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# Maternal serum ferritin level during pregnancy as a predictor of intrauterine fetal growth restriction

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#### Abstract

**Background:** Ferritin is synthesized by a number of tissues, including the liver as a major site. Placental tissue makes a form of ferritin (Placental isoferritin), and levels of this isoferritin or ferritin(s) in circulation have been correlated with pregnancy outcome. Iron storage concentrations decrease with advancing gestation, hence the values of ferritin also decrease up to 32% in the first trimester, 39% in the second and even 53% during the third trimester. As far as there is no causal therapy of IUGR, the prediction of IUGR is one of the priority tasks of perinatal protection. 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 descriptive cross-sectional study was conducted at department of Obstetrics and Gynecology at Tanta university hospital & Elmenshawy Hospital in the period from August 2020 till December 2021. This study included 100 healthy pregnant women between 30 and 32 gestational weeks who were subjected to estimation of serum ferritin levels.

**Results**: The mean Gestational age by LMP was  $30.94\pm0.802$  weeks and the mean estimated fetal weight at 1st visit was  $1240.90\pm168.691$  gm. and resistance index (RI), the mean RI of UA was  $0.60\pm0.119$ , the mean RI of MCA  $0.54\pm0.083$ , as regard pusatility index (PI), the mean PI of UA was  $1.0\pm0.256$ , the mean PI of MCA  $1.33\pm0.425$ , and as regard systolic to diastolic duration ratio (S/D), the mean S/D of UA was  $2.50\pm0.438$ , the mean S/D of MCA  $2.99\pm0.622$  and mean gestational age at delivery was  $37.81\pm1.169$  weeks, the mean Fetal weight at birth was  $3059.20\pm623.356$  gm and as regard APGAR score, the mean at 1 minute was  $7.03\pm1.243$ , the mean at 5 minutes  $8.80\pm1.206$  and the mean Gestational age by LMP was  $30.90\pm0.826$  weeks, the mean AFI was  $10.28\pm3.634$  cm, the mean FL was  $5.90\pm0.173$  cm, the mean AC was  $1309.27\pm89.702$  gm.

**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%.

Keywords: Serum ferritin, pregnancy, intrauterine, growth restriction

#### Introduction

Tibial plateau fractures are one of the commonest intra-articular fractures. They results from indirect coronal or direct axial compressive forces. They comprise of 1% of all fractures <sup>[1]</sup>. These fractures encompass many and varied fracture configurations that involve medial, lateral According to American College of Obstetricians and Gynecologists (ACOG) guidelines, a fetus with intrauterine growth restriction (IUGR) is a fetus with an estimated weight less than the 10th centile for gestational age <sup>[1]</sup>. The incidence of IUGR is 3.3-10% in the developed countries and 6.7-17% in developing ones <sup>[2]</sup>.

A fetus with IUGR is exposed to increased intrauterine risks of fetal distress and death, neurologic developmental disorders as well as meconium aspiration at birth. Neonatal risks include hypoglycemia, long admission to intensive care units, hypothermia, polycythemia, jaundice, feeding difficulties, necrotizing enterocolitis, late-onset sepsis, hypoxic-ischemic encephalopathy, and pulmonary hemorrhage. These infants also have increased risks of type 2 diabetes, obesity, autoimmune diseases, cardiovascular diseases, and hypertension in adult life <sup>[3, 4]</sup>. The incidence of IUGR varies from 5% in healthy mothers to 25% in high-risk groups <sup>[5]</sup>.

The etiology is frequently unknown. However; two types of IUGR are recognized <sup>[6]</sup>.

The asymmetric IUGR which represents about 80% and is caused by decreased nutrient supply to the fetus as in maternal hypertension, anti-phospholipids syndrome, placental insufficiency and extreme low BMI <15, and the symmetric IUGR which represents about 20% and is caused by chromosomal abnormalities especially trisomies 21, 18 and 13, congenital anomalies and congenital infection of the fetus as toxoplasmosis and cytomegalovirus. Hence, antenatal care, serial clinical and ultrasound examinations are essential for prediction, diagnosis and types of IUGR <sup>[7, 8]</sup>; however other biochemical markers were also studied <sup>[9]</sup>.

