FEDERATION OF OBSTETRIC & GYNAECOLOGICAL SOCIETIES OF INDIA

FOGSI GCPR on Fetal Growth Restriction

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INTRODUCTION

The evaluation of fetal growth is one of the key objectives of the prenatal care. Identification of a small fetus, classifying fetal growth restriction(FGR), understanding the etiology and risk factors , formulating a comprehensive strategy and timing of delivery is imperative to have a successful perinatal outcome. These recommendations have been drafted by a panel of experts from across the country based on the ideal practice while at the same time certain modifications have been suggested to adapt to the varied resource settings in the country. These guidelines provide a road map to practice and by no means are binding for the management of a case of fetal growth restriction where physician experience and individual patient characteristics may warrant deviation from the protocols.

DOCUMENT OUTLINE

SECTION 1. DEFINITION AND CLASSIFICATION

Definition:

FGR is defined as the failure of the fetus to meet its biological growth potential due to a pathological factor.[1] However, assessment of fetal growth potential is very difficult to determine. More often than not, estimates of fetal weight at a given point in time are more readily available than multiple observations of fetal size over time. In clinical practice, small for gestational age (SGA) is defined when the size (biometric evaluation) of the fetus falls below a predefined threshold for its gestational age. This is commonly defined as estimated fetal weight (EFW) or abdominal circumference (AC) below a certain threshold such as the 10th percentile and is used interchangeably quite frequently with FGR. Thus, there is more controversy than consensus about the definition, classification and diagnosis of FGR.

The main distinction between SGA and FGR is that a SGA fetus may be small but not at increased risk of adverse perinatal outcome.[1] In order to differentiate between SGA and FGR in cases in which the fetal size is below the 10th percentile, additional biophysical parameters are required. Many methods have been proposed for this purpose, such as evaluation of fetal growth velocity, use of customized growth charts, however, Doppler velocimetric evaluation of placental and fetal circulations is the most useful criteria to differentiate between the two.

The use of SGA as a surrogate for FGR has several limitations:[1]

- Most SGA fetuses are constitutionally healthy small fetuses, whose smallness is the result of their predetermined growth potential (i.e. false-positive diagnosis of FGR).
- Some growth-restricted fetuses, depending on their original growth potential and timing of insult, may remain above the percentile threshold described above and may thus not be SGA (i.e. false-negative diagnosis of FGR).
- Use of SGA in place of FGR is limited by the accuracy of sonographic fetal weight estimation, which has an estimation error of up to ± 15%–20%.
- The diagnosis of SGA is highly dependent on the growth chart being used, which can therefore have a considerable effect on the proportion of fetuses or infants termed as SGA in a given population.

Table 1.1 Definition of SGA and FGR as proposed by different societies

The definition of FGR varies between different guidelines and author groups.[2]

	SOGC, 2013	RCOG, 2014	French College of Gynecologists and Obstetricians 2015	ACOG and SMFM, 2013	ISUOG 2020	FIGO 2020
Definition of SGA	EFW <10th population centile	Birthweight <10th customized centile	EFW or birthweight <10th population centile	Birthweight <10th population centile	A fetus is considered to be SGA when its size (biometric evaluation) falls below a predefined threshold for its gestational age.	EFW or birth weight below the 10th percentile for gestational age
Definition of FGR	EFW <10th or AC <10th population centiles	EFW <10th customized centile, or AC <10th population centile	EFW <10th customized centile	EFW <10th population centile	FGR is a condition that is frequently, but unhelpfully, defined as the fetus failing to reach its genetically predetermined growth potential. (Recommend to use Delphi consensus defined below)	Small fetus that has failed to achieve its growth potential because of a pathologic process. (Recommend to use Delphi consensus defined below)
Definition of high risk FGR	Not specified	EFW <3rd centile	Evidence of reduced/ arresting of growth with or without abnormal UA or cerebral Doppler, oligohydramnios	Not specified	Not specified	Not specified

The criteria proposed by an international Delphi consensus represent the most recognized definition of FGR. The two main phenotypes of FGR, early and late, differ significantly in many aspects, such as prevalence, prediction by first-trimester ultrasound, gestational age at onset, placental histopathological findings, Doppler velocimetric profile, associated maternal disease, severity and perinatal outcome. The distinction between early and late FGR is usually based on diagnosis before or after 32 weeks gestation.

Table 1.2 Delphi Consensus Criteria for Fetal Growth Restriction and Classification[3]

(In absence of congenital anomalies, based on international Delphi consensus)

Early FGR (Gestational age < 32 weeks) in absence of congenital anomalies	**Late FGR** (Gestational age ≥ 32 weeks) in absence of congenital anomalies
AC/EFW < 3rd centile or UA – AEDF OR 1.AC/EFW < 10TH centile combined with 2.Ut A PI > 95th centile and / or 3.UA PI > 95th centile	AC/EFW < 3rd centile Or at least two out of three of following 1.AC/EFW < 10TH centile 2.AC/EFW crossing centiles > 2 quartiles on growth centiles 3.CPR < 5th centile or UA PI > 95th centile

FGR – Fetal Growth Restriction, AC – Abdominal Circumference, EFW – Estimated Fetal Weight, UA – Umbilical Artery, Ut A – Uterine Artery, PI – Pulsatility Index, CPR – Cerebroplacental ratio

Table 1.3 Main clinical characteristics of early- and late-onset fetal growth restriction[1]

Characteristic	Early-onset FGR	Late-onset FGR
Main clinical challenge	Management	Detection
Prevalence	30%	70%
Gestational age at manifestation	<32 weeks	≥32 weeks
Ultrasound findings	Fetus may be very small	Fetus not necessarily very small
Doppler velocimetry	Spectrum of Doppler alterations that involves umbilical artery, middle cerebral artery and ductus venosus	Cerebral blood flow - redistribution
Biophysical profile	May be abnormal	May be abnormal
Hypertensive disorders of pregnancy	Frequent	Not frequent
Placental histopathological findings	Poor placental implantation, spiral artery abnormalities, maternal vascular malperfusion	Less specific placental findings, mainly altered diffusion
Perinatal mortality	High	Low

SECTION 2: ETIOLOGY AND RISKS FACTORS FOR FGR

ETIOLOGY

FGR is a result of one or more maternal, placental or fetal disorders with significant overlap among these entities, that interfere with the normal mechanisms regulating fetal growth.

