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Original Research Article

A Hospital Based Prospective Study to Determine the Role of Maternal Serum Ferritin as a Predictive Marker in Intrauterine Growth Restriction

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Abstract

Aim: The aim of the present study was to assess the role of maternal serum ferritin as a predictive marker in intrauterine growth restriction.

Methods: This was a prospective study conducted in the Department of Obstetrics and Gynaecology, Netaji Subhas Medical College, Bihta, Patna, India. Total 250 antenatal women visiting the antenatal clinic were enrolled in the study at 25th week.

Results: The difference between mean ages of both groups was not significant statistically. The difference in mean birth weight between two group was statistically significant (P<0.05). 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). 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). The 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.

Conclusion: 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

Iron (Fe) is essential for physiological functions, including hemoglobin (Hb) synthesis, and cell growth and development. [1] Iron deficiency results from depletion of stored iron. Increased iron demand during pregnancy can worsen this, resulting in iron-deficient erythropoiesis and, eventually, iron deficiency anemia. [2] If the body iron store is deficient at conception, it is unlikely that dietary iron would be able to match the pregnancy-induced increase in demand. [3] Therefore, assessment of body iron status during pregnancy is crucial. While ferritin is the most commonly used indicator [4], providers often rely on Hb levels to assess iron deficiency at the population level. This use of Hb levels is problematic for two reasons. First, decreased Hb levels can result from causes other than iron deficiency. [5,6] Second, physiological expansion of plasma volume during pregnancy leads to a lowering of hemoglobin (Hb) concentration, irrespective of the iron status. However, the appropriate size of the iron store needed during pregnancy to ensure optimal outcomes for both mothers and neonates remains unknown. [7]

Several studies have evaluated the associations between maternal iron status and fetal iron status [8] and growth. [9,10] However, the findings remain inconsistent. A recent review suggests that low and high hemoglobin concentrations in early pregnancy may lead to a heightened risk of adverse birth outcomes such as low birth weight, preterm birth, and stillbirth. However, the risk of adverse birth outcome was weaker or non-significant when Hb was measured in the second or third trimester. [11] The study also reported less evidence of the association between maternal iron status assessed

by serum ferritin in different trimesters and adverse birth outcomes. [11]

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. [12] 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. [13,14] In pregnancy ferritin level decreases with advancing gestation. [15] Its lowest level is seen around 30- 32 weeks of gestational age after which its concentration reaches plateau level. [15]

The aim of the present study was to assess the role of maternal serum ferritin as a predictive marker in intrauterine growth restriction.

Materials and Methods

This was a longitudinal prospective study conducted in the Department of Obstetrics and Gynaecology, Netaji Subhas Medical College, Bihta, Patna, India. There were total 286 women included in the study. 28 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, 5 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 250 women were taken for analysis. There were total 200 (80%) women in group A having average for gestational age neonates, and 50 (20%) women in group B having neonates small for gestational age. 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 25th 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 10th percentile for corresponding gestational age were included as average for gestational age. In group B neonates with birth weight less than 10th 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. [16,17] 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.

Results

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

Characteristics	Group A	Group B	P value
Number of women	200 (80%)	50 (20%)	
Mean age (years)	23.97	23.7	0.75
Period of gestation at delivery	38.04	37.93	
Mean birth weight (gm)	2565.4	2190.5	<0.05
Mean ferritin level (ng/ml)95% CI	15.49 (13.67-17.32)	19.71 (16.90-22.54)	<0.03
Mean hemoglobin(gm%)95% CI	10.46 (10.32- 10.68)	11.91 (11.23-12.5)	<0.05

The mean age of women in group A was 23.97 years and in group B was 23.7 years. The difference between mean ages of both groups was not significant statistically. Mean gestational age of delivery in group A was 38.04 weeks, in group B was 37.93 weeks. Mean birth weight in group A was 2565.45 gm, and in group B was 2190.5 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 2: Distribution of women according to different range of mean serum ferritin value and their association

Mean serum ferritin values	Asymmetrically growth restricted babies	P value	Symmetrically growth restricted babies	P value
>20 ng/ml	20	<0.0001	10	0.0022
10-20 ng/ml	2		6	
<10 ng/ml	8		4	

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. 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 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

The 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

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 10th percentile for gestational age corrected for parity and gender, as per population growth chart. [18] An annual incidence of around 24% of IUGR of all newborns has been reported worldwide. [19,20] 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. [21]

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. [22,23] 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. [24] This iron deficiency lead to increase in

fetal corticotrophins' 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. The mean age of women in group A was 23.97 years and in group B was 23.7 years. The difference between mean ages of both groups was not significant statistically. Mean gestational age of delivery in group A was 38.04 weeks, in group B was 37.93 weeks. Mean birth weight in group A was 2565.45 gm, and in group B was 2190.5 gm. [25]

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). The value of maternal serum ferritin in predicting asymmetric IUGR was previously investigated, for few times, on small numbers of cases, i.e. 7 cases in Ozgu-Erdinc et al[25], 18 cases in Milasinovic et al. [26] 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. 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). The 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. Soubasi et al [27] found high maternal ferritin levels to correlate significantly with higher rates of gestational diabetes mellitus and IUGR, but did not define a cutoff to differentiate IUGR from AGA neonates. Bindal et al [28] concluded that maternal serum ferritin >20 ng/ml predicted IUGR with an odds ratio of 6.6. Akkurt et al [29] took one step further and showed a role for maternal serum ferritin measurements in distinguishing pregnancies with asymmetric IUGR from those with simple small for gestational age babies and no signs of placental insufficiency.

Conclusion

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.

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