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Clinical Obstetrics

A Case-based Approach

An Official Publication of
Department of Obstetrics & Gynecology
Maulana Azad Medical College (MAMC)

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4

CHAPTER

Fetal Growth Restriction

Simar Kaur, Sangeeta Gupta

Fetal growth restriction (FGR) is associated with significantly increased perinatal mortality as well as immediate and long-term morbidity. Moreover, according to pregnancy audits, most instances of avoidable stillbirth are related with a failure to antenatally detect FGR.[1] One of the most challenging aspects of this condition is the ability to accurately define and adequately diagnose it in order to determine appropriate clinical management.

CASE SCENARIO

Mrs X, 22 years, booked case, married for 1.5 years, G3A2 at 33+1 weeks period of gestation came to OPD for a routine absolute neutrophil count (ANC) visit.

Last menstrual period (LMP)—9/12/2016, Estimated date of delivery (EDD)—16/9/2017, previous cycles regular, sure of dates, pregnancy was confirmed by urine pregnancy test (UPT) at 10 days overdue. First scan done at 9w6d showed a crown-rump length (CRL) corresponding to 9 weeks. Dual marker at 12 weeks was low risk for trisomies. First trimester of pregnancy was uneventful. In second trimester, patient had regular oral hematinic intake. Quickening was appreciated at 20 weeks. Anomaly scan at 20 weeks was corresponding with no gross congenital anomalies. Blood pressure (BP) readings were within normal limits. OGTT done was normal. Thyroid stimulating hormone (TSH) was normal. Clinically growth of the baby had been normal till the previous visit. Weight gain in present pregnancy until now was 7 kg. Patient had adequate daily fetal movement count.

Past Obstetric History

- G1—spontaneous abortion at 2 months of gestation. Medically managed.
- G2—spontaneous abortion at 2.5 months of gestation, followed by D and E.
- No significant family history.

On Examination

No pallor, no pedal edema, BP—120/80 mm Hg, PR—82/min.

Systemic Examination

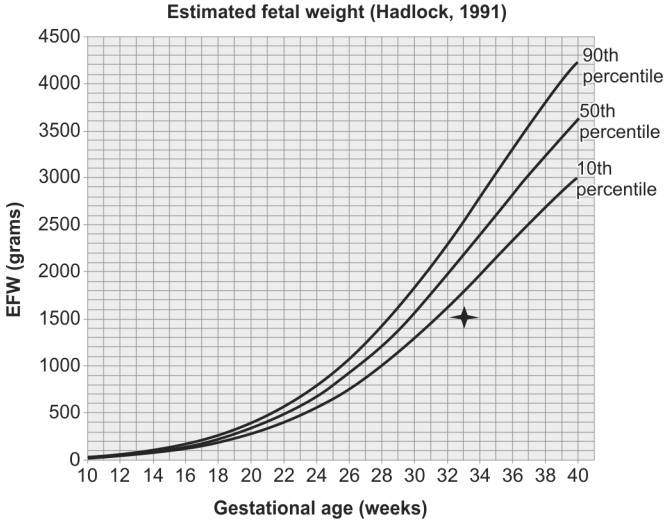
Normal.

Per Abdomen

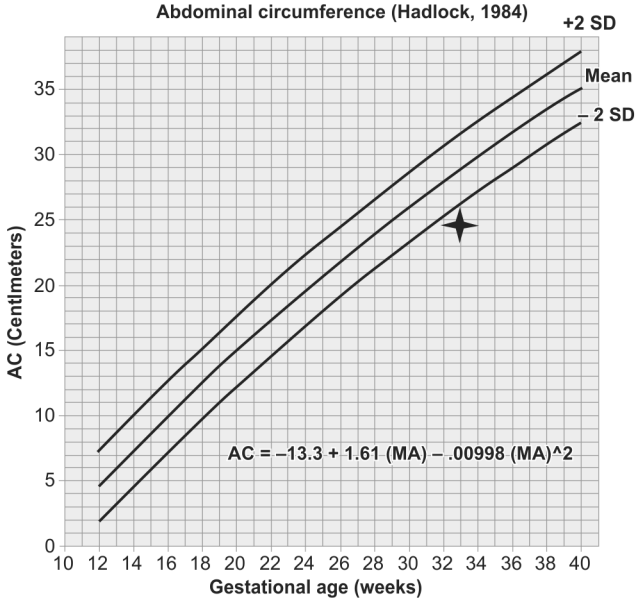
Uterus—30 weeks of gestation, SFH—31 cm, cephalic presentation, FHS +, 130 bpm, clinically FFW ~ 1.4 kg baby, liquor adequate.

Investigations

- Routine blood test and biochemistry was within normal limits.
- Ultrasound (33w1d)—Single live intrauterine fetus (SLIUF), Cephalic presentation, BPD—32 w6d, HC 33 w, AC—30 w2d, FL—33 w1d, EFW—1.45 kg, liquor adequate, UA Doppler PI—1.4 (>95th centile), S/D—3.7, placenta—upper segment, grade 3.



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Q1. How will you define 'fetal growth restriction'?

Fetal growth restriction (FGR) is defined as pathological inhibition of fetal growth and failure of the fetus to attain its growth potential.[2] Placental dysfunction is the leading cause of this condition, which affects approximately 3% of the pregnancies.[3] A major clinical challenge of FGR is the ability to accurately identify the truly growth restricted fetus.

Q2. What do you understand by 'small for gestational age' (SGA) fetus?

Small for gestational age birth is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th centile and severe SGA as an EFW or AC less than the 3rd centile. Fetal growth restriction (FGR) is not synonymous with SGA. Some, but not all, growth restricted fetuses/infants are SGA while 50–70% of SGA fetuses are constitutionally small, with fetal growth appropriate for maternal size and ethnicity.[4] The likelihood of FGR is higher in severe SGA infants.

