3. Removal of [illegible] in case of McDonald suture.
4. **Expedition of delivery** by inducing labour or by cesarean delivery depending upon the case (refer to the section on PPROM) is the most important treatment.

FOETAL GROWTH RESTRICTION (FGR) (SYN: INTRAUTERINE GROWTH RESTRICTION [IUGR])

Normal foetal growth is discussed in Chapter 5.

Previously called intrauterine growth retardation (IUGR), low birth weight infants who are small for gestational age (SGA) are now termed as suffering from foetal growth restriction. The term intrauterine growth retardation used in the past has now been discarded as retardation implies retarded mental function. FGR is **defined as failure of a fetus to reach its genetic growth potential inutero putting it at risk of perinatal mortality and morbidity.** Using the World Health Organization (WHO) cut-off, the term SGA is used when the newborn baby's weight is below the tenth precentile for its gestational age (ACOG).

Incidence

About 3 to 10% infants are growth restricted (12–40% in twin pregnancy). Many infants with birth weight less than the 10th percentile are preterm or small due to neonatal biological factors rather than being pathologically growth retarded.

Types

Delphi Consensus Criteria is used now for FGR and its classification and is shown in Table 34.9 and Table 34.10.

Table 34.9: Delphi Consensus Criteria for Foetal Growth Restriction and Classification (In absence of congenital anomalies, based on international Delphi consensus)

Early FGR (Formerly symmetrical FGR) (Gestational age < 32 weeks in absence of congenital anomalies)	Later FGR (Formerly asymmetrical 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 > 95 th 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: Foetal Growth Restriction, AC: Abnorminal Circumference, EFW: Estimated foetal weight, UA: Umbilical artery,	

Etiology

The various causes of foetal growth restriction are shown in Table 34.11.

Pathophysiology

There is reduction in the available nutrients and micronutrients to the fetus either due to their less availability to the mother (poverty or malnutrition) or their reduced placental transfer. In some cases there is faulty utilization of nutrients by the fetus. The end result is a small fetus with scanty liquor and reduced glycogen and fat stores.

There seems to be absence of invasion of trophoblast in media of spiral arteries with reduced cytotrophoblastic proliferation and impairment of placental angiogenesis in placenta of growth-restricted fetuses like in pre-eclampsia (see Fig. 32.1).

In the early stages of hypoxia, the fetus uses adaptive techniques such as growth reduction, decreased foetal movements and vascular redistribution to reduce its oxygen requirements, in an attempt to prevent hypoxic injury. There is stimulation of erythropoiesis with an increase in foetal hematocrit.

As the fetus becomes increasingly hypoxemic, there may be a decrease in flow to other organs and a corresponding increase in foetal blood flow to the brain, heart and adrenals. Failure of compensatory mechanisms cause abnormal foetal heart rate patterns (Fig. 34.4).

Complications

Maternal

Mother is usually not affected by FGR. However, various maternal diseases like pre-eclampsia, renal or other medical diseases causing FGR may adversely affect her general condition. There is increased incidence of FGR and stillbirths in subsequent pregnancies.

Table 34.10: Main clinical characteristics of early- and late-onset foetal growth restricton

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 - Typically sparing umbilical artery and ductus venosus
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 finding, mainly altered diffusion
Perinatal mortality	High	Low. However due to poor tolerance to hypoxia, more chances of still birth and poor long term outcomes.

Table 34.11: Causes of FGR

Causes of early onset of symmetrical FGR

1. Genetic factors; constitutional chromosomal and single gene defects (e.g. trisomy 21)
2. Congenital anomalies
3. Inborn errors of metabolism
4. Foetal infections (TORCH and CMV virus)
5. Exposure to teratogens
6. Radiation exposure

Causes of late onset of asymmetrical FGR

1. Hypertensive disorders of pregnancy
2. Anaemia
3. Hemoglobinopathies
4. Vasculopathies
5. Chronic renal disease
6. Cyanotic heart disease
7. Chronic partial separation of placenta
8. Extensive placental infarctions
9. Placenta previa
10. High altitude
11. Antiphospholipid antibody syndrome
12. Extrauterine pregnancy

Causes of Combined Type of FGR (Both early symmetrical and late asymmetrical)

1. Cigarette smoking
2. Drug abuse
3. Abruptio placentae
4. Placental infarcts
5. Circumvallate placenta
6. Velamentous insertion of umbilical cord
7. Multiple pregnancy

Foetal Complications

1. Risk of stillbirth due to chronic placental insufficiency
2. Non-reassuring foetal status (foetal distress) due to intrapartum hypoxia, acidosis and meconium aspiration.

