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Intrauterine Growth Retardation - A Review Article

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Abstract

Intrauterine growth restriction (IUGR) is defined as fetal growth less than the normal growth potential of a specific infant because of genetic or environmental factors. The terms IUGR and Small for Gestational Age (SGA) are often used alternatively to describe the same problem, although there exists subtle differences between the two. The burden of IUGR is concentrated mainly in Asia which accounts for nearly 75% of all affected infants. Various maternal, placental, neonatal, environmental and genetic factors are contributing to the preponderance of IUGR infants in Asia. These newborns are unique because of their peculiar and increased risk of immediate and long term complications in comparison with the appropriate gestational age born infants. In this review we would like to present the types of IUGR infants; possible etiology related to maternal, fetal and placental causes; short term and long term neurodevelopmental outcomes, and evidence based preventive interventions effective in reducing the IUGR burden. This review also highlights the genetic contribution of the mother to the fetus and the placenta in the genesis of unexplained or idiopathic intrauterine growth restriction.

Introduction

Intrauterine growth restriction (IUGR) is defined as fetal growth less than the normal growth potential of a specific infant because of genetic or environmental factors. The terms IUGR and Small for Gestational Age (SGA) are often used to describe the same problem, although there are subtle differences between the two. SGA is diagnosed as birth weight less than (less than 10% for that particular gestational age, parity and gender) the population norms on the growth chart. IUGR is a clinical definition and applied to neonates with clinical evidences of malnutrition [1]. World over, IUGR is observed in about 24% of newborns; approximately 30 million infants suffer from IUGR every year [2,3]. The burden of IUGR is concentrated mainly in Asia which accounts for nearly 75% of all affected infants. Africa and Latin America account for 20% and 5% cases respectively. National Neonatal Perinatal Database of India reported the incidence of IUGR to be 9.65% among hospital born live birth infants [4]. In our own observation, the incidence of IUGR with very low birth weight infants is 43% [5]. In this review we used the words IUGR, SGA and FGR interchangeably.

Definition

Small gestational age (SGA) refers to weight below the 10 percentile for gestational age, corrected for parity and gender, as per the population growth charts [1]. It can be further classified as [6]

- **Moderate:** Birth weight in the 3 to 10 percentile (or 5th to 10th centile)

- **Severe:** Birth weight less than 3 percentile (or <5th centile)

Ponderal Index (PI) is also used to determine the degree of fetal malnutrition. It is defined as the ratio of body weight to length expressed as (PI=[weight (in g) x 100]÷[length (in cm)^3]). PI of less than 10 percentile reflects fetal malnutrition; PI of less than 3 percentile indicates severe fetal wasting [7,8]. In a term infants, PI less

than 2.2 and Mid Arm/ Head Circumference (MAC/HC) less than 0.27 are also considered as features of fetal malnutrition [9].

Clinical Assessment of Nutrition Score (CAN Score)

Metcoff J [10] developed a scoring system, CAN score, for the assessment of nutritional status of the newborns at birth. It includes 9 parameters namely hair, cheeks, neck and chin, arms, legs, back, buttocks, chest and abdomen. A neonate with CAN score of less than 25 is considered malnourished (Table 1) [10]. In a cross sectional study on 637 newborns, Mehta et al. evaluated the ability of CAN score in comparison with PI, MAC/HC ratio and weight for age for the detection of fetal malnutrition (IUGR). They reported that CAN score <25 identify 40% of their study population as malnourished. In their study they have observed that weight, age, PI, MAC/HC ratio, and odds ratio (95% CI) are identified as indicators of malnutrition using CAN score, which was 8.5 (5.5-13.3), 4.6 (3.1-6.7) and 11.5 (7.7-17.4), respectively. When compared to PI, CAN score have a sensitivity of 65.6% and a specificity of 75.5% for detection of fetal malnutrition [9].

Epidemiology

The incidence of Intrauterine Growth Restriction (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 raise in the IUGR cases in the developing countries can be attributed to the babies born at home are more likely to be low birth weight (LBW: Birth weight <2500grams). Country specific rates of IUGR-LBW can be categorized as percentages of all births, as follows: low (<5%), moderate (5-10%), high (10-15%) and very high (>15%). For LBW and IUGR-LBW respectively, the highest incidences are found in South Central Asia (28%, 33%). At the national level, the highest incidences for LBW and IUGR-LBW respectively are: Bangladesh (50%, 39%), India (28%, 21%) and Pakistan (25%, 18%). For other Asian countries, the

corresponding data is: Sri Lanka (19%, 13%); Cambodia (18%, 12%); Vietnam and the Philippines (11%, 6%); Indonesia and Malaysia (8%, 4%); Thailand (8%, 3%), and the People's Republic of China (PRC) (6%, 2%) [2].

Classification

There are 3 types of IUGR [11,12]. The type one is

1. Symmetrical IUGR (Hypoplastic small for date) [11,12]

Symmetric growth restriction begins early in gestation

Cell number is reduced

Caused by intrinsic factors such as congenital infections or chromosomal abnormalities

Infants with symmetric growth restriction have reductions in all parameters including weight, length and the head circumference. In such cases there will be less than 3 cm difference between the head and the chest circumference.

PI is more than 2

2. Asymmetrical IUGR (Malnourished babies) [11,12]

Abnormal growth typically begins in the late second or third trimesters

The cell numbers are normal but cell size is reduced

Reductions in fetal nutrients that limit glycogen and fat storage, caused usually due to placenta disorders.

