INTRA-UTERINE GROWTH RESTRICTION – OBSTETRICIAN'S PERSPECTIVE

Sharad Gogate*

ABSTRACT

Intra Uterine Growth Restriction (IUGR) is a serious anomaly in the antenatal period, responsible for many folds increase in the pregnancy wastage, neonatal morbidity and mortality as well as long-term serious complications like dyslipidaemia, type 2 diabetes, atherosclerosis and premature death. The aetiology of IUGR is very diverse and the presentation insidious and confusing hence diagnosis can be quite difficult especially in early stages. The IUGR can be asymmetrical or symmetrical depending upon the aetiology and time of onset.

Detailed history taking, looking out for the high risk factors and vigilant clinical monitoring, along with use of Ultrasonography, and Doppler studies, are essential for early and accurate diagnosis. Once the diagnosis of IUGR is reached the mother and foetus should be under close scrutiny, any complicating factors identified should be ameliorated (whenever possible) and all attempts should be made to take the pregnancy to viability and maturity (30 weeks or more). The delivery of these high risk, delicate foetuses should be handled with extreme care as these babies can not stand prolonged labour. Presence of expert neonatal support is also essential for resuscitation as well as follow-up to look for long-term complications.

Although many treatment modalities are advocated in IUGR, none have come true in critical evaluation, hence there is urgent need for further intensive research in IUGR.

KEY WORDS : IUGR, Foetal programming, Foetal biometry, Cordocentesis.

INTRODUCTION

The development of a fertilised ovum into a complex, fully formed and healthy foetus is one of the most fascinating wonders of the nature. As the health care provider, it is the obstetrician who is responsible for taking the pregnant woman and her baby through this wonderful sojourn.

At cellular level the formation of the foetus consists of multiplication and differentiation of body cells into various organ systems (phase of organogenesis), hyperplasia of cells and hypertrophy of cell organelles and cytoplasm. The first of these, i.e. multiplication and differentiation, takes place in the first trimester, hyperplasia continues in second trimester, while cell hypertrophy takes place in the late second trimester and third trimester resulting in the increase in the body weight and size, as well as maturation of various systems. Proper foetal programming, successful adaptations of the maternal metabolism to the pregnancy and absolute fine tuning of the interplay between maternal and foetal metabolisms, are the essential pre-requisites for the successful culmination of pregnancy.

Although the foetus is a total parasite dependent on the maternal metabolism, it is not a passive recipient accepting whatever comes it's way. It takes what ever is needed by it's metabolism actively from the mother, by modulating the placental function and maternal metabolism. The placenta plays multiple roles in the development of the pregnancy as an organ of transfer of nutrients and metabolic waste products, performs complex and hitherto ill understood metabolic functions and acts as the paracrine and endocrine arm of the foeto-placental unit (1).

INTRA-UTERINE GROWTH RESTRICTION

Definition:

When the hyperplasia and hypertrophy in the second and third trimesters take place in a sub-optimal manner it results in deficient growth in the foetal weight, size and maturation of the foetal metabolism, which is called as Intra-Uterine Growth Restriction (IUGR). Despite vast scientific research done on the topic, the exact definition of IUGR still eludes us. In the most frequently followed definition, emphasis is on the post delivery weight of the foetus i.e. < 5-10 percentiles of the birth weight along with anthropometric measurements like ponderal index (PI), mid arm circumference (MAC), skin fold thickness and abdominal and head circumferences (AC, HC). There are many confounding variables like maternal height and weight, race, foetal sex, and birth weight of previous pregnancies, which make the diagnosis of IUGR more difficult (2).

Foetal Medicine Clinic, LTM Medical College & Hospital,Surlata Hospital, L.J. Road, Mumbai 400016, India.

