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MINI REVIEW

Fetal Growth Restriction

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Abstract
Fetal growth restriction (FGR) is a failure of fetus to reach its expected biological growth, based on its genetically predetermined potential. Whenever effective fetal weight is less than, 10th percentile or 2 standard deviation of population-specific growth curve, it is considered small for gestational age (SGA). The FGR is associated with poor somatic growth with concomitant changes in placental and cerebral blood flow and/or biochemical markers along with EBW < 3rd percentile. It is an important cause of perinatal mortalities and morbidities. Ultrasound plays a definitive role in diagnosis and its management. This article is aimed to mini review the published guidelines on FGR and SGA and summarize the areas of consensus.

Keywords FGR · SGA · IUGR · Growth potential

Definition

The definition of fetal growth restriction (FGR) is a controversial issue [1]. With the advent of higher-resolution ultrasound machines, understanding has been in a constant state of evolution. "The term small for gestational age (SGA) is used for fetus with a birth weight < 10th customized percentile or less than 2 standard deviation for that population reference, and it **may not** be pathological. FGR is pathological state, based on additional criteria of EBW < 3rd percentile, poor somatic growth and compensated umbilical/cerebral blood flow [2]. Recently, however, additional parameters such as placental biomarkers, biochemical factors, markers of inflammation in the mother and biometrics including skin fold thickness and other anthropometric parameters of the neonate have been added to assess this condition [3, 4].

The term low birth weight fetus is described as birth weight < 2.5 kg irrespective of gestational age, gender, ethnicity and other associated clinical conditions. It includes constitutionally small, premature, SGA and FGR babies."

The ACOG 2013 Guidelines [3, 5] replaced the term "IUGR" with "FGR," but NICE and Barcelona protocols still continue to use the term "IUGR."

Incidence

The incidence is around 3–9% in higher socioeconomic group, whereas the rate is as high as 30% in low socioeconomic group [6]. Almost 20–50% stillborns are growth retarded. After prematurity, this is the second commonest cause for perinatal mortality [5].

Pathophysiology

Fetal growth is a complex and ill understood interplay of (a) maternal metabolism/substrate availability (b) placental functions and inflammation; and fetal adaptability to both. Normal fetal growth up to 20 weeks of gestation is mainly by cellular hyperplasia, from 20 to 28th weeks is by hyperplasia and hypertrophy and from 28 weeks onwards, by hypertrophy with rapid accumulation of fat, muscles and connective tissues. Ninety percent of fetal weight gain happens in later half of pregnancy. Fetal growth accelerates from about 5 g per day at 14–19 weeks of gestation to 10 g per day at 20–29 weeks, peaks at 25–35 g per day at 30–36 weeks and afterwards growth rate decreases to 15 g per day.

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Symphysiofundal height increases by about 1 cm per week between 14 and 32 weeks. Abdominal girth increases by 1 inch per week after 30 weeks. Growth of the fetus is a complex process and is dependent on various factors. It includes the interplay of pancreatic hormone, i.e., insulin, hormones secreted by the thyroid, adrenal and pituitary glands. Among these, insulin-derived growth factor-I (IGF-I) is probably the most significant. IGF-1 influences amino acid and glucose transport across the placenta [7] and plays a role in neurodevelopment of the fetus by promoting brain growth, by increasing the number of oligodendrocytes, neuronal number and increasing fine branching of axons at their terminal ends [8]. Some other factors proven to influence the pathogenesis of FGR are vasoactive intestinal polypeptide (VIP), insulin-like growth factor-II and insulin-like growth factor binding proteins-2 and 3 [9, 10].

Pregnancy-associated plasma protein-A [PAPP-A] is secreted by the decidua into the maternal circulation. Low circulating levels of it, in early stages of pregnancy, is associated with increased risk of FGR [10].

Pathophysiologically the FGR is symptom of underlying disorder inhibiting the growth potential of fetus. Conversion of spiral artery into utero-placental sinuses and its proper invasion by trophoblastic villi is fundamental for utero-placental circulation; hence, blood flow study by color Doppler is of great help in understanding the severity of it.

Three main types of causative factors associated with FGR are as per Table 1.

Classification

FGR is classified in the existing literature by various ways. For easier understanding, following classification can be considered:

1. According to fetal biometry [12]

   (a) Type I/symmetric:
   Incidence is 20–30%, usually early onset with intrinsic genetic disorder or infections to fetus. Ponderal index is normal, whereas biparietal diameter (BPD), femur length (FL), head and abdominal circumference (HC and AC) are proportionally reduced. Prognosis is poor.