Reduction in the weight and length occurs due to Brain sparing.

Features of malnutrition are pronounced in the form of loose skin fold, loss of buckle fat, featuring aged people

Ponderal Index (PI) is less than 2

3. Mixed IUGR [11, 12]

Decrease in the number of cell and cell size

Occurs mostly when IUGR is affected further by placental causes in late pregnancy

Represents the clinical features of both symmetrical and asymmetrical IUGR.

Infants with the the normal cell numbers experience better and immediate neonatal and long term growth with improved neuro-developmental outcomes.

Cephalization Index:

Harel et al. [13], coined the term cephalization index, a ratio of head circumference to body weight. They postulated that higher the brain: body ratio, the more severe is the IUGR. They opined that the higher cephalization index reflected a greater degree of brain vulnerability and increased likelihood of cerebral palsy and severe psychomotor retardation. The cephalization index may serve as an additional screening device for the risk categorization of an IUGR infant.

Causes

Intrauterine growth restriction may be caused by maternal, placental, or fetal factors. Nearly one-third of IUGRs are due to genetic causes, and two-thirds are related to the fetal environment [11]

Maternal factors [14-20]

Both young (<16years) and advanced maternal age (>35 years)

High altitude

Lower socioeconomic status

Maternal substance abuse, including cigarette smoking, alcohol consumption, and illicit drug use.

Toxic exposures, including various medications such as warfarin, steroids, anticonvulsants, antineoplastic agents, anti-metabolite, and folic acid antagonists.

Maternal pre pregnancy short stature and thinness

Nulliparity or grand multiparty

Previous delivery of a SGA newborn

Assisted reproductive technologies

Failure to obtain normal medical care during pregnancy

Severe maternal starvation during pregnancy.

Poor maternal weight gain during the latter third of pregnancy

Hematologic and immunologic disorders like system lupus erythematous, sickle cell disease, anti-phospholipid syndrome

Maternal medical disorders (nephropathy, collagen vascular disease)

Pathological conditions in pregnancy like preeclampsia and diabetes associated with vasculopathy

Infection and parasite infestations such as TORCH, malaria, tuberculosis, urinary tract infections and bacterial vaginosis

The WHO Collaborative Study found that women in the lowest quartile of both low pre- pregnancy weight, and pregnancy weight gain were at highest risk (to week 20, odds ratio 5.6; or to week 36, odds ratio 5.6) of producing an IUGR infant [20]. Pregnancy weight gains of women in Asia tend to be low. It has been estimated that most women in South Asia gain little more than 5 kg as against the 10-15 kg weight gain among the women in the developed countries. The other factor identified by them was Body Mass Index (BMI). They found that mothers with a BMI in the lowest quartile had double the risk of producing an IUGR infant. Environmental factors like exposure to nicotine also lead to lower birth weight. Kharrazi et al. [21] evaluated the magnitude and shape of the relations between the environmental factors like exposure to tobacco and adverse pregnancy outcomes among 3000 pregnant women in a prenatal screening programme. In their study, there was a linear dose dependent effect of log cotinine levels on mean birth weight and mean infant length. Infants' body mass index declined with nicotine exposures above 0.5ng/ml. Similarly Goel et al. [23], performed a cross-sectional study to study the effects of passive smoking on outcome in pregnancy. They studied 576 non-smoking women delivering a singleton live baby. They used pre-designed structured questionnaire to record the details of exposure to Environmental Tobacco Smoke (ETS) at home. One hundred and forty one women had ETS exposure and these mothers had

significantly higher incidence of pre-term birth (24.1% vs. 16.1%; P=0.027) and small-for-gestation babies (31.9% vs.17.2%; p<0.001) as compared to unexposed mothers. The mean birth weight of infants was smaller by gram among ETS exposed mothers.

Although heavy maternal drinking is associated with fetal alcohol syndrome, moderate alcohol consumption may be associated with intrauterine growth restriction. Yang Q et al. [24] in their case-control study examined the association of maternal alcohol consumption with the risk ofIUGR among 701 case and 336 control infants born during 1993-1995 in Monroe County, New York. They reported the odd ratio of 1.4 (95% CI 0.7-2.6) among mothers that were heavy drinkers (more or equal to 14 drinks in week) around the time of conception and 1.3 (95% CI: 0.4-4.5) for heavy drinkers during the first trimester.

2. Placental Causes

Any mismatch between fetal nutritional or respiratory demands and placental supply can result in impaired fetal growth. Various causes include [25-28]

Abnormal uteroplacental vasculature

Placental dysfunction (PIH, pre-eclampsia)

Thrombophilia-related uteroplacental pathology

Avascular villi

Decidual or spiral artery arteritis

Multiple infarctions

Partial molar pregnancy

Syncytial knots

Chronic inflammatory lesions

Abruptio placenta

Velamentous umbilical cord insertion

Placental hemangioma

Placental infections

Infectious villitis (as with TORCH infections)

Multiple gestation (limited endometrial surface area, vascular anastomoses)

Genetic causes include increased expression of placental endoglin gene and vascular endothelial growth factor

Heinonen et al. [29] conducted a study to evaluate the association between the placental weight and the birth weight in appropriate (AGA) among the Small Gestational Age (SGA) infants. The study analyzed the placental weight and birth weight of 1569 SGA and 15047 AGA infants. They reported that placenta of SGA infants was 24 per cent smaller in size than that of AGA infants. Placental actual weight was also lower in SGA infants than in AGA infants of the same birth weight (P<0.001).