Small fetuses are divided into normal (constitutionally) small, nonplacenta-mediated growth restriction, for example; structural or chromosomal anomaly and fetal infection, and placenta-mediated growth restriction.[4]

The first clinically relevant step is the distinction of 'true' fetal growth restriction, associated with signs of abnormal fetoplacental function and poorer perinatal outcome, from constitutional small-for-gestational age, with a near-normal perinatal outcome.

Q3. How will you differentiate a constitutionally small fetus from a fetus with true FGR? Is the fetus mentioned in above case constitutionally small or has true FGR?

Fetuses with true FGR are at higher risk of in utero deterioration, stillbirth and overall poorer perinatal outcome as compared with normally grown fetuses. FGR is associated with Doppler signs suggesting hemodynamic redistribution as a reflection of fetal adaptation to placental dysfunction.[5] On the contrary, SGA fetuses do not show any Doppler changes and have virtually normal perinatal outcome. The fetus in the above case has true growth restriction as there are Doppler changes in umbilical artey suggesting increased resistance to blood flow.

Q4. What are the causes of fetal growth restriction?

The causes of FGR are fetal, maternal, environmental, and placental.[6]

Fetal

- Aneuploidy (trisomy 13, 18 and 21, triploidy, uniparental disomy)
- Fetal malformations (heart disease)
- Multiple gestation
- Infection (toxoplasmosis, rubella, cytomegalovirus, herpes).

Maternal

- Gestational hypertension, pre-eclampsia, chronic hypertension
- Diabetes with vasculopathy
- Chronic kidney disease
- Hypoxia (pulmonary disease, cardiac disease)
- Systemic lupus erythematosus, antiphospholipid syndrome
- Thrombophilia (Factor V Leiden heterozygote, prothrombin gene G20210A heterozygote, *MTHFR* heterozygote).

Placental

- Placenta previa
- Placental tumors
- Mosaicism.

Environment

- Low socioeconomic status
- Malnutrition
- Smoking
- Alcohol
- Drugs (cocaine, heroin).

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Q5. What is the normal rate of fetal growth in utero?

Fetal growth in utero depends on two components—genetic potential and substrate supply. The genetic potential is derived from both parents and is mediated through growth factors such as insulin like growth factor. An adequate substrate supply is essential to achieve the genetic potential. This supply is derived from the placenta which is dependent on uterine and placental vascularity.

Fetal growth accelerates from about 5 g per day at 14–15 weeks to 10 g per day at 20 weeks, peaks at 30–35 g per day at 32–34 weeks, after which the growth rate decreases.

Q6. Elaborate the important points in history taking of a patient with suspected FGR.

History of Present Pregnancy

- Determining the period of gestation with accuracy is crucial for diagnosing FGR
- Date of last menstrual period, surety of dates, and history of regular cycles or any prolonged or irregular cycles prior to conception
- An ultrasound in first trimester with pregnancy dated by crown-rump length (CRL) would help to date the gestation more accurately.

First Trimester

- History of fever with or without rash to rule out infections like rubella, herpes, chickenpox, malaria which can lead to FGR if transmitted to the fetus in utero.
- History of exposure to drugs or radiation.

Second/Third Trimester

- History of poor weight gain
- History of excessive swelling of feet as in preeclampsia
- History of perceiving fetal movements.

Obstetric History

- History regarding outcomes in previous pregnancies, including birth weight of previous babies
- Any complications like preeclampsia, previous growth restricted babies, history of previous still births.

Q7. What are the maternal risk factors that can lead to development of FGR?

Maternal Characteristics

Extremes of maternal age, nulliparity or grand multiparity, history of FGR in previous pregnancy and low pre-pregnancy maternal weight contribute to an increased risk of FGR.

Maternal Diseases

Uteroplacental insufficiency resulting from medical complications such as hypertension, renal disease, autoimmune disorders, thyroid disorders or long-term insulin dependent diabetes with vasculopathy place the fetus at an increased risk of FGR. These conditions influence fetal growth primarily by reducing blood supply via the uterine arteries, depriving substrate supply to the fetus.

Congenital heart disease, particularly cyanotic heart disease is associated with growth restricted infants. Maternal respiratory diseases such as asthma and bronchiectasis also affect fetal growth.

Thrombophillias

Antiphospholipid antibody syndrome and hereditary thrombophillias are also associated with growth restriction. The likely mechanisms are placental thrombosis and impaired trophoblastic function.

Smoking, Alcohol and Drugs

Active and passive smoking, especially in the second and third trimesters, is an important cause of FGR. Mothers who smoke during pregnancy generally deliver infants weighing 100–300 g less than children born to nonsmoking mothers.

Excessive alcohol intake can result in fetal alcohol syndrome when consumed in early pregnancy and FGR during second and third trimester. Cocaine and opiates are potent vasoconstrictors. Their use in pregnancy has influence on the uterine vasculature to cause fetal growth constriction. Therapeutic medications such as warfarin, anticonvulsants, etc. are also implicated in growth restriction.

Nutritional Deficiency

Nutritional deficiency in pregnancy is also one of the common causes of FGR.

Q8. Elaborate important points in the examination of a patient with FGR.

General Build and Nutritional Status of Mother

- Height, weight and body mass index (BMI) of mother—a constitutionally small mother may have a constitutionally small fetus
- Blood pressure
- Pallor, cynaosis, pedal edema
- Thyroid swelling
- Jugular venous pressure.

Systemic Examination

Cardiovascular and respiratory system.

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Per Abdomen Examination

Fundal height in weeks and SFH in cms, abdominal girth in inches

- Clinical estimation of fetal weight and liquor
- Auscultation of fetal heart rate.

Q9. What are the clinical methods to detect a growth restricted fetus?

Clinically, the most commonly used method of detecting FGR is the serial measurement of fundal height, symphysiofundal height and abdominal girth.

A lag in fundal height of 4 weeks is suggestive of moderate FGR, while a lag of over 6 weeks suggests severe FGR. However, this method has low sensitivity when used alone because of variables such as maternal habitus, amount of amniotic fluid and examiner bias.

Symphysiofundal height is measured from upper border of symphysis pubis to the level of uterine fundus. It is expressed in centimeters and corresponds to period of gestation in weeks. It increases by approximately 1 cm per week between 14 and 32 weeks.

