Could be Intrauterine Growth Restriction correlated with Maternal Serum Ferritin?

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Abstract

Background

Classically, intrauterine growth restriction (IUGR) is defined as an estimated fetal weight (EFW) or fetal abdominal circumference (AC) measured by ultrasonography below the 10th percentile. An EFW or AC below the 3rd percentile is defined as severe IUGR. Cases starting under 32 weeks of gestation should be defined as early-onset, and cases starting after 32 weeks of gestation should be defined as late-onset IUGR. A fetus with IUGR is exposed to increased intrauterine risks of fetal distress and death, neurologic developmental disorders as well as meconium aspiration at birth. Neonatal risks include hypoglycemia, long admission to intensive care units, hypothermia, polycythemia, jaundice, feeding difficulties, necrotizing enterocolitis, late-onset sepsis, hypoxic-ischemic encephalopathy and pulmonary hemorrhage. These infants also have increased risks of type 2 diabetes, obesity, autoimmune diseases, cardiovascular diseases and hypertension in adult life. In fetuses with growth restriction, mortality around birth is 6-10 times more common and 35% of stillbirths occur in preterm fetuses. Also, the rate of asphyxia reaches 50%, however the prevention of these events can be achieved by recognizing cases of growth restriction and optimal care. People affected by IUGR had a high risk of obesity, cardiovascular disease, hypertension, and diabetes in their later years. Overall, growth-restricted fetuses have a higher rate of conditions associated with prematurity, experience worse neurodevelopmental outcome and are at increased risk of non-communicable diseases in adulthood, such as hypertension, metabolic syndrome, insulin resistance, Type-2 diabetes mellitus, coronary heart disease and stroke

Keywords: Carotid Stenting, High Surgical Risk Patients.

INTRODUCTION

Classically, intrauterine growth restriction (IUGR) is defined as an estimated fetal weight (EFW) or fetal abdominal circumference (AC) measured by ultrasonography below the 10th percentile. An EFW or AC below the 3rd percentile is defined as severe IUGR **(1).**

Cases starting under 32 weeks of gestation should be defined as early-onset, and cases starting after 32 weeks of gestationshouldbe defined as late-onset IUGR **(1).**

In other definitions, an estimated fetalweight below the third percentile is often considered to besufficient for the diagnosis of IUGR **(2).**

A fetus with IUGR is exposed to increased intrauterine risks of fetal distress and death, neurologic developmental disorders as well as meconium aspiration at birth **(3).**

Neonatal risks include hypoglycemia, long admission to intensive care units, hypothermia, polycythemia, jaundice, feeding difficulties, necrotizing enterocolitis, late-onset sepsis, hypoxic-ischemic encephalopathy and pulmonary hemorrhage. These infants also have increased risks of type 2 diabetes, obesity, autoimmune diseases, cardiovascular diseases and hypertension in adult life **(3).**

In fetuses with growth restriction, mortality around birth is 6-10 times more common and 35% of stillbirths occur in preterm fetuses. Also, the rate of asphyxia reaches 50%, however the prevention of these events can be achieved by recognizing cases of growth restriction and optimal care **(4).**

People affected by IUGR had a high risk of obesity, cardiovascular disease, hypertension, and diabetes in their later years. Overall, growth-restricted fetuses have a higher rate of conditions associated with prematurity, experience worse neurodevelopmental outcome and are at increased risk of non-communicable diseases in adulthood, such as hypertension, metabolic syndrome, insulin resistance, Type-2 diabetes mellitus, coronary heart disease and stroke **(5).**

Prenatal recognition of fetal growth restriction (FGR) is a major factor identified in strategies aimed at preventing stillbirth, in which up to 30% of cases are associated with FGR or small-for-gestational age (SGA) in the late third trimester **(5).**

