Intrauterine Growth Restriction: A Perspective for Pakistan

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Abstract

Background: Intrauterine growth restriction (IUGR) is the second leading contributor to the prevailing perinatal mortality and morbidity. It affects 23.8% of newborns around the world and 75% of these affected infants are born in Asia. In Pakistan the incidence of IUGR is around 25%, more than the WHO criteria for triggering a public health action.
Introduction: IUGR is implicated with profound long-term impacts in adult life; like coronary heart disease, NIDDM and abnormal cortisol levels. The effects of the short and long term sequelae are reviewed. Etiology: IUGR is associated with a wide variety of etiological factors. But the factor unique in its importance to Pakistan is maternal malnutrition. The fetal gene expression is under the influence of nutrition. Growth projection curves showing the interaction between the genetic and environmental factors are discussed. Surveillance: Identification of IUGR baby in a primary care setting and the options in diagnosis in secondary and tertiary care settings are overviewed.
Conclusion: The roots of this problem, with multi factorial causes are in the socioeconomic infrastructure. This calls for a synergistic approach of reducing this public health issue. Women empowerment can help us to get out of this intergenerational cycle of growth failure. Availability of resources aside, it is also a matter of political will to change things for the better. (JPMA 49:50, 1999).

Introduction

Intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) is the second leading contributor to the prevailing perinatal mortality and morbidity[1]. A fetus, which suffers from IUGR, has a 6 to 8 times higher perinatal mortality rate as compared to grown counterpart[1]. We are all aware of the early outcomes of IUGR; these infants are more likely to suffer from conditions such as meconium aspiration and birth asyphxia. However, the effects of FGR are not simply restricted to the neonatal time period. Studies now show that IUGR has profound long-term impacts in adult life; it has been linked to coronary heart disease, NIDDM, and abnormal cortisol levels in adult life[2-4]. In addition, recent studies link FGR with a negative impact on the neurodevelopmentai outcome of such children[5,6]. By definition, infants suffering from IUGR are, whose weight falls in or below the tenth percentile of mean weight for gestational age[7]. Falling within these limits, will be a small group of infants who are low birth weight, but are not suffering from IUGR. These infants, unlike IUGR children are genetically determined to be small and have reached their growth potential. In contrast, children with IUGR who fall in this range are those who fail to reach their potential growth because of a pathological process. IUGR, affects 23.8% of newborns arouiid the world and 75% of these affected infants are born in Asia[8]. In Pakistan, specifically in Karachi the prevalence of IUGR was found to be 24.4%[9].

Sequelae of IUGR

IUGR has both short and long term sequelae. The immediate outcome of these babies is poor. The babies born after 34 weeks of gestation are prone to meconium aspiration and many suffer from birth asphyxia. These infants are at risk of hypoglycemia because of inadequate glycogen reserves secondary

to fetal malnutrition and because their gluconeogenic pathways are not as responsive to hypoglycemia[10]. in response to the hypoxia during intrauterine life the fetus increases RBC production and there is a transfer of blood which in turn leads to hyperbilirubinemia when the red The infants are also more prone to volume from the placental circulation to fetal circulation10. The result is polycythemia, hyperviscosity and blood cells breakdown. hypothermia because of inadequate fat reserves[10].

The impact of FGR does not simply end with the neonatal time slot. Studies have now shown that effects continue into adulthood. The overall concept is that fetal gene expression is under the influence of nutrition. Nutrition in turn also controls the hormonal environment within the fetus; Should the nutrition be inadequate, there are certain developmental adaptations which take place. These adaptations may be a decrease in cell number or preferably shunting of blood to the brain. It is the persistence of these adaptations, which is thought to be the link between IUGR and adult onset diseases[11-14].

A link exists between poor school performance and FGR6 These children were also shown to have more emotional and behavioral problems. The neurologic outcome of these children is dependent on the degree of growth restriction (mild, moderate, severe), time of onset and immaturity at birth. Those fetus affected by early onset IUGR between 10-17 weeks have serious neurologic sequelae. It is during this time that neuronal cellular multiplication takes place and because of the malnutrition the multiplication is limited, leading to profound neurological damage. If IUGR sets in during the third trimester when glial multiplication, establishment of synaptic connections and myelination take place, processes which continue up to the age of 2 years, the outcome is not as severe, provided that the child has adequate nutrition during the early years of life[10].

Coronary heart disease is one other long-term complication of IUGR[14-17].Men who were born with IUGR and then “caught up” in reference to weight by the age of 7 were at the highest risk of cardiovascular disease[18]. It has been postulated that in utero because of IUGR there are changes in the hormonal milieu; coronary heart disease is a reflection of those persisting changes[18].