Abdominal girth is measured at the level of umbilicus and is expressed in inches. It is about 30 inches at 30 weeks in an averagely built woman. It increases on an average by 1 inch per week after 30 weeks.

All three parameters—fundal height, symphysiofundal height and abdominal girth should be checked every weekly while monitoring a patient with fetal growth restriction.

Q10. Can abdominal examination alone diagnose FGR in all patients?

Abdominal examination alone has a limited role in the diagnosis of FGR. Abdominal palpation has a sensitivity of 30% for detecting SGA fetuses.[6] The symphysis-fundal distance has a sensitivity of 65% and specificity of 80–93% for detecting SGA, with variations depending on the methodology used and the presence of factors like high maternal BMI, uterine tumors (leiomyoma) or multiparity.

Q11. What are the various ultrasound parameters used for fetal growth assessment?

Commonly used parameters for calculating estimated fetal weight include biparietal diameter, head circumference, abdominal circumference and femur length.

- *Biparietal diameter (BPD):* It is measured in the transthalamic plane of head which includes thalami, cavum septum pellucidum and midline falx. It is measured at the level of thalami from the outer border of the proximal calvarium to inner border of the distal calvarium.
- *Head circumference (HC):* It is also measured in the transthalamic plane by measured the outer circumference of the calvarial margin.
- *Abdominal circumference (AC):* It is measured in a transverse section at the level of birfurcation of main portal vein into right and left branch (boomerang appearance). AC is the most affected parameter in fetuses with growth restriction.
- *Femur length (FL):* It is measured by measuring the diaphysis of femur, leaving the epiphyseal ends.

Fetal weight is calculated by a variety of formulae—Hadlock, Ott, Shepherd using ultrasound parameters like BPD, HC, AC and FL.

Q12. What are the various ultrasound parameters used for assessment of gestational age?

An accurate determination of the gestational age is fundamental for the management of pregnancies with fetal growth restriction.

Mean Sac Diameter (MSD)

In the early first trimester, when no structures are visible within the gestational sac, gestational age may be estimated from the sac diameter. A common method is to measure the mean sac diameter, by calculating the mean of the 3 sac diameters. An alternative simpler method is to add 30 to the sac size in millimeters, to give GA in days. By the time the embryo becomes visible on ultrasound the sac diameter is no longer accurate in estimating gestational age.

Crown Rump Length (CRL)

Measurement of CRL in first trimester of pregnancy is the most accurate method to determine gestational age. The crown-rump length is the longest straight line length of the embryo from the outer margin of the cephalic end to the rump.

Biparietal Diameter (BPD)

The BPD is the most accurate measurement to determine the gestational age in the second trimester of pregnancy. It is measured in a transverse plane of the head at the level of the thalamus. If the fetal head looks flattened or elongated, it is necessary to measure the cephalic index which is the ratio of BPD divided by occipitofrontal diameter (OFD).

Head Circumference (HC)

The HC is measured in the same transverse plane as is used to measure the BPD and is not altered by brachycephaly or dolicocephaly of the head.

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Femur Length (FL)

The FL is an excellent parameter to calculate the gestational age, because it is not significantly affected by alterations in the fetal growth.

Transverse Cerebellar Diameter (TCD)

It is often measured as an additional fetal biometric parameter. It is measured as the maximal diameter between the cerebellar hemispheres on an axial scan. The value of the transverse cerebellar diameter in mm's is considered roughly equivalent to the gestational age in week (particularly between the 14–26 weeks of gestation). The TCD is not altered by the presence of FGR.

Q13. What is the accuracy of various ultrasound parameters for estimating gestational age?

Ultrasound parameter	*Error*[7]
MSD	4–11 days
CRL	3–8 days
BPD (1st trimester)	3–8 days
BPD (2nd trimester)	7–12 days
FL	7–17 days

Abbreviations: MSD, mean sac diameter; CRL, Crown-lump length; BPD, biparietal diameter; FL, femur length

Q14. What is symmetrical and assymetrical FGR?

The main differences between the two include:[8]

Symmetrical FGR	*Asymmetrical FGR*
Incidence—20–30%	70–80%
Growth inhibition occurs early in pregnnacy	Onset late in pregnancy, usually after 32 weeks
Hyperplastic stage is affected	Hypertrophic stage is affected
Reduced number of cells	Reduced cell size
Causes: Intrauterine infections; TORCH Chromosomal abnormalities Fetal structural anomalies Early onset severe preeclampsia	Cause: Uteroplacental insufficiency Associated with chronic hypertension, renal disease, etc.
All parameters (BPD, HC, AC, FL) are below the 10th centile for gestational age	Only AC is below the 10th centile Liver size reduced due to diminished glycogen stores
Normal ponderal index	Low ponderal index

Abbreviations: BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length

Q15. What are the various parameters used for assessment of fetal well-being?

Fetal well-being tests and indices can be roughly classified as chronic or acute. Whilst the former become progressively abnormal due to increasing hypoxemia and/or hypoxia, the latter correlate with acute changes occurring in advanced stages of fetal compromise, characterized by severe hypoxia and metabolic acidosis, and usually precedes fetal death in a few days.

Various parameters monitored are:

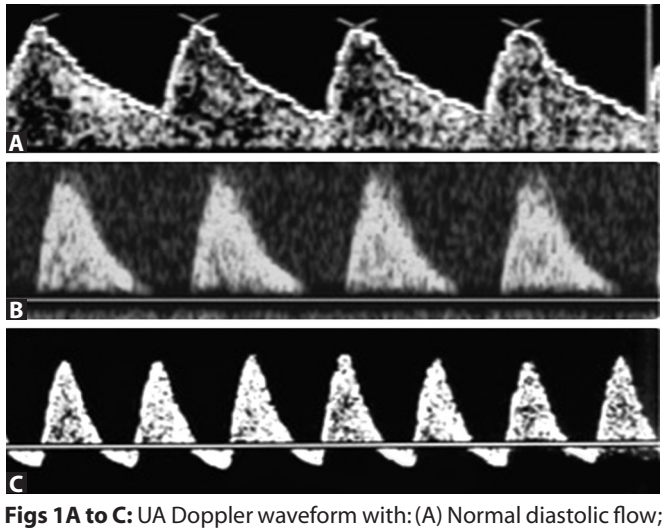
- Doppler: Umbilical artery, middle cerebral artery, cerebroplacental ratio, ductal venosus, aortic isthmus
- Biophysical profile
- Fetal heart rate analysis by conventional and computerized cardiotocography
- Amniotic fluid index.

