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Original Research Article

A Study to Evaluate the Level of Serum Ferritin in Pregnant Women between 30 and 32 Weeks of Gestation & its Value in the Prediction of Intra-Uterine 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. The aim of this study is to evaluate the level of serum ferritin in pregnant women between 30 and 32 weeks of gestation & its value in the prediction of intra-uterine growth restriction.

Methods: This retrospective study was conducted at the Department of Obstetrics and Gynaecology, Katihar Medical College and Hospital, Katihar, Bihar, India for 9 months. The study included 100 healthy pregnant women at 30-32 weeks of gestation who underwent serum ferritin level estimation.

Results: The mean gestational age by last menstrual period (LMP) was 30.94 ± 0.802 weeks. The mean estimated foetal weight at the first visit was 1240.90 ± 168.691 grams. Doppler ultrasound findings included mean resistance index (RI) values of 0.60 ± 0.119 for umbilical artery (UA) and 0.54 ± 0.083 for middle cerebral artery (MCA), mean pulsatility index (PI) values of 1.0 ± 0.256 for UA and 1.33 ± 0.425 for MCA, and mean systolic to diastolic duration ratio (S/D) values of 2.50 ± 0.438 for UA and 2.99 ± 0.622 for MCA. The mean gestational age at delivery was 37.81 ± 1.169 weeks, and the mean fetal weight at birth was 3059.20 ± 623.356 grams. Apgar scores were measured with a mean of 7.03 ± 1.243 at 1 minute and 8.80 ± 1.206 at 5 minutes. Other foetal biometric parameters included a mean biparietal diameter (BPD) of 7.48 ± 0.190 cm, femur length (FL) of 5.90 ± 0.173 cm, abdominal circumference (AC) of 25.17 ± 2.509 cm, and amniotic fluid index (AFI) of 10.28 ± 3.634 cm. The mean estimated fetal weight at the first visit was 1309.27 ± 89.702 grams.

Conclusions: Maternal serum ferritin levels between 30 and 32 weeks of gestation were significantly higher in pregnancies that later developed intrauterine growth restriction (IUGR) compared to normal pregnancies. A cutoff serum ferritin level >15.25 ng/mL had 90% accuracy in predicting IUGR, with a sensitivity of 83.3%, specificity of 91.4%, positive predictive value (PPV) of 68.3%, and negative predictive value (NPV) of 96.2%.

Introduction

Asymmetric, late-onset (type II) intrauterine growth restriction (IUGR) is characterized by pathological foetal growth slowing that typically begins in late pregnancy due to inadequate uteroplacental function [1,2]. This differs from Small for Gestational Age (SGA), which denotes a birthweight below the 10th percentile for gestational age, regardless of health status.

The incidence of IUGR ranges from 3.3% to 10% in developed countries and from 6.7% to 17% in developing nations [3,4,5]. Foetuses affected by IUGR face heightened intrauterine risks such as fetal distress, neurological developmental disorders, and the potential for meconium aspiration at birth. Neonatal complications include hypoglycaemia, prolonged intensive care unit stays, hypothermia, polycythaemia, jaundice, feeding difficulties, necrotizing enterocolitis, late-onset sepsis, hypoxic-ischemic encephalopathy, and pulmonary haemorrhage. Furthermore, these infants have increased susceptibility to type 2 diabetes, obesity,

autoimmune diseases, cardiovascular diseases, and hypertension in adulthood [2,6].

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. Metas tin [7-9]. Apart from being expensive, laboratories at majority of centres 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 [10].

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 [11, 12]. In pregnancy, ferritin level decreases with advancing gestation [13]. Its lowest level is seen around 30-32 weeks of gestational age after which its concentration reaches plateau level [13].

The aim of this study was to evaluate the level of serum ferritin in pregnant women between 30 and 32 weeks of gestation & its value in the prediction of intra-uterine growth restriction.

Methods: This retrospective study was conducted at Department of Obstetrics and Gynaecology, Katihar Medical College and Hospital, Katihar, Bihar, India for 12 months.

This study included 100 healthy pregnant women between 30 and 32 gestational weeks who were subjected to estimation of serum ferritin levels.

Inclusion Criteria

- Maternal age: 20:40 years old.
- 30–32 gestational-week pregnancy (Estimated on the date of the last menstrual period), regular menstrual cycle, gestational week confirmed by ultrasonographic examination in the first trimester (between 8 and 13 gestational weeks).
- Normal laboratory findings in the first and second trimester of pregnancy.
- Singleton.

Exclusion Criteria

- Presence of chronic diseases (nephropathy, hypertension, ischemic cardiopathy, malignant tumours, chronic anaemia, diabetes mellitus, infection in pregnancy and smoking during pregnancy).
- Congenital malformations of the newborn.

