Intra Uterine Growth retardation

Shobhana Mohandas

Intra uterine growth retardation is one of the most vexing problems facing the obstetrician. IUGR could cause concern in two ways. A seemingly uneventful pregnancy with both the obstetrician and the patient in a positive mood could suddenly turn topsy-turvy, with IUGR setting in slowly at first, with either foetal loss in the end or endless days of monitoring and sometimes more days in the neonatal nursery with hopeful anticipation.

Etiology of IUGR:

Intra uterine growth retardation can occur due to fetoplacental or maternal causes.

Fetoplacental:.

Foetal causes: Various chromosomal anomalies, genetic syndromes, congenital malformations and intrauterine infections like Cytomgalovirus or Toxoplasmosis could cause IUGR. IUGR sets in before 20 weeks in the case of anomalies and soon after infection is contracted in the case of intra-uterine infections. It is important to rule out the presence of abnormalities before treating the patient, as it would be a fruitless exercise otherwise.

Placental pathology: An absolute or relative decrease in placental mass affects the quantity of substrate the fetus receives and has been recognized ultrasonographically to antedate fetal growth restriction.

Maternal factors: History of fetal growth restriction, Hypertension, Diabetes mellitus,Elevated MSAFP/hCG, Antiphospholipid syndrome,Chronic medical illnesses, Low maternal prepregnancy weight (<90% IBW), Poor maternal weight gain,Twin gestation,Substance abuse (tobacco,alcohol, drugs),Preterm labor, Abnormalities of placentation,Vaginal bleeding,Maternal anemia (Hgb < 10) ,Maternal hypoxia (cyanotic cardiac, or pulmonary disease, altitude),Maternal hemoglobinopathies & Drug ingestion (hydantoin, coumarin).

Maternal malnutrition: There is a controversy on whether maternal malnutrition can cause IUGR, but in one study, it was proved that protein malnutrition before 26 weeks can cause IUGR. Glucose is a critical fetal nutrient, and if its supply is reduced growth restriction may result. Sokol et al and Langer et al have confirmed that a flat maternal response to glucose loading is associated with an increased risk for fetal growth restriction. Langer et al demonstrated that a "flat" GTT was associated with a 20-fold increase in IUGR in normotensive patients.

Previous H/O IUGR: Women whose first pregnancy results in a growth-restricted infant have a one in four risk of delivering a second infant below the 10th percentile. After two pregnancies complicated by IUGR, there is a fourfold increase in the risk of a subsequent growth-restricted infant. Increased maternal age is not associated with increased incidence of IUGR.

Diagnosis: In women with maternal factors that could lead to IUGR, screening for IUGR should start from the first trimester itself. A gestational age calculated by ultrasound in the first trimester, could help as an index in monitoring further growth of the baby. In case of conditions like Antiphosopholipid syndrome, biochemical testing should start from the first trimester itself. In women who are not at risk to start with, the clinician should have a high index of suspicion to detect the foetus that is not growing on par with its peers. After having decided that the baby is not growing as well as it should, the clinician has to further decide whether the baby is really facing adverse conditions in utero (IUGR) or is merely small by virtue of genetic make up (Small for Gestational Age or SGA).

Clinical examination: Belizan et al. observed that curvilinear fundal height measurements in centimeters from the symphysis pubis could be closely correlated with gestational age: a lag of 4 cm or more suggests growth restriction

Ultrasonography: Ultrasound parameters important in evaluation of IUGR are

1.Oligohydramnios: Oligohydramnios in the absence of PROM or congenital anomalies is suggestive of IUGR.

2. Placental grade. When fetal growth pattern and estimated weight suggest a small fetus, the finding of a Grade III placenta can be used as adjunctive evidence of IUGR. . 3..Suspect IUGR by ultrasound if a.AC falls in the lower 15th percentile. b.Weight falls in the lower 15th percentile. c.FL/AC 23.5%. d.HC/AC 95%.

4..When gestational age cannot be established by the menstrual history, the assessment of fetal risk for IUGR must rely on fetal disproportionality for the determination of asymmetric IUGR, and on serial assessments of fetal growth for symmetric IUGR. Symmetric IUGR may be very difficult to diagnose without serial ultrasound studies.