Q16. What are the various Doppler parameters used for management of FGR fetuses?

Commonly used Doppler assessment in SGA fetus encompasses that of the umbilical artery (UA), middle cerebral artery (MCA), uterine artery and ductus venosus (DV). More specialized and uncommonly performed Dopplers include that of the umbilical vein (UV) and aortic isthmus.

Umbilical Artery Doppler

Umbilical artery (UA) Doppler is most commonly used for the monitoring and timing of delivery of the fetus compromised by FGR. UA Doppler is the only measure that provides both diagnostic and prognostic information for the management of FGR.[9] Increased UA Doppler PI or S/D has a great clinical value for the identification of FGR. The progression of UA Doppler patterns to absent or reverse end-diastolic flow correlates with the risks of injury or death. The PI becomes abnormal when placenta is working less than 50% of its capacity and absence and reversal appear at 70% and 90% deficit respectively. Pattern of absent end diastolic flow (AEDF) appears to be present 12 days preceding acute fetal deterioration.[10] Figures 1A to C demonstrate normal and abnormal UA Doppler waveforms.



Figs 1A to C: UA Doppler waveform with: (A) Normal diastolic flow; (B) Absent end-diastolic flow (AEDF); (C) Reversal of diastolic flow (REDF)[11]

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UA Doppler	*Frequency of monitoring*[5]
Normal	Every 14 days
Reduced diastolic flow	Weekly
AEDF	Biweekly
REDF	1–2 days

Abbreviations: UA, umbilical artery; AEDF, absent end-diastolic flow; REDF, reversal of diastolic flow

Middle Cerebral Artery (MCA) Doppler

In the presence of fetal hypoxemia, central redistribution of blood flow results in increased blood flow to the brain, heart, and adrenal glands, and a reduction in flow to the peripheral circulations. This blood flow redistribution, known as the brain-sparing reflex, is characterized by increased end-diastolic flow velocity (reflected by low Doppler indices) in the middle cerebral artery. MCA Doppler is particularly valuable for the identification of late onset FGR, independently of the UA Doppler, which is often normal in these fetuses.[12] Current role of MCA Doppler in late onset FGR is to guide termination of pregnancy at 37 weeks, if MCA Doppler is deranged.

Ductus Venosus (DV) Doppler

The DV Doppler acts as a marker of cardiovascular deterioration in response to FGR, specifically in cases of early-onset FGR, where the DV typically becomes abnormal after an elevation of the PI in the UA. RCOG recommends that DV Doppler should be used for the surveillance and timing of delivery of the preterm growth-restricted fetus with absence or reversal of EDF on UA Doppler, provided that the fetus is viable and steroids have been administered.[4]

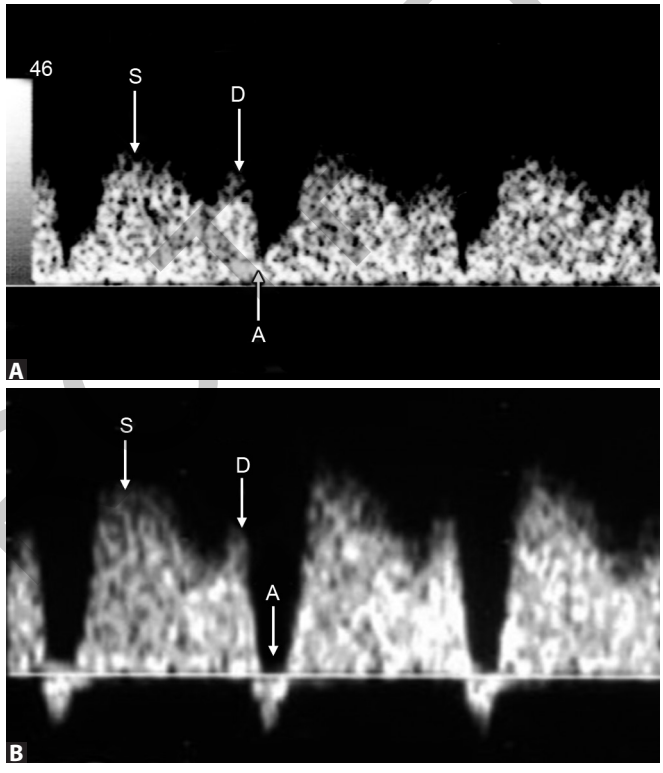
Absent-reversed velocities during atrial contraction are associated with perinatal mortality independently of the gestational age at delivery with a risk ranging from 40% to 100% in early onset FGR.[13] Thus, this sign is normally considered sufficient to recommend delivery at any gestational age, after completion of steroids (Figs 2A and B).

Uterine Artery

Uterine artery has been mainly used as a screening tool for prediction of FGR, but now its role in diagnosis of late onset FGR is being established. Increased uterine artery resistance (uterine artery PI > 95th centile) is being used as parameter to predict adverse outcomes among SGA fetus with normal UA PI.[14]

Aortic Isthmus

The aortic isthmus is the segment of the aorta located between the origin of the left subclavian and the connection of the ductus arteriosus to the descending aorta. Abnormal aortic isthmus Doppler is an important step between placental insufficiency and cardiac decompensation. The aortic isthmus (AoI) Doppler is associated with increased fetal mortality and neurological morbidity in early-onset FGR. Reverse AoI flow is a sign of advanced fetal deterioration and precedes DV abnormalities by 1 week.[15]



Figs 2A and B: Ductus venosus doppler waveform: (A) Normal waveform; (B) Reversal of a wave. S—ventricular systole ; D—ventricular diastole; A—atrial contraction

Q17. What are the various Doppler indices used in the assessment of uteroplacental blood flow?