Methodology

All patients in this study were enrolled in this study after taking informed written consent. Full history taking including (personal, present, complain, menstrual, obstetric, past, family history) was done. Clinical examination including general and abdominal examination was done. Investigations such as complete blood picture (erythrocytes, haemoglobin, haematocrit, and leukocytes), Serum ferritin level were done. SPSS version 22 (IBM©, Chicago, IL, USA) for Windows was utilized. According to the nature of the data, the relevant statistical tests employed A were judged statistically significant (P value ≤ 0.05).

Results:

The mean age of patients was 29.26±5.443 years, the mean height 162.03±4.352 cm, the mean weight was 75.81±4.162 kg, the mean Gravidity was 2.52±1.259, and the mean Parity 1.29±0.977.

Table1: Demographic characteristics of the studied cases.

	Mean &SD	Median	Range	IQR
Age (years)	29.26±5.443	29.0	20.0, 40.0	25.25, 33.0
Height(cm)	162.03±4.352	162.0	154.0, 171.0	158.25, 165.75
Weight(kg)	75.81±4.162	75.40	67.50, 85.0	73.0, 78.80
Gravidity	2.52±1.259	2.0	1.0, 6.0	2.0, 3.0
Parity	1.29±0.977	1.0	0.0, 4.0	1.0, 2.0

Table (2) shows that as regard resistance index (RI), the mean RI of UA was 0.60±0.119, the mean RI of MCA 0.54±0.083, as regard pusatility index (PI), the mean PI of UA was 1.0±0.256, the mean PI of MCA 1.33±0.425, and as regard systolic to diastolic duration ratio (S/D), the mean S/D of UA was 2.50±0.438, the mean S/D of MCA 2.99±0.622.

Table 2: Doppler indices of umbilical artery and middle cerebral artery of the studied cases

		Mean &SD	Median	Range	IQR
RI	UA	0.60±0.119	0.59	0.25, 0.98	0.53, 0.67
	MCA	0.54±0.083	0.55	0.31, 0.72	0.49, 0.60
PI	UA	1.0±0.256	1.03	0.44, 1.89	0.82, 1.14

	MCA	1.33±0.425	1.35	0.36, 2.42	0.99, 1.61
S/D	UA	2.50±0.438	2.53	1.67, 3.80	2.20, 2.70
	MCA	2.99±0.622	3.06	1.67, 4.65	2.55, 3.42

Table (3) shows that the mean gestational age at delivery was 37.81±1.169 weeks, the mean Fetal weight at birth was 3059.20±623.356 gm and as regard APGAR score, the mean at 1 minute was 7.03±1.243, the mean at 5 minutes 8.80±1.206.

Table 3: Fetal assessment at delivery of the studied cases

		Mean &SD	Median	Range	IQR
Gestational age at delivery (weeks)		37.81±1.169	38.00	35.00, 40.00	37.00, 39.00
Fetal weight at birth (gm)		3059.20±623.356	3290.0	1620.0, 3890.0	2935.0, 3457.50
APGAR score	1 minute	7.03±1.243	7.0	4.0, 9.0	6.0, 8.0
	5 minutes	8.80±1.206	9.0	6.0, 10.0	8.0, 10.0

Table (4) shows that in normal group, the mean HB was 11.02±0.533 gm/dl, the mean RBCs count 3.20±0.267 *105/dl, the mean Haematocrit was 30.82±2.509% and the mean Serum ferritin level was 11.15±3.125 ng/ml. In IUGR group, the mean HB was 11.32±0.509 gm/dl, the mean RBCs count 3.38±0.229*105/dl, the mean Haematocrit was 32.79±2.798% and the mean Serum ferritin level was 17.33±4.134 ng/ml. There was high significant difference between both groups as regards laboratory investigations according to presence of IUGR.

Table4: Laboratory investigations according to presence of IUGR.

	Normal group (n= 82)	IUGR group (n=18)	95%CI	P
HB (gm/dl)	11.02±0.533	11.32±0.509	-0.58, -0.03	0.030
RBCs(*10^5/dl)	3.20±0.267	3.38±0.229	-0.3, 0.0	0.010
Hematocrit(%)	30.82±2.509	32.79±2.798	-3.3, -0.6	0.004
Serum ferritin level(ng/ml)	11.15±3.125	17.33±4.134	-7.9, -4.5	p<0.001

Table (5) shows that there was negative significant Correlation between Serum ferritin level and Foetal weight at birth and there was positive significant correlation between serum ferritin and the presence of IUGR**.**

Table5: Correlation between serum ferritin level and fetal weight at birth & correlation between serum ferritin and the presence of IUGR

Serum ferritin level	Correlation coefficient	P
Fetal weight at birth	-0.517	<0.001
IUGR	0.585	<0.001

Discussion:

In the same line with our findings, Hou *et al* [14] determined the relationship between maternal serum ferritin concentrations and specific types of fetal growth restriction (FGR) in Alabama. They observed that among 480 infants, 370 (77%) were appropriate for gestational age (AGA), 58 (12%) had asymmetric FGR, and 52 (11%) symmetric FGR.