Ferritin is a protein, the serum concentrations of which are in correlation with total iron reserves in the human organism, and therefore it can be used as a reliable parameter in the estimation of iron deficiency <sup>[10]</sup>. Ferritin, the main iron storage protein, was suggested to be an adequate alternative as a screening test being a relatively cheap and easily available blood test. Its level is known to rise in response to hypoxia or as an acute phase reactant in infections <sup>[11]</sup>.

Ferritin is synthesized by a number of tissues, including the liver as a major site. Placental tissue makes a form of ferritin (Placental isoferritin), and levels of this isoferritin or ferritin(s) in circulation have been correlated with pregnancy outcomes <sup>[12]</sup>. Iron storage concentrations decrease with advancing gestation, hence the values of ferritin also decrease up to 32% in the first trimester, 39% in the second and even 53% during the third trimester<sup>[13]</sup>. The lowest values of ferritin are recorded between 30 and 32 gestational weeks, after which the concentrations stay on constant levels. The decrease of ferritin levels is in correlation with the decrease of iron reserves in the maternal body resulting from increased uptake (by the mother, placenta and fetus) as well as from hemodilution <sup>[14]</sup>. 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 descriptive cross-sectional study was conducted at department of Obstetrics and Gynecology at Tanta university hospital & Elmenshawy Hospital in the period from August 2020 till December 2021.

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.

# All patients in this study were subjected to the following Informed written consent

- **History taking:** full history taking including (personal, present, complain, menstrual, obstetric, past, family history).
- Clinical examination: General and abdominal examination.

#### Investigation

- Complete blood picture (erythrocytes, haemoglobin, hematocrit, and leukocytes)
- Serum ferritin level.

# Method of estimation of serum ferritin

**Measurement Principle:** The ST AIA-PACK FER is a two-site Immuno-enzymometric assay performed entirely in the ST AIA-PACK FER test cups. Ferritin present in the sample is bound with monoclonal antibody immobilized on magnetic beads and enzyme-labelled monoclonal antibody in the test cups. The magnetic beads are washed to remove any non-bound enzymelabelled monoclonal antibodies and then incubated with fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labelled monoclonal antibody that binds to the beads is in direct proportion to the ferritin concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve.

**Imaging study:** All cases in this study were subjected to transabdominal ultrasound by Mindray Dc -30 ultrasound at 30-32 weeks.

# Measurement of fetal biometry as

- Biparietal diameter (BPD)
- Femur Length (FL)
- Abdominal Circumference (AC)

These ultrasonographic parameters were used to confirm normal growth & correct gestational age to dates of last menstrual period)

- Estimated fetal weight
- Amniotic fluid index (AFI)
- Doppler indices of the fetus (Umbilical artery (UA), Middle cerebral artery (MCA)) Statistical analysis

SPSS version 27 (IBM©, Chicago, IL, USA) for Windows was utilized to evaluate the data Quantitative data was reported as mean SD or median (range) according to normality, whereas qualitative data was expressed as number and percentage. According to the nature of the data, the relevant statistical tests employed A were judged statistically significant (P value  $\leq$  0.05).

**Results:** Table (1) shows that the mean age was  $29.26\pm5.443$  years, the mean height  $162.03\pm4.352$  cm, the mean weight was  $75.81\pm4.162$  kg, and the mean Gravidity was  $2.52\pm1.259$ , the mean Parity  $1.29\pm0.977$ .

**Table 1:** 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	$1.29\pm0.977$	1.0	0.0, 4.0	1.0, 2.0

Data is expressed as mean and standard deviation, median, range and interquartile range.

Table (2) shows that as regard resistance index (RI), the mean RI of UA was  $0.60\pm0.119$ , the mean RI of MCA  $0.54\pm0.083$ , as regard pusatility index (PI), the mean PI of UA was  $1.0\pm0.256$ ,

the mean PI of MCA 1.33 $\pm$ 0.425, and as regard systolic to diastolic duration ratio (S/D), the mean S/D of UA was 2.50 $\pm$ 0.438, the mean S/D of MCA 2.99 $\pm$ 0.622.

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

		Mean & SD	Median	Range	IQR
DI	UA	0.60±0.119	0.59	0.25, 0.98	0.53, 0.67
NI	MCA	0.54±0.083	0.55	0.31, 0.72	0.49, 0.60
DI	UA	1.0±0.256	1.03	0.44, 1.89	0.82, 1.14
F1	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
3/D	MCA	2.99±0.622	3.06	1.67, 4.65	2.55, 3.42

Data is expressed as mean and standard deviation, median, range and interquartile range.

