INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

INTRAUTERINE GROWTH RESTRICTION (IUGR) – A CHALLENGE FOR THE NEONATOLOGIST AND OBSTETRICIANS

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ABSTRACT

Intra uterine growth retardation (IUGR) is a condition in which the foetal growth is less than that of the normal gestational age, due to maternal-placental-fetal factors. IUGR is of two types- symmetric and non symmetric. IUGR is one of the important causes of fetal and neonatal morbidity and mortality. The burden of IUGR is concentrated mainly in developing countries, in that about 75% accounts in Asia. Although the mechanism behind the IUGR is not clear but oxidative stress, genetic, parental, fetal, placental, environmental factors were involved in that. Ultra sound sonography and doppler flow were the common methods adopted for the diagnosis of IUGR. Identification of IUGR is crucial because proper evaluation and management can result in a favorable outcome. Therefore the management and treatment involves use of both pharmacological (antibiotics, corticosteroids, tocolytics, aspirin, l- arginine) and non-pharmacological methods (cerclage, proper diet, bed rest). This review high lights the causes, symptoms, diagnosis and treatment options of the IUGR.

Keywords: Foetal factors, Genetic factors, Intra Uterine Growth Restriction (IUGR), Maternal factors.

INTRODUCTION

Intrauterine growth restriction (IUGR) is also known as intrauterine growth retardation. It is a condition in which poor growth of a foetus, while in the mother's womb during pregnancy. IUGR prevents an infant from obtaining his or her complete growth potential.

Intrauterine growth restriction is the situation in which rate of foetal growth is below the normal growth potential of a specific infant as per the race and gender of the foetus. In other words, it is a reduction in an expected foetal growth pattern and is usually as a result of innate reduced growth potential or because of multiple adverse effects on the foetus.

Normal foetal growth is determined by the genetically predetermined growth potential and further modulated by maternal, foetal, placental, and external factors. The normal neonate is the one whose birth weight is between the 10th and 90th percentile as per the gestational age, gender and race with no feature of malnutrition and growth retardation.

IUGR & Small for gestational age (SGA) were the two commonly used synonymous terms in medical literature, in which SGA is based on the cross-sectional evaluation, that is either prenatal or postnatal and this term has been used for those neonates whose birth weight is less than 10th percentile for the corresponding gestational age. Neonates with a birth weight less than 10 percentile will be SGA not an IUGR, if there are no features of malnutrition, and a neonate with a birth weight greater than 10 percentile will be an IUGR[1,2,3].

Types of IUGR

(i) Symmetric or primary IUGR
(ii) Asymmetric or secondary IUGR

Symmetric or Primary IUGR	Characterized by all the internal organs will be reduced in size than the normal. In this type all the biometric parameters tend to be less than the expected for the given gestational age. Both length and weight parameters are reduced. Early gestational growth retardation will be expected to affect the foetus in a symmetric manner and thus have permanent neurologic consequences for the infant. Etiologies for symmetric growth retardation include genetic or chromosomal defects, early gestational intrauterine infections and maternal alcohol use. About 20 % to 25% cases of IUGR belong to this.
Asymmetric or Secondary IUGR	Characterized by a smaller abdomen, but the head and the brain being normal. Asymmetric IUGR can be recognized by the third trimester only. Most growth retarded infants have asymmetric growth restriction. Firstly there will be restriction of weight and then length, with a relative head sparing effect. This asymmetric growth is more commonly due to extrinsic influences that affect the foetus later in gestation like pre-eclampsia, chronic hypertension and uterine abnormalities [4].

Epidemiology

Globally, IUGR is observed in about 24% of newborns; approximately 30 million infants suffer from IUGR every year. In Asia, IUGR accounts for nearly 75% of all the affected infants, followed by African and Latin American countries. The raise of IUGR in the developed countries is less, when compared to the developing countries. IUGR varies among countries, populations, races and increases with decreasing gestational age. 14 to 20 million infants have been affected with IUGR cases in the developing countries annually. The babies born at home are more likely to be low birth weight (LBW) that is less than 2500 grams. The highest incidences of LBW -IUGR was found in South Central Asia, about 28% -33%. Following are the details of IUGR in various countries. India (21-28%), Bangladesh (39-50%), Pakistan (18- 25%).Sri Lanka (13-19%), Cambodia (12-18%), Philippines (6-11%), Vietnam (11-12%), Indonesia, Malaysia (4-8%) and Thailand (3-7%)[4].