Confined Placental Mosaicism (CPM) refers to chromosomal mosaicism (usually involving a trisomy) found in the placenta, but not in the fetus. It occurs significantly more often in the placentas associated with the FGR than in controls of the normal weight. Wilkins-Haug et al. [27], in their study evaluated the confined placental mosaicism as a risk factor among newborns with fetal growth restriction. They analyzed 70 IUGR infants and 70 AGA infants who were matched by maternal age (±5 years) and gestational age (±7 days). They reported that CPM occurred significantly more in IUGR infants' placenta compared to AGA infants {(11/70 (15.7%) and 1/70 (1.4%) respectively (p=0.008)}. They also found high-level tetraploidy (>20% in a primary culture) among the IUGR placenta. When placentas were examined histological way they showed greater decidual vasculopathy, infarction, and intervillous thrombus formation predominantly in the karyotypically abnormal placenta.

Robinson et al. [30,31] conducted a study assessing the role of placental trisomy in preeclampsia and intrauterine growth restriction. They performed comparative genomic hybridization to 61 placentas obtained from mother with preeclampsia and/or IUGR, 11 cases from mother with elevated maternal serum hCG and/or AFP but no IUGR or preeclampsia, and 85 were control placentas. They observed total of 5 trisomy placenta, four from IUGR group and 1 from abnormal maternal serum screen group. There was no case of mosaicism in control group.

Szentpéteri I et al. [32,33] conducted a study to describe placental gene expression patterns of endoglin in pregnancies with Intrauterine Growth Restriction (IUGR) compared to normal pregnancies. They obtained placental samples from 101 IUGR complicated pregnancies and 140 controled pregnancy cases. They observed that the placental endoglin gene was significantly over expressed in the IUGR group (Ln2 (α): 1.69). The placental endoglin protein level were significantly higher in case of IUGR (endoglin/β-actin ratio: 13.8±2.3) versus the control cases (5.3±1.1). They concluded that increased placental gene expression of endoglin may result in vascular dysfunction leading to chronic fetal hypoxia, which may induce VEGF-A to stimulate angiogenesis which can be explained as feedback response to restore fetal placental circulation. From the same cohort of patients, they reported over expression of VEGF-A gene in IUGR pregnancies in comparison with the normal controls (Ln 2(α) β-actin: 1.32; Ln 2(α) GADPH: 1.56). No correlation was observed between the degree of growth restriction and VEGF-A gene expression (Ln 2(α) (0-5) percentile: 0.58; Ln 2(α) (5-10) percentile: 0.64). They suggested that the hypoxic environment present in the placental tissue in IUGR pregnancy resulted in increased placental expression of the VEGF-A gene and the resultant stimulation of angiogenesis.

3. Neonatal factors [34-36]

Karyotypic abnormalities, such as trisomy 18 and 13, autosomal deletions, ring chromosomes, Uniparental disomy (UD).

Genetic syndromes, such as Bloom syndrome and Russell-Silver syndrome.

Major congenital anomalies such as tracheo-esophageal fistula

Multiple gestation

Congenital infections (e.g., toxoplasmosis, rubella, cytomegalovirus)

Metabolic disorders including agenesis of pancreas, congenital absence of islets of langerhans, congenital lipodystrophy, galactosemia, generalized gangliosidosis type I, hypophosphatasia, I-cell disease, Leprechaunism, fetal phenylketonuria, transient neonatal diabetes mellitus

4. Genetic Causes of Fetal Growth Restriction

Polymorphisms in maternal, placental and fetal genes encoding for proteins and hormones have been shown to affect the fetal growth.

Some of the known genetic associations of intra-uterine growth restriction are

A. Placental genes

Homeobox Genes: These are also known as homeotic genes and were originally discovered in the fruit fly Drosophila. These genes contain highly conserved 180 base pair homeobox sequence, which encodes 60 amino acid homeodomain. The homeobox genes which have been identified to be of potential importance in the human placenta includes DLX3 , DLX4, MSX2 and GAX , ESX1L , and HLX .There is decreased expression of Homeobox genes HLX [37] and ESX1L [38] in FGR-affected placenta.

SERPINA3 Genes: Single nucleotide polymorphism (SNP) which is located in the promoter of SERPINA3 in the placenta is also associated with IUGR [39]

NEAT1 (Nuclear Paraspeckle Assembly Transcript 1) gene: NEAT1 is the core component of a sub-nuclear structure called paraspeckle. This structure is responsible for the retention of hyper-edited mRNAs in the nucleus. In a recent study by Gremlich et al., NEAT1 mRNA expression was 4.14 fold increased in IUGR in comparison with control placenta, which suggest an increase in paraspeckles in IUGR villous trophoblasts. This in turn could lead to an increased retention of important mRNAs in villous trophoblasts nuclei. As these villous trophoblasts are crucial for the barrier function of the placenta, this could in part explain placental dysfunction in idiopathic IUGR foetuses [40]

Placental Growth Factor (PlGF): This has a major role in vasculogenesis and angiogenesis in human placenta. Low concentrations of PlGF and high concentrations of its inhibitor-soluble Fms-like tyrosine kinase-1 (sFlt-1) are linked with impaired angiogenesis [41]

Trophoblastic miRNAs (micro RNA) in the maternal plasma: MicroRNAs, short non-coding RNAs regulate gene expression at the post transcriptional levels. miRNAs are released intracellular to the circulation in conditions with complicating pregnancy. Plasma concentration of placenta-derived miRNAs is increased in plasma of women with pregnancies complicating the fetal growth. [42,43].