Table 2.1 Common Etiologies of Fetal Growth Restriction[4]

Maternal (preplacental) factors	Placental factors	Umbilical cord (post-placental) factors	Fetal disorders
• Hypoxemia (chronic lung disease, high altitude) • Anemia • Smoking, substance abuse (cocaine, methamphetamines) • Malabsorption, poor weight gain • Environmental toxins: air pollution, heavy metals (lead, mercury), perfluorooctanoic acid (PFOA)	• Maternal vascular malperfusion pathology (infarction, fibrin deposition, chronic abruption) secondary to hypertensive disorders in pregnancy • Fetal vascular malperfusion pathology • Chronic placental inflammation (e.g. villitis of unknown etiology) • Confined placental mosaicism	• Increased coiling • Increased cord length • True cord knot • Single umbilical artery • Marginal or velamentous cord insertion	• Genetic disorders (chromosomal, microdeletions/ duplications, single site mutations, epigenetic disorders) • Structural anomalies (e.g. congenital heart disease, gastroschisis) • Congenital infections (cytomegalovirus, toxoplasmosis, herpes, rubella, syphilis, Zika virus, malaria) • Teratogen exposure (drugs, toxins) • Multiple Pregnancy

RISK FACTORS

All women should undergo risk stratification for development of FGR at first visit based on her medical and obstetric history. The predictive value of any individual risk factor is low.

In low resource countries, anemia, undernutrition, hypertensive disorders and malaria are important causes. It is important to assess for risk factors (Table 2) at the first antenatal visit as those pregnant women found to be at high risk can benefit from close surveillance for FGR from 24-28 weeks.

Table 2.2 Risk factors for Fetal Growth Restriction[4]

History-based risk factors			Biochemical markers	Ultrasound-based markers
Maternal demographics	Medical conditions	Obstetric history	• Low PlGF • Low PAPP- A • High AFP	• Uterine artery: pulsatility index >95th percentile • Uterine artery: bilateral notching • Marginal or velamentous cord insertion • Two -vessel cord (single umbilical artery) • Abnormal placental morphology • Decreased fetal growth velocity
• Advanced age • Underweight • Living in high altitude • Severe anemia, hemoglobinopathies • Environmental factors (air pollution, heavy metals, heat)	• Chronic hypertension • Chronic kidney disease • Systemic lupus erythematosus • Inflammatory bowel disease •Antiphospholipid syndrome • Pregestational diabetes (long standing)	Previous pregnancy affected by FGR or pre-eclampsia		

KEY RECOMMENDATIONS

1. All women to undergo risk stratification for FGR at the first antenatal visit to look for high risk factors.
2. Biochemical or USG markers should not be used for universal screening for FGR.
3. Women at high risk for FGR should undergo close surveillance for FGR from 24-28 weeks.

SECTION 3: EARLY PREDICTION AND PREVENTION OF FGR

PREDICTION OF FGR:

The identification of women at high risk to develop FGR is crucial as prenatal detection of FGR will provide an opportunity to employ interventions to reduce the morbidity and mortality associated with this problem. While the predictive value of individual risk factors is low, clinical prediction models based on combinations of the risk factors can considerably improve the prediction of FGR.[5]

Role of risk factors for prediction and prediction models: Current status [4,6]

- Role of history-based risk factors: History based risk factors (Table 2.2) can be identified and FGR can be prevented to a large extent by established interventions for these. Moreover, prevention of exposure from environmental toxins and smoking cessation can be done.
- Role of biochemical markers: There is no role for routine screening with serum biomarkers for FGR. However, when biochemical markers are available as part of prenatal genetic screening for trisomy 21, it may be reasonable to use this information for the purpose of risk stratification for FGR. The combination of low PAPP-A in first trimester and high alpha-fetoprotein in second trimester is particularly predictive of severe FGR.
- Role of ultrasound markers: Uterine artery Doppler, placental morphology and placental volumes have modest predictive accuracy and cannot be recommended for universal screening for FGR as a solitary parameter.
- Role of prediction models: There is no single screening test sufficiently predictive of FGR to recommend for routine clinical use. There are some predictive models based on combination of risk factors but there are wide variations in sensitivity and specificity and none is a gold standard have not been sufficiently validated.

PREVENTION OF FETAL GROWTH RESTRICTION:

- Lifestyle modifications: This should be done ideally in the preconception period wherein; a healthy lifestyle is adopted and medical conditions are optimized. Cessation of smoking, alcohol and illicit drug use should be done.

- Medical interventions: No medical interventions to prevent FGR have been clearly established. Aspirin is recommended for women at increased risk of pre-eclampsia and FGR. However, due to the safety profile of the drug and a significant overlap in the risk factors and pathophysiology of pre-eclampsia & FGR, it is reasonable to consider aspirin to women at high risk of FGR, using the same regimen of aspirin used for prevention of pre-eclampsia. Treatment with aspirin at a dose of 150 mg starting at 12–16 weeks may be considered in selected cases such as women who are at high risk of pre-eclampsia or those with a history of placenta-mediated FGR.[7]

Key Recommendations:

1. Categorizing the risk factors for FGR is very important to determine the further antepartum surveillance methods.

2. Currently, there is no single tool for prediction of FGR. None of the biochemical or ultrasound markers should be used as tools for universal screening for FGR.

3. Prevention of fetal growth restriction is possible by preconception lifestyle modifications. There is no evidence based medical intervention, however aspirin may be tried in selected cases such as women with a history of placenta-mediated FGR or high risk of pre-eclampsia.

SECTION 4. SCREENING AND DIAGNOSIS OF FETAL GROWTH RESTRICTION

Approach to screening and diagnosis of FGR

Screen for FGR → **Identify a small fetus** → **SGA vs FGR**

A. Screening for FGR

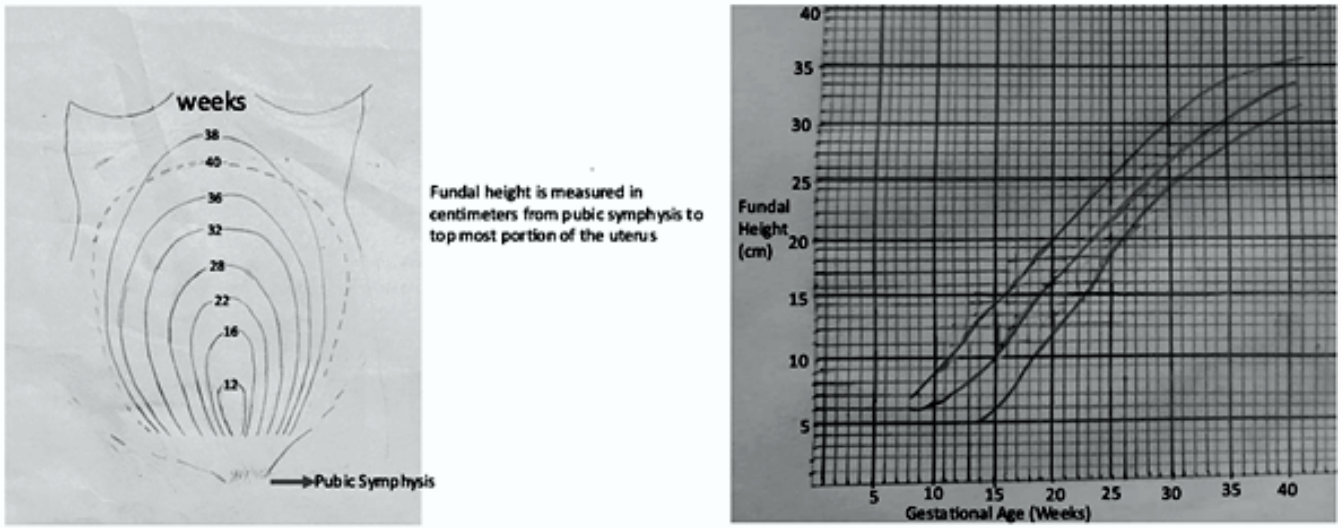
I. Screening for high risk factors: (as described previously in Table 2.2)