Causes for IUGR

IUGR is the common end result of maternal, placental, foetal, genetic or environmental factors, various maternal factors such as age of the mother, inter-pregnancy interval (less than 6 months or 120 months or more), maternal health, behavioral habits and maternal infection affect the growth of the foetus are responsible for causing IUGR. Any mismatch between the supply of nutrient by the placenta and the demand of the foetus also leads to IUGR. Foetal malformations, inborn error of metabolism and chromosomal abnormalities are also responsible for IUGR in few cases. With the recent advances in molecular biology and genetics, the role of various maternal, foetal, and placental genes polymorphisms has become important and has now been implicated as a cause of IUGR.

1.	**Maternal causes**	**Maternal age**: (If the mothers age is less than 16 years and more than 35 years then the chances for IUGR is high). **Maternal pre-pregnancy height and weight**: (If BMI less than 20, weight less than 45 kg and more than 75 kg then the chances for IUGR is high). **Inter pregnancy interval**: (If the pregnancy interval is less than 6 months or 120 months or more then the chances for IUGR is high). **Assisted reproductive technologies (ART)**. **Maternal medication**: (Use of Warfarin, Steroids, Anti-convulsants, Anti-neoplastic , Anti-metabolite and Folic acid antagonists). **Previous delivery of a SGA newborn**. **Pregnancy poor weight gain**. **Hematologic and immunologic disorders.** **Maternal medical disorders**: (Hypertensive disorders, diabetes, chronic renal disease, systemic lupus erythematous, sickle cell disease). **Pathological conditions in pregnancy like pre-eclampsia**. **Maternal infection and parasite infestations**: (Malaria, tuberculosis, urinary tract infections and bacterial vaginosis). **Moderate to heavy physical work**. **Maternal substance abuse**: (Smoking both active and passive, alcohol, illicit drugs like marijuana or cocaine).
2.	**Placental causes**	**Placental weight**: (If weight is less than 350 gram). **Placental dysfunction**. **Placental infections**: (Placental malaria). **Multiple infarctions**. **Multiple gestations**. **Chronic inflammatory lesions**. **Abnormal uteroplacental vasculature** **Thrombophilia-related uteroplacental pathology**.
3.	**Foetal factors**	**Chromosomal abnormalities**: (Congenital heart disease, congenital diaphragmatic hernia, neural tube defect like anencephaly and ano-rectal malformation). **Multiple gestations**: (Twin to twin transfusion). **Metabolic disorders**: (Congenital absence of islets of langerhans, galactosemia, foetal phenyl ketonuria, neonatal diabetes mellitus). **Congenital infections**: (Malaria, congenital HIV infection, Syphilis).
4.	**Genetic factors**	**Foetal Genes**: The following are the some foetal genes factors that cause IUGR. **A**. Insulin-like growth factors 1 receptor (IGF-1R) mutation leading to decreased IGF-I-receptor function and **B**. N-terminal parathyroid hormone-related protein under-expression. **Placental Genes**: Variations in the placental genes will result in IUGR. The various placental gene factors includes: **A**. Placental growth factor under-expression, **B**. Placental Insulin-like growth factor 1 (IGF1) under-expression, **C**. Placental Insulin-like growth factor 2 (IGF2) over-expression, **D**. Insulin like growth factor binding protein-3 over-expression and **F**. Epidermal growth factor (EGF) under-expression. **Maternal Genes**: The Maternal gene factors includes: **A**. Endothelin-1 over-expression, Thrombophilia genes mutation, **B.** soluble vascular cellular adhesion molecule-1 higher level and C. higher maternal serum, neonatal umbilical cord asymmetric dimethyl arginine.
5.	**Endocrine factors**	Hormones such as insulin, thyroid, adrenal hormones and pituitary hormones affect the foetal growth. These hormones promote the growth and development of the foetus and any disruption in these hormone levels leads to IUGR[5, 6].

