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INTRAUTERINE GROWTH RETARDATION: POTENTIAL CAUSE OF CHRONIC DISEASE

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ABSTRACT

Intrauterine growth retardation (IUGR) refers to the growth rate of a fetus that is less than normal for the growth potential. As one of the leading causes of mortality and morbidity, intrauterine growth retardation has immense implications for the short term and long term growth of children. It is an important public health concern in developing countries. Various maternal, placental, neonatal, genetic and environmental factors lead to IUGR and babies with low birth weight. Maternal nutrition, pathophysiological and life style factors are leading causal factors of growth retardation in the uterine life of fetus which develops a bridge towards chronic diseases through an irreversible change in the programming during intrauterine life. These changes result in the distribution of cell types, hormonal feedback, metabolic activity and organ structure and ultimately lead to birth of infants with low birth weight. These infants are more likely to develop chronic diseases such as coronary heart disease, diabetes and neurodevelopment diseases in their adult life.

KEYWORDS: Intrauterine Growth Retardation (IUGR), Programming, Chronic Diseases

INTRODUCTION

Intrauterine growth retardation (IUGR) is a term used for neonates who could not achieve their optimal growth potential [1] which is a major clinical and public health problem in developing countries [2] which is associated with increased risk of neonatal death [3]. Intrauterine growth retardation (IUGR) is the term used to describe the intrinsic growth potential of a fetus with a birth weight at or below the 10^{th} percentile for gestational age in weeks & sex [4]. Intrauterine growth retardation (IUGR) and Small for Gestational Age (SGA) are terms, used to convey the same condition although there are subtle differences in these. IUGR is a clinical aspect which is applied to neonates with clinical evidence of malnutrition and SGA is low birth weight less than 10% for particular gestational age, parity and gender, as per the population growth chart [5]. SGA is further classified as Moderate (birth weight in the 3 to 10 percentile) and Severe (birth weight below 3 percentile) [6].

EPIDEMIOLOGY

Globally, the burden of IUGR is around 24% which shows that approximately 30 million infants are affected from IUGR every year [7], mainly it is concentrated in Asia which accounts for nearly 75% while Africa and Latin America account for 20% and 5% cases, respectively [8]. Increased incidences in the cases of IUGR, in developing countries can be attributed to babies born at home because they are more likely to be low birth weight (LBW: Birth weight <2500grams). The highest prevalence of LBW (28%) and IUGR-LBW (33%) are found in South Central Asia. 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 OF IUGR

There are 3 types of IUGR: Symmetrical IUGR, Asymmetrical IUGR and Mixed IUGR [9, 10].

- Symmetrical growth restriction begins early in gestation in which the total cell number is reduced. Infants with Symmetrical IUGR are characterized by reduction in all physical parameters such as weight, height, and head circumference. The difference between head and chest circumference will be less than 3 cm in such cases. Symmetrical IUGR is generally caused by intrinsic factors such as congenital infections or chromosomal abnormalities.
- Asymmetrical growth restriction typically begins in the late second or third trimesters in which the cell numbers are normal but cell size is reduced. Infants with Asymmetrical IUGR have reduction in weight and length due to brain sparing. Features of malnutrition are well-defined in the form of loose skin fold, loss of buckle fat, featuring aged people. Placental disorder is the major cause of asymmetrical IUGR.
- Mixed type of IUGR is represented by a decrease in the number of cells and cell size which occurs mostly when IUGR is affected further by placental causes in the later stages of pregnancy. This represents the clinical features of both symmetrical and asymmetrical IUGR. Infants with normal cell numbers experience better and immediate neonatal and long term growth with improved neuro developmental outcomes.

CAUSES OF IUGR

The occurrence of IUGR is accountable by different causes which include maternal factors, placental factors, fetal factors and genetic factors [11]. Among all these factors, one third of IUGR are caused by genetic factors and two third is caused by fetal environment [9].