Risk factor assessment should be done:

- Preconceptionally
- At booking in antenatal clinic
- At every antenatal visit

II. Symphysio-fundal height (SFH) :[8]

- Primary screening tool
- Simple, inexpensive tool for low risk pregnancies
- Distance from upper border of symphysis pubis to top of uterine fundus
- SFH increases by 1 cm/week between 14 and 32 weeks
- Lag in SFH of ≥ 3 cm can help diagnose FGR
- Measure SFH every 2-4 weeks and at every antenatal visit from 24 weeks onwards and plot it on growth charts.
- Various local charts are available
- When SFH is less than 10th centile or on clinical suspicion of slow or static growth on serial SFH measurements, perform ultrasound to confirm FGR.
- When SFH is likely to be inaccurate as in multiple fibroids, polyhydramnios or high BMI, consider ultrasound evaluation.



III. Routine third trimester USG for growth:[9]

- Universal ultrasonography in late pregnancy (after 24 weeks) is not generally recommended because the test has low sensitivity and a clear outcome benefit has not been seen.

- Routine USG for fetal growth is an alternative method for screening for growth restriction. Although the protocols are not well laid out, scans can be done between 32 and 36 weeks with the scans closer to 36 weeks having greater predictive ability.

- It is reasonable to perform serial symphysio-fundal height measurements for screening in low risk population and recommend a third trimester growth scan for screening in women who are at high risk for fetal growth restriction.

B. Diagnosis of FGR

I. Sonographic fetal weight estimation[10]

- Fetal biometry by ultrasound – cornerstone for detection of FGR

- Assess biparietal diameter (BPD), Head Circumference (HC), Abdominal Circumference (AC), Femur Length (FL) and Estimated Fetal Weight (EFW) from combination of these parameters

- EFW or AC:

    - AC may be more susceptible to bias because measurement can be technically challenging, but it reflects liver size and abdominal subcutaneous fat storage and is strongly related to fetal nutritional status.

- EFW is based on multiple measurements and hence susceptible to inherent measurement errors of each, thus potentially resulting in an overall worse predictive performance. However, EFW is more consistent with the newborn standards used to define small for gestational age since paediatricians do not typically measure AC.

- Combining the two approaches may be reasonable (i.e. FGR should be suspected if either AC or EFW is < 10th percentile)

II. Fetal Growth Velocity (FGV) and Role of Growth charts

- FGR can be detected by plotting FGV on charts and any deviation from trajectory helps in the diagnosis.

- The objective is to evaluate the fetal growth trajectory and identify those fetuses that are deviating from their individual trajectory, indicating a failure to reach their growth potential. There is evidence to suggest that reduced fetal growth velocity in the third trimester is associated with increased risk of adverse outcome.
- Fall of > 50 percentiles for AC or EFW between 2 consecutive scans is considered as reduced growth velocity.

Universal versus Customized growth charts

- Universal charts are based on assumption that all fetuses are expected to have same growth potential under optimal conditions irrespective of race or origin. Examples include Intergrowth - 21st and World Health Organization (WHO) charts.[11,12]

- Indian babies are small as compared to west with mean birth weight at term of 2.6-2.9 kg whereas it is 3.5-3.7 kg in white caucasian populations in high-income countries. Hence, the use of customized growth charts adapted according to local population should be used to reduce over or underestimation of FGR. FIGO Safe Motherhood and Newborn Health Committee recommends local or regional growth charts over universal chart.

III. Doppler Velocimetry

Doppler velocimetry is an integral tool for diagnosis and surveillance of FGR fetuses.

III. 1 Dopplers for uteroplacental insufficiency

- Uterine artery doppler:

  When uterine arteries fail to transform from high- to low-resistance circulation due to inadequate trophoblastic invasion of the spiral arteries, this is reflected as a persistence of high uterine artery mean pulsatility index (PI) (above 95th percentile) and is associated with placental insufficiency and maternal vascular malperfusion of the placenta.

- Umbilical artery doppler:

  An umbilical artery pulsatility index of more than 95th centile for that gestation reflects a raised value. It indicates reduction in placental surface area available for gas and nutrient exchange and placental vascular insufficiency. Increasing severity of placental vascular insufficiency results in absent end diastolic flow (AEDF) or reverse end diastolic flow (REDF).

III. 2 Doppler for fetal adaptation

- Middle cerebral artery doppler:

  Reduced puslatility index (less than 5th centile), reflects a hemodynamic response in the fetus to hypoxemia which results in vasodilation and preferential shunting of blood flow (brain-sparing effect).

- Ductus venosus doppler:

  Alterations in the ductus venosus flow velocity waveform, especially absent or reversed a-wave, may be a consequence of increased intra-atrial pressure due to high cardiac afterload and/or a direct effect of fetal acidemia on myocardial cell function.

- Cerebroplacental Doppler ratio (CPR) : CPR is ratio of middle cerebral artery pulsatility index divided by umbilical artery pulsatility index. A low CPR indicates fetal blood flow redistribution (brain sparing) and is predictive of adverse neonatal outcome. This has a significance beyond the individual parameters of umbilical and middle cerebral artery doppler .

Consensus definition for diagnosis of Small for gestational Age (SGA) and FGR

Delphi Consensus Criteria for Fetal Growth Restriction

Delphi Consensus involves both biometric and functional parameters for the diagnosis of FGR. In most of the studies, EFW < 10th centile is taken as cut off for diagnosis of FGR. But this may encompass diagnosis of SGA fetuses. SGA fetuses are constitutionally small fetuses, not at

increased risk of adverse outcome whereas FGR fetuses are pathologically small with increased risk of adverse perinatal outcome may lead to over detection of SGA and under detection of FGR fetuses. Thus, SGA fetuses will be over-diagnosed and FGR fetuses will be under diagnosed in fetuses with an EFW > 10th centile. Hence in order to reduce this, Delphi consensus came into being. In Delphi consensus, congenital anomalies must be absent. The absolute size measures used were defined at lower cut off values of 3rd centile than 10th centile which is commonly used. Functional parameters were added either alone (AEDF in UA) or in combination (UA or Ut A PI > 95th centile). It helps in proper diagnosis of FGR and to differentiate between early and late FGR. The lower cut off of 3rd centile for size measurements reflect that the long-term outcome of severe SGA fetuses is unfavorable even in the absence of abnormal functional doppler parameters. (Table 1.1)

Key Recommendations:

1. Symphysis–fundal height is a simple and inexpensive tool that can be used as the primary screening strategy for FGR in low-risk pregnancies in both low- and high-resource setting.