   (b) Type II/asymmetric
   Usually later onset, 70–80%, utero-placental insufficiency/extrinsic factors are associated. Ponderal index is low (< 3), whereas BPD, HC and FL are normal. Abdominal circumference is decreased. Brain sparing growth is there, with advancing pregnancy, and features of malnutrition are exaggerated. Prognosis is better.

   (c) Type III
   Initially symmetric but later on asymmetric. Etiology is mixed.

2. According to etiological factors

   - Intrinsic due to fetal factors
   - Extrinsic due to placental/maternal/environment factors
   - Combined
   - Idiopathic

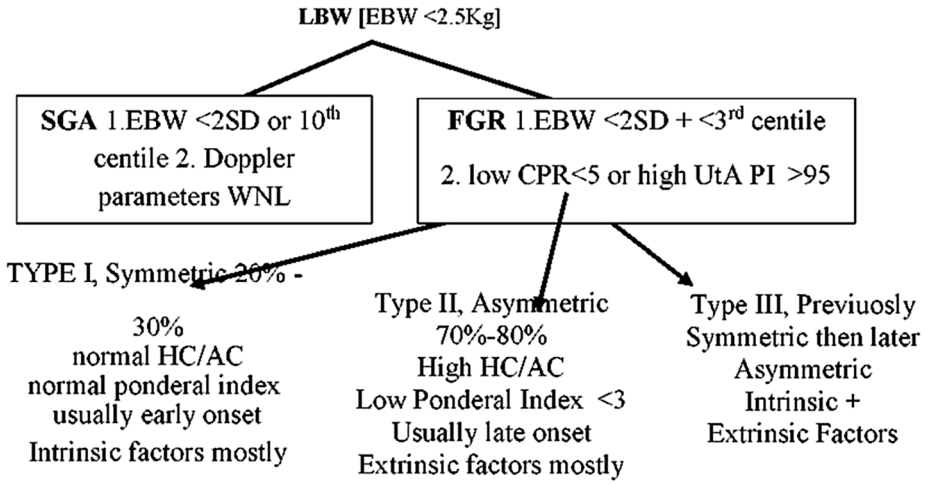
3. According to Barcelona study group [13], FGR has been divided into two categories:

   FGR = Low CPR (< 5) or, High UtA PI (> 95)
   or, EFW < 3rd centile

   - Early onset—onset is less than 32 weeks, disease is of genetic or fetal origin. Hypoxia is present and significant; however, fetus tolerates the hypoxia due to cardiovascular adaptations. It is associated with high mortality. Management is relatively more complex.
   - Late onset—onset is more than 32 weeks, placental/maternal disease or idiopathic hypoxia may be present. The adaptive mechanisms in this case are mainly by the cardiovascular system, but tolerance to hypoxia is low as no natural history is present. The mortality rates are low; however, the morbidity is high and is associated with poor long-term outcomes.

Table 1 Causative factors for FGR

Group I: associated with maternal utero-placental insufficiency	Group II: alterations in the feto-placental circulations	Group III: genomics and fetal growth inability to reach genetic potential
Chronic hypertension	Weight of placenta (weight < 350 g at term)	Constitutional small
Preeclampsia	Abnormalities in trophoblastic invasion: preeclampsia and placenta accreta	Genetic abnormalities like trisomy 13, 18 or 21, turner's syndrome, triploidy. autosomal deletions, ring chromosomes and uniparental disomy
Chronic renal disease	Chronic low-grade abruption leading to multiple subchorionic hemorrhages, abruption, infarction, calcifications, villitis, chronic villitis of unknown etiology, hemorrhagic endovasculitis, avascular villi, syncytial knots	Congenital abnormalities, including: cardiac, e.g., TOF, transposition of the great vessels and gastroschisis
Diabetes with vascular lesions	Congenital infection, including: CMV, rubella, toxoplasmosis, malaria, congenital HIV infection, syphilis	Genetic syndromes like, Rubenstein-Taybi syndrome, Russell-Silver syndrome, Seckel syndrome, Cornelia de Lange syndrome, Brachmann-de Lange syndrome, Bloom syndrome, Dubowitz syndrome, Johanson–Blizzard syndrome, Roberts syndrome, Fanconi syndrome and Mulibrey Nanism syndrome
Heart disease class III or IV	Placental location/structure: placenta praevia, velamentous cord, single umbilical artery, multiple gestation	Placental genes: over-expression of IGFBP-3 and placenta IGF-2 and under-expression of placental IGF1 and epidermal growth factor (EGF) [11]
Sickle cell anemia and other haemoglobinopathies	Tumors: chorioangiomas, placental haemangiomas, abnormal umbilical cord or cord insertion	Maternal genetic factors: phenylketonuria, leptin under-expression, over-expression of thrombophilia genes, endothelin-1 (ET-1) over-expression [11]
Autoimmune diseases, including: APS, thrombophilia of pregnancy, connective tissue disorder		Fetal genetic factors: low nitric oxide, genetic deletion of IGF1, under-expression of N-terminal parathyroid hormone-related protein, high urinary protein S100B [11]
Severe maternal malnutrition		
Smoking, alcohol ingestion and recreational drugs		