Fetal growth accelerates from about 5 g per day at 14–19 weeks of gestation to 10 g per day at 20–29 weeks, peaks at 25–35 g per day at 30–36 weeks, and afterwards growth rate decreases to 15 g per day. Almost 90% of fetal weight gain happens in later half of pregnancy. Growth of the fetus is dependent on various factors. It includes the interplay of hormones (insulin; hormones secreted by the thyroid, adrenal, and pituitary glands;and others). Among these, insulin-derived growth factor-I (IGF-I) is probably the most significant IGF-1 influences amino acid and glucose transport across the placenta and plays a role in neurodevelopment of the fetus by promoting brain growth, by increasing the number of oligodendrocytes, neuronal number, and increasing fine branching of axons at their terminal ends. There are various causes for fetal growth restriction, which are divided into three categories: maternal (maternal hypertension, diabetes, heart disease, connective tissue diseases), fetal (exposure to teratogens and viral infections of the fetus, fetal abnormalities), and placental (placental diseases such as heart attack and placental abruption and placenta previa) **(6).**

Fetal growth is a dynamic process and its assessment requires multiple observations of fetal size over time. Fetal size is determined through biometric evaluation of the head circumference, biparietal diameter, abdominal circumference (AC) and femur length and/or derivation of estimated fetal weight (EFW) computed by different formulae **(7).**

Classification:

IUGR is classified in various and different ways: -

1.According to fetal biometry:

(a) Type I: Symmetric:

Usually, early onset with intrinsic genetic disorders or infections to fetus.Ponderal index is normal, whereas biparietal diameter (BPD), femur length(FL), head and abdominal circumference (HC and AC) are proportionally reduced. Often the prognosis is poor. Incidence is 20–30% **(8).**

(b) Type II: Asymmetric

Usually, later onset and occurs by uteroplacental insufficiency. Ponderal index is low (< 3), whereas BPD, HC, and FL are normal. Abdominal circumference is often decreased. Brain growth is often preserved. Prognosis is better. Incidence 70–80%.

(8).

2. According to etiological factors:

- Intrinsic due to fetal factors
- Extrinsic due to placental/maternal/environment factors.
- Combined
- Idiopathic

(8).

3. According to gestational age:

- Early onset: onset is early in pregnancy, usually before 32 weeks. Usually the disease is of genetic or fetal origin. Hypoxia is present and significant;however, fetus tolerates the hypoxia due to cardiovascular adaptations. It is associated with high mortality. Management is relatively more complex **(8).**
- Late onset: onset is later in pregnancy (more than 32 weeks), placental/maternal disease, or idiopathic hypoxia may be present. The adaptive mechanisms are mainly by the cardiovascular system, but tolerance to hypoxia is low. The mortality rates are lower; however, the morbidity is high and is associated with poor long-term outcomes **(8).**

Risk Factors and Causes of IUGR

I. Foetal causes of IUGR:

1. Genetic/Chromosomal Anomalies:

Among liveborn neonates withautosomaltrisomies, trisomy 21 is associated with an SGA prevalence of 15 to 30 percent,Withtrisomies 13 and 18, therisk of SGA is significantly greater, 50 percent and >80 percent, In trisomy 18, the combination of fetal abnormalities plusFGR and hydramnios is particularly common**(9).**

2. Foetal Structural Abnormalities

In a recent review of 1789 singleton neonates with isolatedcongenital cardiac abnormalities, the prevalence of SGA was 13 percent,which was 3 percent higher than the general-population risk **(10).**

3. Congenital Infections

Viral, bacterial, protozoan, and spirochetal infections have been implicatedin up to 5 percent of FGR cases, *rubella* and cytomegalovirus infectionpromote calcifications in the fetus that are associated with cell death, andinfection earlier in pregnancy correlates with worse outcomes,tuberculosisandsyphilisalso are associated with poor fetal growth,toxoplasmagondiiis associated with FGR **(11).**

4. Placental/Umbilical Cord Disorders

Several placental abnormalities are associated with poor fetal growth, whichis presumed secondary to uteroplacental insufficiency and include chronic placental abruption,extensive infarction, chorioangioma, velamentous cord insertion, andumbilical artery thrombosis **(12).**

5. Multiple Gestation

Pregnancy with two or more fetuses is more likely to be complicated bydiminished growth of one or more fetuses compared with that of singletons **(13).**

