INTRODUCTION

Intrauterine growth restriction (IUGR) is defined as fetal growth slower than the normal growth potential of a specific fetus because of genetic or environmental factors ***(Murki and Sharma, 2014).*** IUGR is associated with a high incidence of perinatal morbidity and mortality ***(Muhammad et al., 2010).*** IUGR neonates have a greater risk of hypoxic-ischaemic encephalopathy, intraventricular hemorrhage and necrotizing enterocolitis with longer hospital stay and higher health care costs ***(Ross, 2008).*** Incidence of a fetus developing a small size for gestational age (SGA) is about 8% ***(Višnjevac et al., 2011).***

Fetal growth is regulated by the balance between fetal nutrient demand and maternal-placental nutrient supply. 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. In the developing world, IUGR is likely to be a consequence of poor maternal nutritional status prior to or during pregnancy ***(Zhang et al., 2015).***

There are two general patterns of growth abnormalities: symmetric and asymmetric. Symmetric growth inhibition arises during the first half of gestation, when fetal growth occurs primarily through cellular division and produces an undersized fetus with fewer cells of normal size. Asymmetric growth inhibition occurs during the second half of gestation and is

usually the consequence of an inadequate availability of substrates for fetal metabolism ***(Moh et al., 2012).***

To prevent the previously mentioned complications of IUGR, it is important to establish markers which can identify pregnancies at risk of IUGR early enough. Recently several studies have highlighted the role of many biomolecules as markers for IUGR like leptin, adiponectin, endothelin-1, lactate dehydrogenase, s-endoglin, soluble FMS tyrosine kinase receptor 1(sFTL1), pregnancy associated plasma protein, metastin ***(Wang et al., 2010).*** Apart from being expensive, laboratories at majority of centers are not equipped with facilities of measurement of these markers. Measurement of maternal serum ferritin has also been used as a predictive marker for increased risk of IUGR in one previous study on a limited number (seventeen) of cases ***(Višnjevac et al., 2011).***

Ferritin is an intracellular protein consisting of 24 H (heavy) and L (light) subunits surrounding a core that can store up to 4,500 iron atoms. The two subunits are highly conserved during evolution, but only the H subunit has ferroxidase activity ***(Arosio et al., 2008).*** Ferritin is released by infiltrating leukocytes, in response to acute and chronic infection. Ferritin as an acute phase reactant is well known for its intracellular iron sequestration and storage abilities during immune activation ***(Nandini et al., 2015).***

Plasma (or serum) ferritin concentration is positively correlated with the amount of total body iron stores in the absence of inflammation. Serum ferritin is considered a valuable biomarker for body iron status in healthy subjects ***(Milman, 2015).***

Iron deficiency has its known deleterious effect in pregnancy but iron loading may be associated with oxidative damage to cells and tissues. It has been shown in various studies that lower level of transferritin receptor expression in placenta is associated with preeclampsia and IUGR. This can lead to decrease extraction of iron by placenta from maternal serum leading to increase maternal serum ferritin. This fetal iron deficiency leads to increase in fetal corticotropins and fetal cortisol, causing inhibition of fetal growth ***(Bindal et al., 2015).***

AIM OF THE WORK

This study aims to assess the accuracy of maternal serum ferritin level in predicting the development of IUGR in pregnant woman.

INTRAUTERINE GROWTH RESTRICTION

Definition:

The use of the term small for gestational age (SGA) and intrauterine growth retardation (IUGR) has been confusing. They are often used interchangeably, although infants born following IUGR may or may not be SGA ***(Kurjak et al., 2010).***

SGA is a statistically descriptive term that correlates birth length and/or weight with gestational age (G.A.) and is, therefore, a postpartum diagnosis. It does not refer to fetal growth, and is not a synonymous with IUGR although it may be a consequence of diminished fetal growth ***(Hillman, 2014).***

It is important to distinguish between infants who experienced in utero growth restriction from infants with normal in utero growth but constitutionally small (i.e. no loss in percentiles throughout gestation) ***(Speer et al., 2008).***

Intrauterine growth restriction (IUGR) describes a decrease in fetal growth rate that prevents an infant from obtaining his or her complete growth potential ***(Aziz et al., 2012).***

A fetus with IUGR may be born small for gestational age (SGA) or appropriate for gestational age (AGA) according to population reference charts ***(Grisaru-Granovsky et al., 2012).***

Additionally, in developing countries, there is a direct correlation between the incidence of low birth weight (<2500 g) and IUGR because in developing countries, the high incidence of low-birth-weight (LBW) infants is almost exclusively due to the incidence of IUGR. Data from developed countries show the opposite, rates of low birth weight being explained almost exclusively by prematurity rates ***(De Onis et al., 2008).***

Some women have a tendency to have constitutionally small babies although both parent's gene affect childhood growth and adult final size, maternal genes mainly influence birth weight. Unfortunately, it can be concluded that a fetus is constitutionally small only after a pathological process has been excluded, which requires examination of new born. Therefore, identification of a constitutionally small baby is usually made in retrospect after the infant is born ***(Bernstein et al., 2010).***

The Ponderal index arrived at by the following formula, can be used to identify infants whose soft tissue mass is below normal for the stage of skeletal development.