Apoptosis Bcl-2 and Bax gene in human placenta: Bcl -2 is a family member of anti-apoptotic gene group whereas Bax is pro-apoptotic gene. Börzsönyi B et al. [44] in their study assessed the Bcl-2 and Bax gene expression patterns in human placental samples from IUGR pregnancies using normal controls. The study consisted of 241 placental samples (101 in the IUGR pregnancy group and 140 in the normal pregnancy group). Bcl-2 gene were under expressed In IUGR group when compared to normal pregnancy. There was no difference in the Bax gene activity in the two groups. The degree of growth restriction within the IUGR group did not relate to Bcl-2 or Bax gene activity. They concluded that the reduced inhibitory activity of the Bcl-2 gene rather than an enhanced stimulatory activity of the Bax gene was responsible for the increased apoptosis observed in IUGR.

Placental Insulin-like growth factor (IGF1 & IGF2) and the insulin like growth factor binding protein (IGFBP)-3 genes: Börzsönyi B et al. [45] in their same cohort of 241 placental samples also assessed the insulin-like growth factor (IGF), -gene expression patterns, characteristics of glucose and insulin metabolism in human placenta of IUGR pregnancies. They reported that in normal pregnancies the values of umbilical cord glucose and insulin levels were significantly higher than the IUGR complicated pregnancies. There was an over expression of IGF-2 and the insulin-like growth factor binding protein (IGFBP)-3 genes in IUGR complicated placentas. The overexpression of IGF-2 in the placentas of IUGR pregnancies reflects its physiological role in optimizing energy distribution in a low-energy environment.

Placental Gene of Epidermal Growth Factor (EGF): The same group from Hungary which reported the role of growth factors and anti-apoptotic genes in IUGR placenta, compared the human placental gene expression patterns of epidermal growth factor (EGF). They have reported underexpression of EGF in the IUGR group compared to normal pregnancy (Ln2(α):-1.54; p<0.04) and concluded that the decrease of EGF level partly explain the smaller placental size and placental dysfunction commonly seen with IUGR [46].

B. Maternal

Increased level of Endothelin-1 and Leptin: Inadequate uteroplacental perfusion is the most common reason for IUGR ET-I. Vasoactive mediator is produced primarily by endothelial cells; is a potent vasoconstrictor, with its receptors expressed in the human placenta. Ischemia is a potent stimulus to ET-1 production [47,48]. Leptin is a peptide hormone that regulates energy homeostasis, reproductive functions and immune reactions. It regulates appetite and body weight. Leptin is mainly produced in the adipose tissue of non-pregnant woman. On the other hand, leptin is produced from human placental trophoblastic cells, so plasma leptin level increases in pregnancy [49,50]. Nezar et al. [51], conducted a study to see Endothelin-1(ET 1) and leptin as markers of intrauterine growth restriction. They studied 43 IUGR mothers out of which 23 cases had severe preeclampsia and rest had non-pre-eclamptic IUGR. Control group comprised of 15 cases with uncomplicated pregnancy. They found significant increase in the mean maternal and fetal ET-1 level in IUGR group. The mean maternal leptin level was also significantly higher in pre-eclamptic mother than non-preeclamptic and control mothers.

Visfatin: Visfatin, a 52-kd visceral fat–specific adipocytokine, results in expansion of adipose depot to insulin resistance. Visfatin, is identical to pre–B-cell colony-enhancing factor (PBEF), and found in both normal and infected human fetal membranes and increased levels are seen during labour. Malamitsi-Puchner et al. [52], evaluated perinatal circulating visfatin levels (an adipocytokine) in intrauterine growth restriction. They measured serum visfatin levels in 40 mothers and their full term neonates on postnatal days 1 and 4. Twenty neonates were IUGR and rest was AGA. They found that visfatin levels were significantly high in mothers who had IUGR babies. Similarly visfatin levels in neonates who were IUGR were also elevated.

Thrombophilia genes and IUGR: Grandone et al. [53] in their retrospective study saw the relation between birth-weight of neonates and presence of factor V G1691A and factor II A 20210 mutations in the mothers. They analyzed 755 women, including 194 with a history of unexplained recurrent pregnancy loss, 202 with gestational hypertension with or without proteinuria and 359 with at least one uneventful pregnancy. Out of 1100 neonates, they found 980 neonates from mothers without mutations, 136 (13.9%) neonates weighed <2500 grams whereas 34 (27.6%) out of 123 mothers carrying the factor V G1691A or factor II A(20210) mutation had an infant with low birth weight (OR: 2.4, 95%CI: 1.5- 3.7).

C. Fetal Genes

Increased level of Protein S100B: Florio et al. [54] conducted a study of urinary S110B protein concentrations in IUGR. They evaluated 42

IUGR infants and 84 controls. They reported significantly higher level of S100B in urine of IUGR infants. They also reported it as having 95% sensitivity with 99.1 % specificity in predicting adverse neurological outcomes in these newborns.

Genetic deletion of Igf1 (Insulin Like growth factor 1) and SHOX gene: Caliebeet al. [55], found SHOX, IGF-1, IGF1R defects in 6 IUGR neonates. They found gene variants in SHOX and its pseudo autosomal region (PAR) and IGF1R; other mutation of SHOX associated with IGF1R defect whose locus was on Xp22.3.