Doppler parametres: Doppler USG helps in determining foetal well being. . The 3 commonly used indices are the Systolic/Diastolic ratio(S/D ratio), the resistive index and the pulsatility index.

Umbilical vessel: The most commonly studied vessel is the umbilical artery as it is one of the easiest target to visualize.

Umbilical artery Doppler study

(Normal range)

Weeks of Gestation	Pulsatiliy index(PI)	Resistive index(RI)	Systolic/ Diastolic(S/D) Ratio
28 weeks	0.80-1.30	0.58-0.76	2.1-4.72
30weeks	0.76-1.25	0.56-0.74	2.0-4.0
32weeks	0 .72-1.20	0.54-0.72	1.9-3.8
36weeks	0.68-1.10	0.48-0.68	1.8-3.3
38weeks	0.64-1.00	0.46-0.66	1.8-3.0
40weeks	0.60-0.95	0.44-0.64	1.7-2.8

The cerebral vessels:Study of the middle cerebral vessel as it exits the circle of willis adds to the information provided by studying the umbilical artery. The hypoxic fetus tries to maintain the normal oxygen supply to the brain

by dilating the cerebral vessels. This is called the brain-sparing effect.The dilatation of middle cerebral vessels in addition to abnormal Doppler indices in the umbilical artery should prompt the obstetritian to intensively monitor the fetus. As hypoxemia progresses, in absence of any interventions, the cerebral vessels also constrict, and this is a sign of imminent fetal demise. The ratio of the middle cerebral artery to umbilical artery Doppler systolic-to-diastolic ratios (the cerebroplacental ratio) is possibly a better predictor of adverse outcome than the ratio in either of the vessels on their own (i.e., a cerebroplacental ratio of <1.0)

Biochemical markers: . Erythropoietin, identified in the cord blood of growth-restricted fetuses by cordocentesis, amniotic fluid, or cord blood at delivery, Fetal cord blood glycine/valine ratios, decreased levels of Pregnancy-Associated Plasma Protein A as early as 14 weeks are all useful in identifying IUGR.

Management:

Once IUGR is suspected , the parameters for fetal well being should be clearly studied to distinguish it from the normally growing small baby. The normal fetuses should be left alone. Again if IUGR has developed very early, it is usually associated with congenitally abnormal fetuses or irrevocable fetal infections. It is only in the remaining group, where IUGR is detected in the late trimester that some fetoplacental deficiency can be deemed to be responsible for the situation. Here corrective measures may be undertaken and the fetus should undergo intensive antenatal surveillance. When the fetus is found to be in jeopardy in utero and one is reasonably sure of it's surviving outside, it should be taken out and nurtured in the nursery.

IUGR in the first half of pregnancy:

In patients at high risk for IUGR, routine screening for IUGR should be started from the beginning of pregnancy itself.

Antiphospholipid antibodies: Antiphospholipid antibodies being a common and treatable cause of IUGR, it should be looked for in the first trimester by testing the maternal serum for Anticardiolipin antibodies and Activated Partial Thromboplastin time. There are many other tests for the screening of this condition, but the above 2 tests are the locally available tests.

Treatment options for Anticardiolipin antibody syndrome:

The treatment options are:

1.Low dose Aspirin.

2.Heparin : Heparin can be given as unfractionated heparin, 5000IU 12 hrly. However, this is being replaced by low molecular weight heparin currently. It is more expensive, but has the advantage of lesser incidence of thrombocytopenia and osteoporosis and has a longer half life, necessitating only a once daily dosage regimen. The commonly used Low molecular weight heparin preparations are, Enoxaparin, Dalteparin and Nadroparin.. The doses are: Enoxaparin: 40mg/day, Dalteparin 5000U/day, Nadrroparin:0.3-0.6ml/day. There is no advantage of one preparation over another. Treatment has to be continued till delivery. Patients could be treated either with Aspirin 75mg daily till delivery or by a combination of Aspirin and low molecular weight heparin. The most significant risk of heparin therapy is osteopenia and the patient must take 1 gm of calcium and walk for at least 30 minutes a day. Platelet count should be done periodically to look for thrombocytopenia.

