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**Research Article**

# Role of maternal serum ferritin as a predictive marker in intrauterine growth restriction

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## ABSTRACT

**Background:** Intrauterine growth restriction (IUGR) is most common and distressing complication for both obstetrician and neonatologist. Measurement of maternal serum ferritin has also been used as a predictive marker of increase risk of IUGR. In pregnancy, ferritin level decreases with advancing gestation. Its lowest level is seen around 30-32 weeks of gestational age after which its concentration reaches plateau level.
**Methods:** Total 326 antenatal women enrolled in the study. Maternal serum samples of all women were taken at 25$^{th}$ week and again at 30-32 weeks in trace free mineral evacuated tubes for assessment of serum ferritin by chemiluminescence. Mean of both values was calculated.
**Results:** Mean ferritin value of women with average for gestational age neonates was 15.49 ng/ml and women with growth restricted neonates was 19.71 ng/ml. The women with mean serum ferritin above 20 ng/ml, were 6.26 times more likely to have asymmetrically growth restricted baby and 4.47 times more likely to have a symmetrically growth restricted baby when compared to women with serum ferritin value less then <20 ng/ml.
**Conclusions:** In our study negative correlation was found between the value of serum ferritin and neonatal birth weight. In future large randomized control trial is needed to found association between maternal serum ferritin and IUGR.

**Keywords:** Intrauterine growth restriction, Ferritin, Ponderal index, Alpha feto protein, Amniotic fluid lactate dehydogenase

## INTRODUCTION

Intrauterine growth restriction (IUGR) is most common and distressing complication for both obstetrician and neonatologist. The term IUGR and Small for Gestational Age (SGA) is often used interchangeable. Small for gestational age is defined as fetal birth weight less than 10$^{th}$ percentile for gestational age corrected for parity and gender, as per population growth chart.[1] An annual incidence of around 24% of IUGR of all newborns has been reported worldwide.[2,3] 40% of these are constitutionally small but healthy, 40% have asymmetrical IUGR with low ponderal index and 20% have symmetrical IUGR with normal ponderal index.[4] Fetuses with restricted growth are at increased risk of many intrapartum, post natal and long term complication as fetal distress, intrapartum asphyxia, meconium aspiration, intrauterine death, postnatal hypoglycemia, neurologic developmental disorders development of type 2 diabetes, obesity, autoimmune diseases, cardiovascular diseases and hypertension in adult life.[5-8] To prevent all these complication it is important to establish such markers which can predict those pregnancies very early who are at the risk of developing future IUGR. Recently many studies have highlighted the role of many

biomolecules as markers of IUGR like leptin, adiponectin, endothelin-1, lactate dehydrogenase, s-endoglin, soluble FMS tyrosine kinase receptor 1(sFTL1), pregnancy associated plasma protein,metastin.[9-16] Apart from being expensive, laboratories at majority of centers are not equipped with facilities of measurements of these markers. Measurement of maternal serum ferritin has also been used as a predictive marker of increase risk of IUGR.[17] Ferritin is a globular protein complex consisting of 24 protein subunits and is the primary intracellular iron storage protein. It is an acute phase protein and its serum concentration increases in stresses like anoxia and infection.[18,19] In pregnancy ferritin level decreases with advancing gestation.[20] Its lowest level is seen around 30-32 weeks of gestational age after which its concentration reaches plateau level.[20]

## METHODS

This was a longitudinal prospective study conducted in the department of obstetrics and gynaecolgy in our hospital between January 2011 and December 2012. Total 326 antenatal women visiting the antenatal clinic were enrolled in the study at 25$^{th}$ week. Exclusion criteria were BMI <18, placental abnormalities like velamentous insertion, antepartum hemorrhage, multiple pregnancies, patients with acute infection, patients with positive CRP, raised TLC count, congenital malformation, and fetuses with chromosomal or genetic syndrome. Gestational age was defined as completed weeks from the onset of last menstrual period, if there was mismatch between the dates and USG reports by more than two weeks then the ultrasonographic dating (first trimester) was considered for calculating gestational age. Maternal serum samples of all women were taken at 25$^{th}$ week and again at 30-32 weeks in trace free mineral evacuated tubes for assessment of serum ferritin by chemiluminescence. Mean of both values was calculated. Hemoglobin was estimated of all women at the time of inclusion in the study and again in late third trimester. All patients were serially followed up till delivery. Mode of delivery, gestational age at delivery, birth weight and crown rump length of all neonates were assessed at time of birth. Ponderal index of all neonates with fetal growth retardation was calculated. Rohrer's ponderal index is defined as 100 times birth weight (in grams) divided by the cube of birth weight.[21] Based on the above measurement babies were divided in two groups. In group A neonates with birth weight more than or equal to the 10$^{th}$ percentile for corresponding gestational age were included as average for gestational age. In group B neonates with birth weight less than 10$^{th}$ percentile for corresponding gestational age were included as small for gestational age. Group B was again divided in two parts, group B1 included women having neonates with ponderal index less than 2 (between 29 to 37 weeks) and less than 2.25 (>37 weeks) as asymmetrical FGR, group B2 included neonates with ponderal index more or equal to2.25 at birth as symmetrical FGR.[21,22] Depending upon maternal serum ferritin value women were divided in three groups. Group 1 included women with mean serum ferritin <10 ng/ml, group 2 included women with mean serum ferritin value between 10ng/ml-20ng/ml and group 3 consisted of women with mean serum ferritin value >20 ng/ml. Sensitivity, specificity, positive and negative predictive value at various cut off of serum ferritin were calculated and ROC curve was analyzed (Table 3).