The parameters used in the assessment of uteroplacental blood flow include:

- **S/D:** Systolic/Diastolic ratio
- **PI:** Pulsatility index
- **RI:** Resistive index.

Systolic/Diastolic (S/D) Ratio

This is calculated by:

- Peak systolic velocity/end diastolic velocity.

Pulsatility Index (PI)

This is calculated by the following equation:

PI = (peak systolic velocity – end diastolic velocity)/time averaged velocity = (PSV – EDV)/ TAV

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Resistive index (RI)

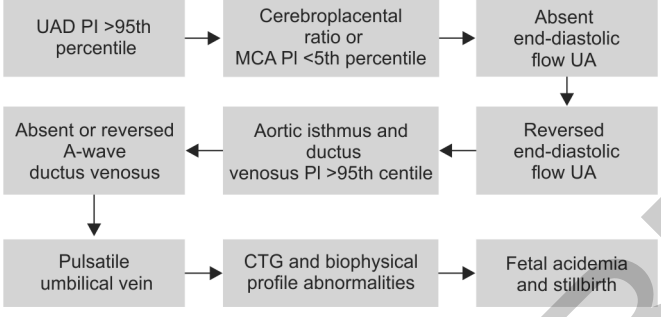
This is calculated by the following equation:

RI = (PSV-EDV)/PSV = (peak systolic velocity—end diastolic velocity)/peak systolic velocity

Among these parameters PI is the recommended parameter for assessment of Doppler changes. In cases of AEDV, S/D ratio cannot be calculated. Hence, PI is considered better.

Q18. What is the sequence in which various Doppler changes occur in an FGR fetus?

Though this is the sequence of Doppler changes occurring in FGR fetuses most of the times, we may not always find this exact sequence of alterations.[16]



Abbreviations: UAD PI, umbilical artery Doppler pulsatility index; MCAPI, middle cerebral artery pulsatility index; CTG, Cardiotocography; UA, umbilical artery

Q19. What is the role of cardiotocography (CTG) in management of FGR?

Spontaneous decelerations on conventional CTG represent a very late event preceding fetal demise, and therefore measures that allow earlier identification and delivery must be used. A main limitation of conventional CTG is the subjective interpretation of the FHR, which is extremely challenging in very preterm fetuses with a physiologically reduced variability.

Computerized CTG (cCTG) has provided new insights into the pathophysiology and management of FGR. cCTG evaluates short-term variability (STV) of the FHR, an aspect that subjective evaluation cannot assess. cCTG is sensitive to detect advanced fetal deterioration, and it provides a value similar to DV reverse atrial flow for the short-term prediction of fetal death.[17]

Q20. What is the role of biophysical profile (BPP) in management of FGR?

Biophysical profile (BPP) has a high false-positive rate of 40% to 50%. Fetal heart rate variability decreases first followed by fetal breathing. Loss of fetal movements and tone are late events. Changes in BPP occur much later than changes in Doppler. Consequently, whenever Doppler expertise and/or cCTG are available, the use of BPP is questionable. It may be more useful when UA Doppler is abnormal as it has a high negative predictive value in high-risk cases.

Amniotic fluid volume is believed to be a chronic parameter. In fact, among the components of BPP, it is the only parameter that is not considered to indicate acute asphyxia. Because of the limited evidence, the inclusion of oligohydramnios in the management protocols of SGA/FGR is doubtful.[14]

Q21. What do you understand by cerebroplacental ratio (CPR)?

Cerebroplacental ratio is the ratio of MCA PI and UA PI. This index reflects in a combined fashion mild increases in placental resistance with mild reductions in fetal brain vascular resistance. CPR is more sensitive to hypoxia than its individual components and correlates better with adverse outcome in pregnancy.[18]

Q22. Constitutionally small fetuses can be distinguished from fetuses with true FGR by Doppler velocimetry. Which is the best Doppler parameter for the same?

For almost 20 years, UA Doppler has been widely accepted as the standard to identify true FGR. However, current evidence demonstrates that constitutionally small fetus, as defined by a normal UA PI, contains a large proportion of fetuses with worse perinatal outcomes than normally grown fetuses. Thus, UA Doppler cannot be used as a standalone criterion to differentiate the two. The CPR improves the sensitivity of UA and MCA alone because it is already decreased when its individual components are still within normal range. The cerebroplacental ratio (CPR), which combines the pulsatility index of the MCA and UA, is affected in about 25% of small fetuses at term. The CPR is more sensitive to hypoxia than its individual components and it correlates better with adverse outcome.[15]

Q23. SGA fetus with normal UA PI can be reclassified as true FGR based on cerebroplacental ratio. What are the other new criteria proposed for the same?

Aside from CPR, the uterine artery Doppler PI (UtA PI) can be abnormal in the presence of a normal UA Doppler in small fetuses and predicts a poorer outcome in small fetuses. Another predictor of poor outcome is a very small EFW. Among fetuses below the 10th centile, those with an EFW <3rd percentile have a much higher risk of adverse

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perinatal outcome irrespective of the CPR and UtA Doppler indices.[15]

Q24. What is stage-based classification of FGR?

Stage[5]	*Pathophysiological correlate*	*Criteria (any of)*
I	Mild placental insufficiency	EFW <3rd centile UA PI > p95 MCA PI < p5 CPR <p5 Ut A PI >p95
II	Severe placental insufficiency	UA AEDV
III	Low-suspicion fetal acidosis	UA REDV DV PI >p95
IV	High-suspicion fetal acidosis	DV reversal a wave cCTG <3 ms FHR decelerations

Q25. How frequent fetal monitoring should be done for an FGR fetus and what is the ideal gestational age for delivery?

