmune conditions
Fetal	Infection, malformation, aneuploidy
Placental	Chorioangioma, infarction, circumvallate placenta, confined placental mosaicism, obliterative vasculopathy of placental bed

Decrease in umbilical venous volume & liver size
 Abdominal circumference (AC) lag – 1st biometric sign
 Increased umbilical artery doppler resistance
 Flow redistribution – Middle Cerebral Artery (MCA)
 compensatory vasodilatation
 Decreased amniotic fluid
 Absent end diastolic velocity (AEDV) in umbilical artery
 Loss of fetal movement, variability
 Reversed end diastolic flow in umbilical artery
 Ductus venosus [a-wave absent or reversal]
 Biophysical profile (BPP) or score (BPS) decline
 non reactive NST, late decelerations
 Fetal circulatory collapse & death

Compensation to Decompensation

Fig. 1 Sequence of changes in response to hypoxia/chronic deprivation of fetus

redistribution can occur with normal umbilical artery Doppler. Decreased cerebroplacental ratio (CPR) precedes middle cerebral artery (MCA) dilatation. Such a decrease should alert the obstetrician that brain sparing is imminent. Late onset FGR is a significant clinical problem that frequently goes undetected and can contribute to over 50 % of unanticipated still births [2, 4].

Management

First step in the management is correct dating, for which known last menstrual period (LMP), regular cycles, clinical examination in early pregnancy, and most importantly, ultrasound dating in first or early second trimester, are the tools.

Second step is to establish the presence of FGR by using fetal weight or biometry less than 10th, 5th or 3rd centile preferably on a customized growth chart which takes into account fetal growth potential based upon mother's height, prepregnancy weight, parity and ethnicity. A 10th centile, cutoff is the usual practice in establishing FGR.

Third step is to differentiate between true growth restriction (FGR and abnormal Doppler flows) and constitutionally small fetus—small for gestation age (SGA) (FGR and normal Doppler flows). Fetuses at 3rd centile or less are usually true FGRs.

The Porto study [5] has indicated that between 3rd and 10th centile FGR incidence of adverse outcome is 2 %, at 3rd centile, it is 6.2 % and if 3rd centile growth and Dopplers >95th centile, absent or reverse flows in umbilical arteries, it is 16.7 %.

Fourth step FGR is established; viable gestation less than 34 weeks, careful search for fetal anomalies (ultrasonography and fetal echocardiography), and selective investigations for maternal and fetal causes should be done.

Ten per cent of FGRs have congenital malformations; 10–40 % of structurally malformed fetuses will have chromosomal abnormalities as against only 2 % of normally formed fetuses. Chromosomal studies in the fetus are recommended.

Work up for fetal infection should also be undertaken, if clinically suspected. Infections account for less than 5 % of all FGRs.

Needless to say that underlying maternal disease such as hypertension disorders, autoimmune disease etc., if present, should be treated.

Fifth step is the most important step of management, that is, monitoring for fetal hypoxia. An integrated surveillance approach using multivessel Doppler—arterial and venous, BPS, and fetal growth assessment is the recommended practice. Figures 2, 3, 4 indicate a rough management protocol in different scenarios.

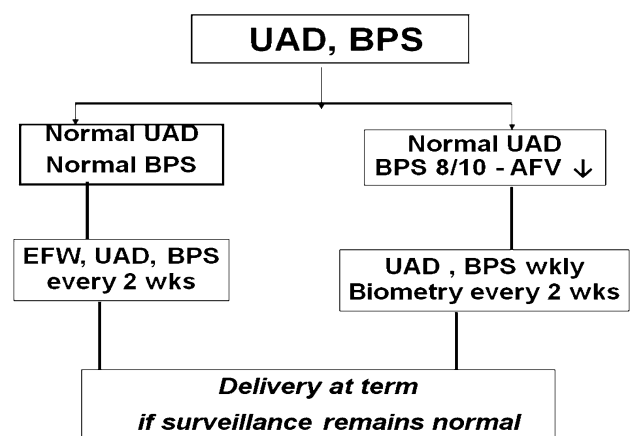
**Fig. 2** Scenario 1. AFV amniotic fluid volume, BPS biophysical score, EFW expected fetal weight, UAD umbilical artery Doppler

