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Original Research Article

To Assess the Importance of Maternal Serum Ferritin as a Predictive Marker for Intrauterine Growth Restriction

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Abstract

Aim: To assess the importance of maternal serum ferritin as a predictive marker for intrauterine growth restriction.

Material and Methods: This study was conducted in the Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India. A total of 326 pregnant women attending the prenatal clinic were included in the research during the 25th week of pregnancy. The exclusion criteria included a body mass index (BMI) below 18, placental anomalies such as velamentous insertion, antepartum hemorrhage, multiple pregnancies, patients with acute infection, patients with a positive C-reactive protein (CRP) test result, elevated total leukocyte count (TLC), congenital deformity, and fetuses with chromosomal or genetic syndrome. Gestational age was determined by counting the completed weeks from the start of the previous menstrual period. If there was a discrepancy of more than two weeks between the dates and the ultrasound reports, the ultrasound dated from the first trimester was used to calculate the gestational age.

Results: The patients were categorized into three groups based on their serum ferritin levels. The data above indicates that the subgroup of women who had a mean serum ferritin concentration of >20 ng/ml during pregnancy had the highest proportion of growth limited kids. The results presented indicate that women with a mean serum ferritin level over 20 ng/ml had a 6.26 times higher likelihood of having kids with asymmetric growth restriction and a 4.47 times higher likelihood of having babies with symmetric growth restriction, compared to women with a serum ferritin level below 20 ng/ml. The study yielded a statistically significant result ($P<0.0001$) for asymmetrical growth restriction as an outcome and a statistically significant result ($P<0.05$) for symmetrical growth restriction as an outcome. A blood ferritin value of 20.2 ng/ml was found to have the greatest Yuden's index, indicating that it may be used as a threshold for screening prenatal patients for the risk of fetal growth limitation. This threshold has a sensitivity of 61.5% and a specificity of 80.1%.

Conclusions: Our investigation revealed a negative connection between the levels of serum ferritin and neonatal birth weight. In the future, a comprehensive randomized control study is necessary to establish a correlation between maternal blood ferritin levels and intrauterine growth restriction (IUGR).

Keywords: Alpha feto protein, Amniotic fluid lactate dehydrogenase, IUGR

Introduction

Intrauterine growth restriction (IUGR) is a notable obstetric issue when a fetus fails to achieve its genetically programmed development potential. It is linked to higher rates of illness and death during childbirth, as well as long-lasting health effects. Precise and prompt detection of IUGR is crucial for the management of afflicted pregnancies and enhancing newborn outcomes. Serum ferritin, a protein that stores iron and reacts during acute-phase responses, has gained interest as a possible predictive marker for intrauterine growth restriction (IUGR). This is because it is involved in inflammatory processes and oxidative stress, both of which have a role in the development of IUGR. [1-4] Ferritin is a widely present protein found within cells that serves as a storage unit for iron and releases it in a regulated manner. During pregnancy, there is a large increase in the amount of iron needed

to support the growth and development of the fetus, as well as the increased volume of blood in the mother. Ferritin levels serve as an indicator of the amount of iron stored in the body and may provide valuable information about iron metabolism and inflammatory condition. Increased levels of ferritin in the bloodstream have been connected to negative outcomes during pregnancy, such as preeclampsia and gestational diabetes, both of which are related with intrauterine growth restriction (IUGR). [5-13] Intrauterine growth restriction (IUGR) often occurs as a result of placental insufficiency, which is characterized by the inadequate provision of nutrients and oxygen from the placenta to the developing baby. This inadequacy may initiate inflammatory reactions and oxidative stress, resulting in cellular harm and hindered embryonic development. Ferritin, as an acute-phase reactant, elevates in reaction to inflammation and oxidative stress. Thus, increased levels of ferritin in the bloodstream may suggest an underlying medical condition that contributes to intrauterine growth restriction (IUGR). Recent research has examined the possibility of using serum ferritin as a biomarker to forecast intrauterine growth restriction (IUGR). The discovery that serum ferritin may be used as a prognostic indicator for intrauterine growth restriction (IUGR) has important implications in clinical practice. It provides a non-intrusive and very straightforward approach for early identification of pregnancies that are at risk. This may enable more rigorous surveillance, prompt treatments, and enhanced perinatal results. Furthermore, combining ferritin readings with other diagnostic techniques, such as Doppler ultrasonography and fetal biometry, might provide a more thorough evaluation of the health of the fetus. [14-19]

Material and Methods

This study was conducted in the Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India for 12 months. Total 326 antenatal women visiting the antenatal clinic were enrolled in the study at 25th 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 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 isdefined 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 ponderalindex 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 inthree groups. Group 1 included women with mean serumferritin <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 differencebetween 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 oftwo 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 babiesand 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 serumcut 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

ROC curve 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 screeningantenatal 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.

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

Name	Serum ferritin cutoff for prediction as per ROC curve	Sensitivity	Specificity	Odds of growth restriction with serumferritin above the defined cut off
Nimanja Vinjevac et al.[17]	13.6 ng/ml	64.7%	91.7%	>15 ng/ml OR 4.5
J. Hou et al.[23]	13 ng/ml			>13 ng/ml OR 4.5 for low birth weight
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 othermarkers 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 alsoassociated 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 onthe value of maternal serum ferritin; there by evaluating the role of solely serum ferritin on intra uterine growth restriction.

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.

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