1. Early Neonatal Complications

The neonates may have congenital malformations or chromosomal abnormalities. FGR neonates have very less subcutaneous fat and reduced muscle mass and are prone to following complications.

1. Metabolic complications
   - (i) Hypothermia: FGR fetuses are particularly susceptible to hypothermia due to reduced subcutaneous fat and small body mass.
   - (ii) Hypoglycemia due to reduced glycogen content.
   - (iii) Hypocalcemia from relative hypoparathyroidism.
   - (iv) Polycythemia from enhanced erythropoiesis due to chronic intrauterine hypoxia.
   - (v) Hyperviscosity syndrome from polycythemia
2. Complications due to asphyxia
   - (i) Hypoxic ischemic encephalopathy
   - (ii) Persistent foetal circulation
   - (iii) Meconium aspiration syndrome (due to oligohydramnios)
   - (iv) Necrotizing enterocolitis
   - (v) Pulmonary haemorrhage
   - (vi) Electrolyte imbalance
   - (vii) Metabolic acidosis

II. Late Neonatal Complications

1. Symmetrical growth restricted babies tend to grow slowly after birth. The asymmetrical growth restricted babies tend to catch up growth in early infancy.
2. Increased chances of retarded neurological, intellectual, cognitive and behavioural development and cerebral palsy in infancy especially in symmetrical FGR.
3. *Increased risk of cardiovascular disease, type 2 diabetes and hyperlipidemia in adulthood (Barker's hypothesis 1992) as such a fetus is programmed to exhibit a 'thrifty phenomenon' with increased food intake, fat deposition and decreased energy output. However, other authors have challenged this concept.*

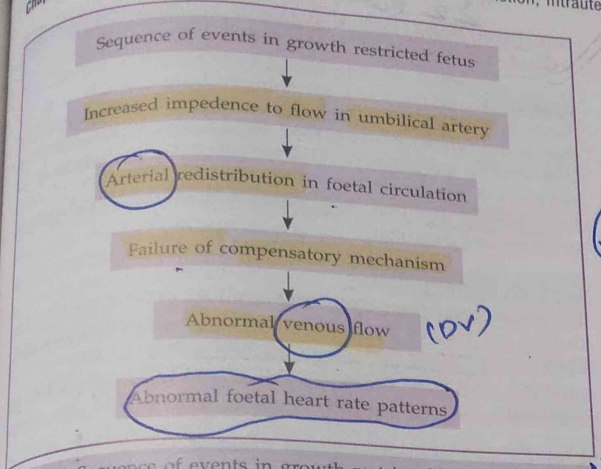

Fig. 34.4: Sequence of events in growth restricted fetus

Mortality

There is 6 to 8 fold increase in intrapartum and neonatal deaths. Most of the deaths occur within first 24 hours.

Prediction and Screening

Accurate prediction of the pregnancies destined to develop FGR would allow increased vigilance and foetal monitoring to enable interventions to improve outcome.

History and Examination

The various risk factors and causes should be enquired and observed.

Maternal Serum Screening

Various biochemical markers (AFP, uE_3, hPL and hCG) in the maternal serum in the second trimester have been used to detect foetal growth restriction in later pregnancy. PAPP-A <0.4 MoM in the first trimester is also used as a predictor for development of FGR later.

Ultrasound Markers

Abnormal uterine artery Doppler velocimetry and bright or echogenic foetal bowel in the second trimester are associated with an increased risk of subsequent FGR. The combination of unexplained elevated maternal AFP with abnormal uterine artery Doppler velocimetry or echogenic bowel is a better predictor of adverse perinatal outcome.

Scoring Systems

Several different scoring systems utilizing various risk factors for reduced foetal growth have been devised to better predict women at particular risk of having an FGR baby. Due to poor specificity and sensitivity, they are of limited clinical use.

Diagnosis

Clinical Examination

1. On obstetric palpation, if the height of the uterus is less by 4 weeks or more than the estimated gestation, foetal growth restriction should be suspected. An early accurate estimation of gestational age is needed for this method.
2. Symphysisfundal (symphyseofundal) height: Carefully performed serial fundal height measurement throughout pregnancy is a simple, safe, inexpensive, and reasonably accurate method to detect small for gestational age fetuses (see Chapters 8 and 9 for details). The uterine height in centimeters coincides with weeks of gestation between 18 and 30 weeks. If the measurement is 2–3 cm less, foetal growth restriction may be suspected. ACOG found it to be 70–85% sensitive and 96% specific. Serial measurements are needed.
3. Static or falling maternal weight after 20 weeks may indicate in FGR.
4. Static or falling abdominal girth measured at umbilicus may indicate FGR. The stage based classification and management of FGR is given in Table 34.12.