Fig. 3 Scenario 2. *AFV* amniotic fluid volume, *BPS* biophysical score, *MCA* middle cerebral artery, *MCAPI* middle cerebral artery pulsatility index, *UAD* umbilical artery Doppler, *UAPI* umbilical artery pulsatility index

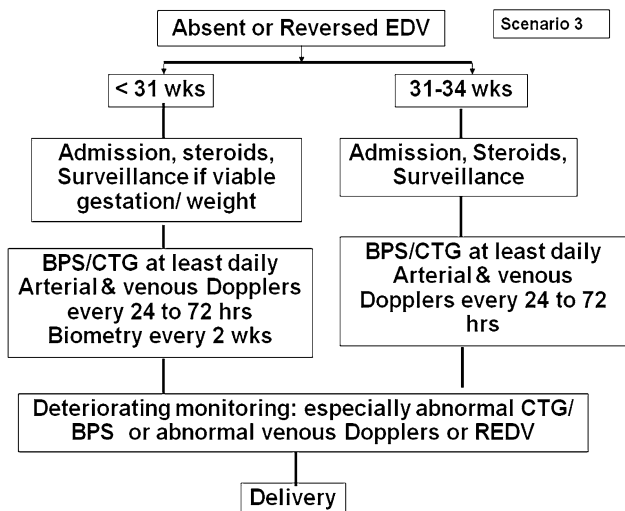
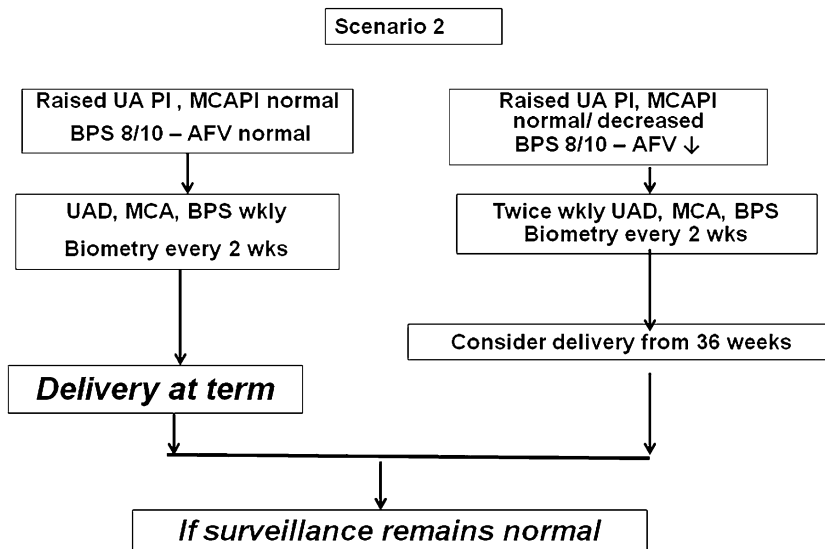


Fig. 4 Scenario 3. *BPS* biophysical score, *CTG* cardiotocography, *REDV* reverse end diastolic velocity

Scenario 1

FGR Fetus with Normal Umbilical Artery Doppler and BPS

This, most probably, is an SGA fetus that can be safely monitored every 2 weeks with umbilical artery Doppler, BPS and growth assessment. Pregnancy can be taken to term in the event of normal findings.

FGR Fetus with Normal Umbilical Artery Doppler but Reduced Amniotic Fluid Volume

This fetus needs weekly surveillance. Pregnancy can also be taken to term.

Scenario 2

FGR Fetus with Increased Umbilical Artery Resistance but not Absent Flow, Normal MCA Doppler and Normal Amniotic Fluid Volume

This case scenario depicts a fetus which is compromised but has not redistributed its cardiac output. Weekly monitoring is required with umbilical artery Doppler, MCA Doppler and BPS. Fetal growth check is recommended every 2 weeks. Pregnancy can be taken to term if surveillance remains normal.

FGR Fetus with Raised Umbilical Artery Doppler, Dilated Middle Cerebral Artery and Reduced Amniotic Fluid Volume

FGR fetus that has raised umbilical artery Doppler, dilated MCA and reduced amniotic fluid volume is a fetus which has redistributed its cardiac output, therefore has some degree of hypoxemia. Fetus must be monitored biweekly with a plan to deliver by 36 weeks.