Maternal Causes of IUGR

1. Maternal Malnutrition and Malabsorption:

Maternal weight gain during pregnancy is positively correlated with fetal size **(14).**

2. Pregestational Diabetes:

Fetal-growth restriction in newborns of women with diabetes may be relatedtocongenital malformations or may follow substrate deprivation fromadvanced maternal vascular disease, The likelihood ofrestricted growth increases with worsening White classification, particularly as in diabetic nephropathy. **(14).**

3. Maternal Anaemia:

In most cases, maternal anemia does not impair fetal growth. Exceptionsinclude sickle-cell disease and other inherited anemias **(14).**

4. Vascular Disorders:

Maternal vascular disease as evidenced by abnormal uterine artery Dopplervelocimetry early in pregnancy is associated with higher rates ofpreeclampsia, SGA neonates, and delivery before 34 weeks.**(11)**

5. Uterine Abnormalities:

Some uterine malformations are linked to FGR. **(11)**

6. Maternal Hypoxic Conditions:

Conditions associated with chronic hypoxia include asthma, maternalcyanotic heart disease, other chronic pulmonary disease, cigarette smokingand living at high altitude lead to FGR. **(13)**

7. Socioeconomic Factors

Food insecurity, late entry into prenatal care, and limited access tohealthcare are all contributors to fetal-growth restriction. **(13)**

8. Antiphospholipid Syndrome

Adverse obstetrical outcomes including fetal-growth restriction have been associated with three types of antiphospholipid antibodies: anticardiolipin antibodies, lupus anticoagulant, and anti-β2 Glycoprotein-I antibodies **(15).**

Management of intrauterine growth restriction

If FGR is detected, efforts are made to assess the fetal condition and search for possible causes. **(16).**

General tenets of management include serial evaluation of fetal growth every 3 weeks and at least weeklyevaluation of amnionic fluid and umbilical artery dopplervelocimetry. Afetus with slow but progressing EFW is more reassuring than one that hasplateaued growth. This is supplemented with antepartum evaluation of fetalwell-being, which is usually nonstress testing or biophysical profile **(16).**

Measurement of maternal serum ferritin has also been used as a predictive marker of increased risk of IUGR (17).

Antenatal Testing for IUGR

1. Fetal kick counts

Fetal kick counts are performed daily by the mother—she should feel her fetus kick ten times in one hour, this period can be extended to two hours. If kicks are not met the patient can then call for advice, present to her physician or go to the hospital for further evaluation **(15).**

2. Non-stress Test (NST)

Non-stress tests are typically performed in a clinic setting and involve placing the fetus on the cardiotocographic monitor while also monitoring contractions. Non-stress tests are either reactive or non-reactive. A reactive NST contains 2 or more accelerations in fetal heart rate in a 20-minute period **(15).**

3. Biophysical profile (BPP)

Biophysical profiles are performed using ultrasonography and can require up to 30 min to complete the testing. A score of 8 or 10 out of 10 is reassuring for fetal well-being**(15).**

Biophysical profile scoring

	Normal (2points)	Abnormal(0points)
Fetal Breathing	One or more episodes of fetal breathing lasting at least 30 seconds	No episodes of fetal breathing lasting at least 30 seconds
Gross body movements	3 or more discrete limb or body movements	2 or less discrete limb or body movements
Tone	One or more episodes of active extension and flexion or opening and closing of a hand	No episodes of active extension and flexion or opening and closing of a hand
Amniotic fluid	A single deepest pocket of fluid measures 2 cm or greater	A single deepest pocket of fluid is less than 2 cm
Non-stress test	Reactive	Non-reactive

(15).