Maternal Factors

Maternal health status is a good predictor of fetal growth. Various maternal physiological factors, biological factors, socioeconomic factors and life style factors are found to be the significant maternal determinants of intrauterine growth restriction [12]. Physiological factors include age, height, weight, mid arm circumference and skin fold thickness at the time of conception [13, 14]. Maternal young age (<16) yrs and advanced age (>35) yrs, are considered as risk factors for developing babies with low birth weight [15, 16]. Maternal biological factors, like parity, previous spontaneous abortion, direct and indirect obstetric morbidity are found to be significantly associated with intrauterine growth restriction [17]. Maternal pathological conditions like diabetes, anemia and preeclampsia are closely associated with IUGR [18, 19]. Maternal socioeconomic condition is unswervingly related to maternal nutrition, education and knowledge regarding antenatal care, which can ultimately cause lower weight gain during pregnancy followed by IUGR [16, 17, and 20].

It has been reported that women in the lowest quartile of pre pregnancy weight and weight gain during pregnancy were highly associated with increased risk of IUGR; similarly body mass index (BMI) in the lowest quartile had double the

risk of producing an IUGR infant [16]. A cross sectional study, was conducted to evaluate maternal factors associated with intrauterine growth restriction in Goa, India. In this, 200 live new born infants with IUGR were examined and reported a strong association of maternal factors such as age, parity, socioeconomic status, BMI, pregnancy induced hypertension, anemia and previous IUGR with the birth of an IUGR infant [21]. Maternal life style factors such as cigarette smoking, alcoholism and use of illicit drugs affects the antenatal growth during pregnancy [17, 18], although, heavy consumption of alcohol during pregnancy can lead to fetal alcohol syndrome and moderate consumption can lead to IUGR. Yang Q et al (2001) conducted a case-control study to scrutinize the relationship of maternal alcohol consumption with the risk of IUGR among 701 case and 336 control infants born during 1993-1995 in Monroe County, New York. They reported an odd ratio of 1.4 (95% CI: 0.7-2.6) among mothers that were heavy drinkers (more or equal to 14 drinks in a week) around the time of conception and 1.3 (95% CI: 0.4-4.5) for heavy drinkers during the first trimester [22].

Apart from all these factors, an environmental factor like failure to obtain normal medical care during pregnancy is one of the major contributors of IUGR [13]. Toxic exposure of mother including various medications such as steroids, anticonvulsants, wasfarin, anti-metabolites, antineoplastic agents and folic acid antagonists have shown adverse effect on fetal growth. Kharrazi et al (2004) studied the magnitude and shape of the relation between environmental factors like exposure to tobacco and adverse pregnancy outcomes from 3000 pregnant women in a prenatal screening programme. They found that there was a linear dose dependent effect of blood nicotine levels on mean birth weight and mean infant length. They also observed that the Infants' body mass index declined with nicotine exposure above 0.5ng/ml [23].

Placental Factors

Fetal growth is a reflection of the placental supply of key nutrients from the maternal body through its own demand for metabolism of important nutrients and production of hormones that influences fetal development. Growth of the placenta occurs mainly during the first half of pregnancy; in contrast to fetal growth which is more rapid in the second half. As a result, the ratio of placental to fetal weight normally decreases as gestation progresses. Inequity in these can result into impaired fetal growth [24].

A placenta that is either too small or too large may adversely affect fetal growth. If the placenta is disproportionately small, the fetus may suffer as a result of an impaired placental supply capacity. Conversely, if the placenta is too large, the fetus may suffer by experiencing fetal catabolism and wasting to supply amino acids to the placenta as a source of lactate [25]. Placental ratio was positively associated with several maternal factors, including lower socioeconomic status, anemia, and increasing number of cigarettes smoked daily. Also in Australia, it was found that maternal smoking was negatively associated with placental weight and with growth and bone mass of children at the age of 8 years [26]. Association of smoking with growth and bone parameters may be mediated by placental size and function, since these effects were no longer significant when adjusting for placental weight. Infectious villitis (TORCH infection) is associated with recurrent abortion, intrauterine growth retardation, intrauterine death, preterm labor, early neonatal death and congenital malformation [27]. Along with these, placental infections, placental dysfunction, placental hemangioma, abnormal uteroplacental vasculature, uteroplacental pathology (thrombophilia), chronic inflammatory lesions and multiple infractions are contributory factors causing impaired fetal growth [22, 24, 25, 28].