Fetal Consequences

At intrauterine stage, FGR feti are predisposed to an increased risk of fetal morbidity or stillbirth. After birth, they are susceptible to multiple neonatal morbidities leading to early neonatal death [14–16]. The long-term consequences of intrauterine adverse events lead to various metabolic effects, which manifest in extrauterine life. These impacts during the childhood and adult life [17, 18] mainly affect the cardiovascular and central nervous system [19, 20].

Management

Management of FGR is a double-edged sword, a critical decision between avoiding fetal damage or death in utero due to prolongation of pregnancy and the consequences of iatrogenic preterm delivery. This has to be based on assessment of maternal and familial risk factor and nutritional status of the mother, accurate dating of gestational age, plotting of gravidogram, fundal height, cardiotocography (CTG), accurate estimated fetal weight measurement and ultrasound biometric parameters (AC, HC, BPD and FL).

A Doppler ultrasound study to evaluate uterine artery, umbilical artery, middle cerebral artery, ductus venous blood flow velocities and cerebro-placental perfusion ratio give significant outcome prediction and further help in making decision for termination of pregnancy.

In spite of recent advances in the field of FGR, there are no absolute clinical tests for the accurate prediction of it, especially when present in late gestation [14] The high-risk factors [15] for mothers are as per Table 2.

Screening for FGR: To All High-Risk Women

Dual-marker test in maternal serum Idiopathic low PAPP-A or human chorionic gonadotropin (hCG) levels have been correlated with an increased predisposition to placenta-related pathologies. **Erythropoietin** level in cord blood and amniotic fluid is high, which supports the concept of early damage of placenta sufficient to cause erythroblastic response.

Triple/Quadruple marker Increased levels of serum alpha-fetoprotein, hCG or inhibin-A in second trimester.

All the high-risk mothers should be subjected to proper first trimester dating scan by **crown-rump length**. Lagging growth pattern between the first and second trimester plotted using **ultrasound-based growth charts** calibrated for the fetal gender and maternal factors, i.e., parity, height, weight, ethnic origin, presence of hypertension, GDM, smoking, tobacco chewing, etc. Serial fundal height assessment, DFMC, BPP and routine/intermittent third-trimester ultrasound biometry are gold standards.

Uterine artery Doppler Screening for early-onset FGR using Doppler analysis of uterine artery in the second or third trimester leads to detection rate of about 75% and 25%, respectively, The sensitivity is higher in case of early FGR, more so if preeclampsia is also present. The sensitivity, however, is lower in case of late-onset FGR.

Various permutations and combinations comprising of risk factors of the mother, blood pressure and biochemical parameters have been employed for identifying early-onset FGR.

Table 2 High-risk factors [15] for mothers

S. no.	High-risk factors
1	Maternal extreme of ages [< 16 and > 35 years], low socioeconomic and nutritional status, pre-pregnancy BMI < 20, wt < 45 kg and > 75 kg and heavy manual workers
2	Maternal active or passive smoking, alcohol intake, teratogenic drug intake anticancer, anticonvulsants, antimetabolite drugs and folic acid antagonists or illicit/substance abuse in past and present
3	History of growth-restricted fetus or still birth in a previous pregnancy predisposes to a 50% increase in risk of severe growth restriction in subsequent pregnancies, the risk being higher if the past stillbirth had occurred before 32-week gestation
4	Nulligravida and parity more than 5, < 6 months or > 10 years interval between two pregnancies
5	Medical disorder—maternal hypertensive disorders, sickle cell disease, Type II diabetes mellitus, reno-vascular disorders, SLE, antiphospholipid antibody syndrome, bronchial asthma and CVS anomalies
6	Hematologic and immunologic disorders (acquired thrombophilias)
7	Maternal infection (malaria, TORCH, tuberculosis, bacterial vaginosis and UTI)
8	IVF/multiple pregnancy

Diagnosis

Proper Diagnosis is Based on Clinical Monitoring, Serial USG biometry and Doppler Studies

Clinical Monitoring Stationary or falling maternal weight gain during second half of pregnancy, palpation of SFH, abdominal girth, lag in fundal height of 4–6 weeks, easily palpable fetal parts and liquor volume appearing less.