Effects of IUGR:

It has been well documented that IUGR results in several fold increase in stillbirth, and pre-term labour. There is increased neonatal morbidity and mortality due to birth asphyxia, respiratory distress syndrome (RDS), meconium aspiration, neonatal sepsis, hypoglycaemia and hypothermia. There are immediate neurological abnormalities and deficiencies, but there are no major developmental handicaps on 2-4 years follow-up. The pioneering work of Prof Barker and the extensive retrospective and prospective studies of IUGR babies has conclusively proved that there is definite link IUGR (with insulin resistance) and increased risk of dyslipidaemia, type two diabetes mellitus, hypertension, coronary heart disease and premature death.

Incidence:

The incidence of IUGR varies from region to region and even in the same region it varies in different sub populations. In India , according to recent UNICEF surveys, the incidence of IUGR is 25-30%.

Aetiology:

IUGR has got very mixed aetiology and in large percentage of cases one cannot identify the exact cause. Some of the important causes of IUGR are,

- **Maternal:** Chronic malnutrition/starvation, severe anaemia, mal-absorption syndrome, excessive energy consumption by mother like athletes/heavy manual labour, addictions (alcohol, smoking, drugs), cyanotic heart diseases, chronic respiratory diseases, pregnancy induced hypertension with/without proteinuric hypertension, antiphospolipid antibody syndrome, sickle cell disease, chronic renal and collagen diseases, recurrent ante-partum haemorrhages, high altitude with resultant hypoxia and constitutionally small mother.

- **Placental:** Chronic placental separation and placental infarcts, chorioangioma of placenta, veilamentous insertion of cord, circumvallate placenta, utero-placental insufficiency.

- **Foetal:** *Chromosomal anomalies* e.g. Trisomy 18,13.21, Trisomy 16 (confined to placenta), *structural anomalies* e.g. congenital heart disease, NTD, collagen and musculo-skeletal disorders, *Foetal infections* e.g. viral infections like rubella, cytomegalovirus, hepatits A and B, listeriosis, tuberculosis, protozoan infections like toxoplasma, malaria, *teratogens* like anticonvulsants, anticoagulants, alcohol, narcotics. Multiple gestations are associated with moderate IUGR.

The list is far from complete and more than one etiological factors may be responsible in any given case. Conventionally the IUGR is classified into two types, *Symmetrical IUGR*, where there is symmetrical reduction in foetal measurements of body and head. This is because the restriction in growth starts early in second trimester (hyperplasia, hypertrophy stage). constitutionally small foetus, chromosomal anomalies, teratogens and foetal infections in early pregnancy are the likely causes. In contrast in *asymmetrical IUGR*, the restriction in growth starts in late second and third trimesters (hypertrophy phase) due to utero-placental insufficiency and due to the brain sparing foetal physiological changes. there is continued growth of head while rest of the body growth is restricted resulting in disparity between head and rest of the body growth i.e. *asymmetrical IUGR*. In actual practice we find an overlap in these two varieties in many cases (3).

MANAGEMENT OF IUGR:

The basic management of IUGR consists of,

- Early and reliable diagnosis of IUGR

- Close ante-natal monitoring, amelioration of causative pathology (if identified), therapy to prevent IUGR.

- Optimum timing, mode of delivery, intra-partum management.

- Neonatal management.

- Prevention/ reduction of IUGR in subsequent pregnancies.

Diagnosis of IUGR:

1. A detailed history elicitation to look for any of the aetiological factors and relevant investigations.

2. Accurate dating of the pregnancy with detailed menstrual history, first trimester/early second trimester USG scan for accurate dating.

3. Meticulous record of maternal weight gain and fundal height measurement.

4. Ultrasonography parameters like abdominal circumference (AC) < 5th centile, foetal growth lagging by >1.5SD in two weeks, amniotic fluid index (AFI) <5centile and abnormal Doppler studies of uterine arteries and umbilical artery.

5. Cerebellar diameter is another important measurement, as it is largely unaffected even in moderate to severe IUGR and is dependable measurement between 18-40 weeks of pregnancy.

The percentile birth weight graph is shown in Fig.1.

