



Acknowledgement

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Enisar Desoki Mostafa Ali

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَأَنْزَلَ اللَّهُ عَلَيْكَ
الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ
مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا

صِرَاطُ اللَّهِ الْعَظِيمِ

سُورَةُ النِّسَاءِ (آيَةُ ١١٢)

INTRODUCTION

Intrauterine growth restriction (IUGR) is defined as a failure of the fetus to achieve its optimal growth potential (*ACOG Practice Bulletin, 2001*) and constitutes a major clinical and public health problem, mainly in the developing world (*de Onis et al., 1998*).

It is considered a heterogeneous syndrome associated with hypertensive disorders of pregnancy, smoking, infection, under nutrition and unexplained factors (*Villar et al., 2006*).

IUGR fetuses are at greater risk of perinatal death, birth hypoxia, neonatal complications, impaired neuro development and manifestations of the metabolic syndrome in adult life such as type 2 diabetes, coronary heart disease and hypertension (*Kady, 2004*).

Although no preventive interventions are available at present, being able to predict IUGR reliably would be valuable because:

- (i) It would identify fetuses that require early referral to secondary care and closer surveillance.
- (ii) Identifying at-risk fetuses would allow specific preventive interventions to be tested.

- (iii) Studies of predictors of IUGR could improve our understanding of the biological and pathological mechanisms that cause fetal growth restriction, leading potentially to better interventions
- (iv) Identifying low risk fetuses would avoid the use of unnecessary interventions, and
- (v) Accurate prediction, and prevention, of IUGR could be an early stage in a public health strategy that aims to avoid the adult consequences of fetal growth restriction.

(Villar et al., 2006)

IUGR is one of the leading causes of perinatal morbidity and mortality several causes of IUGR have been proposed involving cytotrophoblast dysfunction ***(Ruebner et al., 2010)***.

It is widely accepted that, next to infections, maternal disease and chromosomal abnormalities, a lack of nutrients and oxygen and impaired fetal-placental angiogenesis could lead to IUGR ***(Ruebner et al., 2006)***.

Endothelial dysfunction may lead to impaired uteroplacental function or nutrient deficiency ***(Riabna et al., 2009)***.

The regulation of vascular growth and remodeling is considered to be central to normal placental and fetal growth and development (**Chaiworapongsa et al., 2008**).

Endoglin, also known as CD105, is one of the key proteins that is synthesized and released by the placenta. It is highly expressed on the vascular endothelium and syncytiotrophoblast and is known to play a role in angiogenesis and in the regulation of the vascular tone through its interaction with endothelial nitric oxide synthase (eNOS) (**Robinson et al., 2007**).

Endoglin was also found to have a crucial role in monocyte-Mediated vascular repair (**Van Laake et al., 2006**).

In addition, endoglin is expressed in syncytiotrophoblasts of term placenta, and in pre-eclampsia its expression is highly elevated (**Levine et al., 2006**). While endoglin in normal smooth muscle cells is low, its expression is strongly up regulated in vascular smooth muscle cells in atherosclerosis (**Conley et al., 2000**).

Levine et al. (2008) demonstrated that the levels of soluble maternal endoglin in small-for-gestational-age (SGA) fetuses in normotensive pregnancies increased in the second trimester, with a large increase after the 37th week, resulting in the same high concentrations as in term preeclampsia.

AIM OF THE WORK

The aim of our study is to measure the level of the serum soluble endoglin in pregnant women at high risk to develop Intra -Uterine Growth restriction between 26th to 30th weeks of pregnancy.

Research hypothesis

Research question: Does the level of serum soluble endoglin will be useful in prediction of IUGR in patients at high risk to develop IUGR?

Research hypothesis: the serum soluble endoglin will be high in patients who will develop IUGR than the patient which not develops IUGR.

Medical application: if the serum soluble endoglin high in patients which develops IUGR this will help in the prediction of IUGR in these patients.

FETAL GROWTH RESTRICTION

Definition

Battaglia and lubchenco (1967) defined small for gestational age infants as those whose weights were below the 10th percentile for their gestational age. Such infants were shown to be at increased risk for neonatal death.