Salafia et al (1995) conducted a study on intrauterine growth restriction in infants of less than thirty-two weeks gestation associated with placental pathologic features. They reported that cases with intrauterine growth restriction had

lesions of uteroplacental insufficiency ($p<0.001$) or chronic villitis ($p<0.02$). The cases with asymmetric intrauterine growth retardation tended to have more lesions as compared to appropriate for gestational age. Overall, uteroplacental fibrinoid necrosis circulated nucleated erythrocytes, avascular terminal villi and villous infarct were significantly independent predictors of fetal growth and with addition of preeclampsia, and all these were independent predictor of fetal growth [29].

Neonatal Factors

Neonatal factors play a secondary role in developing fetal growth retardation along with primary maternal factors like nutrition, pathophysiological condition and antenatal care throughout during pregnancy [30]. These maternal primary factors can cause abnormality in the fetus at genetic level such as karyotypic abnormalities (trisomy 18 and 13, autosomal deletions, ring chromosomes and uniparental disomy (UD), Bloom and Russell-Silver syndrome and major congenital anomalies like tracheo-esophageal fistula [30, 31]. Metabolic disorders during pregnancy can cause congenital absence of islets of langerhans, congenital lipodystrophy, hypophosphatasia, agenesis of pancreas, galactosemia, generalized gangliosidosis type I, I-cell disease, Leprechaunism, fetal phenylketonuria, transient neonatal diabetes mellitus [30-32].

INTRAUTERINE GROWTH RETARDATION ONSET ADULT DISEASE

It is absolute that IUGR is one of the influences which programs the human body and has lifelong consequences. Intrauterine fetal life is a critical period of growth and development in which, the tissues and organs of the fetal body, develop through rapid cell division [33]. The rapid cell division affects directly through undernutrition along with other maternal, placental and neonatal factors. According to the fetal origins hypothesis, alterations in fetal growth result in developmental adaptations that “programme” vulnerability to cardiovascular, metabolic and endocrine disease in later life [34]. “Programming” is a phenomenon whereby a long-term and irreversible alteration in structure or metabolism is induced by a relatively brief stimulus [35]. During the rapid fetal growth and developmental period, changes in the nutrient and hormonal milieu of the conceptus at critical periods may alter the expression of the fetal genome, leading to permanent effects on a range of physiological functions and structures [36]. Programming reflects a general principle of developmental biology, and a wide range of organs and systems may be programmed by the intrauterine environment [37]. Rickets linked with calcium deficiency, neural tube defects linked with folate deficiency and altered mental development in iodine deficiency is the paradigm of programming during intrauterine life [38].

Fundamentally, there are two reasons of long term consequences of chronic diseases during intrauterine life. First, infants with IUGR have reduced function in key organs, such as the kidney [39]. Retarded growth during fetal life results in lower metabolic rate, redistribution of blood flow and changes in the production of fetal and placental hormones which control growth [40]. This can ultimately lead to a disproportion in organ size since organs and tissues that are growing rapidly at the time are affected the most. The kidney develops rapidly at late gestational period. Reduced replication of kidney cells may permanently reduce cell numbers and ultimately reduce functional capacity [41]. Secondly, they have altered amendment in their metabolic and hormonal feedback. Fetal insulin hormone and the insulin-like growth factors (IGFs) are reflection to have a fundamental role in the regulation of growth. Reduced maternal insulin and IGF results in lower concentration of glucose, insulin and IGF in the fetus followed by reduced transfer of amino acids and glucose from mother to fetus, and ultimately to reduced rates of fetal growth. In late gestation and after birth the fetus’ growth hormone and IGF axis take over, from insulin, a central role in driving linear growth [35, 41]

The numerous animal experiments suggests that growth retardation in uterine life leads to persisting changes in blood pressure, cholesterol metabolism, insulin response to glucose, and a range of other metabolic, endocrine, and immune functions known to be important in human disease [38,42].