2. Local or regional growth charts should be preferred over universal charts. Alternatively, universal standards may be used with locally adjusted thresholds to avoid under- or overdetection of FGR.

3. Criteria from Delphi consensus including both biometric and functional parameters should be used to define FGR.

SECTION 5. INVESTIGATIONS FOR CAUSES OF FGR

- Systematic investigation should be performed with an aim to identify the underlying etiology. However, confirmation of gestational age should be first step when FGR is suspected in order to prevent a false diagnosis of growth restriction.

- Causative factors are broadly categorized into maternal, fetal and placental disorders and a significant overlap can be found in these causes. Relevant investigations should be done based on factors on history or examination findings only.

- The exact cause may not be identified even after investigations and the couple should be counselled about the same.

- Establishing the likely etiology is essential to allow for proper counselling, surveillance, and interventions. It can also aid in preconception counselling for future pregnancies.

Table 5.1 Components Of History Taking[13]

History	
Maternal	**Family**
Age Ethnic group Height, weight, BMI Nutritional status Socioeconomic status Medications Personal history of cigarette smoking and use of recreational drugs Address the risk of congenital fetal infection with TORCH: History of febrile disease or rash in the pregnancy or periconceptional period, recent travel to endemic areas, frequent exposure to domestic animals Detailed previous obstetric history including details of birth weight of previous children Chronic medical conditions Thrombophilia Genetic disorders	Thrombophilia Genetic disorders

Table 5.2: Relevant investigations based on history and clinical examination[13]

Investigations for maternal factors		
Evaluation	**Investigation**	**Remarks**
Haematological	• Full blood count • Peripheral blood smear • Coagulation screening with PT/aPTT	For diagnosis and monitoring of pregnancy-related morbidities like anaemia, hypertensive disorders in pregnancy
Biochemical	• Blood sugar (Fasting/Postprandial) including HbA1c • Liver function test • Renal function test • Urine analysis	For diagnosis and monitoring of maternal medical conditions like pregestational diabetes mellitus, renal insufficiency, hypertensive disorders in pregnancy, undernutrition
Autoimmune	• Nonspecific antinuclear antibody (ANA) for initial screening • Anti dsDNA antibody - specific for SLE	For diagnosis and monitoring of maternal autoimmune conditions when clinically suspected.

Thrombophilia	• Anticardiolipin antibody (ACA), Lupus anticoagulant (LA) and Anti β_2 glycoprotien-I	In patients with history of recurrent pregnancy loss, preterm preeclampsia, placental insufficiency, unexplained intrauterine fetal death and current or past DVT/CVT To be done in interconceptional period preferably May be subject to facilities and resources available for testing
Infections	**Maternal Serology** • Cytomegalovirus and Toxoplasmosis screening • Screening may also include for Rubella, Varicella and Syphilis in cases at high risk for these infections.	It should not be offered routinely in all cases of FGR. It is only indicated when there is positive background of risk factors, based on history or ultrasound findings or in cases of unexplained FGR or early onset FGR.
	• In the context of endemic prevalence or travel history testing for Malaria should also be included[1]	
Ultrasound	• Uterine artery Doppler • Identify multiple gestation • Identify any morphological abnormalities of uterus or fibroid	Uterine artery Doppler is indicated if severe SGA is identified at the 18–20 weeks scan. High mean pulsatility index (above 95th percentile) of uterine artery denotes placental insufficiency and maternal vascular malperfusion of the placenta.

Table 5.3 : Investigations for fetal factors [4,13]

Evaluation	Investigations	Remarks
Detailed anatomy scan	● Detailed anatomic survey: Structural anomalies, soft markers, disorders of amniotic fluid ● Fetal echocardiography to detect major cardiac anomalies and to evaluate cardiac function. ● Doppler velocimetry	Structural anomalies, soft sonographic markers or disorders of amniotic fluid (e.g., polyhydramnios) should prompt genetic counselling for possibility of chromosomal, or single gene abnormalities as the cause of FGR. Findings that are associated with congenital infections, especially in women with a relevant history can also be detected on a detailed anomaly scan. Small fetus with excess amniotic volume suggests aneuploidy or fetal infection.
Genetic evaluation by invasive prenatal diagnostic procedures	● Karyotype ● Chromosomal microarray (CMA) ● Whole exome sequencing or Clinical Exome sequencing based on couple history or index child to identify the genetic basis for FGR	·Genetic consultation and genetic testing by amniocentesis should be offered to women with FGR, especially in cases of early-onset or severe FGR (<3rd percentile), co-presence of sonographic findings (such as structural anomalies, soft markers, or polyhydramnios), and the absence of obvious signs of placental dysfunction such as abnormal uterine or umbilical artery Doppler.

Infections	When fetal infection is highly suspected based on serology results or clinical findings, further testing should be offered by means of amniocentesis for the detection of viral DNA in the amniotic fluid using polymerase chain reaction. In these cases, amniocentesis should be delayed until after 21 weeks of gestation and at least 6–8 weeks following the estimated onset of maternal infection to minimize the risk of false negative results.	Screening for congenital infections should be offered when FGR is suspected, especially in cases of early-onset FGR or when infection is possible based on history of ultrasound findings like small head circumference, ventriculomegaly, brain or liver calcifications, periventricular hyperechogenicity, cortical brain malformations, echogenic bowel, hydrops, or placentomegaly. Testing should be focused on cytomegalovirus and toxoplasmosis, but may also include rubella, varicella, and syphilis in cases at high risk for these infections.
		Testing for Zika virus and malaria should also be considered in the relevant travel history or location context.

Table 5.4: Investigations for placental factors

Evaluation	Investigations	Remarks
Placenta, cord and membrane	● Gross examination of placenta and umbilical cord ● Histopathology (HPE) of placenta	Gross examination of placenta and umbilical cord to detect developmental abnormalities like circumvallate placenta, chorioangioma and hemangioma or umbilical cord abnormalities such as velamentous or marginal cord insertion and single umbilical artery. HPE will be useful to detect infarction, fibrin deposition, and thrombosis.

