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Original Research Article

A Retrospective Assessment of the Significance of Maternal Serum Ferritin as a Prognostic Indicator for Intrauterine Growth Restriction

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Abstract

Aim: To determine the significance of maternal serum ferritin as a prognostic indicator for intrauterine growth restriction

Material and Methods: This retrospective study was conducted in the Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India from April 2019 to March 2020. 326 antenatal women visiting the antenatal clinic were enrolled in the study on the 25th week. Exclusion criteriawere BMI <18, placental abnormalities like velamentous insertion, antepartum haemorrhage, multiple pregnancies, patients with acute infection, positive CRP, raised TLC count, congenital malformation, and foetuses with chromosomal or genetic syndrome. Gestational age was defined as completed weeks from the onset of the last menstrual period, if there was a mismatch between the dates and USG reports by more than two weeks then the ultrasonographic dating (first trimester) was considered for calculating gestational age.

Results: Patients were divided into 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 having a 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 symmetrically growth-restricted babies when compared to women with serum ferritin value less than <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). Serum ferritin value at 20.2 ng/ml was associated with the 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.

Conclusions: In our study, a negative correlation was found between the value of serum ferritin and neonatal birth weight. In the future, a large randomized control trial is needed to find an association between maternal serum ferritin and IUGR.

Keywords: Intrauterine growth restriction, Ferritin, Ponderal index, Alpha-fetoprotein, Amniotic fluid lactate dehydrogenase

Introduction

Intrauterine growth restriction (IUGR) is a significant obstetric complication, characterized by a fetus not reaching its genetically predetermined growth potential. It is associated with increased perinatal morbidity and mortality, as well as long-term health consequences. Accurate and timely identification of IUGR is essential for managing affected pregnancies and improving neonatal outcomes. In recent years, serum ferritin, an acute-phase reactant and iron storage protein, has garnered attention as a potential predictive marker for IUGR due to its involvement in inflammatory processes and oxidative stress, which are implicated in the pathophysiology of IUGR. [1-5] Ferritin is a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion. During pregnancy, iron requirements increase significantly to support foetal growth and development, as well as increased maternal blood volume. Ferritin levels reflect the body's iron stores and can provide insights into iron metabolism and inflammatory status. Elevated serum ferritin levels have been associated with adverse pregnancy outcomes, including preeclampsia and gestational diabetes, both of which are linked to IUGR. [6-9] IUGR is often a consequence of placental insufficiency, where the

placenta fails to provide adequate nutrients and oxygen to the growing foetus. This insufficiency can trigger inflammatory responses and oxidative stress, leading to cellular damage and impaired foetal growth. Ferritin, being an acute-phase reactant, increases in response to inflammation and oxidative stress. Therefore, elevated serum ferritin levels may indicate an underlying pathological process contributing to IUGR. [10-12] Recent studies have investigated the potential of serum ferritin as a biomarker for predicting IUGR. Identification of serum ferritin as a predictive marker for IUGR has significant clinical implications. It offers a non-invasive and relatively simple method for early detection of at-risk pregnancies. This can facilitate closer monitoring, timely interventions, and improved perinatal outcomes. Moreover, integrating ferritin measurements with other diagnostic modalities, such as Doppler ultrasound and fetal biometry, could provide a more comprehensive assessment of foetal well-being. [13-15]

Material and Methods

This retrospective study was conducted in the Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India from April 2019 to March 2020. 326 antenatal women visiting the antenatal clinic were enrolled in the study on the 25th week. Exclusion criteriawere BMI <18, placental abnormalities like velamentous insertion, antepartum haemorrhage, multiple pregnancies, patients with acute infection, positive CRP, raised TLC count, congenital malformation, and fetuses with chromosomal or genetic syndrome. [16-20] Gestational age was defined as completed weeks from the onset of the last menstrual period, if there was a 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 samplesof all women were taken on the 25th week and again on 30-32 weeks in trace-free mineral evacuated tubes for assessment of serum ferritin by chemiluminescence. The mean of both values was calculated. Haemoglobin was estimated in all women at the time of inclusion in the study and again in the 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 the 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 into 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 into two parts, group B1 included women having neonates with a 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 intthree 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, and positive and negative predictive values at various cut-offs of serum ferritin were calculated and the ROC curve was analyzed (Table 3).

Results

326 women were 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, and 20 patients developed pre-term labor. These high-risk pregnancies were excluded from the study to remove any confounding factors from the study and finally, data from 257 women were taken for analysis. 204 (79.37%) women in group A have an average for gestational age neonates, and 53 (20.62%) women in group B have neonates small for gestational age. In group B1 asymmetrically growth restricted was 30 (11.67%) and symmetrically growth restricted was 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 the mean ages of both groups was not significant statistically. The mean gestational age of delivery in group A was 38.03 weeks, and in group B was 37.91 weeks. The 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 the two groups was statistically significant (P<0.05). The mean ferritin value of group A was 15.49 ng/ml and that of group B was 19.71 ng/ml. There was a statistically significant difference between the mean ferritin values of the two groups (P=0.03). The mean haemoglobin in group A was 10.46 gm% and in group B was 11.91%, the difference between the 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 into 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 having a 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 symmetrically growth-restricted babies when compared to women with serum ferritin value less than <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 ranges 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, and negative predictive value of various serumcut-offs to predict foetal 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 the highest Yuden's index which means that it can be taken as a cut-off for screeningantenatal patients for the development of fetal growth restriction with 61.5% sensitivity and 80.1% specificity.

Discussion

Fetal growth restriction is not only a short-term worry during the antenatal period but also has long-term effects affecting the 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
Nemanja 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, a 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 the 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. Table 5 shows the comparison between various othermarkers and serum ferritin as a predictor of fetal growth restriction. Although amniotic fluid LDH value boasts ofbetter sensitivity and specificity, it is more invasive, costly and associated with greater procedural side effects when compared to serum ferritin assessment. [12] Elevated levels of serum alpha-fetoprotein (>2.5 Mom) are alsoassociated with intrauterine growth restriction with an odds ratio ranging from 1.6-4.0, But no specific treatment protocol was suggested for its increased level. [24]

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

Study	Name of predictor	Measured in	Sensitivity as a predictor	Specificity	PPV as a predictor
Audibert et al.[28]	Alpha-fetoprotein	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 a Lower level of Trans ferritin receptor expression in the placenta is associated with preeclampsia and IUGR. [25,26] This can lead to a decrease in the extraction of iron by the placenta from maternal serum leading to an increase in maternal serum ferritin. Placental iso-ferritin levels were also found to be decreased in IUGR and preeclampsia in some studies. [27] This iron deficiency leads to an increase in fetal corticotrophins and fetal cortisol, causing inhibition of fetal growth. In the present study smoking, hypertension, and very low BMI <18 have been taken as exclusion criteria to negotiate their confounding effect onthe value of maternal serum ferritin; thereby evaluating the role of solely serum ferritin on intrauterine growth restriction.

Conclusions

In our study, a negative correlation was found between the value of serum ferritin and neonatal birth weight. In the future, a large randomized control trial is needed to find the association between maternal serum ferritin and IUGR.

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