Coronary Heart Diseases

An important clue symptomatic of coronary heart disease which originated during fetal development came from studies of death rates among babies in Britain during the early 1900s. The usual certified cause of death in newborn babies at that time was low birth weight. One possible conclusion suggested by this observation was that low rates of growth before birth or IUGR are in some way coupled to the development of coronary heart disease in adult life [43]. The incidence of coronary heart disease is now rising in other parts of the world to which Western influences are extending, including China, India, and Eastern Europe [44]. Associations have been established between small size at birth and coronary heart disease and its risk factors, hypertension, non-insulin dependent diabetes, and abnormalities in lipid metabolism and blood coagulation. These associations are independent of adult lifestyle, including smoking, obesity and social class, and have led to the hypothesis that the disease is programmed in uterine life. These and other associations between fetal growth and the risk of degenerative disease have been extensively reviewed by Barker [41].

Vijayakumar et al (1995) [45] conducted a study in southern India which showed that LBW and CHD were coupled. The prevalence of CHD in men and women aged 45 or older reached 18% in that weighing ≤2.5 kg at birth, to 4% in those weighing ≥3.2kg. Short birth length and low head circumference at birth were also associated with raised prevalence of the disease. Furthermore, CHD was related to low maternal weight in pregnancy thus the highest rates were found in persons with LBW and thin mothers. Coronary heart disease was associated with the conventional risk factors including age, diabetes, and high blood pressure, adverse serum lipid profiles, short stature, and smoking, but not with raised fibrinogen concentrations or obesity. Simultaneous regression analyses suggested that the associations between reduced fetal growth and conventional coronary risk factors did not suppress the association between birth length and CHD. Lack of birth weight in formation resulted in a very low participation rate, which highlights the difficulty of such studies in developing countries.

In a subset of the Hertforshire cohort of men born in the ’20s and ’30s and still living there in the ’90s, They also observed that left ventricular mass was not related to birth weight, but it was highest in men with the lowest weight at the age of one year, after controlling for current age, body size, and systolic blood pressure. The enlargement was concentric, which is a known risk factor for CHD. Similarly, in French subjects aged 8–24 years [46], a concentric increase of left ventricular mass was found to be inversely related to weight at the ages of 9 months and at 2 years, but not to birth weight. These data suggest that poor postnatal growth may be an independent risk factor.

Serum Cholesterol

Disproportion in body length relative to head size is a reflection of IUGR during late gestation. The fetus uses an adaptive response present in mammals and diverts oxygenated blood away from the trunk to sustain the brain. This affects the growth of the liver, two of whose functions, regulation of cholesterol and of blood clotting, seem to be permanently perturbed. Disturbance of cholesterol metabolism and blood clotting are both important features of coronary heart disease [41].

In a large retrospective cohort study on Jamaican schoolchildren [47], serum cholesterol was found to be inversely related to length at birth and current height but not birth weight, in addition to being directly related to current triceps skinfold. Cook et al. [48] found that fibrinogen and factor VII were related to adiposity in British children aged 10 to 11 years, but not to fetal growth. In UK children aged 11–14 years, Morley et al [49] found a significant inverse association between birth weight and serum triglycerides, but not with other lipids. Social deprivation was associated with higher fibrinogen, but not lipid levels.

Blood Pressure

Possible mechanisms relating reduced fetal growth and raised blood pressure are persisting changes in vascular structure, including loss of elasticity in vessel walls, and the effects of glucocorticoid hormones. In animals, modest glucocorticoid excess retards intrauterine growth and programs raised blood pressure. An excess may occur either from feto-placental stress or from deficiency in the normal placental enzyme barrier that protects the fetus from its mother's glucocorticoids [41].

Law & Shiell reviewed 34 studies describing the relationship of blood pressure with birth weight in quantitative terms and in non-pathological groups, representing 66,000 individuals. Nearly all reported an inverse association, with a few exceptions in adolescents and newborns. There were 25 cohort studies, 4 case-control or comparative studies and 5 longitudinal studies. Nearly half the studies were from UK, and only 4 included nonwhite subjects. Roughly half of the studies reported multiple regression analyses, controlling for current size which was the most important potential confounder [50]. Blood pressure was typically 2–3 mmHg lower per kg increase in birth weight. In only one study in adolescents in Israel, and only in girls, there was a positive correlation between birth weight and blood pressure [51].