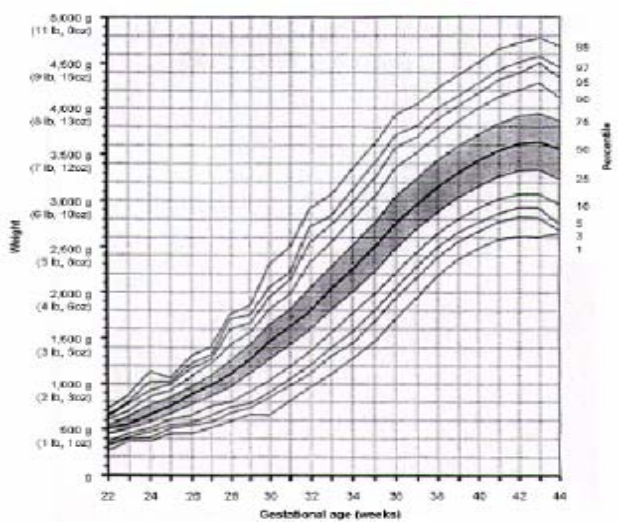

Figure 1 : Percentile birth weight graph (3)

Close ante-natal monitoring and treatment:

Once a diagnosis of IUGR is made, the pregnancy should be closely monitored by frequent clinical check-ups, serial ultrasound scans, Doppler studies and invasive tests like cordocentesis or placental biopsy (to rule out chromosomal defects, infection, biochemical studies). As the IUGR foetuses tolerate cordocentesis poorly and Doppler studies correlate quite well with foetal acidosis/hypoxia, it is not recommended for evaluating the severity of IUGR. Biophysical profile, non stress test are also used to monitor foetal well being and to decide the optimum time and mode of delivery. One has to strike a compromise between risk of intra uterine foetal demise and risk of gross prematurity (<32weeks).

The Doppler studies should include uterine artery, umbilical artery, middle cerebral artery and foetal aorta. Notches in diastole in the uterine artery, abnormal pulsitility index (PI), and resistance index (RI) point toward possibility of IUGR. Calculation of PI between middle cerebral artery and foetal descending aorta / umbilical artery, is useful to evaluate the deterioration in IUGR and brain sparing effect. Reduction/ reversal of end-diastolic flow in the umbilical artery is a very serious sign of severe foetal compromise and impending foetal death and is an indication for urgent intervention (4).

Treatment of IUGR:

Amelioration of any aetiological factor identified is most vital. There is no proven effective therapy for IUGR till date.

Amongst the foetal infections Toxoplasmosis can benefit from therapy with spiramycin /sulfadiazine and pyrimethamine provided an early diagnosis and prompt treatment is possible.

Bed rest has been the mainstay of IUGR therapy as it reduces the catacholamine release, improves central intravascular volume and improves uterine perfusion, resulting in better foetal nutrition.

Nutritious diet has been advised with some improvement, provided it is started early in pregnancy. The Woman Infant Clinic program has shown that interpregnancy food assistance has better impact on foetal growth than just antenatal supplementation. Studies using parenteral solutions of 10% dextrose/fructose and 17% aminoacids have shown an increase in the birth weight with some reduction in perinatal mortality in undernourished mothers. Folic acid and zinc supplementation has been shown to be associated with some benefit in IUGR prone patients. fish oil contains high levels of eicosapentanoid acids which reduce synthesis of thromboxane and increase the prostacyclin levels, thus promoting vasodilatation. Hence it is recommended as a therapeutic option by some workers.

Low dose aspirin therapy has been tried as ante-platelet agent, as it shifts the balance of thromboxane-prostacyclin in favour of latter, but reports of its efficacy are quite contradictory. The CLASP trial failed to show any benefit in low risk mothers, but several other studies showed improvement in birthweights in the treated groups as compared to the controls, in high risk population. To be effective, aspirin therapy should be started in first trimester itself (5).