The frequency of fetal monitoring and gestational age for delivery will depend on the stage of FGR.[5]

Stage	*Pathophysiological correlate*	*Monitoring*	*Gestational age*
I	Mild placental insufficiency	Weekly	37 weeks (IOL)
II	Severe placental insufficiency	Biweekly	34 weeks (CS)
III	Low-suspicion fetal acidosis	1–2 days	30 weeks (CS)
IV	High-suspicion fetal acidosis	12 hours	26 weeks

Stage I fetal growth restriction (mild placental insufficiency): UtA, UA or MCA Doppler, or the CPR are abnormal. In the absence of other abnormalities, evidence suggests a low risk of fetal deterioration before term. Labor induction beyond 37 weeks is acceptable, but the risk of intrapartum fetal distress is increased.[19] Weekly monitoring seems reasonable.

Stage II fetal growth restriction (severe placental insufficiency): This stage is defined by UA absent-end diastolic velocity (AEDV). Delivery should be recommended at 34 weeks. The risk of emergent cesarean section at labor induction exceeds 50% and, therefore, elective cesarean section is a reasonable option. Monitoring twice a week is recommended.

Stage III fetal growth restriction (advanced fetal deterioration, low-suspicion signs of fetal acidosis): The stage is defined by reverse absent end-diastolic velocity (REDV) or DV PI >95th centile. There is an association with a higher risk of stillbirth and poorer neurological outcome. However, since signs suggesting a very high risk of stillbirth within days are not present yet, it seems reasonable to delay elective delivery to reduce as possible the effects of severe prematurity. Delivery is recommended by cesarean section after 30 weeks. Monitoring every 24–48 hours is recommended.

Stage IV fetal growth restriction (high suspicion of fetal acidosis and high risk of fetal death): There are spontaneous FHR decelerations, reduced STV (<3 ms) in the cCTG, or reverse atrial flow in the DV Doppler. Spontaneous FHR deceleration is an ominous sign, normally preceded by the other two signs, and thus it is rarely observed, but if persistent it may justify emergency cesarean section. cCTG and DV are associated with very high risks of stillbirth within the next 3–7 days and disability. Deliver after 26 weeks by cesarean section at a tertiary care center under steroid treatment for lung maturation. Intact survival exceeds 50% only after 26–28 weeks, and before this threshold parents should be counseled by multidisciplinary teams. Monitoring every 12–24 hours until delivery is recommended.

In cases with associated maternal morbidity like pre-eclampsia, timing of delivery is determined by both maternal and fetal parameters.

Q26. How will you manage the pregnancy in the case scenario? What is the ideal time to deliver and mode of delivery?

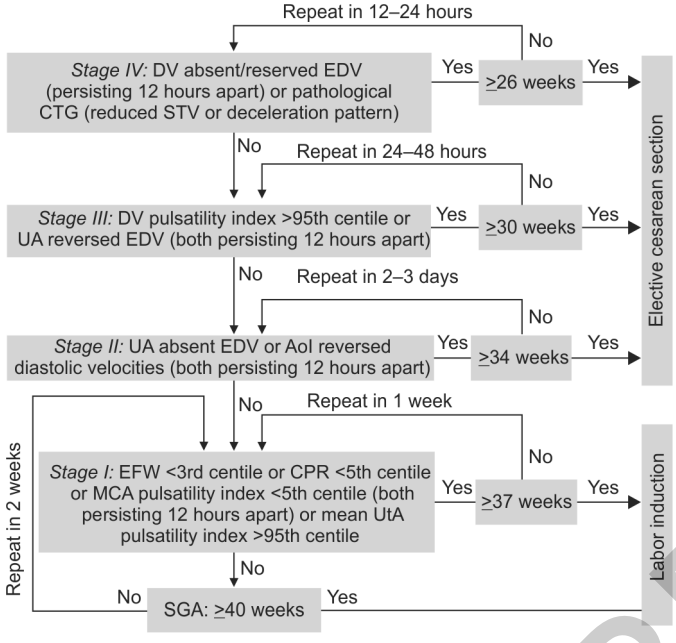
The above-mentioned patient is 33 weeks pregnant with SFH of 30 weeks, EFW less that 10th centile (1.4 kg), UA PI >95th centile. These findings suggest that this is a case of true FGR (late onset type), with mild placental insufficiency (stage I).

The patient should be admitted and monitored weekly for fundal height, SFH, abdominal girth and maternal weight gain. Though, her BP is currently normal, daily BP monitoring should be done, as there could be coexisting hypertensive disorder. Corticosteroids should be administered for fetal lung maturity. Twice weekly biometry for estimated fetal weight should be done and plotted on a growth chart to assess the fetal growth. Fetus should be monitored weekly with UA Doppler, biophysical profile (BPP), amniotic fluid volume. If there is absence or reversal of end-diastolic flow on UA Doppler or BPP <4 consider termination of pregnancy. If these changes do not occur, pregnancy can be continued up to 37 weeks. Plan a vaginal delivery at 37 weeks, by inducing labor.

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Q27. Draw a flowchart to depict stage-based decision algorithm for the management of FGR.

Flowchart 1: Stage-based decision algorithm for the management of fetal growth restriction



Abbreviations: DV, ductus venosus; EDV, end-diastolic velocity; UA, umbilical artery

CASE SCENARIO

Mrs N, 28 years, primigravida referred from a private hospital at 28 weeks period of gestation in view of severe pre-eclampsia with blood pressure records of 150/100–160/110 with a urine albumin of 1+.

Married for 9 months, LMP–16/4/2016, EDD–23/1/2017, previous cycles regular, sure of dates, pregnancy confirmed by a scan at 6 weeks which showed a CRL of 5w5d. She was started on regular folic acid intake. Nuchal translucency scan at 12w5d was normal and corresponding. Dual marker at 12 weeks showed a low PAPP A, however, there was no overall increase in the risk for trisomies. First trimester was uneventful. In second trimester, she had regular oral hematinic intake. Quickening was appreciated at 20 weeks. Anomaly scan at 18 weeks was normal and corresponding. OGTT at 24 weeks was normal. BP readings had been normal until 28 weeks period of gestation. At 28 weeks she was found to have two high blood pressure readings of 150/100 and 160 /110. Urine albumin was 1+. Patient had complaints of slight headache, but no complaints of blurring of vision, nausea, and vomiting or epigastric pain. She was appreciating fetal movements well.