Intrauterine growth restriction (IUGR) is also defined as a failure of the fetus to achieve its optimal growth potential and constitutes a major clinical and public health problem, mainly in the developing world (*de Onis, et al., 1998*).

Risk factor

- (a) Poor maternal nutrition: in the woman of average or low body mass index, poor weight gain throughout pregnancy may be associated with fetal growth restriction (*Rode et al., 2007*). Lack of weight gain in the second trimester especially correlates with decreased birth weight (*Abrams et al., 1995*) marked restriction of weight gain after mid pregnancy should not be encouraged. Even so, it appears that caloric restriction to less than 1500 kcal/day adversely affects fetal growth only minimally (*Lechtig et al., 1975*).

- (b) Social deprivation; the effect of social deprivation on birth weight interconnected to the effects of associated lifestyle factors such as smoking, alcohol or other substance abuse, and poor nutrition. In a study of 7493 British women. **Wilcox et al. (1995)** found that the most deprived mother had the smallest infants.
- (c) Maternal and fetal infection; viral, bacterial, protozoan and spirochetal infections have been implicated in up to 5 percent of cause of fetal growth restriction. The best known of these are infection caused by rubella and cytomegalovirus (**Stagno et al., 1977**).

Mechanisms affecting fetal growth appear to be different with each. cytomegalo virusis associated with direct cytolysis and loss of functional cells. Rubella infections causes' vascular insufficiency by damaging the endothelial of small vessels and it also reduces cell division (**Pollack and Divon, 1992**). Hepatitis A and B are associated with preterm delivery but may also adversely affect fetal growth (**Waterson, 1979**). Listeriosis, tuberculosis and syphilis have also been reported to cause fetal growth restriction.

- (d) Congenital mal formations; in a study of more than 13,000 infants with major structural anomalies,

22percent had accompanying growth restriction (*Khoury et al., 1988*).

- (e) Chromosomal aneuploidies;
- (f) Disorder of cartilage and bone; numerous inherited syndromes such as osteogenesis imperfecta and various chondrodystrophies are associated with fetal growth restriction.
- (g) Drugs with teratogenic and fetal effects; a number of drugs and chemicals are capable of adversely affect fetal growth. Examples include anticonvulsants agents and antineoplastic agent. In addition, cigarette smoking, opiates and related drugs, alcohol and cocaine may cause growth restriction. Either primarily or by decreasing food intake. Caffeine use throughout pregnancy has recently been linked to fetal growth restriction. Diminished growth may be related to a phenotypic enzyme expression that slows caffeine metabolism (*CARE study group, 2008*).
- (h) Vascular disease: especially when complicated superimposed preeclampsia, chronic vascular disease commonly cause growth restriction. preeclampsia may cause fetal growth failure and is indicator for its severity, especially when the onset is before 37 weeks (*Gainer et al., 2005*) in a study of more than 2000women, vascular diseases evidenced by abnormal

uterine artery Doppler velocimetry early in pregnancy was associated with increased rate of preeclampsia small for gestational age neonates, and delivery before 34 weeks (**Groom et al., 2009**).

- (i) Renal disease; chronic renal insufficiency is often associated with underlying hypertension and vascular disease chronic nephropathies are commonly accompanied by restricted fetal growth (**Cunningham et al., 1990**).
- (j) Pregestitional diabetes; fetal growth restriction women with diabetes may be related to congenital malformations or may follow substrate derivation from advanced maternal vascular disease. The degree of growth restriction is related to malformation severity. Also the likelihood of growth restriction increase with development nephropathy and proliferative retinopathy especially in combination (**Haeri et al., 2008**).
- (k) Chronic hypoxia; conditions associated with chronic Utero placental hypoxia include preeclampsia, chronic hypertension, asthma, smoking and high altitude. When exposed to chronically hypoxic environment some fetuses have significantly reduced birth weight (**Bahtiyar et al., 2007**).

