

Intrauterine Growth Restriction: A Perspective for Pakistan

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Pages with reference to book, From 82 To 85

Pathophysiology (in relation to maternal malnutrition)

As previously discussed, nutrition sets the growth trajectory. Once the trajectory is set, environmental factors determine whether the fetus will meet the full potential of the trajectory or will fall short. In Pakistan, maternal malnutrition is of great importance, so the answer to the following question shall occupy us: what are the required nutrients of the maternal blood, and how does a deficit of these nutrients biochemically affect the fetus?

Three major substrates must be available for placental transfer - oxygen, glucose, and amino acids. Severe oxygen deficit is generally independent of nutrition, but rather on any co-morbidities such as chronic lung disease or severe anemia - though mild nutritional anemia is common in Pakistan. In fact, it is the other two substrates that more directly concern us; these are glucose and amino acids. Glucose crosses the placenta by facilitated diffusion, while amino acids are actively transported across the placenta, causing higher fetal amino acid levels. Maternal nutrition will affect both the amount of glucose as well as amino acids that are available for transfer. The signals eliciting alterations in the fetal growth pattern in response to a compromised maternal supply have not been elucidated in detail yet, although details are slowly emerging.

Current theories

An IUGR fetus is sometimes hypoinsulinemic due to hypoglycemia in utero, and the low insulin levels will slow the growth rate in insulin-sensitive tissues such as skeletal muscle and liver, whereas brain growth is relatively spared. Recently, concentration has been given to the insulin like growth factors (IGF) because the IGFs seem to play a crucial role in fetal growth. They have been found to cause stimulation of fetal cell proliferation and anabolism. They have also been found to have a capacity to direct nutrients from the placenta towards the fetus³⁶. Direct correlation between umbilical cord serum IGF-I levels with birth weight have repeatedly been reported^{37,38,39}. Evidence of the role of IGFs in fetal growth have been found in mice -in whom targeted mutagenesis of the genes encoding IGF-I and IGF-II have produced profound embryonic, fetal, and postnatal growth retardation in mice^{40,41}. In humans, a patient with severe IUGR due to the deletion of IGF-I has been recently described as well⁴². It has been postulated that the growth-promoting machinery of the fetus - an integral link of which are the IGFs is frozen in IUGR fetuses to minimize energy expenditure for growth and to favor survival and development of vital organs⁴³.

Another area currently being actively explored is the role of amino acids in IUGR, how the concentrations change throughout pregnancy, and how specific amino acids contribute to the growth of various organ systems. The information in this area is not yet as advanced as that for the IGFs. Experiments have mostly been done on animals, including rats and cats. An important example is taurine - deficiency of taurine in cats has been found to be directly linked to IUGR⁴⁴, suggesting that taurine plays a role in regulating fetal growth. In human fetuses, taurine is an essential amino acid^{45,46}. It has been found recently that IUGR is associated with a reduced activity of placental taurine transporters, both in the microvillous membrane and the basement membrane⁴⁷. Correlating this with the role that it is thought to play in animals, it has been recently postulated that this could be yet another link in the pathophysiology of some forms of IUGR.

Identification and Surveillance of an IUGR fetus

A thorough clinical assessment and appropriate laboratory investigations are the two broad-based tools available. Regarding the clinical assessment, a detailed history should be focused at the identification of risk factors. Wennergren⁴⁸ classified the risk factors into 5 broad categories:

- 1) Low maternal pre-pregnancy weight and height. and low weight gain during pregnancy,
- 2) Poor prior obstetric history (high parity, previous LBW, stillbirth/NND).
- 3) Pregnancy complications (hypertension, bleeding etc.).
- 4) Maternal medical diseases (vascular, renal diseases etc.).
- 5) Environmental factors (malnutrition, low socioeconomic status etc.).

The environmental factors seem to be most relevant to the broader context of our population.

The physical examination should be directed to assess the general medical condition of the mother as well as the measurement of symphysis-fundal height which if found to have a discrepancy of more than 3 cm has a very high sensitivity and specificity for IUGR detection. The identification of risk factors together with Small Fetal Height measurement may screen out positively up to 85% of fetuses who have a higher probability of being growth-restricted⁴⁹.

From a primary care setting, these cases can then be referred to secondary or tertiary care centers where more expertise and sophisticated techniques should be at hand for further management.

The tools of investigation available are TORCH titers, U/S biometry, biophysical profile, non-stress test, fetal doppler U/S and then certain invasive techniques such as amniocentesis, chorionic villus sampling and cordocentesis.

TORCH titers and invasive procedures are important to find out the etiology of a symmetrical growth restriction, if present.

1. Ultrasound for gestational age should be done no later than 20th week with 8-13 weeks being the most appropriate time⁵⁰. Fetal weight should be measured to see if it is less than 10th percentile and Abdominal Circumference is less than 2.5th percentile. It is important to select the appropriate percentiles depending on the sensitivity required for a particular population or center.
2. Crown-Rump Length (5-12 weeks), Biparietal Diameter (12-18 weeks)⁵¹ and Femur Length (>15 weeks)⁵⁰, are very accurate in determination of gestational age. Abdominal Circumference has >95% sensitivity for IUGR detection⁵¹ whereas HC/AC has >70% sensitivity for the detection of asymmetric IUGR⁵².
3. Biophysical profile has a sensitivity of 65-100% for the identification of acidemia⁵³. Doppler ultrasound of fetal circulation is still in the experimental stage⁵⁴ even in western countries and its utility lies in identifying a compromised fetus⁵⁵ and then intervening at a step where the degree of damage to the fetus is not irreversible.
4. Non-stress test is also an important tool for assessment of fetal well-being but has the disadvantage of missing the intermittent stage of partial decompensation which could be the appropriate time for intervention.