3. Intravenous immunoglobulins: There are conflicting reports about the added advantage of adding intravenous immunoglobulins. Thus IVIG may be used when pregnancy failure has occurred despite heparin use. A dose of 0.3g/kg immunoglobulin given every four weeks till 32 weeks is commonly used.

5.Corticosteroids: Use of Prednisone 40mg/day, in combination with Aspirin has been shown to be effective in reducing ACL. However, the incidence of osteoporosis is higher with this regime. I have given this regimen to a

few ACL moderately positive patients with satisfactory patients. In patients from lower socio-economic strata, who cannot afford the heparin therapy, it could be taken as an alternative. In my patients prednisone was tapered by 5th month, aspirin continuing.

Foetal infections,Rh isoimmunisation,Chromosomal anomalies: Role for Foetal transfusion:

Other than The APL syndrome, IUGR in the first half of pregnancy is commonly associated with fetal infections, chromosomal anomalies or Rh isoimmunisation. If the woman is Rh negative, isoimmunisation should be looked for. In cases of Rh isoimmunisation, as also in cases of suspected fetal infections, if there are signs of hypdrops fetalis, seen on ultrasound, cordocentecis should be done . The cord blood obtained should be used to look for fetal anaemia. The same sample could be sent for chromosomal analysis. After ruling out fatal congenital anomalies/chromosomal anomalies. Giving intrauterine transfusions can treat fetal anaemia, repeated periodically if necessary. Some cases of hydrops could be salvaged thus.

Treatment of Maternal conditions : When a maternal medical problem such as inflammatory bowel disease is contributing to poor growth, specific therapy should be instituted. Alleviation of hypoxia, therapy of high blood pressure and anemia, and hyperalimentation are three examples.

IUGR in later pregnancy: Once growth restriction is suspected, maternal conditions like hypertension, anemia,malnutrition,etc should be diagnosed and treated.

Role of protein supplementation and micronutrients:

1.Protein: Investigation of Guatemalan Indian tribes has indicated that

protein malnutrition before 26 weeks can result in symmetric growth restriction.

Protein restriction after 26 weeks did not limit fetal growth.

2.Vitamin E therapy: In one study, Vitamin E supplementation was found to be associated with a significant decrease in the incidence of preeclampsia and the intervention group had fewer SGA babies

3.Folic acid: Although better-quality trials, all in developed countries, have shown no effect of folic acid supplementation on birth weight, two from developing countries [India and South Africa] showed large increases.

4. Vitamin C: Several observational studies showed positive correlations between maternal vitamin C status and birth weight.

5. Iron: Evidence from developing countries, where iron deficiency anemia is common, shows that maternal iron deficiency is associated with low birth weight and poor obstetric outcome.

6. Zinc: A large well-conducted study of 580 U.S. women with low serum zinc concentrationsshowed a significant increase in birth weight (+126 g), head circumference (+0.4 cm) and limb length in the supplemented group

7. Calcium: Belizan et al found that children whose mothers were supplemented with calcium in pregnancy had lower bloodpressures. Other studies have also proved that in a women with low calcium intake, calcium therapy is useful in preventing pre-ecclampsia

8. Magnesium: The Cochrane review included 6 trials of magnesium, mainly focusing on hypertension as an outcome. The meta-analysis showed a beneficial effect on low birth weight and smallness for gestational age.

Omega 3 fatty acids and Arginine:

Omega –3 fatty acids: Patients supplemented with either 920 mg of DocasoHexanoic acid (DHA) and 1.3 g of Ecisopentanoic acid (EPA) per day (total n-3 fatty acid intake of 2.7 g per day) were found to have fewer low-birth-weight infants (LBW), preterm infants. On average, gestational length was increased from 4 to almost 6 days in women taking the omega-3 fatty acids.