Genetic mutation in Igf1r (Insulin-like growth factors 1 receptor): Kawashima et al. [56] in their study analyzed nucleotide sequence of IGF-1R gene of a family. They prepared R (-) cells expressing wild type or R431LIGF-IR and performed analysis. They identified family with IUGR mother and infant that had heterozygous missense mutation at the L2 domain of IGF-IR (R431L). They hypothesized that this mutation leads to decreased cell division and decreases IGF effects

Fetal Growth in Normal and IUGR Fetuses

The fetal growth restriction occurs in any trimester which results in either symmetrical or asymmetrical IUGR. Growth occurs primarily by increased cell number during the first trimester whereas cell size increases with number in the second trimester. In later gestation, the rate of cell division declines, but cell size continues to increase. Growth of tissues like adipose tissue and skeletal muscle etc. are developed during the later gestation period and spare other organs and tissues, such as the brain and heart, whose growth rate already has taken place. Growth hormone may be used to treat the children of IUGR at birth [57].

1. Water

Total body water content in the normal fetus increases with gestation but percentage of water as per body weight decreases as there is an increase in protein, adipose tissue and mineral content of the fetus with gestation. ECF water also decreases with gestation due to increase in cell number and size. IUGR that are mild-to moderate usually have normal ECF water. Adipose tissue, skeletal muscle, and mineral accretion all are decreased to the same extent as per the gestational age. In severe IUGR, there is marked decrease in fat content and is characterized by higher fractional contents of body water [58].

2. Minerals

No difference is traced in mineral content per body mass and bone mass in IUGR fetuses. However, calcium content increases exponentially with increase in fetal length and bone density in the IUGR fetuses. The increase in content of other minerals like sodium and potassium depends on body weight and their distribution in the body compartments [59].

3. Nitrogen and Protein

Non-fat dry weight and nitrogen content (predictors of protein content) increases with gestational age. The increase has a linear relationship with fetal weight and an exponential relationship with gestational age. Majority of fetal nitrogen content is found in protein and the rest is composed with urea, ammonia, and free amino acids. Nitrogen and protein contents are reduced among IUGR infants,, as these neonates have deficient muscle growth [59].

4. Glycogen

Glycogen synthetic rates are low in the human fetus which account for less than 5% of fetal glucose utilization. Insulin acts with glucose to increase hepatic glycogen stores of the fetus till term and as the newborn is born cortisol, epinephrine, and glucagon induce glycogenolysis and increase the glucose levels. Most tissues in the fetus, including brain, liver, lung, heart, and skeletal muscle produce glycogen over the second half of gestation leading to progressive accumulation of glycogen in the organs. IUGR fetuses have reduced glycogen storage both in the liver and in the skeletal muscles because of lower fetal plasma concentrations of glucose and insulin. IUGR fetuses frequently have intrauterine episodes of hypoxia which stimulate epinephrine secretion and deplete glycogen further by activating glycogen phosphorylase and increasing glycogenolysis [60].

5. Adipose Tissue

The fat content of newborns at times contains 15% to 20%. Adipose tissue accretion begins in the late second to early third trimester of gestation. In the first half of gestation, non-fat and fat components are almost equal in content and contribute equally to the carbon content of the fetal body. In later part of pregnancy there is rapid fat accretions and at birth constitute major content of carbon content of the body. IUGR fetuses have deficiency in fat content because of decreased fatty acid, triglyceride and glucose levels. Insulin hormone is also decreased which limits fat synthesis because of decreased stimulation of fatty acid synthase in adipocytes [61].

6. Total Energy Balance and Tissue Mass

The total energy storage of IUGR babies is decreased as they are depleted in fat, protein and glycogen [61].

Clinical Features

IUGR newborns have typical but varied clinical features. These include [11]

Weight less than expected for the gestational age

Relatively large heads for the size of the body in asymmetrical IUGR

Large Anterior fontanelle

Loss of buccal fat, face has a typical shrunken or "wizened" appearance (Old Man Look)

Small or scaphoid appearing abdomen, thin umbilical cord often stained with meconium

Decreased skeletal muscle mass and subcutaneous fat tissue with thin and arms and legs.

Long finger nails.

Relatively large hands and feet with increased skin creases

Loose folds of skin in the nape of neck, axilla, inter-scapular area and groins

Diminished breast bud formation and immature female genitalia due to loss of subcutaneous fat.

Gestational age is difficult to determine as the physical criteria are often unreliable when used alone but reliability improves along with neurologic assessment, especially in the absence of neurological insults [11]. The fallacies of physical examination include

Mature sole crease pattern: Decrease in vernix production leads to continuous exposure of skin to amniotic fluid leading to its desquamation.

Immature Breast nodule: Diminished breast bud formation due to decreased blood flow, low estradiol level and low subcutaneous fat

Under-developed female external genitalia lead to reduced fat deposit in the labia majora.

Thin Ear cartilage

All infants with features of IUGR must be examined closely to identify features of chromosomal anomalies, TORCH infections and major malformations. Polyhydraminos, absent stomach bubble and IUGR occur in trachea-oesophageal fistula. Hepatosplenomegaly, skin rash including blue berry muffin lesions, ocular findings such as cataract, cloudy cornea, chorioretinitis and thrombocytopenia occur when IUGR is due to TORCH infections [11]. IUGR with facial dysmorphism, cardiac defects and skin crease abnormalities occur with syndromes and chromosomal anomalies.