The incidence of newborn infants with IUGR differs from one country to another. Uberos *et al* [15] analyzed the blood ferritin concentration in pregnant women and measured the risk of low birth weight and the impact of various blood ferritin levels on growth rates in Spain. Of the 226 pregnant women included in their study, 19 (8.4%) presented low birth weight and 201 (88.9%) had a baby with normal birth weight for gestational age [15].

In contrast to our findings, Višnjevac *et al [16]* conducted a prospective study of healthy pregnant women between 30 and 32 gestational weeks, who were estimated for ferritin values. Out of 210 pregnant women who completed the investigation, 17 (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. The deviation from our findings may be attributed to difference of participant ethnicity as we assessed Egyptian women while Višnjevac *et al* [16] evaluated Serbian women.

In the present study, laboratory investigations (HB, RBCs, hematocrit, and serum ferritin level) were significantly higher in IUGR group compared to normal group (P value <0.05). In agreement with our findings, Salem *et al*., (2019) [17] conducted a

prospective longitudinal study included 64 women at 30-32 gestational weeks. Out of 328 pregnancies, the first 32 cases of IUGR and 32 appropriate for gestational age (AGA) controls were included in data analysis. Serum ferritin was then measured in the stored serum samples. Ultrasound scanning was performed at 30-32 weeks then at 37 weeks. Umbilical and MCA Doppler scans were added at 37 weeks. Serum ferritin, at 30-32weeks, was higher in women delivering IUGR babies with significant difference between the two groups (19.3±6.83 vs 14±5.18 ng/ml, $p<0.01$).

Our results agreed with Akkurt *et al [18]* who compared maternal serum ferritin levels across pregnancies with fetal growth restriction including SGA and IUGR compared to appropriate for gestational age (AGA). Three groups were enrolled: AGA, SGA (birth weight below 10th percentile for gestational age with no placental insufficiency findings), and IUGR (birth weight below 5th percentile for gestational age accompanied by abnormal umbilical artery Doppler waveforms and/or oligohydramnios). Maternal serum ferritin samples were obtained at gestational weeks 34 through 36, and delivery occurred at or beyond36 weeks. A total of 126pregnancieswith AGA (36%), SGA (40%), and IUGR (24%) were enrolled. The mean maternal serum ferritin level was higher in the IUGR group than in the AGA group (59 ng/ml versus 32.5 ng/ml, p<0.001). One possible explanation for the association between high ferritin levels and asymmetric FGR was that high serum ferritin levels might serve as a marker for either non-infectious vascular inflammatory response or infection and the second possible explanation for high ferritin levels in mothers of asymmetric-IUGR infants was that they were relatively hypovolemic.

In the same line with our findings, Višnjevac *et al [19]* reported that laboratory markers: hemoglobin, hematocrit and serum ferritin level were significantly lower in control group compared to IUGR group (P value <0.05). In this study, as regarding gestational age by LMP and ultrasonic fetal assessment of biparietal diameter (BPD), femur length (FL), abdominal circumference (AC), amniotic fluid index (AFI) and initial assessment of fetal weight we found BPD and FL were insignificantly different between both groups while AC, AFI and estimated fetal weight were significantly lower in IUGR group than normal group (P-value<0.05).

Our results are confirmed by Salem *et al [20]* who stated that gestational age at delivery was insignificantly different between IUGR group and control group. In our study, Doppler indices of umbilical artery and middle cerebral artery showed that RI, PI and S|D of umbilical artery of normal group were significantly lower than IUGR group (P value <0.05). RI, PI and S|D of middle cerebral artery of IUGR group were significantly lower than normal group ($p<0.05$).

Also, Salem *et al [21]* stated that birth weight (gm) was significantly lower in IUGR group than control group (2134±143 vs 3419±325; p<0.001). Also, APGAR score at 1 minute and 5 minutes was significantly lower in IUGR group than control group (p=0.04 and 0.03 respectively). In our study, there was significant negative correlation between maternal serum ferritin level and fetal weight at birth (r =-0.517; $p<0.001$) and significant positive correlation between serum ferritin level and IUGR (r= 0.585; $p<0.001$). Our results are compatible with Rahman *et al*., (2021) [22][23] who conducted a prospective cohort study.

Conclusions

Maternal serum ferritin between 30 and 32 weeks of gestation were significantly higher in pregnancies destined to develop IUGR at a later gestational age than in normal. A cutoff of serum ferritin >15.25 ng/mL had an accuracy of 90% to predict IUGR with sensitivity of 83.3%, specificity of 91.4%, a PPV of 68.3% and NPV of 96.2%.

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