KEY RECOMMENDATIONS:

1. Confirmation of gestational age should be the first step when FGR is suspected.
2. Women with suspected FGR should undergo systematic assessment that includes the following : detailed history; detailed sonographic assessment for structural anomalies, soft markers, and sonographic signs related to fetal infection; doppler studies that include at least the umbilical artery and, when available, also the uterine and middle cerebral arteries; and maternal screening for relevant congenital infections, which should be focused on cytomegalovirus and toxoplasmosis, but may also include rubella, herpes, syphilis, malaria, and Zika virus in cases at high risk.
3. In Low resource settings, the extent of investigation may be limited by available resources. Assessment should include screening for infections such as malaria and Zika virus in endemic areas.
4. Amniocentesis for karyotype (as well as microarray and polymerase chain reaction for infectious agents when available and indicated) should be offered to women with suspected FGR, especially in cases with early-onset severe (estimated fetal weight <3rd percentile) FGR, in the presence of sonographic findings associated with genetic or infectious etiologies or polyhydramnios and no obvious signs of placental dysfunction, and when the findings are likely to affect management.

SECTION 6: MEDICAL MANAGEMENT OF FGR

Table 6.1 Summary of treatment with unproven benefit

Intervention	Mechanism of Action	Recommendation
Bedrest	• Reduces the catecholamine release • Improves central intravascular volume • Improves uterine perfusion	Unproven benefit
Low Dose Aspirin	• Suppress production of prostaglandins and thromboxane through its irreversible inactivation of the cyclooxygenase enzyme • Cytoprotective mechanisms • Antioxidant mechanisms	• Low-dose aspirin prophylaxis is not recommended for prevention of fetal growth restriction, in the absence of risk factors for preeclampsia. (ACOG 2018) • No role in treatment once FGR sets in.
Heparin and LMWH	• Anticoagulant properties and ability to prevent placental thrombosis and subsequent infarction • Anti-inflammatory	• Currently LMWH therapy for the prevention of FGR should be limited to the research setting. • No role in treatment once FGR sets in.

Table 6.2 Summary of treatment for FGR under investigation

Intervention	Mechanism of action	Current stage of investigation
Phosphodiesterase type -5 inhibitors	Selective vascular smooth muscle relaxation and vasodilatation	Phase II/III clinical trials, however neonatal pulmonary hypertension has been reported as an adverse effect and caution has been advised.
Statins	Anti-inflammatory, antioxidant, and angiogenesis	Phase II/III clinical trials
Nitric Oxide donors	Selective vascular smooth muscle relaxation and vasodilatation	Phase II nonrandomized trials
Proton pump inhibitors	Angiogenesis	Phase II/III clinical trials
Maternal VEGF gene therapy	Local vasodilatation and angiogenesis	Phase I/IIa clinical trial
Nanoparticles	Uterine blood flow, placental function	Preclinical
microRNAs	Uterine blood flow, placental function	Preclinical
Hydrogen sulphide	Selective vascular smooth muscle relaxation and vasodilatation	Preclinical
Melatonin	Antioxidant	Phase II nonrandomized trial
Creatine	Cellular energy homeostasis	Preclinical
N- acetlycysteine	Selective vascular smooth muscle relaxation and vasodilatation	Phase II randomized trial

Summary of treatment to optimise perinatal outcome

A. Role of antenatal corticosteroids:[14]

- Reasonable to administer when pre-term delivery is anticipated, ideally within 1-7 days before birth and up to 34 weeks

- It is important to know that the "improvement" in umbilical artery Doppler that is commonly noticed following administration of antenatal corticosteroids is transient, and is thought to be the result of vasodilation of the fetoplacental arterial tree and increased fetal cardiac output rather than a true decrease in placental resistance. Therefore, these transient changes should not be interpreted as an improvement in fetal status and should not affect the management plan.

B. Role of magnesium sulphate:[15]

- Reasonable to administer for neuroprotection in women at risk of preterm birth with FGR up to 32 weeks

- Seen to decrease the risk of perinatal mortality, cerebral palsy, and gross motor dysfunction.

KEY RECOMMENDATIONS

1. There is no medical therapy with proven benefit for treatment of FGR
2. Antenatal corticosteroids and magnesium sulphate can be used when indicated to optimise perinatal outcomes due to prematurity in cases of FGR.

SECTION 7: MANAGEMENT OF PREGNANCIES WITH FGR : MONITORING

Introduction

The purpose of monitoring pregnancies with FGR is to ensure continuation of the pregnancy till it is safe for the fetus to remain in utero and plan delivery when the risks of in utero environment exceed the risks of ex-utero environment. India is a large county with wide variations in facilities available across the country. It is expected that ultrasound and Doppler facilities with or without computerised cardiotocography machine (cCTG) or non-stress test (NST) will be present. Nevertheless, we have to accept the fact that in India the health care facilities are still not equitably distributed and hence rational modifications to monitoring protocol have to be made based on the practical availability of resources.

Rationale for plan of monitoring:

In early onset FGR, doppler changes follows classic cascade of doppler changes in uteroplacental insufficiency. The umbilical artery Doppler (UA) has an important role to play as abnormalities in UA vessel flow precede others and a cascade of Doppler abnormalities corelates well with the worsening clinical situation.

In late onset FGR the changes in umbilical artery Doppler (UA) may be minimal but there is a decrease in PI of Middle cerebral artery (MCA) due to reduction in resistance in cerebral circulation such that the cerebroplacental ratio shows the first signs of change and indicates onset of hypoxia. As the gestational age is past 32 weeks, decisions for monitoring have to be devised in order to ensure "intact survival" when delivered and to avoid "sudden intrauterine death" as this group of fetuses is less well compensated. This group may not follow the 'classic cascade' of doppler changes.

Modalities for fetal monitoring in FGR:

- **Fetal movement count:**

It is a simple, inexpensive and reasonable tool for fetal monitoring in FGR pregnancies in the home setting. Reduced fetal movement (FM) is defined as less than 10 movements in 2 hours during focused maternal counting on 'rest' in left lateral position. This method can be of use, especially in rural settings. It increases patient involvement and provides a basic safety net as an alarm can be raised when there is reduced perception of FM. It is a well-known fact that as fetal hypoxia sets in, fetal activity is reduced. So decreased fetal movement can trigger a hospital visit for further investigations of USG and or NST, while normal activity can help reassure the mother. Disadvantage of this method is lack of objectivity, hence risks of false alarms or false perception of movement despite fetal inactivity.