Impaired glucose tolerance and NIDDM have also been associated with impaired fetal development[14,19,20]. According to one study, a three fold decrease in prevalence of NIDDM and impaired glucose tolerance in men who weighed 9.5 lbs. as compared to those weighing less than 5.5 Ibs[21]. The men at most risk were those who were thin at birth and later obese as adults. During fetal life, insulin stimulates cell division in areas such as the skeletal muscle. insulin resistance arises in skeletal muscle when the fetus needs to conserve glucose. In the short term the fetus would be thin because of decreased muscle mass and glucose would preferentially be shunted to the brain. In the long run the persistence of insulin resistance at the peripheral skeletal muscle would lead to impaired glucose tolerance or NIDDM[14]. Preliminary evidence also suggests that impaired fetal nutrient supply may lead to alterations in fetal neuroendocrine development, leading to raised cortisol levels in childhood[22]. This effect persists into adulthood causing altered sympathoadrenal function, which is indirectly assessed by a high pulse rate in the subjects[23]. A study of 60 years old men revealed that birth weight was inversely related to adult fasting plasma cortisol levels[24].

Etiology

Over the past decades, Intrauterine Growth Restriction has been associated with a wide variety of etiological factors (Table I).

Table. Factors associated with IUGR.

Placental
Small placenta in hypertensive women
Circumvallate placenta]
Abnormal implantation site
Placental infarcts
Abruptio placentae
Fetal
Congenital abnormalities
Trisomies
Intrauterine infection
Aids
Torch
Maternal factors
Chronic lung disease
Cyanotic lung disease
Severe anemias
Malnutrition
Low calorie absorption
Surgical bypass procedures
Smoking
Drug addiction

In contrast to the United States, where smoking may be the cause of 30-40% of cases of IUGR[25], the factor most unique in its importance to Pakistan is maternal malnutrition. Malnutrition of the mother may be manifested as low maternal height and weight at pregnancy[26-28] as well as low weight gain during pregnancy - all of which have been strongly associated with IUGR.

To understand the pathophysiology of the relationship between malnutrition and IUGR, one must understand how the fetus grows in utero and the process by which its nutrient demands are met by the mother. Recent research continues to shed more light on the pathophysiology of this association.

Environmental demands and factors

After birth, it is understood that subsequent growth is dependent upon both environmental and genetic factors. The same is true of the developing fetus. Genetic factors determine the maximal height to which the fetus can aspire, whilst environmental factors determine the extent to which the fetus approaches that goal. Less obvious, however, is that the importance of environmental factors far outweigh that of genetic factors. Studies of animal cross breeding[29], half-siblings[30], as well as more recent embryo transfer[31] studies give strong evidence in this regard[14,32]. Environmental factors being paramount, fetal nutrition is dependent upon the following series of events:

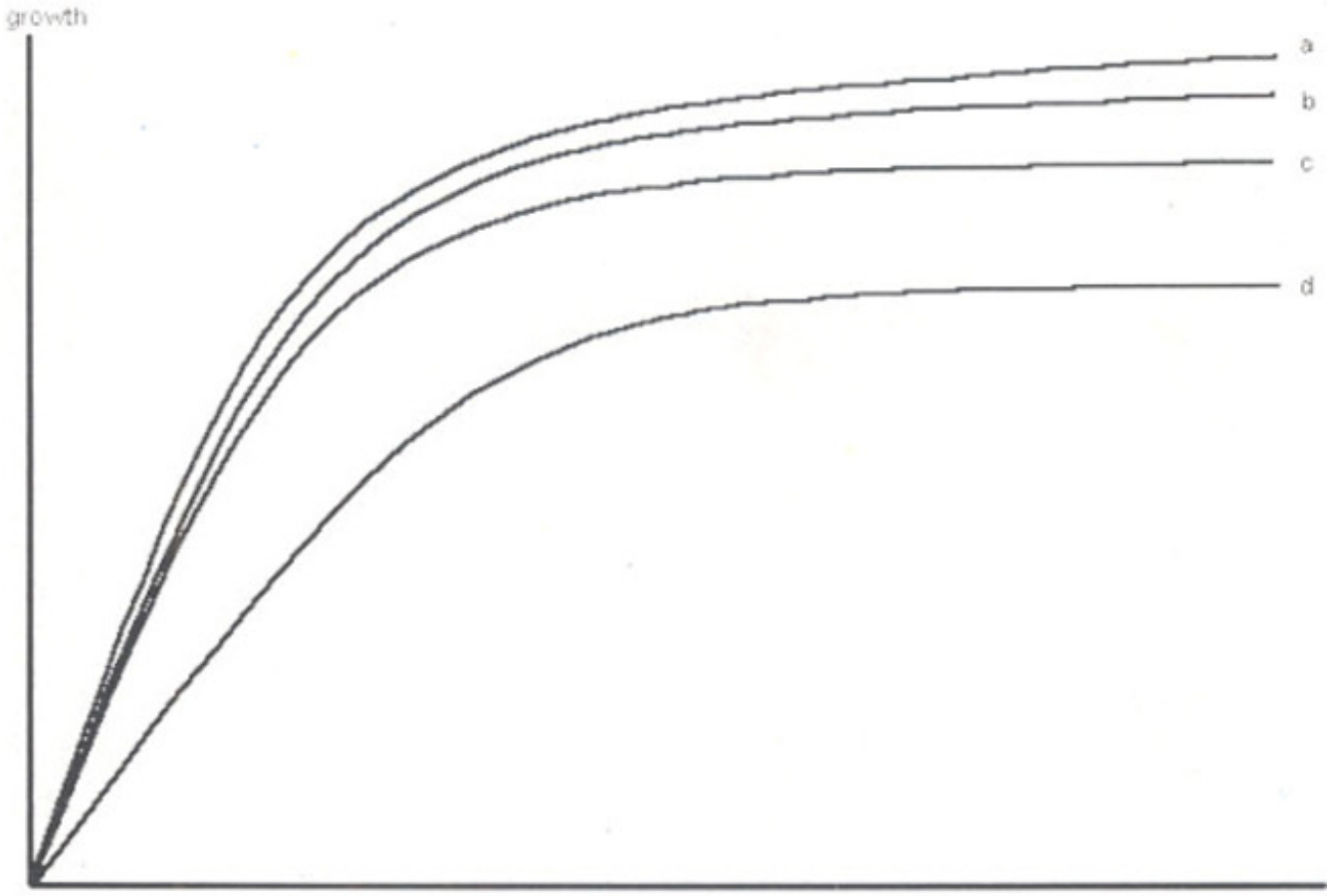
1) An adequate quantity of substrate present in the maternal blood.