Ponderal index= (Birth weight (gm)/Crown-heel length $(cm)^3$) ×100.

Thus a ponderal index below the 10^{th} percentile may be used to identify IUGR infants, thus all IUGR may not be SGA, and all SGA infants may not be small as a result of growth restricted process ***(Stoll et al., 2010).***

The two components that are necessary to define a SGA fetus are:

a) Birth weight < 10^{th} percentile.

b) Absence of pathogenic process ***(Stoll et al., 2010).***

To document adequately impaired fetal growth and diminished growth velocity in utero, at least 2 intrauterine size assessments must be performed ***(Petrini et al., 2009).*** Thus, IUGR should be considered a prenatal diagnosis, based primarily on serial measurements of fetal ultrasound parameters including estimates of fetal weight, head circumference, abdominal circumference and femur length ***(Petrini et al., 2009).***

Incidence:

Approximately one-third of low birth weight infants are SGA ***(Lee and Kimberly, 2008).*** In accurately dated pregnancies, approximately 80–85% of fetuses identified as being SGA are constitutionally small but healthy, 10–15% are 'true' IUGR cases, and the remaining 5–10% of fetuses are affected by chromosomal/structural anomalies or chronic intrauterine infection ***(Saleem et al., 2011).***

IUGR has a prevalence of 10% for all pregnancies. However, the figure varies in different patient populations, with rates of 3-5% for healthy mothers and 25% or higher for some high risk groups, such as hypertensive mothers ***(Melchiorre et al., 2009).***

The incidence of IUGR varies according to the reference population (with higher rates of IUGR in developing countries) and the percentile determined as indicating clinically significant growth restriction. While <10th centile is usually considered to indicate SGA, it may be that <3rd to 5th centile is more relevant in indicating the group with an increased risk of an adverse perinatal outcome ***(Vayssière et al., 2015).***

The perinatal mortality rate is 5-20 times higher for growth restricted fetuses, and serious short or long term morbidity is noted in half of the affected surviving infants ***(Gomella et al., 2009).***

Infants born prematurely who are also severely IUGR have higher neonatal morbidity and mortality when compared to infants of similar GA ***(Kristensen et al., 2006).***

It is estimated that one third of the infants with birth weight < 2500gm are in fact growth retarded and not premature ***(Gomella et al., 2009).***

The recurrence risk was found in one study to be 29% if the first pregnancy was affected, and 44% if two pregnancies have been affected. Recent research has shown that insulin-like growth factor 1 receptor (IGF-1R) gene mutations leading to disordered function of IGF-1 may result in restricted intrauterine growth and suboptimal development in postnatal life ***(Abuzzahab et al., 2003).***

Classification:

Two main patterns of fetal growth restriction that observed are symmetric or asymmetric ***(Militello et al., 2009).***

Symmetric IUGR:

The head circumference (HC), length (Ht), and weight (Wt) all are proportionately reduced for GA. Symmetric IUGR is due to either decreased growth potential of the fetus (congenital infection or genetic disorders) or extrinsic conditions that are active early in pregnancy ***(Stoll et al., 2010).***

Asymmetric IUGR:

Head circumference and height equally affected, both are less affected than weight and all the three measures are below the 10^{th} centile". In these infants, brain growth is usually spared. The usual causes are utero-placental insufficiency, maternal malnutrition, or extrinsic conditions appearing late in pregnancy ***(Stoll et al., 2010).***

With no nutritional reserve, the fetus redistributes blood flow to sustain function and help in development of vital organs. This is called the brain sparing effect and results in increased relative blood flow to brain, heart, adrenals, and placenta, with diminished relative flow to the bone marrow, muscles, lungs, GIT, and kidneys. This head sparing phenomenon is the most common form of IUGR (70%-80%) and may result in different fetal growth patterns ***(Garite et al., 2004).***

Table (1): Specific Distinctions between Symmetric and Asymmetric IUGR.

	Asymmetric	Symmetric
Incidence	70-80%	20-30%
Period of growth restriction	Begins third trimester	Begins first or second trimester
Physical characteristics	Large head size relative to small abdomen	Small head and abdominal size
Pathophysiology	Impaired cellular hypertrophy Decreased cell size	Impaired cellular embryonic division Impaired cellular hyperplasia± hypertrophy Decreased cell number± size
Etiology	Mostly extrinsic: placental and maternal vascular factors	Mostly intrinsic: chromosomal abnormalities, congenital malformations, infection.
Outcome	Lower morbidity and mortality	Greater morbidity and mortality

(Militello et al., 2009)

Causes and risk factors:

Causes include:

- Incorrect dating of the pregnancy.
- Constitutionally small size.
- Genetic/chromosomal defects in the fetus.
- Intrauterine infection.

- Intrauterine growth restriction (IUGR) related to an inadequacy in the supply of nutrients and/or oxygen to the fetus through the utero-placental unit.