Low dose anticoagulants (low molecular weight heparin), low dose steroid and nitric oxide donor therapy like nitro-glycerine patch therapy, has been used in cases of IUGR with anti-phospolipid antibody syndrome, with mixed results.

Use of hyperbaric oxygen and amino acid infusions given to mother have been tried as well, but there is no proven benefit and sudden discontinuation of hyperbaric oxygen can result in serious foetal hypoxia.

Betamimetics, Insulin like growth factor, thyroxin, atrial natriuretic factor and intra amniotic infusions of aminoacids have been tried, but with questionable benefits. Intermittent abdominal decompression with Heyn's suit has shown improved perinatal outcome in small studies (6).

We have used Ayurvedic herbal preparations (Sujat, Torchnil), which have natural herbal micronutrients, immunomodulators and nitric oxide donor molecules, in fair number of PIH/IUGR cases, with quite encouraging results.

Optimum timing, mode of delivery and intra-partum management : The suggested guidelines for timing of delivery are shown in table 1,

Size	Normality	Growth/ Doppler/ Liquor	Gestation	Plan of delivery
SGA	Abnormal	Abnormal	<24 wks	ConsiderMTP
		Abnormal	>24wks	Non interference
SGA	Normal	Normal (?const. IUGR)	Any	Follow to term
SGA	Normal	Abnormal (true IUGR)	<26wks	Wait
			26-30wks	Wait/Steroids prior to delivery if needed
			30-32wks	Steroids for 24-48hrs, deliver
			>32wks	Deliver
SGA	Normal	Investigations mismatch	Any	Repeat investigations, follow-up action

Table 1 : Guidliness for timing of delivery.

Each diagnosed case should be closely monitored for severity of IUGR, foetal growth and maturity as well as foetal well being. Depending upon the condition of the foetus appropriate decisions should be taken by joint consultations between the obstetrician, neonatologist and ultra-sonologist.

Intrapartum and Neonatal management:

As the IUGR foetuses have fivefold increase in the stillbirth rate as well as threefold increase in neonatal mortality and morbidity, a very close monitoring of the labour is warranted. Electronic surveillance by cardiotocography should be used. Wherever available, foetal scalp blood sampling should be used to monitor foetal blood gases and pH. Vaginal delivery can be offered in mild to moderate IUGR with no other contraindications. in severe IUGR with <32wks gestation, elective LSCS should be opted for, as these babies cannot stand labour pains. Problem of meconium aspiration should be anticipated and treated vigorously.

A senior paediatrician should be available for skilled resuscitation and careful evaluation of the foetus for foetal infections/abnormality. Associated problems like hypoglycaemia, hypothermia, coagulation defects and polycythaemia should be tackled immediately.

`Short term and long term follow-up of these babies is essential, as there is several fold increase of hypertension, dyslipidaemia, coronary heart disease in the IUGR babies, in their future life.

Prevention/reduction of IUGR in subsequent pregnancy:

As the chance of IUGR babies in subsequent pregnancies is higher, these patients should be followed up post-nataly. Thorough evaluation of all possible causative factors should be done, any therapeutic measures available should be administered to remove them or reduce their severity, before planning for the conception. Genetic and metabolic studies of the couple should be done whenever indicated. Infection screen like TORCH assay and immunological investigations like antiphospolipid antibody assays should be done whenever indicated and appropriate treatment should be started.

Pre-conception prophylaxis with low dose aspirin, zinc and folic acid supplementation should be given and should be continued during the pregnancy. These patients should be closely monitored and treated aggressively whenever required.

CONCLUSION:

IUGR has attracted lot of attention of the scientific community, extensive research is going on in many centres. With better understanding of the patho-physiology of IUGR better foetal monitoring and therapeutic modalities will be available to us in future to tackle this serious problem more effectively. Prevention and better management of IUGR will not only stop the reproductive wastage and reduce infant morbidity/mortality but reduce the

incidence of serious cardiac and metabolic disorders thus preventing premature deaths.

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