Ultrasound Measurements

1. Foetal Biometry

In foetal biometry, foetal biparietal diameter (BPD), head circumference (HC), femur length (FL) and abdominal circumference (AC) are measured to estimate the approximate foetal size. Of all these measurements, AC is considered to correlate with foetal weight. An AC within normal range for gestational age rules out FGR while an AC of < 5th percentile is highly suggestive of FGR (ACOG, 2000). It should be measured at the level of bifurcation of hepatic veins in the center of foetal liver. HC should be measured at the level of thalami.

2. Head Circumference (HC) and Abdominal Circumference (AC) Ratio

It is a useful ratio to diagnose and classify FGR especially late growth restriction. Normally, the HC/AC ratio is > 1.0 before 32 weeks, 1.0 at 32–34 weeks and < 1.0 after 34 weeks. In an late FGR fetus, the HC remains bigger, HC/AC ratio is increased. In early FGR the HC/AC ratio remains normal due to reduced HC and AC. Using HC/AC ratio, 85% FGR fetuses are diagnosed with reduced false negative rate. **AC is the most sensitive parameter to diagnose FGR.** Serial measurements are more useful.

3. Femur length

Femur length (FL) is relatively spared in late FGR. The normal FL/AC ratio is 22 from 21st weeks till term and does not need accurate gestation. A ratio > 23.5 diagnosis FGR.

4. Amniotic Fluid Volume

Amniotic fluid volume is usually reduced in late FGR. Vertical pocket of amniotic fluid < 2 cm and amniotic fluid index (AFI) less than 5 indicates oligohydramnios and FGR (see Chapters 4 and 15 for details).

5. Ponderal index (PI)

It is rarely used now. Ponderal index (PI) is calculated by dividing the estimated foetal weight in grams by the cube

of crown-heel length in centimeters (weight/length³). PI below 10th percentile is taken as FGR. It is usually < 2 in late FGR and 2 or more in early FGR and normal growth.

6. Other ultrasonic parameters

Reduction in fetal facial fat stores has been associated with FGR. Foetal structural abnormalities can also be excluded by ultrasonographic evaluation. Ultrasound does not predict all cases of FGR but has high negative predictive value. Transverse cerebellar diameter and AC (TCD/AC) ratio (normal 0.137) can be used for diagnosis of FGR.

Doppler Velocimetry

Elevated uterine artery systolic/diastolic (S/D) ratio (> 2.6) and/or presence of diastolic notch are associated with development of FGR. In a normal pregnancy, the diastolic flow increases with time. In a pregnancy complicated by placental vascular insufficiency, diastolic flow decreases leading on to increased in UA S/D ratio to more than 2 standard deviation (SD) above the mean for the gestational age. However, with worsening placental vascular insufficiency, UV waveform can show absent end diastolic flow and finally reversal end diastolic flow indicating foetal hypoxia and need to deliver the fetus urgently (see Chapter 15, Figs. 15.5–15.10 and Chapter 46 and Fig. 46.4 for details). Pulsatility index and sequential changes are used.

Physical features at birth

See Chapter 28 for details.

MANAGEMENT

Uncomplicated FGR before 37 weeks of gestation

If intrauterine restriction is suspected or diagnosed before 37 weeks of gestation, the objective of management will be to monitor the further growth of the fetus and assess foetal well-being. Any major foetal malformations must be excluded as they may be associated with FGR.

1. Rest

Rest is particularly important in developing countries like India where women may not be able to get adequate rest during pregnancy. At times it may be necessary to hospitalise her to ensure adequate rest. However, there is no evidence that bed rest causes accelerated foetal growth or improves outcome.

2. High Protein Diet

Inadequate and poor nutrition resulting in poor weight gain during pregnancy leads to intrauterine growth restriction. Hence, improving dietary intake with adequate calories and proteins may help in the further growth of fetus. Balanced diet with 300 extra calories per day should be given

3. Avoidance of Smoking and Alcohol

4. Pharmacological Interventions

Low dose aspirin, essential amino acids, arginine and lycopene are often used in FGR but their role is doubtful. Progestogens especially allylestrenol have been used in various studies to prevent FGR and preterm labour by increasing placental blood flow and secretion of placental enzymes, relaxing uterine muscles with accelerated foetal growth by its beta-adrenergic action. They can be given as allylestrenol (oral), 10 mg twice daily, oral natural micronized progesterone 200–400 mg daily, dydrogesterone 10 mg twice daily in second and third trimester.