4. Umbilical artery (UA) Doppler

Umbilical artery Doppler flow studies are central to the evaluation and management of the fetus with growth restriction. Abnormalities represent the negative progression from fetal adaptation to failure **(*18*).**

Specifically, initially increased impedance to flow in the umbilical artery may progress to absent end-diastolic flow and then reversed end-diastolic flow. This negative progression correlates with hypoxia, acidosis, and fetal death **(*18*).**

The stillbirth risk in the setting of absent and reversed end-diastolic flow is 7 percent and 19 percent, respectively.Because of these findings, theAmerican College of Obstetricians and Gynecologists (2021a,b) and Societyfor Maternal-Fetal Medicine (2020) recommend serial umbilical artery doppler studies in the management of FGR**(*18*).**

Management of the Near-term Fetus

Delivery of a suspected growth-restricted fetus with normal umbilical artery Doppler velocimetry, normal amnionic fluid volume, and reassuring fetal testing can likely be deferred until 37 to 38 weeks' gestation **(16).**

Expectant management can be guided using antepartum evaluation of fetalwell-being. If

oligohydramnios is present, delivery between 37 and 38 weeks' gestation is recommended.With a normal fetal heart rate pattern, vaginaldelivery is planned.Notably, some of these fetuses do not tolerate labor **(16).**

Management of the Fetus Remote from Term

If growth restriction is identified in a fetus before 34 weeks, and amnionic fluid volume and fetal surveillance findings are normal, observation is recommended. As long as interval fetal growth and fetal surveillance test results are normal, pregnancy is allowed to continue **(16).**

Reassessment of fetal growth is typically made no sooner than 3 weeks later.Weekly outpatient assessment of umbilical artery Doppler velocimetry and amnionic fluid volume is combined with fetal well-being testing. If umbilical artery doppler studies indicate absent or reversed end-diastolic flow,inpatient surveillance is under taken **(16).**

During hospitalization, more frequent sonographic evaluations and ante natal testing of fetal well-being and close proximity to labor and delivery are advantages.With growth restriction remote from term, no specific treatment ameliorates the condition **(16).**

Evidence does not support diminished activity or bed rest to accelerate growth or improve outcomes. Nutrient supplementation, attempts as plasma volume expansion, oxygen therapy,anti-hypertensive drugs, heparin, and aspirin are all ineffective **(16).**

Intrapartum Management

When lagging fetal growth is the result of placental insufficiency due to poor maternal perfusion or reduction of functional placenta, the fetal condition may be aggravated by labor. Equally important, oligohydramnios raises the likelihood of cord compression during labor **(19).**

For these and other reasons, the frequency of cesarean delivery is increased.The risk of neonatal hypoxia or meconium aspiration is also greater.Thus, care for the newborn should be provided immediately by an attendant who can skillfully clear the airway and ventilate a neonate as needed **(19).**

The severely growth-restricted newborn is particularly susceptible to hypothermia and may also develop other metabolic derangements such as hypoglycemia, polycythemia, and hyperviscosity. Risk is greatest at the lowest extremes of birth weight **(19).**

Prevention

Ideally, prevention begins before conception. Maternal medical conditions are treated, and medications are modified to help lower FGR risks. Smoking cessation is critical. Other risk factors are tailored to the maternal condition,such as antimalarial prophylaxis for women living in endemic areas and correction of nutritional deficiencies**(16).**

Treatment of mild to moderate hypertension does not reduce the incidence of SGA newborns. Currently, no pharmacologic therapies prevent growth restriction **(16).**

Serum Ferritin & IUGR

Unger et al, **(20).** measure serum ferritin concentrations at approximately 25 and 36 weeks gestation in 480 multiparas with singleton fetuses who participated in a study of risk factors for repeated IUGR. Among 480 infants,370 were appropriate for gestational age (AGA), 58 had asymmetric IUGR, and 52 had symmetric IUGR **(20).**

Higher ferritin concentrations were associated with mothers of asymmetric IUGR infants whereas mothers of symmetric IUGR infants had significantly lower ferritin levels so they concluded that high maternal

serum ferritin levels are associated with asymmetric IUGR, whereas loe serum ferritin levels are associated with symmetric IUGR **(20).**

Goldman et al, **(21).** conducted prospective study 226 healthy pregnant women between 29-34 gestational weeks. Maternal serum ferritin was found to be correlated later with birth weight of baby after birth.