Problems of the Small-for-Gestational Age Neonate

Immediate Mortality and Morbidities

These newborn are faced with many problems after birth. Severely affected IUGR infants, deprived of oxygen and nutrients, may have difficult cardiopulmonary transition with perinatal asphyxia, meconium aspiration, or persistent pulmonary hypertension. Immediate neonatal complications include hypothermia, hypoglycemia, hyperglycaemia, hypocalcaemia, polycythaemia, jaundice, feeding difficulties, feed intolerance, necrotizing enterocolitis, late onset sepsis, pulmonary haemorrhage and so on [11] (table 2).

Katz et al. [73] in a pooled analysis of 20 cohorts (total population 2 015 019 live births) from Asia, Africa, and Latin America studied the mortality risk in preterm and small for gestational age infants in low income and middle income countries. They recorded data for birth weight, gestational age, and vital statistics through 28 days of life. In comparison with term AGA infants, the RR for neonatal mortality was 1·83 (95% CI 1·34-2·50) and post-neonatal mortality RR was 1·90 (1·32-2·73) for SGA infants. The risk of neonatal mortality was maximum in babies who were both preterm and SGA in comparison to babies who were either SGA or preterm alone (15·42; 9·11–26·12).

Deorariet al. [74], in their study on 144 SGA babies, the most common morbidities was hypoglycemia (17%) and polycythaemia (10%). Dogra et al. [75], conducted a prospective observational study to measure the incidence of feed intolerance and Necrotizing Enterocolitis (NEC) in preterm Small for Gestational Age (SGA) neonates with normal umbilical artery doppler flow in comparison with gestation matched Appropriate for Gestational Age (AGA) neonates. Fifty consecutive singleton SGA preterm between 28 and 34 weeks gestation with normal Doppler were enrolled and 50 gestation matched AGA served as controls. There was a trend toward more feed intolerance (22% vs. 12%, p=0.183), NEC (12% vs. 6%, p=0.295) and mortality (8% vs. 2%, p=0.362) in SGA group and these babies also had significantly more hypoglycemia (p=0.000) and polycythaemia (p=0.032) and longer hospital stay (p=0.017).

Padidela et al. [76], evaluated the neuro-behaviour of the babies that are born during Appropriate gestational age and Small gestational

during their first two weeks of life in a tertiary care hospital. Forty eight appropriate and thirty small for gestation age babies were evaluated using Brazelton neurobehavioral assessment scale on 3rd, 7th and 14th day of life. The behavior performance of SGA babies on day 3, compared to AGA babies, was lower in all the clusters except orientation where they performed much better. By day 14 SGA babies were scoring higher than AGA babies in orientation, autonomic stability and regulation of state.

Mukhopadhyay et al. [77] evaluated the iron status at birth and at 4 weeks in preterm-SGA infants in comparison with preterm and term-AGA infants. Fifty mother-infant pairs in each group were enrolled. Cord serum ferritin levels were less in preterm-SGA group as compared to preterm-AGA group (median [interquartile range]: 68 (30 113) vs. 120 (73 127), p=0.002). The proportion of the infants with "low" serum ferritin was more in preterm-SGA than in preterm-AGA (16 [32%] vs. 5 [10%], p=0.01). The serum ferritin levels at follow-up were also less in preterm-SGA as compared to preterm-AGA (143.5 ± 101 vs. 235.1 ± 160, p=0.004).

Figueras F et al. [78] conducted a study to evaluate the neurobehavioral outcomes of preterm infants with intrauterine growth restriction (IUGR), with and without prenatal advanced brain-sparing. Brain sparing was defined as MCA pulsatility index <5th centile recorded 72 hours before birth. They included 126 preterm newborns (64 controls and 62 IUGR) in their study. Neonatal neurobehavior was evaluated at 40 weeks' (±1) corrected age using the Neonatal Behavioral Assessment Scale. They reported that when IUGR were compared with AGA infants after adjusting for maternal smoking, socioeconomic level, , gestational age at delivery, preeclampsia, illness severity score, infant sex and mode of delivery; newborns in the IUGR subgroup with abnormal MCA Doppler had significantly lower neurobehavioral scores in the areas of habituation, motor system, social-interactive and attention.

Long term morbidities

Small Gestational Age (SGA) infants are at risk for impaired growth and neurodevelopment. Subsequent disorders in adults may also result from Fetal Growth Restriction (FGR).

Long term Physical Growth

Postnatal growth after IUGR depends in part on the cause of the growth retardation, the postnatal nutritional intake, and the social environment. Neonates who are symmetrical IUGR i.e. who have growth retardation in first trimester remain small throughout life. Those infants whose intrauterine growth was inhibited late in gestation (asymmetrical IUGR) will have catch-up growth after birth and approach their inherited growth potential when provided with an optimal environment and adequate postnatal caloric intake [79-81].

Chaudhari et al. [82] in their study assessed the growth and sexual maturation of low birth weight infants at 12 year of age. They evaluated 180 LBW infants who were grouped as preterm SGA (n=73), full term SGA (n=33) and preterm AGA (n=74).Ninety full term AGA infants were taken as controls. Among the three cohorts, preterm SGA children had significantly less height, weight and head circumference (P<0.001) compared to the others. There was no significant difference in sexual maturity and onset of menarche.