## RESULTS

There were total 326 women included in the study. 36 women lost to follow up. Out of all cases that were followed up till term 2 patients had sudden intrauterine death, 3 patients developed jaundice, 8 patients developed preeclampsia, 20 patients developed pre-term labor. These high risk pregnancies were excluded from study to remove any confounding factor from the study and finally data from 257 women were taken for analysis. There were total 204 (79.37%) women in group A having average for gestational age neonates, and 53 (20.62%) women in group B having neonates small for gestational age. In group B1 asymmetrically growth restricted were 30 (11.67%) and symmetrically growth restricted were 23 (8.94%).The mean age of women in group A was 22.9 years and in group B was 23.1 years. The difference between mean ages of both groups was not significant statistically. Mean gestational age of delivery in group A was 38.03 weeks, in group B was 37.91 weeks. Mean birth weight in group A was 2674.41 gm, and in group B was 2199.81 gm. The difference in mean birth weight between two group was statistically significant (P<0.05). Mean ferritin value of group A was 15.49 ng/ml and that of group B was 19.71 ng/ml. There was statistically significant difference between mean ferritin value of two group (P=0.03). The mean hemoglobin in group A was 10.46 gm% and in group B was 11.91%, the difference between two was statistically significant (P<0.05).

**Table 1: Clinical characteristics and their values of two different groups.**

| Characteristics | Group A | Group B | P value |
|---|---|---|---|
| Number of women | 204 (79%) | 53 (20.6%) | |
| Mean age (years) | 22.94 | 23.1 | 0.83 (not significant) |
| Period of gestation at delivery | 38.03 | 37.91 | |
| Mean birth weight (gm) | 2674.9 | 2199.8 | <0.05 (significant) |
| Mean ferritin level (ng/ml) 95% CI | 15.49 13.67-17.32 | 19.71 16.90-22.54 | <0.03 (significant) |
| Mean hemoglobin (gm%) 95% CI | 10.46 10.32-10.68 | 11.91 11.23-12.5 | <0.05 (significant) |

As shown in Table 2, patients were divided in three groups depending on the serum ferritin value. The above data shows that the maximum percentage of growth restricted babies is seen in the subgroup of women who had mean serum ferritin value of >20 ng/ml during pregnancy. The data above depict that women with mean serum ferritin above 20 ng/ml, were 6.26 times more likely to have asymmetrically growth restricted babies and 4.47 times more likely to have a symmetrically growth restricted babies when compared to women with serum ferritin value less then <20 ng/ml. The analysis was statistically significant P<0.0001 for asymmetrical growth restriction as an outcome and P<0.05 for symmetrical growth restriction as an outcome).

**Table 2: Distribution of women according to different range of mean serum ferritin value and their association.**

| Mean serum ferritin values | Asymmetrically growth restricted babies | Odds ratio | CI | P value | Symmetrically growth restricted babies | Odds ratio | CI | P value | Average for gestational babies |
|---|---|---|---|---|---|---|---|---|---|
| >20 ng/ml | 21 (69%) | 6.26 | 2.86-13.69 | <0.0001 | 10(50%) | 4.47 | 1.66-11.99 | 0.0029 | 45(21.8%) |
| 10-20 ng/ml | 2 | 1.0 | | | 6 | 1.0 | | | 72 |
| <10 ng/ml | 8 | 1.0 | | | 4 | 1.0 | | | 89 |

**Table 3: Data showing sensitivity, specificity, positive predictive value, negative predictive value of various serum cut offs to predict fetal growth restriction.**

| Serum ferritin cut off | Sensitivity | Specificity | +LR | -LR | +PV | -PV |
|---|---|---|---|---|---|---|
| ≥4.02 | 100.0 | 0.00 | 1.00 | | 20.2 | |
| >4.5 | 92.31 | 6.31 | 0.99 | 1.22 | 19.9 | 76.5 |
| >6.95 | 92.31 | 19.90 | 1.15 | 0.39 | 22.5 | 91.1 |
| >7.1 | 84.62 | 19.90 | 1.06 | 0.77 | 21.5 | 83.7 |
| >9.91 | 84.62 | 43.20 | 1.49 | 0.36 | 27.3 | 91.8 |
| >10.32 | 69.23 | 43.20 | 1.22 | 0.71 | 23.5 | 84.8 |
| >13.4 | 69.23 | 60.68 | 11.76 | 0.51 | 30.8 | 88.7 |
| >13.87 | 61.54 | 60.68 | 1.57 | 0.63 | 28.3 | 86.2 |
| >20.2 | 61.54 | 80.10 | 3.09 | 0.48 | 43.8 | 89.2 |
| >21.1 | 53.85 | 82.04 | 3.00 | 0.56 | 43.1 | 87.6 |
| >21.55 | 46.15 | 82.04 | 2.57 | 0.66 | 39.3 | 85.8 |
| >21.94 | 38.46 | 83.98 | 2.40 | 0.73 | 37.7 | 84.4 |
| >23.2 | 38.46 | 85.92 | 2.73 | 0.72 | 40.8 | 84.7 |
| >23.6 | 15.38 | 85.92 | 1.09 | 0.98 | 21.6 | 80.1 |
| >28.14 | 15.38 | 94.17 | 2.64 | 0.90 | 40.0 | 81.5 |
| >39.42 | 0.00 | 94.17 | 0.00 | 1.06 | 0.0 | 78.9 |
| >83.1 | 0.00 | 100.00 | | 1.00 | | 79.8 |