L Arginine:In one study,3 groups of nine pregnant women each were infused i.v. with 30 g ARG, for 30 minutes. This was followed by a significant decrease of non-placental side resistances in IUGR-B women. The pulsatility index was lowered by 14%, in respect of baseline value. These findings suggest that L-Arginine infusion affects utero-placental circulation in patients with IUGR associated with increased uterine resistances. Such an action is specific and appears possibly to be mediated by a release of nitric oxide.In another study, L-arginine 3 x 1 g oral dose daily in IUGR patients was found to reduce the oxidative stress risk,and the total antioxidative activity in blood serum decreased in pregnancies connected with IUGR. Oral L-Arginine is marketed in Kerala.

Other interventions:

1.Glyceryle trinitrate patches: In one study, Transdermal glyceryl trinitrate (Nitroderm TTS; Ciba-Geigy) at a dose of 5 mg/16 h daily until delivery in 51 pregnant women (gestational age, 27–35 weeks) with IUGR fetuses and impaired uteroplacental blood flow was associated with a significant decrease in uterine artery RI and the UA PI , whereas no significant difference was found in MCA PI This produced a higher mean gestational age at delivery in the treated group.

2.Hydration therapy: Oligohydramnios is an almost invariable accompaniment of IUGR. The simple measure of drinking 2 litres of fluids per day in several studies have shown to increase the Amniotic fluid index and prevent oligohydramnios.

3. Low dose Aspirin: One famous study, the CLASP study did not show any significant dcrease in IUGR or Pre-ecclampsia with routine administration of low dose aspirin, but acknowledged that, "low-dose aspirin may be justified in women judged to be especially liable to early-onset pre-eclampsia severe enough to need very preterm delivery. " Higher doses (100 to 150 mg/day) may be significantly more effective in preventing IUGR than

lower doses (50 to 80 mg/day. In another study, efficacy of aspirin seemed optimal when bleeding time increased by 2 minutes with treatment, indicating a more powerful antiplatelet effect.. The dose of aspirin has to be increased till the effect of increasing Bleeding time is achieved. Use of low-dose Aspirin (100 mg) at night, rather than in the morning, was more effective in reducing Blood pressure for women at high risk for pre-eclampsia in a recent study .

4.Maternal oxygen therapy: Ribbert et al provided maternal oxygen therapy (2.5 L/min nasalprong) to four growth-restricted infants at 27 to 28 weeks and found they could prolong pregnancy by 9 days. Overall, maternal hyperoxygenation may be of value for the safe, short-term prolongation (For a week or so) of pregnancy

5. Rest in lateral position has been shown to improve placental circulation.

6.Amnioinfusion: In a study where 113 pregnant women at 16-34 weeks gestation, with severe oligohydramnios were treated by amnioinfusion, and was found to be beneficial to the course of pregnancy with no adverse side effects. Basically amnioinfusion consisted of injecting a 0.9% lactated Ringer solution at an infusion rate of 30-50ml/minunder ultrasound guidance through a 150mm 20 g needle. The volume infused was 10ml/gestational week. Amnioinfusion was repeated whenever te AFI reduced to </+5, except when it occurred within 12 hours of infusion, as this indicated a large membrane rupture. Prophylactic antibiotics were given. Tocolytic therapy was given only on indication.

Fetal surveillance: While all correctable medical factors are being corrected, the fetus should be closely observed for signs of hypoxia.

The foetus should be assessed using biophysical profile and amniotic fluid volume on ultrasound and the Non Stress Test(NST) using electronic fetal monitor.

Biophysical profile: Manning in 1980 devised a scoring system to know fetal well being on ultrasound: It is as follows:

-- Fetal BPP Scoring According to Manning

Variable	Score 2	Score 0
FBM	The presence of at least 30 sec of sustained FBM in 30 min of observation	<30 sec of FBM in 30 min
FM	Three or more gross body movements in 30, min of observation simultaneous limb and trunk movements are counted as a single movement	Two or fewer gross body movements in 30 min of observation
FT	At least one episode of motion of a limb from a position of flexion to extension and a rapid return to flexion	Fetus in a position of semi- or full-limb extension with no return to flexon with movement: absence of fetal movement is counted as

absent tone

Fetal reactivity

The presence of two or more FHR accelerations of at least 15 bpm and lasting at least 15 sec and associated with FM in 40 min	No acceleration or less than two accelerations or the fetal heart rate in 40 min of observation

Qual AF volume

A pocket of amniotic fluid that measures at least 1 cm in two perpendicular planes	Largest pocket of amniotic fluid measures <1 in two perpendicular planes.