No significant past or family history.

On Examination

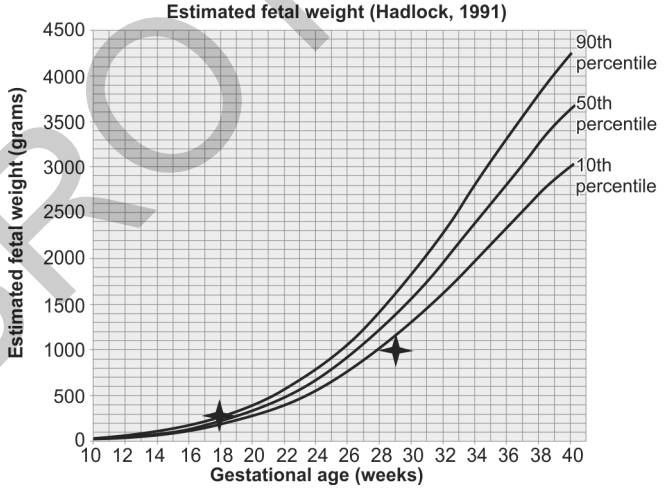
- No pallor, pedal edema +
- BP—160/110 mm hg, PR—80/min
- Cardiovascular system and respiratory examination was within normal limits.

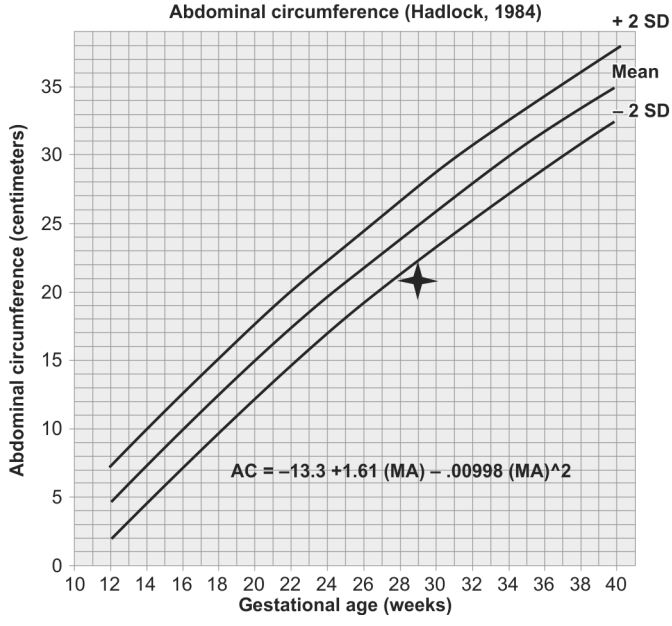
Per Abdomen Examination

Uterus—26 weeks, SFH—27 cm, cephalic, relaxed, FHR—132 bpm, clinically fetus—1 kg

Per Vaginal Examination

- Cervix long, os closed, Vertex—3
- Urine albumin (By Dipstick 1+)





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Investigations

- CBC—WNL, RFT/LFT—WNL, 24 hours urine protein—450 mg/24 hours, Fundus—normal
- Ultrasound (29 weeks)—SLIUF, cephalic presentation, BPD—29w1d, HC—29 w, AC—26w1d, FL—28w5d, placenta posterior grade 2, AFI—8, EFW—1 kg
- UA Doppler—S/D—3.6, PI—1.5 (> 95th centile).

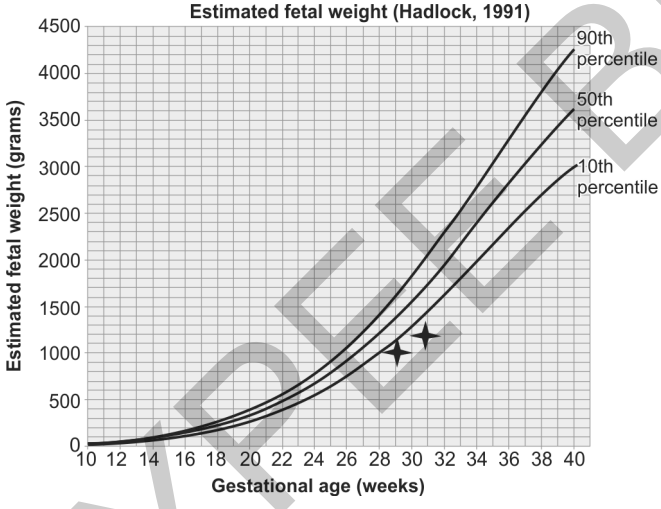
Course in Hospital

Patient was admitted. Injection labetalol 20 mg IV stat given. BP checked after 20 minutes—130/94 mm Hg, patient was started on T Labetalol 200 mg TDS. Injection $MgSO_4$ was started prophylactically as per Pritchard's regimen.

BP readings were controlled on oral labetalol. Weekly monitoring of Hb, platelets, renal and liver function was done.

Weekly fetal growth monitoring with fundal height SFH was done. Tests for fetal well being— UA Doppler and biophysical profile were done weekly.

Ultrasound (31 weeks)—SLIUF, cephalic, BPD—30w2d, HC—31w, AC—27w2d, FL—30w5d, AFI—5, UA Doppler AEDV, EFW—1.16 kg.



Q1. What are the types of FGR based on the gestational age at onset?

Fetal growth restriction presents under two clinical patterns, as determined by the gestational age at onset—early onset and late onset FGR.