Chaudhari et al. [83], in another study evaluated LBW infants till their age of 18 years. The cohort of LBW infants consisted of preterm

SGA (n=61), full term SGA (n=30) and preterm AGA (n=70) infants. Seventy one full term AGA infants were the controls. . They found out that preterm SGA males had height which was significantly less than that of controls (P=0.02). Preterm GA children had short stature in spite of normal mid-parental height. Preterm SGA and AGA children had smaller head circumference.

Long term Neurodevelopmental Outcome

Cognitive and neuro-developmental abnormalities are more common in IUGR infants compared with those who were AGA and born at the same gestational age. Intellectual and neurologic functions in these infants depend heavily on the presence or absence of adverse perinatal events, in addition to the specific cause of IUGR. Under-nutrition that affects head circumference before 26 weeks of pregnancy (symmetrical IUGR) has a greater impact on neurologic function than does asymmetrical IUGR. Neurodevelopmental outcome will be worsened in IUGR who have associated illness such as hypoxic-ischemic encephalopathy [84,85] and hypoglycaemia.

Apart from restricted growth, the premature children are more likely to have [11,86,87]:

Lower scores on cognitive testing

School difficulties or require special education

Gross motor and minor neurologic dysfunction

Behavioral problems (attention deficit hyperactivity syndrome)

Growth failure

Reduced strength and work capacity

Grantham et al. [88] in their review of the 3 studies showed association between IUGR and cognitive development and behavior in the first six years of life and reported that deficits in performance of the IUGR group began to appear between 1 and 2 years of age. These deficits were larger in high risk subgroups (those who were born smallest, or when IUGR occurred early in pregnancy) and however the size of the difference was less at 4 to 7 years of age Martorell et al. [89] in their systematic review of 12 studies including Guatemala longitudinal study, observed that IUGR males and females, at an average of 15 years of age, performed poorly on tests of strength and they could apply approximately 2 to 3kg less force to a hand grip dynamometer and had lower work capacity in comparison to their normal counter-parts .

In a cohort from Pune, India, 161 low birth weights (weight <2000g at birth) were followed from birth till 18 years of age. The cohort consisted of preterm SGA (n=61), full term SGA (n=30) and preterm AGA (n=70). Seventy one full termed AGA infants were controls. Among the enrolled infants PTSGA subjects had the lowest IQs (percentile 35.5) although within the normal range for age. PTSGA infants were also poor in visuo-motor perception, motor incompetence, reading and mathematics learning [90].

Leitner Y et al. [91] conducted a prospective study to characterize the neurodevelopmental and cognitive difficulties specific to children with IUGR and to detect early clinical predictors of these difficulties. In their study they enrolled 81 IUGR infants who were followed up to 6 to 7 years of age using biometric parameters, perinatal risk questionnaires, and detailed neurodevelopmental and cognitive assessments. Forty-one children served as age-matched, appropriate for gestational age controls. They reported a significant difference in growth parameters (weight in kgs; 19.3± 4.4 vs. 22.2 ± 5, p<0.005; Height in cms; 114.3±5.5 vs.118.6±6.7, p<0.001; Head circumference in cms: 50±1.6 vs.51.3±1.7, p<0.001), neurodevelopmental score (85.6±11.5 vs. 89.2±6.1, p<0.05), and IQ (101.38±14.1 vs. 107±13.9, p<0.05) in IUGR infants. The most frequent early intervention in IUGR infants was their referral for occupational therapy (27% vs. 17.8%). IUGR infants had specific profile of difficulties including coordination, lateralization, spatial and graphomotor skills. The clinical parameters best predicting neurodevelopmental outcome were the neonatal risk score (P<0.05) and the weight and height at 6 years of age (P<0.05). The children with IUGR with neonatal complications had lower neurodevelopmental scores (78.7±18 vs. 86.1±9, p<0.05) than the controls but there was no difference in IQ scores (98±14.9 vs. 102.4±13.5, p>0.05).

Geva R et al. [92] analyzed the memory functions of children born with asymmetric IUGR using a long-term prospective paradigm. They enrolled 110 IUGR and 63 AGA infants and followed them prospectively from birth till 9 year of age. Memory functions (short-term, super- and long-term spans) for different stimuli types (verbal and visual) were evaluated using Visual Auditory Digit Span tasks (VADS), Rey Auditory Verbal Learning Test (Rey-AVLT), and Rey Osterrieth Complex Figure Test (ROCF). They reported that IUGR children's had short-term memory difficulties that hindered both serial verbal processing system and simultaneous processing of high-load visuo-spatial stimuli. Recognition skills and benefits from reiteration, typically affected by hippocampal dysfunction were preserved in both groups. They concluded memory profile of children born with IUGR was characterized by a short-term memory deficit that does not necessarily comply with a typical hippocampal deficit, but rather may reflect an executive short-term memory deficit characteristic of anterior hippocampal-prefrontal network.

In a longitudinal study by Leitner Y et al. [93], the neurodevelopmental outcome of children with intrauterine growth retardation was evaluated at 10 years of age. They enrolled 123 IUGR and 63 AGA infants in their study and assessed their specific neurodevelopment, school achievement and cognitive difficulties. They reported significant differences in growth (weight in kgs; 27.9±7.1 vs. 31.1± 6.1, p<0.005; height in cms; 131.3±6.1 vs. 135±6.8, p<0.001; head circumference in cms: 51.2±1.8 vs.52.1±2.6, p<0.01), neurodevelopmental score (85.9±9.6 vs. 91.2±5.1, p<0.01), intelligence quotient (IQ: 98.39±12.9 vs. 107.5±10.4, p<0.001), and school achievements which was measured using Kaufmann Assessment Battery for Children (588.6±80.2 vs. 636.63±55.7, p<0.001) in IUGR children. Overall, approximately 18% to 20% of the children that participated in the study were below the 10th growth percentile for their age in at least one of the biometric parameters at age 9 to 10. Children with IUGR had a specific profile of neurocognitive difficulties at school age, accounting for lower school achievements. The best perinatal parameter predictive of neurodevelopment and IQ was the Cephalization Index (P<.001).