USG biometry and plotting the finding in growth charts, detection of malformations, biophysical activity and then color doppler. Manning's BPP includes non-stress test, fetal breathing movements, fetal movements, fetal tone and amniotic fluid index with score ranging from 0 to 10. However, if oligohydramnios is present it is suggestive of an abnormal BPP regardless of the total score, as stated in modified BPP.

On USG, margin of error is ± 1-week up to 20-week gestation, ± 2 weeks from 20 to 36 weeks, beyond which the error is ± 3 weeks. Abdominal circumference (AC) is the most sensitive indicator.

On color Doppler, four important Doppler flow markers are uterine artery PI, umbilical artery PI, middle cerebral artery flow and ductus venosus flow.

High **uterine artery PI is an** indicator of high resistance flow. High **PI at umbilical artery** signifies placental dysfunction or insufficiency. **MCA Doppler abnormality** is an indicator of fetal hypoxia. RCOG recommends MCA Doppler to time delivery in terms of FGR with normal UmA Doppler [21].

Cerebro-placental ratio (CPR) is calculated as the ratio of MCA-PI/umbilical artery PI and is useful marker for cerebral hypoxia. A value < 1 at term is abnormal. This is the best indicator to pick up vascular insufficiency throughout the pregnancy, i.e., irrespective of gestational age [22, 23].

The constant arterial pressure changes that take place during the cardiac cycle are indirectly understood by studying and interpreting the **ductus venosus (DV)** flow patterns. In case reversal of flow has been established in the umbilical vein and DV, one should consider it as ominous sign of the onset of overt fetal cardiac compromise.

Aortic isthmus (AoI) AoI Doppler is an additional parameter used to study the correlation between the impedance of the systemic vascular system and the vascular supply of the brain. Reversal in the AoI flow is associated with an increased occurrence of fetal mortality and in case of survival, neurological morbidity.

Management

There is no definitive management for FGR except for correction of maternal factors and timely delivery. Supportive management helps to some extent while waiting for fetal lung maturity.

Supportive Management

- Adequate bed rest, preferably in left lateral position to increase blood flow to the uterus.
- Low-dose aspirin 150 mg/day.
- Maternal oxygen therapy, 55% oxygen at a rate of 8 L/min to decrease resistance in placental circulation.
- Maternal hyperailmentation by amino acids, Zn and calcium.
- Nitric oxide donor like L-arginine
- Maternal volume expansion may improve placental perfusion.
- Sildenafil—phosphodiesterase inhibitors, causes more vasodilatation. Dosage is 25–50 mg BD per vaginal or oral.
- Betamethasone/dexamethasone, 48 h prior to planned birth at < 34 weeks.
- Administration of magnesium sulfate as a neuroprotective agent in early-onset FGR.

Decision of timing for termination and mode of delivery is critical for preventing the fetus from further brain injury and risk of prematurity. **An algorithm as per** Fig. 1 can be followed for management. Overall LCSC is considered safe, but vaginal delivery can be planned at tertiary care center for near-term non-compensated feti. Continuous oxygenation of mother, left lateral position, maintaining proper nutrition and hydration, continuous CTG monitoring, no prolongation of first stage of labor, amnioinfusion and cutting short of second stage are mainstay of **vaginal delivery**. The placenta of FGR baby should be examined by a pathologist as it may provide evidences regarding the etiology.

Neonatal Outcome

The features of FGR newborns are quite peculiar; they have a larger head with a wide anterior fontanel, typical facies with an anxious and alert look (old man look), thin umbilical cord, scaphoid abdomen, low subcutaneous fat and muscle mass, loose skin folds, dry-rough skin and long finger nails.

The female neonate is born with poor breast nodule and immature female genitalia. Immediate consequences include hypoxic ischemic encephalopathy, meconium aspiration syndrome, hypoglycemia, hyperglycemia, hypocalcemia, hypothermia, polycythemia, feeding difficulties, jaundice, necrotizing enterocolitis, sepsis, pulmonary hypertension and pulmonary hemorrhage.

Later in life, these children are prone for poor growth and neurodevelopment outcome. They are also predisposed to developing late-onset diseases in their infancy, early childhood and adolescence.

Barker hypothesis [24, 25] suggests that these children in adulthood have a relatively higher incidence of coronary heart disease, hypercholesterolemia, type II diabetes mellitus and hyperinsulinemia.