Fetal growth is influenced by fetal, placental and maternal factors ***(Brodsky and Christou, 2004).***

A- Maternal factors:

1- Maternal size and nutrition:

Maternal constitutional factors have a significant effect on fetal growth ***(Sankaran and Kyle, 2009).*** The major risk factors for IUGR include small maternal size (height and pre-pregnancy weight) and low maternal weight gain. Low body mass index, defined as BMI= (weight [kg]/height [m2]) ×100, is a major predictor of IUGR ***(Zenk et al., 2004).***

Underweight mothers are more likely to give birth to lower birth weight infants. Similarly, obese women are more likely to give birth to larger infants, even in situations of poor pregnancy weight gain ***(Siza, 2008).***

Maternal nutritional status is affected by many factors. Women at risk of poor nutrition and poor fetal growth include adolescents, women of low socioeconomic status, women with short inter-pregnancy intervals, women with unusual dietary restrictions, and women doing heavy physical work during pregnancy ***(Sankaran and Kyle, 2009).***

Maternal nutrition and supply of nutrients to the fetus affect fetal growth. Evidence shows a relationship between maternal nutrition during pregnancy and infant birth weight ***(Martinez and Simmons, 2005).***

The effects of micronutrients on pregnancy outcomes and fetal growth have been less well studied. It has been shown that maternal intake of certain micronutrients can affect fetal growth ***(Martinez and Simmons, 2005).***

Zinc deficiency has been associated with fetal growth restriction as well as other abnormalities, such as infertility and spontaneous abortion. Additionally, dietary intake of vitamin C during early pregnancy has been shown to be associated with an increase in birth weight ***(Taeusch et al., 2005).***

Others have shown strong association between maternal intake of folate and iron and infant and placental weight. In developing countries, the effects of nutritional deficiencies during pregnancy are more prevalent and easier to detect ***(Gleason and Juul, 2011).***

2- Maternal illness:

Maternal hypoxia and vascular disease is believed to account for 25-30% of all IUGR infants, it is the most common cause of IUGR in the non-anomalous infants ***(Resnik, 2002).*** Maternal disorders such as pre-eclampsia, eclampsia, antiphospholipid syndrome**,** chronic reno-vascular disease,

diabetes mellitus and chronic hypertensive vascular disease often result in decreased utero-placental blood flow and associated IUGR ***(Tellechea et al., 2015)*** Impaired delivery of oxygen and other essential nutrients is thought to limit organ growth and musculoskeletal maturation. Mothers with hemoglobinopathies, especially sickle cell disease, often have IUGR infants ***(Zenk, 2004).***

Women with systemic lupus erythematosus (SLE) have a higher prevalence of fetal growth restriction. Some researchers have shown that the majority of adverse fetal outcomes associated with SLE are related to maternal antiphospholipid antibodies ***(Tellechea et al., 2015).***

3- Maternal exposure to environmental/extrinsic factors:

The fetus may be exposed to chemical agents via the mother from several different avenues, including recreational (drugs of abuse), therapeutic, and occupational exposure (maternal exposure to environmental hazards) ***(Thompson et al., 2009).***

Maternal medications associated with fetal growth restriction (FGR) include anticonvulsants, anticoagulants, and folic acid antagonists. The two most commonly associated anticonvulsants with IUGR are diphenylhydantoin (phenytoin) and trimethadione ***(Alberry and Soothill, 2007).***

4- Multiple pregnancies:

There is a progressive decrease in placental and fetal weight as the number of fetuses increases in multiple gestations cause of crowding and abnormalities with placentation, vascular communications, and umbilical cord insertions ***(Doom et al., 2012).***

5- Recurrence rate & Parity:

Women who were born SGA were shown to be at increased risk of giving birth to SGA infants. Parity of the mother also affects fetal size, nulliparous women having a higher incidence of SGA infants ***(Kozuki et al., 2013).***

B- Placental factors:

Placental factors are known to influence fetal growth. The transfer of nutrients across the placenta depends on uterine blood flow, which normally increases throughout gestation ***(Gaccioli et al., 2013).***

Fetal size and placental growth are directly related, and placentae from pregnancies yielding growth retarded infants demonstrate a higher incidence of smallness and abnormality than from pregnancies with appropriately grown infants ***(Taeusch et al., 2005).***

Table (2): Different fetal and placental weights throughout gestation

Gestational age (wk)	Placental weight (mg)	Fetal weight (g)
14	45	-
16	65	59
18	90	155
20	115	250
22	150	405
24	158	560
26	217	780
28	250	1000
30	282	1270
32	315	1550
34	352	1925
36	390	2300
38	430	2850
40	470	3400

(Taeusch et al., 2005)

Abnormal placentation comprises a broad range of pathologies that ultimately comprise utero-placental circulation; including velamentous cord insertion, vasa previa, placenta previa, and uterine anomalies, such as large sub-mucous myomas, synechiae, and septate uterus ***(Ananth and Wilcox, 2011)***.

Premature placental separation may reduce the surface area exchange, resulting in impaired fetal growth. An adverse intrauterine environment can affect both placental and fetal development; hence, IUGR infants usually have small placentas ***(Brett et al., 2014).***