- **Fetal heart rate monitoring:**

FGR is a universal indication to check for fetal wellbeing. Fetal heart rate characteristics reflect fetal oxygenation, gestational age, and maturational state of the nervous and cardiovascular systems. These features can be studied on an antepartum cardiotocograph (CTG) also known as non-stress test (NST). A normal baseline heart rate (110-160 bpm) with periodic accelerations (raise of 15 bpm above baseline lasting for 15s) defines a normal or "reactive" CTG. Absence of normal variability or presence of decelerations are non-reassuring. A reactive CTG is reassuring and has a good negative predictive value for fetal hypoxia (99.8%). In unselected pregnancies the rate of stillbirth in the week following a reactive CTG/NST is 1.9/1000. Conversely, an abnormal CTG has low specificity for predicting fetal hypoxia and further tests will be needed to ascertain the exact fetal condition.

- **Computerised CTG (cCTG):**

It is known to be better than the traditional CTG in predicting fetal hypoxia. cCTG can look into "short term variability" (STV) of fetal heart rate and reduced STV correlates well with fetal hypoxia increasing the sensitivity of this modality in fetal monitoring. However, the availability of cCTG in India is extremely limited and non-standardised. Hence in Indian context, unless the accessibility to cCTG 'standardised modality' (Dawes-Redman CTG Analysis) increases, incorporation of cCTG in fetal monitoring protocols is limited.

- **Fetal biophysical profile (BPP):**

It is a test that helps assess the possibility of fetal acidosis. The traditional BPP includes a 30 minute fetal ultrasound assessment of movements, breathing movements, tone and amniotic fluid level. In an unselected population the negative predictive value for fetal death with one week of a normal BPP is 99%. Since the traditional BPP takes time, a modified BPP with a CTG and amniotic fluid assessment has been suggested. If this this abnormal, a 30 minute BPP can be done. Thus, BPP is a more accurate predictor of fetal acid-base status at the time of testing than CTG/NST. Therefore, a five-component BPP can be used to clarify fetal acid base status when a nonreactive CTG/NST is obtained.

- **Fetal Dopplers:**

They are extremely important and easily available tool for monitoring pregnancies with FGR. Doppler studies of fetal vessels provide vital information about fetal hemodynamics and can be correlated to fetal cardiovascular response to the hypoxic/ metabolic changes happening in FGR.

The important vessels studied are described in the table below:

Table 7.1 : Important Vessels in monitoring of FGR

Vessel	Relevance	Remark
Umbilical artery	**Placental resistance, fetal cardiac afterload**	Increased resistance correlates with risk of hypoxia, absent or reversed diastolic flow indicates high risk of acidosis.
Middle cerebral artery	**Cerebral hypoxia**	Low PI indicates brain sparing effect & possible fetal hypoxia
Ductus venosus	**Inflow of oxygenated blood to fetus**	Absent or reversed a wave associated with risk of fetal mortality and morbidity very near future.
Aortic Isthmus	**Interface of oxygenated and deoxygenated blood – indicates oxygenation in the cranial supply**	Abnormal flows indicate compromise of cerebral oxygenation – increased risk of neurological injury
Maternal uterine artery	**Placental resistance from maternal side**	High resistance indicates high placental resistance and suggests etiology of poor uteroplacental perfusion

COMPREHENSIVE MONITORING STRATEGY [1,4,16,17]

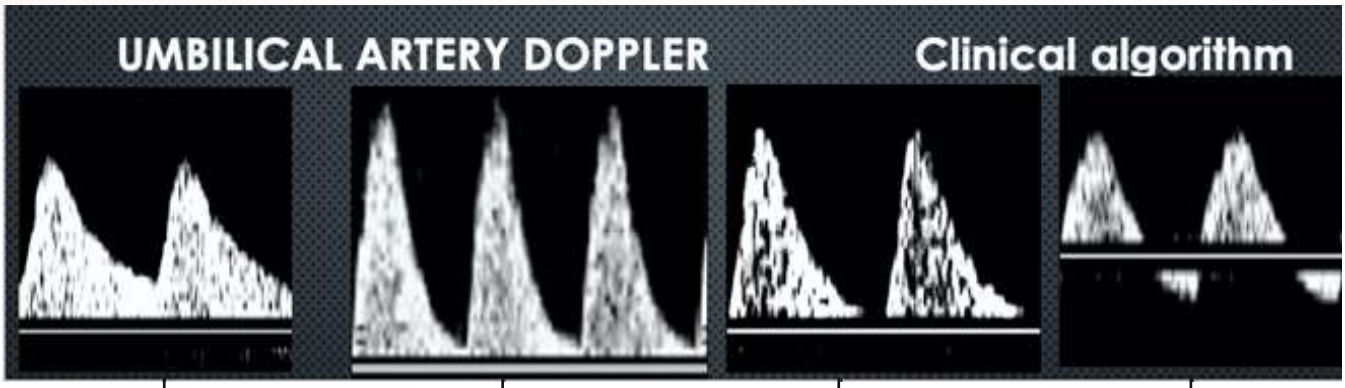
A combination of surveillance modalities is needed to accurately determine fetal acid base status at the time of testing, as well as allowing anticipation of future deterioration.

Table 7.2 : Suggested Monitoring protocol according to Doppler Abnormality

Category	Risk of stillbirth	Monitoring
SGA (EFW at 3rd –10th percentile, normal fluid and Doppler studies)	Low	● Growth scan every 2 weeks ● Doppler (UA, MCA) every 1–2 weeks, BPP/NST once a week ● At ≥37 weeks consider BPP/NST 1–2 times per week.
Uncomplicated FGR at <3rd Percentile or fall of AC/EFW by 2 quadrantile (normal liquor and normal Doppler studies)	Low	● Growth scan every 2 weeks ● Doppler (UA, MCA) 1 –2 times per week, BPP/ NST 1-2 times per week
FGR with mild abnormalities: ● Early Doppler changes: a. UA PI > 95th percentile, or b. MCA PI <5th percentile, or c. CPR < 5th percentile, or d. UtA PI >95th percentile ● Oligohydramnios ● Suboptimal interval growth	Low	Consider inpatient monitoring, especially if other co-morbidities ● Consider steroids for fetal lung maturation if at risk of prematurity ● BPP/NST 2 times per week ● Doppler (UtA, UA, MCA, DV) 2 times per week ● Growth scan every 2 weeks
FGR with umbilical artery AEDF/REDF	Moderate with median time of	● Inpatient monitoring ● Steroids for fetal lung maturation Consider MgSO4, if gestation is below 32 weeks

COMPREHENSIVE STRATEGY FOR DELIVERY DECISION OF FGR FETUS

Option1 : Following with Umbilical artery only



Normal UA

- Repeat Sonogram in 2 week Intervals
- Assess biometry, UA and AFI
- Consider delivery
- Repeat Sonogram in 2 week Intervals

UA Doppler(PI> 95th,+ EDF)

- Repeat Sonogram in 2 week Intervals or more frequently as necessary
- Assess UA, AFI (MCA Optional)
- 2 weekly biometry assesment
- Time corticosteroids < 34 wk