Clinical manifestations

Routine maternal examination alone can prove the IUGR in 50% of cases. Foetus with IUGR will be too small to the corresponding gestational age. Symptoms of IUGR usually appear during the regular checkups at the time of pregnancy. During the regular monitoring of pregnancy the doctor will measure the height of foetus from the pubic bone to estimate the size. Uterine fundal height is measured during the ultrasound imaging and that usually equal to the number of weeks in the pregnancy. If the distance is too short then it is a clear sign of intrauterine growth restriction and the doctor will ask to conduct additional tests. IUGR newborns have typical but varied clinical features, which may be any of the following:

Clinical manifestations
Relatively large heads for the size of the body in asymmetrical IUGR, Weight less than the expected for the gestational age, Large anterior fontanelle, loss of buccal fat, face has a typical shrunken appearance (old man look) smaller abdomen, thin umbilical cord often stained with meconium, Decreased skeletal muscle mass and subcutaneous fat tissue with thin and arms and legs and long finger nails, Thin Ear cartilage, Facial dysmorphism, Cardiac defects, Relatively large hands and feet with increased skin creases, Loose folds of skin in the nape of neck, axilla and inter-scapular area, Diminished breast bud formation due to decreased blood flow, low estradiol level and low subcutaneous fat, Immature female genitalia due to loss of subcutaneous fat, Under-developed female external genitalia lead to reduced fat deposit in the labia majora[6,7].

Diagnosis of IUGR

IUGR can be difficult to diagnose. Last menstrual period (LMP) of the carrying women is important to note, for doing various tests to diagnose any abnormalities to the growing foetus. By taking a detailed maternal history chances for IUGR may be identified. A mother with a previous IUGR will be at a high risk of having another during the subsequent pregnancy. IUGR is generally diagnosed by measuring the mother's uterus, with the fundal height; being less than it should be for that stage of the pregnancy. Detection of IUGR informs the mother that the pregnancy is at increased risk, allowing considerations on the optimal timing for delivery. Depending on severity, babies that are not fulfilling their growth potential have a 5 to 10 fold risk of dying in uterus.

Screening in early pregnancy by Biochemical markers

- In the first trimester, a low level of pregnancy associated plasma protein A or human chorionic gonadotropin (HCG) is associated with an increased risk of placental-related disease such as IUGR.
- A raised maternal serum alpha-fetoprotein (AFP) during the second trimester is usually associated with an increased risk of low birth weight in the absence of structural abnormality or aneuploidy.
- Low levels of maternal serum pregnancy associated plasma protein A (PAPP-A) is associated with an increased risk of an SGA infant.

Role of sonography in the diagnosis of IUGR

Ultrasound is the benchmark for accurate pregnancy dating and diagnosis of IUGR. Ultrasound can be used to determine how much amniotic fluid is in the uterus. A low amount of amniotic fluid could suggest IUGR. Sonography can be used to measure the baby's head and abdomen. The measurements most commonly used are the biparietal diameter, head circumference, abdominal circumference and femur length. Percentiles have been established for each of these parameters, and foetal weight can be calculated.

Doppler flow

Doppler can be done by evaluating the change in the waveform, in which the speed and direction of an object can be determined. In foetal medicine, the doppler principle is used to evaluate changes in sound waves which informs about the direction and velocity of blood flowing through vessels and the heart. There are various methods in doppler such as umbilical artery doppler, middle cerebral artery doppler, ductus venous Doppler and uterine artery doppler.

Amniocentesis

Amniocentesis is a medical procedure used for prenatal diagnosis of chromosomal or genetic abnormalities and any foetal infections. A small amount of amniotic fluid, which contains foetal tissues, is sampled from the amniotic sac surrounding a developing foetus, and then the foetal DNA is examined. This is usually performed when a woman is between 14 to 16 weeks of gestation.

Weight check-up

Doctors routinely check and record the mother's weight at every prenatal checkup. If mother is not gaining weight, it could indicate a growth problem in her baby.