Unfortunately no specific treatment improves outcome in FGR remote from term. Nutrient supplementation, attempting plasma volume expansion, oxygen therapy, antihypertensive therapy, heparin and aspirin have all been found to be ineffective (American College of Obstetricians and Gynecologists, 2000).

Table 34.1: Stage-based classification and management of FGR

Stage	Pathophysiological correlate	Criteria (any of)	Monitoring*	GA/mode of delivery
I	Severe smallness or mild placental insufficiency	• EFW < 3rd centile • UA PI > p95 • UtA PI > p95 • CPR < p5 • MCA PI <p5	Weekly	37 weeks LI
II	Severe placental insufficiency	UA AEDV/Reverse AoI	Biweekly	34 weeks CS
III	Low-suspicion foetal acidosis	UA REDV DV-PI >p95	1–2 days	30 weeks CS
IV	High-suspicion foetal acidosis	DV reverse a flow cCTG < 3 ms FHR decelerations	12 h	26 weeks** CS

All Doppler signs described above should be confirmed at least twice, ideally at least 12 h apart. GA = Gestational age; LI = labour induction; CS = cesarean section. * Recommended intervals in the absence of severe pre-eclampsia. If FGR is accompanied by this complication, strict foetal monitoring is warranted regardless of the stage. ** Lower GA threshold recommended according to current literature figures reporting at least 50% intact survival. Threshold could be tailored according to parents' wishes or adjusted according to local statistics of intact survival.

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5. Clinical Assessment of Foetal Growth

See above for details.

(i) **Clinical assessment of foetal growth.** Clinically, foetal growth is assessed by maternal weight gain and uterine growth charts which are measured weekly.

(ii) **Ultrasound assessment.** Foetal biometry is performed (see above for details) every 2 weeks.

6. Assessment of foetal well-being

The aim of antepartum foetal surveillance is to predict foetal asphyxia and thus prevent foetal death. FGR fetuses are more prone to intrauterine asphyxia. Careful assessment of foetal well-being and timely intervention when asphyxia is suspected improves perinatal outcome.

The tests of foetal well-being are discussed in Chapter 15 and tables 34.13 and 34.14. Dopper has definite role for FGR cases. Doppler studies of uterine arteries, umblical arteries, middle cerebral artery, ductus venosus are done (also see chapters 15 and 46 for details).

(i) **Growth Restriction Intervention Trial (GRIT 2004).** It was a multicentric RCT in European countries to compare effect of immediate delivery within 48 hours of steroid therapy and delayed delivery. There was no significant difference in two groups in perinatal outcome. Hence, delivery is indicated, when foetal danger is anticipated.

(ii) TRUFFLE (Trial of Randomized Umbilical and Foetal Flow in Europe) trial (2015): Ductus venosus Doppler evaluation was compared with foetal heart rate monitoring in 310 pregnancies between 26–32 weeks with FGR. The study concluded that before 34 weeks delaying delivery until ductus venous Doppler or foetal heart rate abnormalities appear is safe and benefits long term outcome.

(iii) DIGITAT (Disproportionate Intrauterine Growth Intervention Trial at Term) study (2010) examined the delivery timing of growth restricted fetuses who were at 36 weeks or older. The women were randomised to induction or expectant management. Neonatal morbidity at birth and neurodevelopmental and behaviour outcomes at 2 years were similar in 2 groups.

Table 34.13: Tests for Foetal Surveillance in IUGR

A. Long term (valid for 2 weeks)
1. Uterine artery Doppler 2. Placental morphology 3. Foetal biometry
B. Medium term (valid for 1 week)
1. Umbilical artery Doppler 2. Amniotic fluid volume and index
C. Short term (valid for 3–4 days)
1. Non-stress test 2. Biophysical profile score 3. Foetal middle cerebral artery (MCA) and ductus venosus Doppler studies

7. Obstetric Intervention

If the foetal growth is satisfactory and the foetal surveillance tests indicate that the fetus is not in distress, then the pregnancy is allowed to continue till 37 weeks. However, if the fetus is not well according to the biophysical profile or for severe degree of FGR, then termination of pregnancy is required as per table 34.12. This decision will have to be taken according to the neonatal care available since these newborns require a good neonatal unit to survive.

Pulmonary maturity tests can be performed and four doses (6 mg each) of dexamethasone or two doses (12 mg each) of betamethasone are given for pulmonary maturation before 34 weeks gestation as they reduce the incidence of hyaline membrane disease, cerebral haemorrhage and death in fetuses weighing less than 1.5 kg.