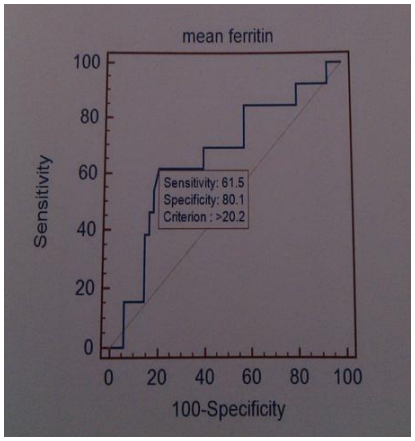


**Figure 1: ROC curve.**

ROC curve (Figure 1) showed that serum ferritin value at 20.2 ng/ml was associated with highest Yuden's index which means that it can be taken as a cut off for screening antenatal patients for development of fetal growth restriction with 61.5% sensitivity and 80.1% specificity.

## DISCUSSION

Fetal growth restriction is not only short term worry during antenatal period but also have long term effects affecting neonatal period, childhood and even adulthood also. Present study reports a 20% rate of growth restricted babies which is higher than most of other studies but comparable to study of J. Hou et al. which reported 23.2% incidence in their study.[2] Table 4 shows various neonatal outcomes studied in different studies.

**Table 4: Comparison of results of our study with other studies.**

| Year | Name | Serum ferritin cut off for prediction as per ROC curve | Sensitivity | Specificity | Odds of growth restriction with serum ferritin above the defined cut off |
|---|---|---|---|---|---|
| 2010-2011 | Nimanja Vinjevac et al.[17] | 13.6 ng/ml | 64.7% | 91.7% | >15 ng/ml OR 4.5 |
| 1996 | J. Hou et al.[23] | 13 ng/ml | | | >13 ng/ml OR 4.5 for low birth weight |
| 2011 | Present study | 20.2 ng/ml | 61.5% | 80.1% | >20.2 OR 6.26 for asymmetric restriction and 4.47 for symmetric |

In our study negative correlation was found between the value of serum ferritin and neonatal birth weight. The coefficient of correlation was -0.36 (significant) which was higher than study of Nemanja Visnjevac et al. (-0.24, significant).[17] In our study cut off point is 20.2 ng/ml (sensitivity 64.7%, specificity 91.7%) while in the study of Nimanja Vinjevac et al. cut off was 13.6 ng/ml (sensitivity 64.7%, specificity 91.75) which is lower than our study.

The Table 5 shows the comparison between various other markers and serum ferritin as a predictor of fetal growth restriction. Although amniotic fluid LDH value boasts of a better sensitivity and specificity but it is more invasive, costly and associated with greater procedural side effects when compared to serum ferritin assessment.[12] Elevated level of serum alpha feto protein (>2.5 Mom) is also associated with intra uterine growth restriction with odds ratio ranging from 1.6-4.0, But no specific treatment protocol was suggested for its increase level.[24]

**Table 5: Comparison between various other marker with maternal serum ferritin.**

| Study | Name of predictor | Measured in | Sensitivity as a predictor | Specificity | PPV as a predictor |
|---|---|---|---|---|---|
| Audibert et al.[28] | Alpha feto protein | Serum; mid trimester | 40% | 82% | 43% |
| Borna S et al.[12] | LDH | Amniotic fluid; mid trimester | 87.5% | 82.4% | |
| Present study | ferritin | Serum; third trimester | 61.5% | 80.1% | 43.8% |

Fetal growth is regulated by the balance between fetal nutrient demand and maternal-placental nutrient supply. 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.[25,26] This can lead to decrease extraction of iron by placenta from maternal serum leading to increase maternal serum ferritin. Placental isoferritin levels also found to be decrease in IUGR and preeclampsia in some studies.[27] This iron deficiency lead to increase in fetal coticotropins and fetal cortisol, causes inhibition of fetal growth. In present study smoking, hypertension, very low BMI <18 has been taken as exclusion criteria to negotiate their confounding effect on the value of maternal serum ferritin; there by evaluating the role of solely serum ferritin on intra uterine growth restriction.

In future large randomized control trial is needed to found association between mataernal serum ferritin and IUGR, including various maternal hematological indices with placental and cord blood ferritin level and the results could help in prevention of unknown adverse effect of iron supplementation in pregnancies.

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