Maximal score= 10 Minimal score:0.{FT=fetal trunk mvt. FB=fetal body mvt}

Non stess test:Fetal heart variabilities of 5-15 per fetal movement is considered a reactive NST and is reassuring.

Doppler studies:

Based on the results of randomized, controlled trials (RCTs), Doppler vascular ultrasound assessment as part of a fetal well-being evaluation may be performed for the following clinical indications:

Fetal umbilical artery (many RCTs)

Suspected fetal growth retardation

Maternal hypertension

Previous complicated pregnancy (fetal growth retardation, fetal death in utero)

Maternal collagen vascular disorders (systemic lupus erythematosus,

antiphospholipid syndrome)

Maternal vascular disease (diabetes mellitus, vasculopathies)

Fetal middle cerebral artery (few RCTs)

Suspected fetal growth retardation

Maternal blood group isoimmunization

Other fetal vessels (no RCTs to date)

Place in clinical management not established .

Frequency of evaluation:Patients should be managed expectantly with

1. Twice weekly nonstress test (NST) and amniotic fluid assessment,

2.Biophysical profile (BPP) in the presence of nonreactive NST,

3. Utrasonographic measurements of fetal biometry every 2 weeks, and

4.Doppler velocimetry studies of the uterine arteries at diagnosis of FGR, and fetal umbilical and middle cerebral arteries every 2 weeks, or more frequently if results are abnormal.

Hospitalisation: In the presence of abnormal Doppler indices , the patient should be hospitalized and monitored every day for fetal well being till delivery at 37 weeks if there is no further deterioration.

Timing of delivery:Delivery should be expedited in the presence of nonreassuring testing of fetal well-being, defined as

1. BPP score of 6 or less on two occasions 24 hours apart with nonreactive NST;

2.Oligohydramnios, defined as the largest amniotic fluid pocket less than 2 × 2 cm; lack of growth of the abdominal circumference over 2 weeks;

3.Absent or reversed diastolic flow in the UA; or preeclampsia.

Intra partum amnioinfusion: In one study, prophylactic intrapartum amnioinfusion after 4cm cervical dilatation in patients with severe oligohydramnios (AFI</= 5) was found to reduce the need for LSCS. Women had an intrauterine pressure catheter (Corometric Trans-cervical intra-uterine kit) through which an infusion was given of 500 ml normal saline solution at 37 °C, as a bolus during a period of 30 min (15–25 ml/min) followed by continuous infusion of 500 ml by gravity . After the end of infusion of 1000 ml ultrasonic re-evaluation of AF was done. There

was a significant increase of AFI from a mean of 3.2±1.3 cm before the procedure to 11.8±1.5 cm after infusion of 1000 ml of saline, with a mean increase of (8.6±1.4 cm). There were no recorded cases of infusion failures. No infusions had to be stopped for fetal distress or delivery.

Elective caesarian section: Elective cesarean delivery should be performed in the presence of nonreassuring testing of fetal well-being .

Neonatal care:

The new born IUGR baby is in danger of developing, Birth asphyxia, Meconium aspiration, Hypoglycemia, Hypocalcemia, Hypothermia,Polycythemia, hyperviscosity, hyperbilirubinemia, Thrombocytopenia, Pulmonary hemorrhage, Malformations, Sepsis, Respiratory distress syndrome and Necrotizing enterocolitis. They need expert neonatal care. Recent studies have shown that IUGR does not provide protection against RDS in the preterm infant. In fact, IUGR in one study, was shown to be one of the factors responsible for preterm labour.

Long term morbidity: The ultimate growth potential for growth-restricted infants appears to be good. The degree of catch-up growth observed in several longitudinal studies suggests that these infants can be expected to have normal growth curves and normal albeit slightly reduced size as adults.

Conclusion: A lot of advances have come up in the field of fetomaternal medicine like improved ultrasound facilities, interventional procedures like fetal transfusion, etc. Increased awareness about these facilities can highly improve the salvage rate of the IUGR infant.