The study was done at the obstetric department at Santa Ana hospital in Montreal Granda,Spain from January 1996 to May 1996. They concluded that women with blood ferritin levels greater than 13 ng/ml were 4.5 times more likely to have a small for gestational age baby at 38 weeks of gestation **(21).**

Soubasi et al, **(22).** prospective, observational study involved 630 mothers and 90 preterm neonates. Full blood counts as well as serum ferritin, soluble transferrin receptor(sTfR) and erythropoietin concentrations were compared across the three study groups based on maternal ferritin levels at the time of delivery **(22).**

Perinatal history, neonatal morbidity and early outcomes were also assessed. High maternal ferritin levels were significantly associated with higher rates of GDM and IIUGR. However, there was no correlation between maternal ferritin and sTfR levels or between maternal and neonatal iron status**(21).**

So they concluded that elevated maternal ferritin is not a reflection of excess iron stores, but is related to an increased risk of GSM or IUGR. Also, maternal ferritin levels are not associated witheither neonatal iron status or neonatal outcomes **(22).**

Visnjevac et al, **(23)** A prospective study was conducted that included 210 healthy pregnant women between 30-32 gestational weeks. Weeks maternal serum ferritin estimation is done to be correlated later with birth weight of baby after birth.

The study was done at the School of medicine in Novi Sad, Serbia from November 2005 to December 2006. Serum ferritin level, hemoglobin, hematocrit and erythrocyte count were determined from blood samples of all pregnant women **(23).**

After term delivery, (8.1%) gave birth to infants of small for gestational age birth weight (birth weight less than 10th percentile adjusted for gestational age), whereas 193(91.9%) delivered infants appropriate for gestational age without anemia **(23).**

The value of ferritin, hemoglobin, hematocrit and erythrocyte was significantly higher in women with low birth weight babies. In mothers with low birth weight newborns the optimal decision threshold for pregnant women blood ferritin values in the period from 30-32 gestational weeks is >13.6 ng/ml. These values cinfirm, with 64.7% sensitivity and 91.7% specificity, the development of IUGR **(23).**

Ljubomir et al, **(24)** prospective syudy included 220 healthy pregnant women between 30-32 gesational weeks. Maternal serum ferritin estimation was correlated later wirth weight.

The study was done at the Clinical Center of Vojvodina, Department of Obstetrics and Gynecology Novi Sad, Serbia and Clinical laboratory from March,2008 to November,2009. Serum ferritin level, hemoglobin, hematocrit and erythrocyte count were determined **(24).**

After term delivery, 8.1% of pregnant women gave birth to low birth weight babies for gestational age without anemia. The value of ferritin, hemoglobin, hematocrit and erythrocyte was significantly higher in women with low birth weight newborns ($p<0.005$) **(24).**

Statistically, ROC curve analysis showed that the pregnant women with the ferritin level above 13.6 μg/L, and with erythrocyte count >32.9%, had a significantly higher probability of having a low birth weight newborn for gestational age ($p<0.05$) **(24).**

Ozgu et al, **(25)** prospective cohort analysis included 107 singleton pregnancies that underwent

amniocentesisat 16-22 weeks according to standard genetic indications. Maternal blood and amniotic fluid obtained from genetic amniocentesis were tested for glucose, alkaline phosphatase(ALP), lactate dehydrogenase(LDH), ceruplasmin, ferritin, high sensitivity c-reactive protein(CRP) and interleukin-6(IL-6) **(25).**

94 pregnancies were followed until delivery. 16 (18.1%) delivered before 37 weeks and 7 (7.5%) delivereda baby below 10th percentile for gestational age. Amniotic fluid glucose levels were significantly lower in patients with preterm delivery than term deliveries (p=0.01) **(25).**

Median amniotic fluid ferritin and IL-6 levels and mean amniotic fluid ALP levels were higher in the preterm group but this is not significant **(25).**

The study concluded that low amniotic fluid glucose levels are associated with risk of preterm delivery, whereas high maternal blood ferritin levels increase the risk for IUGR. Although this result is significant and notable, there is not enough clinical evidence to recommend their use as a screening test for preterm delivery and IUGR in routine practice **(25).**

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