Foetal monitoring

In foetal monitoring sensitive electrodes were placed on the mother's abdomen. The electrodes were held in place by a lightweight stretchable band and attached to a monitor. The sensors measure the rate and pattern of the baby's heartbeat and display them on a monitor[6,7,8].

Treatment

Pharmacological management

Corticosteroids	Dexamethasone and betamethasone were the main corticosteroids used for the treatment of IUGR. They speed up the development of foetal organs. Administration of corticosteroids produces a considerable reduction in respiratory distress, cerebro-ventricular hemorrhage. Repeated doses of corticosteroids are administered for preventing neonatal respiratory disorder.
Tocolytics	Acts by slowing down or stopping the labour contractions, thus helps in prolonging pregnancy. Drugs involved in this category are betamimetics like terbutaline, albuterol, fenoterol and orciprenaline. Betamimetics decreases intracellular calcium levels. And also reduces myometrial contractility and thus act as tocolytics. Magnesium sulphate has also been used as a tocolytic agent.
Antibiotics	IUGR is often manifested by presence of various bacterial infections such as cytomegalovirus. Antibiotics like ampicillin, erythromycin, azithromycin, clindamycin, ceftriaxone, were some of the useful antibiotics used for the management. Administration of antibiotics was found helpful in reducing infections and morbidities.
Calcium Channel Blockers	Nicardipine and nifideipine were the two main calcium channel blockers used during pregnancy. They inhibit the calcium influx into myometrial cells. Lower calcium concentration results in activation of myosin light chain kinase and there by myometrium contraction.
Aspirin	Aspirin is used in the treatment of IUGR to some extent, but its use is still in a controversy. If aspirin is given to the patients before 20 weeks of gestation it was found advantageous in reducing the risk factors of IUGR. But it was found as less effective, if given in the third trimester.
L-Arginine	L-arginine is a semi essential amino acid, which acts as an essential substrate for the synthesis of nitric oxide (NO). NO helps in the prolapse of smooth musculature and consequently the improvement of placental blood circulation. NO has a diverse role in obstetrics as it plays a vital role in labour, cervical ripening, preeclampsia and in IUGR.
Oxytocin Receptor Blockers	Atosiban is an oxytocin receptor blocker. They blocks the oxytocin receptors, inhibiting oxytocin-induced conversion of phosphatidylinositol to inositol triphosphate and release of calcium into the cytoplasm.

Non- Pharmacological Treatment

Cerclage	It refers to the stitch in cervix which may help in keeping cervix closed and preventing early birth of foetus. This stitch gets removed by end of 37th weeks of gestation.
Proper diet	Proper food habits have a direct effect on development of foetus as well as to mother. Improper food habits results in malnutrition which further leads to poor development of foetus in the womb. This may result into preterm delivery, IUGR, neonatal mortality and morbidity. Therefore it is necessary to provide proper diet as well as proper nutrition for the proper development of the foetus.
Bed rest	Bed rest does not seem to have any huge impact on IUGR, but it helps in keeping patient calm and preventing high muscle contractions during pregnancy which may help in prolonging pregnancy.
Practice of a healthy lifestyle habits	Practice of a healthy life style by avoidance of alcohol usage, cessation of smoking for the health of baby.
Balanced diet	Healthy food rich in calories helps in keeping baby well nourished. Calcium, Vitamin, Zinc, Iron supplementation can be given for the proper growth of the baby[9-13].

CONCLUSION

IUGR remains a challenge for the neonatologist and obstetricians. A number of factors that point out towards IUGR, which include age, poor socioeconomic status, genetic factors, placental factors foetal factors maternal factors, poor care of the girl child, medical and obstetric disorders were some among them. IUGR infants face multiple problems from their birth to adolescence, experience long term growth defects and abnormal neuro development. IUGR babies may possibly have a negative effect on brain growth and mental developmental potential. They are also more likely to have poor school performance and childhood behavioral issues. A good coordination among primary, secondary and tertiary health care facilities should be ensured to tackle the problem. For the successful management of IUGR a concerted laison between medical and socials sectors is necessary.

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