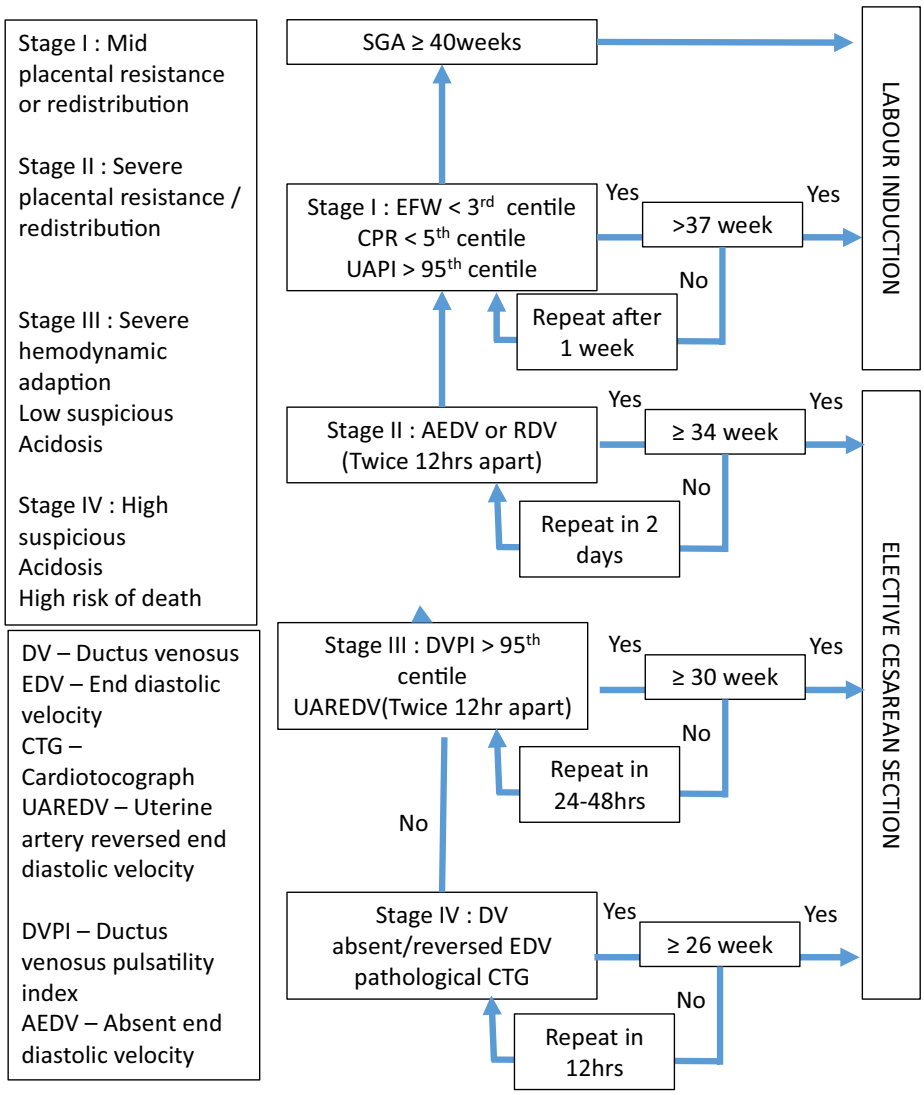


Fig. 1 Comprehensive algorithm of staging and management of FGR

Conclusion

High-risk factors for FGR should be evaluated in all the pregnancies. Accurate diagnosis can be obtained through the use of serial growth charts; DFMC, FHR monitoring by CTG; and Doppler studies of uterine, umbilical, middle cerebral arteries, CPR and flow ductus venosus.

These tests help to differentiate between healthy SGA and pathological FGR and also further prognosis.

The empirical treatment by bed rest in left lateral position, hyperoxygenation, hyperailmentation and nitric oxide donor has limited value. Caesarean section remains the safer mode of delivery.

In FGR babies, early neonatal life may be associated with complications such as HIE, ARDS, hypothermia, hypoglycemia, hyperglycemia, hypocalcemia, exaggerated jaundice, sepsis, necrotizing enterocolitis and pulmonary/intraventricular hemorrhage. Later they are prone for metabolic syndromes, early precipitation of maturity onset disorders and sometimes mental retardation.

The risk stratification coupled with genomic analysis for identification and treatment modalities comprising of nanoparticle delivery designed to modify the specific cell functions may alter the future of FGR pregnancies with improved outcome [14].

Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest.

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