  Consider Delivery at 37wk

UA AEDF*

- Admit, repeat programme in twice weekly intervals or more frequently as necessary
- Assess UA, AFI (MCA Optional)
- Timed corticosteroids
- Deliver no later than 34 wk

  $MgSO_4$ < 32 wk

UA REDF*

- Admit, repeat programme in thrice weekly intervals or more frequently as necessary
- Assess UA, AFI (MCA Optional)
- Timed corticosteroids
- Deliver no later than 30 wk

  $MgSO_4$ < 32 wk

The important vessels studied are described in the table below:

Option 2 : Following with ISUOG guidelines: Umbilical artery, cCTG, CPR & MCA PI

Doppler and cardiotocography examination in FGR fetus

24+0 to 25+6 wks	26+0 to 28+6 wks	29+0 to 31+6 wks	32+0 to 33+6 wks	34+0 to 35+6 wks	36+0 to 37+6 wks	38+0 to 39+0 wks
AEDF or REDF in UA : monitor every 2-3 days unless delivery is indicated						
Personalised Management	Deliver if DV a-wave at or below baseline or STV <2.6 ms	Deliver if DV a-wave at or below baseline or STV <3.0 ms	Deliver if UA-REDF or STV <3.5 ms	Deliver if UA-AEDF or STV <4.5 ms	Deliver if UA-PI > 95th percetilt or AC/EFW < 3rd percentile	Deliver if sign of cerebral redistribution or any other feature of FGR

Deliver if
- spontaneous repeated un provoked decelerations
- altered biophysical profile (score 4)
- maternal indication

Deliver if
- spontaneous repeated unprovoked decelerations
- altered biophysical profile (score 4)
- STV < 4.5 ms
- AEDF or REDF in UA
- Maternal indication

ultrasound obstet Gynecol 2020; 56: 298-312
Published online in Wiley Online Library (Wileyonlinelibrarary.com).
DOI 10.1002/uog.22134

isuog.org GUIDELINES

Umbilical artery MCA - CPR DV

Option 3 : Following with ISUOG guidelines: Umbilical artery, cCTG, CPR & MCA PI

Doppler and cardiotocography examination in FGR fetus

24+0 to 25+6 wks	26+0 to 28+6 wks	29+0 to 31+6 wks	32 wks onwards Not exceeding 39 weeks

CPR below 5th centile or AEDF or REDF in UA monitor every 2-3 days

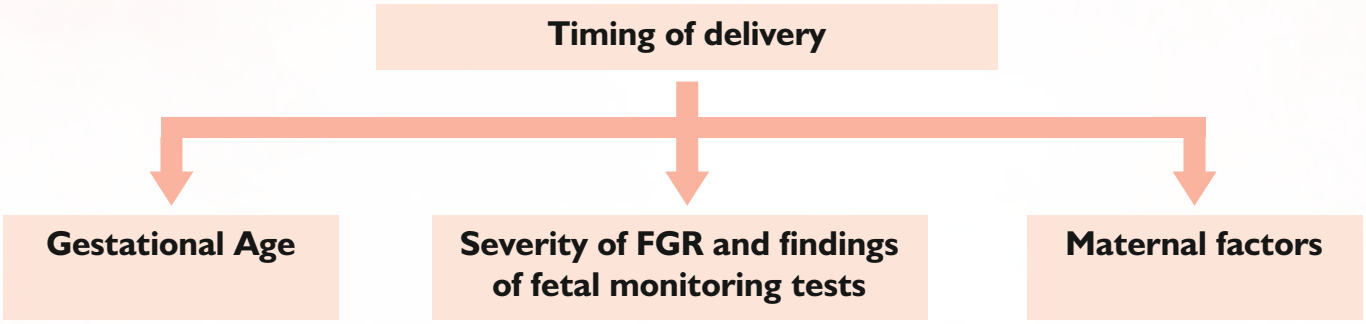
Deliver if GA <32 weeks & if DV below 5th Centile or AEDF /REDF
Spontaneous repeated unprovoked decelerations
Altered BPP < /= 4
Maternal Indication

AEDF / REDF in UA OR
MCA PI <5th centile or
CPR <5th centile or
UT A >95th centile
oligoamnios or interval growth falling 2quadrantile
Suspected severe preeclampsia

more than 32 weeks, CPR< 5th centile AEDF / REDF
Spontaneous repeated unprovoked decelerations
Altered BPP </=4
Maternal Indication
SVT <4.5 ms

Changes proposed for India where Doppler is available	Early OR Late onset	Umbilical artery MCA — CPR DV UT A

SECTION 8 : MANAGEMENT OF FGR: TIMING OF DELIVERY



Key Recommendations:

1. Fetal movement counting is a simple and inexpensive tool monitoring in pregnancies with FGR in both high- and low-resource settings.

2. Surveillance in pregnancies with FGR should follow a uniform protocol that is based on a combination of biophysical profile, fetal heart rate monitoring by NST and Doppler assessment (umbilical artery and middle cerebral artery, with or without ductus venosus Doppler)

Table 8.1 Timing and mode of delivery based on ultrasound findings [4,16,17]

Findings	Timing and mode of delivery
SGA (EFW at 3rd –9th percentile, normal fluid and Doppler studies)	• 37–39 weeks • Mode of delivery: Induction
Uncomplicated FGR at <3rd percentile (normal fluid and Doppler studies)	• 37–38 weeks • Mode of delivery: Induction
FGR with mild abnormalities: • Early Doppler changes: a. UA PI > 95th percentile, or b. MCA PI < 5th percentile, or c. CPR < 5th percentile, or d. UtA PI > 95th percentile • Oligohydramnios • Suboptimal interval growth	• 34 –37 weeks • Mode of delivery: Caesarean section or induction

FGR with umbilical artery AEDF/REDF	• AEDF: 32–34 weeks • REDF: 30–32 weeks • Mode of delivery: Caesarean section
FGR with abnormal ductus venosus Doppler	• 26 –30 weeks • Mode of delivery: Caesarean delivery

AEDF: Absent End Diastolic Flow; REDF:Reversed End Diastolic Flow

Table 8.2: Indications for delivery [4]

Absolute indications (Independent of gestational age)	**Relative indications** (Threshold to deliver varies across various gestational age)
• Maternal conditions needing immediate delivery such as severe pre-eclampsia • Repetitive fetal heart decelerations, sinusoidal tracing, absent FHR variability with late decelerations • Biophysical profile score<4/10 • cCTG STV < 2.6 ms	• Absent ductus venosus a-wave • Biophysical profile <6/10 • cCTG STV based on POG

cCTG STV: computerized CTG Short Term Variability

Key Recommendations:

1. Timing of delivery is based on gestational age, fetal assessment and maternal conditions.
2. The mode of delivery is based on gestational age, bishops score, maternal conditions and acid base status of the fetus.