TERMINATION OF PREGNANCY

Pregnancy is terminated based on stage of disease and also depends on various factors like gestational age, any congenital abnormalities, severity and type of FGR, past obstetric history, severity of foetal compromise by NST, CTG and biophysical profile.

WARNING SIGNS

Prompt intervention to be done:

1. Progression of umbilical artery end diastolic flow (EDF) from reduced to absent and then to reverse flow
2. CTG—Lack of variability, presence of late decelerations

Table 34.14: Interpretation of Antenatal Testing

Antenatal testing	Interpretation
1. Positive UA EDV Normal MCA and DV, amniotic fluid pocket > 2, BPS > 8/10	**Normal. Asphyxia (hypoxia) extremely rare**
2. Same as above with brain sparing MCA	Blood flow redistribution **hypoxia possible**, higher risk of intrapartum distress
3. UA EDV, DV normal, BPS > 8/10, amniotic fluid pocket < 2	Significant redistribution **hypoxia common**, asphyxia/acidemia possible. **Onset of foetal compromise**
4. Significant redistribution, increased DV pulsatility, BPS > 6/10, amniotic fluid < 2	**Foetal compromise, hypoxia common.** Asphyxia and acidemia likely
5. Compromise by above criteria, BPS < 6/10, amniotic fluid < 2	**Foetal decompensation** and cardiovascular/metabolic compromise, **imminent stillbirth, poor outcome**

UA EDV: Umbilical artery end diastolic velocity; MCA: Middle cerebral artery; BPS: Biophysical score; DV: Ductus venosus; REDV: Reversal of end diastolic velocity

3. Biophysical score < 4
4. Abnormal venous Doppler in presence of absent EDF in umbilical artery
5. Oligohydramnios

INDUCTION OF LABOUR

Such women should be delivered in well-equipped centers (tertiary referral hospitals) with facilities for intrapartum continuous foetal heart monitoring, foetal blood sampling and neonatal intensive care unit (NICU) facilities.

Mode of delivery depends mainly upon gestational age and any foetal distress. Vaginal delivery is allowed if there is no indication of cesarean delivery and foetal heart rate is normal. Fetuses with major congenital abnormalities should also be delivered vaginally.

Induction of labour is performed depending upon Bishop's score. If Bishop's score is unfavourable (< 6),

FGR (IUGR) Pregnancy

1. History taking: Smoking, alcoholism, drug addiction, dietary history, regularity of previous menstrual cycle. Rule out mistaken dates.
2. General physical examination: Pallor, malnutrition, medical problem
3. Abdominal examination (4 weeks discrepancy)
4. Confirm the diagnosis and type of FGR by ultrasound; Perform foetal biometry (BPD, HC, FL, AC, Estimated foetal weight, HC/AC. FL/AC ratio), amniotic fluid index, rule out foetal congenital malformation, aneuploidy syndromes and TORCH and other viral infections.
5. Foetal monitoring
   (a) Daily foetal movement count
   (b) Cardiotocography, NST
   (c) Biophysical profile (Manning score)
   (d) Umbilical artery Doppler flow velocimetry, middle cerebral artery, (MCA) Doppler

- Pregnancy < 37 weeks
  - Early onset
    - Inutero transfer to a referral center
      - Admission
        1. Bed rest
        2. Folic acid, iron, calcium and protein supplements
        3. (Betamethasone) therapy if < 34 weeks
        4. Low dose aspirin or antioxidants or arginine or progestogens (doubtful value)
      - Biweekly NST, weekly umbilical artery and MCA Doppler
        - NST, UA/MCA Doppler remain normal
          - Deliver at 37 weeks
        - Normal NST, decreased or absent end diastolic flow on Doppler
          - Deliver at 34 weeks (cesarean is recommended)
        - Reversal of end diastolic flow in umbilical artery, ominous NST or poor biophysical profile (4 and less)
          - Immediate delivery especially if > 32 weeks (usually cesarean is needed)
          - Cesarean delivery for unfavourable cervix and foetal distress
  - Late onset
    1. Bed rest
    2. Iron and folic acid, calcium supplements
    3. Arginine, aspirin, antioxidant and progestrogens (doubtful value)
    4. Foetal surveillance until 37 weeks (NST, Biophysical profile, Doppler studies)
    - Induction of labour
      - Delivery at 38 weeks
      - Cesarean delivery for unfavourable cervix or foetal distress
- Pregnancy ≥ 37 weeks

Flow Chart 34.3: Management of FGR (IUGR)