Scenario 3

Fetus with Absent End Diastolic or Reverse Flow in Umbilical Arteries

When 70 % of placental circulation is affected, absent or reverse flow in umbilical artery occurs. There is significant degree of hypoxemia. When venous circulation gets affected, acidemia is likely. Therefore, daily monitoring with arterial and venous Doppler is recommended, if the fetus is premature. Delivery is planned by 32–34 weeks.

Timing of Delivery

It is an important issue in the management of FGR. Delivery should be considered whenever risk of fetal death exceeds that of neonatal death. Gestational age and individual NICU facilities are important contributors to survival rates.

The growth restriction intervention trial (GRIT) [6, 7], while addressing the issue of immediate versus delayed delivery in severe FGRs, has indicated that early delivery group had fewer stillbirths but more neonatal deaths, whereas, delayed delivery resulted in some antepartum deaths. Long term outcomes at 13 years remained the same.

Generally, reverse end diastolic velocity (REDV) is delivered at 32 weeks, absent end diastolic velocity (AEDV) at 34 weeks and other FGRs with high umbilical artery Doppler indices but not absent and other tests remaining normal, are delivered at 37 weeks.

In general, whenever antepartum monitoring tests indicate imminent hypoxia, such as abnormal cardiotocography (CTG), BPS < 4, severe oligoamnios, ductus venosus $\geq 95\%$ and umbilical vein pulsations—fetus should be delivered. No interval growth in 2–3 weeks, also, is an indication for delivery.

Regarding mode of delivery, cesarean section is the preferred mode because these fetuses are hypoxic, oligoamniotic and, therefore, withstand labor poorly.

Normal delivery can be done if cervix is ripe and facilities for continuous electronic fetal monitoring are available. It is advisable to send umbilical cord blood analysis to establish neonatal base line status.

For late onset FGR, monitoring twice or thrice a week with umbilical artery Doppler, MCA Doppler and CPR is recommended. Delivery should be considered at 37 weeks.

Therapy for Treatment of FGR

Many therapies have been tried. Bed rest, maternal nutrient supplements, calcium channel blockers, beta mimetics, maternal oxygenation, plasma volume expansion, and transcutaneous electrostimulation have not proven to have any benefit for treatment of FGR, by Cochrane systematic reviews [8–14].

Sildenafil citrate therapy for treatment of severe early onset FGR has been reported to have improved fetal growth in a recent study [15]. Strider trial, launched in 2014, will address the issue of sildenafil in improving outcomes, growth velocity, and reducing serious adverse outcomes in severely growth restricted fetuses [16].

Antenatal glucocorticoids confer similar benefits of reducing respiratory distress syndrome and its related morbidities, when given to preterm FGR fetuses, as they do in

preterm adequate for gestational age fetuses. Three studies have shown that fetuses with AEDV often show a transient improvement in blood flow after glucocorticoid administration, and fetuses that did not show improvement appeared to have poorer outcomes [17–19].

Magnesium sulphate used prior to delivery in gestational ages <34 weeks reduces death, cerebral palsy, and gross motor dysfunctions in neonates [20]. The recommended dose is 4 g as a loading dose intravenously, followed by 1 g/h for a maximum of 24 h.

Antithrombotic Therapy and FGR

Aspirin

When started at an early gestational age (<16 weeks), aspirin has shown to reduce perinatal death, pre-eclampsia and adverse outcome in women who are at risk of developing FGR [21–23]. In fact, Royal College of Obstetricians and Gynecologists (RCOG) suggests screening for FGR in early pregnancy by risk factors, and, in the presence of three minor or one major, aspirin prophylaxis is recommended [24].

Heparin

A recent Cochrane review has suggested that use of heparin also appears to be associated with a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 weeks and infant birth weight below 10th centile for gestational age in women considered at risk of placental dysfunction [25].

Conclusion

Optimal management of suspected FGR involves identifying women at risk, correct dating, distinguishing between constitutionally small and true FGRs, monitoring for fetal well being, growth, and a timely intervention.

Conflict of interest None.

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