SECTION 9: POSTPARTUM FOLLOW-UP AND COUNSELLING FOR FUTURE PREGNANCIES

Figure 9.1
Neonate and Infant follow up: [4,18,19]

Baby with growth restriction in-utero

Increased risk of immediate complications	Increased risk of long-term complications
● Complications related to prematurity ● Neonatal mortality (5-fold increase): Independently related to birth weight, irrespective of gestation.	● Affect postnatal growth, can affect height later on. ● Increased risk of adverse long-term neurodevelopmental outcomes. ● Increased risk of future noncommunicable diseases including obesity, diabetes, hypertension, and cardiovascular disease.

Closer follow-up than normally grown infants in the first year of life

Figure 9.2

Maternal Follow-up

Women with a history of pregnancy complicated by FGR or other placenta-mediated complications such as pre-eclampsia

Increased risk

- Maternal CVD and CVD-related morbidities Cerebrovascular events
- Heart failure
- Hypertensive renal disease
- Chronic renal failure and need for renal transplantation

Causal pathway is not clear, however, considerable evidence on the association between birthweight and maternal CVD has been accumulated. It is probable that the association between neonatal birthweight and maternal cardiovascular risk reflects both environmental and genetic influences.

Screen for CVD:[20]

Currently, systematic and population-based follow-up after pregnancy complications for the prevention of future CVD is lacking, even in high-income countries that focus on population-based preventive medicine.

Present: Not clear when follow-ups should be initiated after pregnancy complications, how often follow-ups should be undertaken, or which strategies would be the most cost-effective at a population level.

Recommendation 1:

Consider the following measures at 6–12 weeks after birth, and periodically thereafter, following placental-associated pregnancy complications including fetal growth restriction

- History and physical examination
- Blood pressure measurements
- Consider screening for other cardiovascular risk factors
  - Blood pressure
  - Proteinuria assessment
  - Evaluation of BMI and lifestyle
- Smoking
- Family history of CVD

Recommendation 2:

Once acknowledged, risk-reducing measures are implemented, including lifestyle modification (nutrition and physical activity, treating obesity and overweight, controlling hypertension, and smoking cessation)

Future: Research is needed to discriminate between the specific effects of pregnancy and pre-pregnancy factors, as well as their interaction, on future maternal CVD.

COUNSELLING REGARDING FUTURE PREGNANCIES

Step 1: Assess the risk of recurrence[4]

The underlying etiology, severity and timing of onset, and the presence or absence of modifiable risk factors can all be used to assess the likelihood of recurrence of FGR in subsequent pregnancies.

Risk of recurrence based on severity and onset of FGR	Risk of recurrence based on placental histopathology in cases of placenta mediated FGR
Majority data on the risk of recurrence is based on studies evaluating hypertensive complications of pregnancy. There is evidence for recurrence in cases with early-onset hypertensive complications. Data on the recurrence of FGR is scarce, however risk of recurrence is most often related to the severity of FGR.	Results of the placental histopathological examination may provide valuable information regarding the risk of recurrence, as certain types of placental pathologies are associated with a relatively high recurrence rate.
<u>Conclusion:</u> Counselling regarding the risk of recurrence should be based on the risk factors of the individual patient, severity of FGR as reflected by timing of onset and Doppler findings, co-presence of pre-eclampsia, and placental histopathology.	

Step 2: Preconception counselling and management of future pregnancies[4]

History and Examination	Identify modifiable risk factors for FGR: • Smoking • Poor nutritional status • Chronic medical illness including hypertension
Investigations	**1. Testing for Anti-phospholipid antibody:** - Insufficient evidence to justify routine screening for aPL antibodies in women with prior FGR. - Screening for aPL antibodies is recommended in women with a history of thromboembolism or recurrent pregnancy loss and may be considered in selected cases of women with a history of severe FGR associated with severe early -onset

	pre-eclampsia, when placental examination shows features of severe maternal vascular malperfusion, especially central or multiple areas of villous infarction that are due to multiple spiral arteries thromboses. **2. Routine screening for inherited thrombophilia:** No indication
Interventions	**1. Potential benefit:** Aspirin - Current evidence focused on the prevention of pre-eclampsia as the primary outcome. - Evidence on the prevention of recurrence of FGR in women with a history of FGR are limited. - Recommendation: Aspirin should be considered in women with past history of FGR only if they have risk factors for pre-eclampsia at the time of the next pregnancy. **2. In research setting: LMWH** Data on the role of LMWH to prevent recurrence of placenta mediated complications including FGR are conflicting. LMWH therapy should not be used in women with a past history of FGR except in a research setting. **3. Unproven benefit: Should not be routinely offered** - Bed rest - Nutritional supplements
Advice for future pregnancies	- Optimize chronic medical illness including hypertension ; correct anemia - Manage as high-risk pregnancy - Stratify risk in early pregnancy by means of prenatal screening with biochemical markers (PAPP -A, beta hCG, alpha-fetoprotein, and PlGF) as well as by uterine artery Doppler

	- Recommend monitoring of weight gain and informing women about their target weight gain range - Closer antenatal surveillance, including close monitoring of fetal growth and maternal blood pressure

SECTION 10: SUMMARY

Identify risk of FGR based on history, biochemical and ultrasound markers

Low risk of FGR based on history, biochemical and ultrasound markers

- Routine antenatal care
- Serial measurement of symphysis-fundal height (SFH)
- Ultrasound examination if low SFH or routine examination at 32-36 weeks

High risk of FGR based on history, biochemical and ultrasound markers

- Preventive interventions
- Strict Antenatal fetal surveillance
- Monitor fetal growth at 24-28 weeks by ultrasound examination

Identify a small fetus
Differentiate between SGA and FGR fetus
Define FGR using the Delphi consensus and classify into early or late onset FGR

Investigate the cause of FGR

- History: Detailed history at booking, current pregnancy complications, past obstetric and medical history, family history
- Ultrasound examination

Monitoring and interventions for FGR (based on severity of biometric and functional parameters and maternal status

- Daily fetal movement counting
- Biophysical profile, NST (frequency based on severity of FGR)
- Fetal growth every 2 weeks
- Doppler (frequency based on severity of FGR)
- Antenatal corticosteroids as per standard protocol

Delivery considerations

- Timing of delivery and mode of delivery based on gestational age, maternal and fetal status
- Magnesium sulphate as per standard indications for fetal neuroprotection
- Continuous fetal heart rate monitoring in labour

Postpartum follow up and preconception counselling for future pregnancy

- Infant follow up
- Identify modifiable risk factors and educate regarding the same with an aim to optimize the medical condition before next pregnancy
- Assess regarding risk of recurrence and stratify risk
- Educate about long term maternal and fetal consequences

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