Fetal Origin of Adult Disease (FOAD)

According to Barker Hypothesis, the SGA babies are more prone to develop diseases with the onset of adult age. Barker hypothesized that the associations between small size at birth or during infancy and later cardio-vascular disease reflect permanent effects of fetal undernourishment. Intra-uterine fetus is dependent on the nutrients

from the mother and adapts to this inadequate nutrient supply in a number of ways [94-99]:

Prioritization of brain growth at the expense of other tissues such as the abdominal viscera

Reduced secretion and sensitivity to the fetal growth hormones insulin and IGF-I

Up-regulation of the hypothalamo-pituitary adrenal (HPA) axis

The FOAD hypothesis proposes that although occurring in response to a transient phenomenon (fetal under-nutrition) these adaptations become permanent or 'programmed' because they occur during critical periods of early development. These IUGR infants are susceptible to following disease in adulthood

A. Hypertension [100]

B. Ischemic Heart disease/Stroke [101,102]

C. Type-2 Diabetes [103]

D. Hypercholesterolemia [104]

E. Syndrome X [100]

F. Obesity [105,106]

G. Parkinsonism [100]

Prevention of IUGR

Increased incidence of intrauterine growth restriction in developing countries is often due social reasons and does not appear to reduce with interventions targeted at pregnant women alone. Adolescent nutrition, pre-pregnancy weights, poverty, inter-pregnancy interval are the crucial determinants of fetal growth in low and middle income countries. However some interventions exist to improve maternal nutrition and reduce fetal growth restriction and Small-for-Gestational Age (SGA) births in appropriate settings in developing countries, if scaled up before and during pregnancy [107].The interventions include

a) Balanced energy protein

Kramer et al.,[108] in their systematic review of 16 RCTs and quasi-experimental studies on balanced energy protein supplementation to pregnant women reported reduction in incidence of SGA (RR 0.66, 95% CI 0.49-0.89), stillbirths (RR 0.62, 95% CI 0.40-0.98) and improved birth weight (Mean difference of 73g, 95% CI 30-117).

b) Calcium supplementation

Imdad et al., [109] in their systematic review of 15 RCTs on calcium supplementation to pregnant women from developed and developing countries reported significant effects on pre-eclampsia (RR 0.48, 95% CI 0.34-0.67), birth weight 85 g (95% CI 37-133), and preterm birth (RR 0.76, 95% CI 0.60-0.97). There was no significant effect on perinatal mortality, low birth weight and neonatal mortality.

c) Multiple micronutrient supplementations

Cochrane systematic review of 21 RCTs on multiple micronutrient supplementation to pregnant women in comparison with two or fewer micronutrients resulted in a significant effects on low birth weight (RR 0.88, 95% CI 0.85-0.91), SGA (RR 0.89, 95% CI 0.83-0.96) and preterm birth (RR 0.97, 95% CI 0.94-0.99). [110].

d) Preventive strategies for malaria in pregnancy

Cochrane Systematic review of 16 RCTs comparing anti-malarial drugs given regularly with no anti-malarial drugs for preventing malaria in pregnant women living in malaria endemic areas reported effects in reduction of antenatal parasitemia (RR 0•53, 95% CI 0•33-0•86), increased birth weight (MD 126•7g, 95% CI 88•64–164•75), reduced low birth weight by 43% (RR 0•57, 95% CI 0•46-0•72) and severe antenatal anemia 38% (RR 0•62, 95% CI 0•50–0•78). There were no significant effects on perinatal deaths [111].

The other interventions which can be tried in mother who are diagnosed to have IUGR babies include [112]

Bed Rest to mother

Parenteral nutrition to mother

Nutritional supplementation to fetus

Oxygen therapy

Antibiotic therapy to mother

Pharmacological therapy to mother including aspirin, beta adrenergic agonist, atrial natriuretic peptide

Nitric oxide donor

Intermittent abdominal compression

Conclusion

IUGR newborns are common in the developing countries. A significant global burden of IUGR neonates is contributed by the Asian continent. Poor socioeconomic status, poor care of the girl child, medical and obstetric disorders complicating pregnancy contribute to a significant proportion of IUGR in developing countries. Of late genetic factors affecting the mother, placental and fetus are increasingly reported. IUGR infants face multiple problems from birth to adolescence. They are more prone to immediate mortality and morbidities, apart from experiencing the long term growth deficits and abnormal neurodevelopment. They are also more likely to have poor school performance and childhood behavioral issues. The health policy of the country must be directed towards prevention of IUGR births as they are burden to health infrastructure of the country and add to neonatal mortality. IUGR remains a challenge for the neonatologist/obstetricians. Greater integration and coordination among primary, secondary and tertiary health care facilities should be ensured to tackle the problem. To summarize, the successful management of IUGR requires a concerted liaison of both medical and socials sectors in the developing world.

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