- (l) Anemia: curtailed maternal blood volume expansion has been linked to fetal growth restriction (**Duvekot et al., 1995**).
- (m) Placental and cord abnormalities a number of placental Abnormalities may cause fetal growth restriction. Chronic Placental abruption, extensive infection chorioangioma, marginal or velamentous cord insertion circomevellat placenta, placenta previa, and umbilical artery thrombosis. Growth failure in those cases is presumed to be due to uteroplacental insufficiency some pregnancies with other wise un explained fetal growth restriction and a grossly normal placenta have reduced uteroplacental blood flow compared with that of normally grown fetuses (**Kotini et al., 2003**).
- (n) Infertility; pregnancies in women with a history of infertility have an increased risk of small for gestational age infants with or without infertility treatment (**Zhu et al., 2007**).
- (o) Extra uterine pregnancy.
- (p) Ant phospholipid antibody syndrome.
- (q) Genetics.
- (r) Multiple fetuses.

PREVENTION

Prevention of fetal growth restriction ideally begins preconceptionally with optimization of maternal medical conditions, medications, and nutrition. Smoking cessation is critical. Other risk factors should be tailored to the maternal condition, such as antimalarial prophylaxis for women living in endemic areas and correction nutritional deficiencies. During early pregnancy, accurate pregnancy dating is essential in pregnancies at risk for fetal growth restriction, for example those in women with hypertension or prior fetal growth restriction, prophylaxis with low dose aspirin beginning early in gestation has been shown to reduce growth restriction by only 10 percent (*Berghella, 2007*).

MANAGEMENT

Once fetal growth restriction is suspected, efforts should be made to confirm the diagnosis, assess fetal condition, and evaluate for anomalies. Growth restriction near term is easier to manage but often missed. (*Miller et al., 2008*), although growth restriction before 34 weeks is readily recognized, it presents a management challenge. Cordocentesis allows rapid karyotyping for detection of a lethal aneuploidy, which may simplify management. (*The American college of obstetricians and gynecologists (2000)*) has concluded that there are not enough data to warrant routine cord blood sampling in this situation. the timing of delivery is crucial, and the risks of fetal death versus the hazards of preterm delivery must be assessed as reported in the growth restriction intervention trial (GRIT) by (*Thornton et al., 2004*).

Diagnosis of IUGR

Current thinking on the natural history of growth restriction differentiates between early-onset and late-onset forms, (*Turan et al., 2008*) which have different biochemical, histological, and clinical features (*Crispi et al., 2006*).

Whereas the former is usually diagnosed with an abnormal umbilical artery Doppler and is frequently associated with preeclampsia, the latter is more prevalent, shows less change in umbilical flow pattern, and has a weaker association with preeclampsia (*Crispi et al., 2006*).

Umbilical artery Doppler

Most instances of growth restriction correspond with cases of placental insufficiency (*Lackman et al., 2001*).

Evaluation of placental function by umbilical artery Doppler is a clinical standard to distinguish between SGA and IUGR (*Royal College of Obstetrics and Gynaecology 2003; American College of Obstetricians and Gynecologists, 1997*).

As suggested by animal (*Morrow et al., 1989*) and mathematical. (*Thompson et al., 2000*) models of chronic placental embolization, the obliteration of more than 50% of the placental vessels is required before absent or reversed end-diastolic velocities appear. There is good evidence that umbilical Doppler ultrasound use in these pregnancies improves a number of obstetric care outcomes and reduces perinatal deaths (*Neilson et al., 2000*).

Whereas abnormal umbilical artery Doppler is associated with adverse perinatal and neuro developmental outcome (*McCowan et al., 2000*). Small fetuses with normal umbilical artery Doppler are considered to represent one end of the normal-size spectrum, and the importance of managing them as completely differently from true IUGR babies has been stressed (*Soothill et al., 1999*).

This may not be true for late-onset cases, in which a substantial proportion of cases with a normal umbilical artery may have true growth restriction, and are at risk of adverse perinatal outcome (*Severi et al., 2002*).

Other Doppler parameters because the identification of late-onset SGA fetuses with mild forms of growth restriction cannot only be relied on by umbilical artery Doppler, other vascular territories have been proposed. Abnormal uterine artery Doppler is comparable with umbilical artery Doppler as a predictor of adverse outcome in growth restricted fetuses (*Vergani et al., 2002*).

Up to 20% of SGA fetuses have reduced resistance in the middle cerebral artery (MCA), and this sign is also associated with poorer perinatal outcome and suboptimal neurodevelopmental development at 2 years of age (*Eixarch et al., 2008*).