A rank-ordering for abnormalities of fetal assessments in a progressively deteriorating IUGR fetus has been developed⁵⁶. Abnormal fetal umbilical artery waveforms precede the changes in fetal rest-activity cycle. Subsequently, late decelerations and poor variability appear on NST, followed by a low score on biophysical profile. Growth changes (as measured by AC) occur in between.

A Perspective for Pakistan

Every year out of the 30 million newborns born with IUGR, 75% are born in Asia-mainly in south-central Asia⁸. Whereas 30% of Africa's children are underweight; the corresponding figure for South Asia is over 50%⁵⁷.

Virtually half of the world's malnourished children are to be found in just three countries, namely Bangladesh, India and Pakistan. The fact that the problem is more in this area as compared to sub-Saharan African region indicates that the underlying problem is beyond the more obvious poverty,

agricultural performance and social inequalities.

Ramalingaswami pointed out that the key to this deadlock is the woman of a country⁵⁷. Imagine women as Soil' nourishing the seed of every new generation. So it becomes important that our very foundation should be healthy. According to The State of the World Children 1998, enrollment ratio of females in schools in Pakistan, as a percent of males was around 50% and 81% of the births are not attended by any health personnel. Around 60% of females in South Asia have iron deficiency, anemia, compared to 40% in Sub-Saharan region⁵⁸. The pregnancy weight gain should be ten kilos where as in South Asia it is five kilos". And this is only the tip of the iceberg.

All this comes to prove that the girls in South Asia are less well regarded and less cared for. And it is a fatal mistake on our part for not seriously realizing this issue. According to a community-based study in Karachi, the incidence of term intrauterine growth restriction was 24.4% among 738-singleton births⁹. The major risk factors, with an attributable risk of 20% or more were, low maternal weight, grand multiparity, low level of education, consanguinity and short birth-to-conception interval. A comparable study in Ahmedabad, India, showed similar results⁵⁹. Risk factors suggested were, low mean height and booking weight, low paternal height and weight, anemia (mean Hb 8.1g/dl) and malnutrition (54% consumed less than 1500cal/day). Still another study in India concluded maternal malnutrition as a risk factor for IUGR with an attributable risk of 42%⁶⁰. These facts further reinforce the notion of inequality of women in a society.

According to M de Onis, IUGR is a major public health problem worldwide, which contributes to closing the intergenerational cycle of poverty, disease and malnutrition⁸. A prevalence of IUGR in excess of 20% has been recommended as the cutoff point for triggering public health action⁶¹. The prevalence in Pakistan is around 25%^{8,9}. So a dire need for an immediate intervention is imperative. While evaluating prevention strategies we have to keep in mind the concept of inter generation cycle of growth failure. In this viscous cycle a low birth weight baby grows up to be a small adult woman, who eventually with early pregnancies in turn bears small children. Studies have shown that a woman's birth weight influence the birth weight of the offspring^{62,63}. So the challenge is to reach women well before they become pregnant. This will help adolescent girls to achieve the best nutrition status possible, before they enter the reproductive years.

Intrauterine growth restriction is a problem with a multi factorial cause. A macroscopic view of the situation points out the roots of the problem to be based in our political, cultural, social and economic infrastructure. With basic contributing determinants being family and community resources, information, and education. Personal communication with Bhutta revealed that the underlying determinants like inadequate food, hygiene, sanitation and health services are all interconnected with disease and low birth weight.

This calls for a synergistic approach to reduce multicausal outcome like IUGR⁸. A review of 126 randomized control trials pointed out interventions like balanced protein/energy supplements, anti malarial chemoprophylaxis and smoking cessation⁶⁴. More than this it is a matter of political will. The age-old notion of 'agenda of welfare' is to be changed to 'agenda of rights'. The 'key of keys' is the education of girls⁵⁷. Health services should be affordable, of adequate quality, and reasonable distance from home. Women should be given better status in the family. Women empowerment will give her more decision making power. Especially in the rural setting community awareness and understanding is the basic platform, from which goal oriented targets can be achieved.

Strategies to reduce IUGR in the present generation of infants are for the benefit of the generations to come⁶⁴. A lot of responsibility lies with the doctors and health care workers, it is us who have to make these problems known to the government and the media. We have to sensitize communities to organize themselves. It is the same 'good will', which Dante spoke of in Paradise of his Divine Comedy, which is required today. Otherwise Intrauterine Growth Restriction will remain a testimony to the regression

of a civil society.

Concluded!

Acknowledgements

We would like to extend our gratitude to Dr. Thomas Martin, Professor and Chairman, Department of Obstetrics and Gynecology and Dr. Zulfiqar A. Bhutta, Professor, Department of Pediatrics, The Aga Khan University Hospital, for their guidance and support in this project.

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