In early-onset FGR, there is severe placental dysfunction with abnormalities in UA and venous Doppler parameters to abnormal biophysical parameters, often necessitating preterm delivery. In addition, there is a high association with PE and perinatal mortality. In contrast, late-onset FGR is normally associated with less severe placental disease and normal or minimally elevated UA Doppler indices but abnormal CPR and no obvious cardiovascular adaptation beyond the cerebral circulation.[5]

Early-onset FGR	*Late-onset FGR*
GA <32 weeks	GA >32 weeks
Prevalence: 1%	Prevalence: 3–5%
Severe placental disease: UA Doppler abnormal, high association with pre-eclampsia	Mild-placental disease: UA Doppler may be normal, low association with pre-eclampsia
Severe hypoxia	Mild hypoxia
High mortality and morbidity	Low mortality (but common cause of late still birth)
Challenge: Management	Challenge: Diagnosis

Q2. Is this a case of early-onset or late-onset FGR?

This case of early-onset FGR, presenting at 29 weeks of gestation. It is associated with severe preeclampsia and abnormal umbilical artery Doppler suggesting severe placental insufficiency.

Q3. When should this pregnancy be terminated?

As per the stage-based classification of FGR, this is a case of severe placental insufficiency with AEDV on UA Doppler. Once there is AEDV on UA Doppler in a preterm fetus, the risk of still birth increases. However, at the same time fetus has a high risk of neonatal death due to prematurity if pregnancy is terminated. DV Doppler should be done in these cases to decide the time of termination of pregnancy. As per RCOG guidelines.[4]

- In the preterm FGR fetus with umbilical artery AEDV detected prior to 32 weeks of gestation, delivery is recommended when DV Doppler becomes abnormal provided the fetus is considered viable and after completion of steroids.
- Even when DV Doppler is normal, delivery is recommended by 32–34 weeks of gestation.

However, since there is coexisting severe preeclampsia in this case, pregnancy might have to be terminated earlier in case of uncontrolled BP records, eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome or abruption.

Q4. What will be the ideal mode of delivery in this case?

The ideal mode of delivery in this case will be by an elective cesarean section at 34 weeks. In preterm fetuses with unfavorable cervix with serious fetal compromise like AEDV, BPP <4, delivery is ideally recommended by a cesarean section.

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Q5. Is there a role of therapeutic measures in management of pregnancies with FGR?

Many interventions have been tried to treat FGR, but there is no evidence from randomized controlled trials that any specific antenatal treatment is beneficial. The only interventions likely to be useful include treatment of the undrerlying causes such as hypertension, cessation of smoking and protein supplementation in poorly nourished women.

Bed rest in left lateral position is commonly advised in an attempt to increase uteroplacental blood flow. However, there is paucity of good evidence to draw any conclusion for or against the role of bed rest.[20]

Maternal nutritional supplementation with high caloric and protein diets various mineral and vitamins have all been tried to prevent and treat FGR. There is not enough evidence to recommend routine supplementation of any nutrients except probably protein energy supplements to poorly nourished women.[21]

Maternal Oxygen Therapy

Recent Cochrane review concluded that there is not enough evidence to evaluate the benefits and risks of maternal oxygen therapy for fetal growth restriction.[22]

Pharmacologic Therapy

There is no concrete evidence to support the use of various pharmacological agents like aspirin, beta mimetics, calcium channel blockers for management of FGR.

Q6. What is the role of sildenafil in FGR?

Sildenafil citrate is a phosphodiesterase inhibitor which augments the vasodilatory effects of nitric oxide (NO). Evidence suggests sildenafil citrate as a therapeutic strategy to improve uteroplacental blood flow, fetal growth, and meaningful outcomes in FGR pregnancies. Sildenafil administered at 25 mg 3 times a day in patients with early onset FGR has been shown to be associated with improved fetal growth velocity, as assessed by serial AC measurement by ultrasound.[23] At present the STRIDER (Sildenafil Therapy In Dismal prognosis Early-onset intrauterine growth Restriction) trial is under way to establish with certainty the true health benefits of sildenafil in FGR.[24]

Q7. What is the role of uterine artery Doppler in predicting FGR?

Uterine artery Doppler reflects trophoblastic invasion and identifies impedance on maternal side of placental circulation. It has been extensively evaluated as a screening tool for prediction of FGR with variable results.

At 20–24 weeks of gestation, uterine artery Doppler can detect a fetus at high risk of growth restriction, though its sensitivity is low. Women with an abnormal uterine artery Doppler at 20–24 weeks (defined as a PI >95th centile) and/or notching should be referred for serial ultrasound measurement of fetal size and assessment of wellbeing with umbilical artery Doppler commencing at 26–28 weeks of pregnancy.

In high-risk populations, uterine artery Doppler at 20–24 weeks of pregnancy has a moderate predictive value for a severely SGA neonate. However, screening an unselected population seems to be of limited value.[25] The predictive ability of uterine artery Doppler improves when used in combination with maternal characteristics, previous history and biomarkers. Hence, screening with uterine artery Doppler may be done in pregnancies at high risk of developing FGR.

Q8. What is the role of biochemical markers in prediction of FGR?

Numerous studies have also shown that some maternal biochemical markers [e.g. pregnancy associasted plasma protein-a (PAPP-A); alfa-fetoprotein (AFP); human chorionic gonadotropin, (hCG); inhibin A] are associated with placental function and fetal growth, and their levels are altered in FGR pregnancies . A low level (<0.4 MoM) first trimester PAPP-A should be considered a major risk factor for delivering a SGA neonate. The combination of uterine artery Doppler and maternal serum markers appears promising for improving prediction of SGA fetus, although predictive values are still poor.[26]

Q9. What are the different types of growth charts?

- Population-based growth chart
- Customized growth chart

Population growth charts are based on the analysis of large samples of fetuses starting from the principle that all the fetuses have the same growth potential.

However, there is a possibility that fetal size is influenced by race, ethnicity, sex, parity, maternal size and genetic factors. Customized growth charts were designed to identify the growth potential for individual fetuses. They were customized for maternal characteristics including height, weight, ethnic origin and parity.[27]

The use of customized growth charts is purported to increase the antenatal detection of fetal growth restriction, improving the distinction between normal and abnormal growth, but whether this improves clinical outcomes still has to be demonstrated. Customization is questioned by intergrowth 21st according to which growth patterns in

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