Insulin Resistant

The thin neonate is lacking in skeletal muscle, as well as fat. Muscle is the main peripheral site of action of insulin, which has a key role in stimulating cell division in fetal life. It is thought that at some point in mid-to-late gestation the thin neonate became undernourished, and that in response its muscles became resistant to insulin. Muscle growth was, therefore, sacrificed but the brain was spared [52].

In Beijing, in a study conducted by Mi et al (2000) [53], birth weight of term offspring was negatively associated not only with blood pressure, but also with 2-h serum glucose and insulin, and with triacylglycerol concentrations, in a cross-sectional sample of over 600 men and women aged 45. Current weight and sex were controlled for. There was also a positive association of birth weight with HDL cholesterol levels, but not LDL-cholesterol.

In Pune, India, cohort studies showed that components of the insulin resistance syndrome that are "programmed" *in utero* may already be apparent in childhood. In a group of almost 400 children aged 4 years, those with birth weights >2.5 kg had significantly higher plasma insulin concentrations 30 minutes after a glucose load, independent from their current size [54]. Plasma glucose and insulin were independently and inversely related to birth weight, although current weight and skinfold thickness were positively related to glucose and insulin [55]. At the age of 8 years, LBW was associated in these children with clustering of insulin resistance syndrome factors, although current weight had a stronger effect [56].

Neurodevelopmental Disorder

Neurodevelopmental outcomes are intimately associated with intrauterine life of the fetus. Impaired placental function with increased resistance to blood flow reflects fetal circulation which can further cause IUGR in addition to fetal hypoxia [57, 58]. Abnormal fetal blood flow in IUGR is linked with neurological disfunctions and impaired intellectual functions [59]. Several studies have revealed that children born with low birth weight are at risk for impairment in cognitive and neuromotor skills, and have educational and behavioral problems [60-63]. Adverse neurodevelopmental outcome in children born moderately preterm or term with IUGR and abnormal fetal blood flow has been described by several authors. Neurodevelopmental outcome will be worsened in IUGR who have associated illness such as hypoxicischemic encephalopathy and hypoglycaemia [64, 65]. Children with IUGR are more likely to have 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 and reduced strength and work capacity [9,66,67].

Tideman et al (2007) evaluated the influence of IUGR with abnormal fetal blood flow on cognitive function and psychological development in young adults. In their study, cognitive capacity (Wechsler adult intelligence scale-III (WAIS-III)) and psychological development (symptom check-list and Wender Utah rating scale) were evaluated at 18 years of age in 19 subjects who had a history of IUGR (abnormal fetal blood flow in the descending aorta and birth weight small-for-gestational age) and in 23 control subjects who had had normal fetal aortic blood flow and birth weight appropriate-for-gestational age (AGA). School grades at 16 years of age were also recorded. They found that IUGR subjects had significantly lower results at 18 years of age in the combined subtests of the WAISIII measuring executive cognitive functions ($P = 0.03$) and lower school grades at 16 years of age ($P = 0.03$) compared with the AGA group. IUGR subjects did not exhibit significantly more psychological distress symptoms [68].

Martorell et al (1998) conducted a systematic review of 12 studies and 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 [69].

Leitner et al (2007) studied the neurodevelopmental outcome of children with intrauterine growth retardation at 10 years of age. In their study 123 IUGR and 63 AGA infants were enrolled and assessed for 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 ($P<.001$) [70].

CONCLUSIONS

Children are the prospects of a healthy nation but children born with IUGR are major problem in developing

countries. A significant global burden of neonates with IUGR is contributed by Asian countries. The leading contributory factors are underprivileged socioeconomic condition, lack of education, lack of medical facilities and medical and obstetric disorders during pregnancy as well as negligence of neonatal care, especially girl child which plays a central role in IUGR in neonates. Along with these, maternal nutrition, life style factors and physiological factors transfer irreversible changes to the fetus during intrauterine life and domino effect in chronic disease in later life such as coronary heart disease, diabetes, obesity and neurodevelopment disorder next to malnutrition. A health strategy of the nation must be directed towards prevention of IUGR births by improving antenatal and postnatal health care facilities as they are a burden to the health infrastructure of the nation. The successful management of IUGR requires an intensive liaison of medical and socials sectors in the developing world.

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