2) An adequate uterine blood flow to the intervillous spaces.

3) The presence of a normally developed placenta with adequate surface area for exchange of nutrients.

4) A functioning fetus that can utilize substrate for its development. A disruption in any of these requirements will alter fetal growth - all etiological factors affect one or more of these requirements. It is, however, not quite as simple as this.

At the moment of conception, the genetically determined maximal size of the fetus is programmed. It might be said that the theoretically maximum growth trajectory (Figure 1)



Growth projection curves showing the interaction between genetic and environmental factors. a) Genetically determined optimal growth curve given optimal environmental conditions. b) Growth curve given slightly suboptimal conditions in the first trimester with no deficiencies thereafter. c) Growth curve given slightly suboptimal conditions in the first trimester with nutritional/placental deficiencies in the third trimester causing asymmetrical IUGR. d) Growth curve given severe nutritional/chromosomal deficiencies in the first trimester causing symmetrical IUGR

Figure. Growth projection curve.

for the fetus is produced at the moment of conception - given optimal environmental conditions, fetal growth would follow this curve.

When the placenta is developing in the first trimester, it is at this time that the environmentally influenced growth trajectory for the fetus is determined. If the maternal nutrition is in a good state at this time, then a high growth trajectory will be established, so the maximal growth of the fetus will approach that of the genetically determined maximum. If maternal nutrition is at a poor state at that time, then the trajectory will be set at a lower rate. The trajectory essentially sets the fetal nutritional demands for the remainder of pregnancy - once set, the trajectory can not be altered. A high trajectory equates to faster growth, and greater nutrient demand. A fetus with a low trajectory will demand fewer nutrients. This can Figwe Geowlh projection cwve - ironically present a problem later in pregnancy - if a patient with a high trajectory has problems with supplying the fetus for any reason in the third trimester, then the child begins to waste, because the required deniand is not met[10]. If a child with a low trajectory meets the same condition, it can cope better, because it requires less to grow. Therefor that fetus will not waste.

Animals who have poor nutrition at the time of conception and who suddenly increase their intake have

an increase in the size of the their placenta, but without a concurrent increase in surface area for nutrient exchange[34]. It is not sufficient to increase intake when missing the first menses. The mother must have adequate nutrition throughout her childbearing years, not just when her pregnancy is discovered - a concept that must be kept in mind in Pakistan.

IUGR Phenotypes

The two phenotypes of IUGR may now be appreciated - if a high trajectory is projected at the beginning of the pregnancy, and for whatever reason the demands are not met in the third trimester, then that child, attempting to follow the trajectory, will waste. The child's head and long bones will continue to grow, but at the expense of the rest of the body[35]. This is known as asymmetrical IUGR. If however a child has a low trajectory from the outset, then neither the length, nor the breath of the child will increase at an adequate rate, and as a result the entire fetus is smaller. This condition is known as symmetrical IUGR.

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