Table (3) shows that the mean gestational age at delivery was  $37.81\pm1.169$  weeks, the mean Fetal weight at birth was

 $3059.20\pm623.356$  gm and as regard APGAR score, the mean at 1 minute was  $7.03\pm1.243$ , the mean at 5 minutes  $8.80\pm1.206$ .

Table 3: Fetal assessment at	t delivery of the studied cases
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		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

Data is expressed as mean and standard deviation, median, range and interquartile range or as percentage and frequency.

Table (4) shows that in normal group, the mean HB was  $11.02\pm0.533$  gm/dl, the mean RBCs count  $3.20\pm0.267 *10^{5}$ /dl, the mean Hematocrit was  $30.82\pm2.509\%$  and the mean Serum ferritin level was  $11.15\pm3.125$  ng/ml.

In IUGR group, the mean HB was 11.32±0.509 gm/dl, the mean

RBCs count  $3.38\pm0.229*10^5$ /dl, the mean Hematocrit was  $32.79\pm2.798\%$  and the mean Serum ferritin level was  $17.33\pm4.134$  ng/ml. There was high significant difference between both groups as regards laboratory investigations according to presence of IUGR.

	Normal group (n= 82)	IUGR group (n= 18)	95% CI	Р
HB (gm/dl)	11.02±0.533	11.32±0.509	-0.58, - 0.03	0.030
RBCs (*10 <sup>5</sup> /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	<i>p</i> < 0.001

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when p < 0.05.

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

Table 5: Correlation between serum ferritin level and fetal weight at birth & correlation between serum ferritin and the presence of IUGR.

Serum ferritin level	Correlation coefficient	Р
Fetal weight at birth	-0.517	< 0.001
IUGR	0.585	< 0.001
P is significant when $< 0.05$ .		

Table (6) shows that serum ferritn level at cutoff point 15.25 ng/ml showed that the area under curve (AUC) was 0.896, the sensitivity was 83.3%, the specificity was 91.4%, the positive predictive value

(PPV) was 68.3%, the negative predictive value (NPV) was 96.2% and the accuracy was 90.0% to predict IUGR.

Table 6: Accuracy of maternal serum ferritin level to predict IUGR.

Serum ferritin level	IUGR
AUC	0.896
95% CI of ACU	0.802, 0.989
Р	< 0.001
Cutoff point	15.25
Youden's index	0.748
Sensitivity	83.3%
Specificity	91.4%
PPV	68.3%
NPV	96.2%
Accuracy	90.0%

P is significant when < 0.05.

The receiver operating characteristic curve (ROC) for the

studied cases and results is demonstrated in Fig (1)



Fig 1: ROC curve for the studied cases.

#### Discussion

In the same line with our findings, Hou *et al.*, (2000) <sup>[15]</sup> 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 differ from one country to another. Uberos *et al.*, (2000) <sup>[16]</sup> 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 <sup>[16]</sup>.

In contrast to our findings, Višnjevac *et al.*, (2011) <sup>[17]</sup> 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.*, (2011) <sup>[17]</sup> evaluated Serbian women. Also, different sample size which affect the results.

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) <sup>[18]</sup> 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 30-32 weeks, was higher in women delivering IUGR babies with significant difference between the two groups (19.3 $\pm$ 6.83 vs 14 $\pm$ 5.18 ng/ml, *p*<0.01).

Our results agreed with Akkurt et al., (2017)<sup>[19]</sup> 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 beyond 36 weeks. A total of 126 pregnancies with 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.*, (2011) <sup>[20]</sup> reported that laboratory markers: haemoglobin, 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.*, (2019)<sup>[21]</sup> 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.*,  $(2019)^{[22]}$  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) <sup>[23]</sup> who conducted a prospective cohort study. They randomly selected 573 women recruited into their study who delivered singletons with available birth anthropometric information. The plasma ferritin of each mother was measured at gestational week 14 (GW14; before the start of micronutrient supplementation) and at week 30 (GW30). Multivariable linear regression revealed no association between plasma ferritin at GW14 and birth weight. However, newborns of women in the highest levels of serum ferritin at GW30 (median = 29 ng/ml) had an average about 93 gm lower birth weight (95% CI: -172, -14; p = 0.021) than the newborns of women in the lowest levels (median = 8 ng/ml).

In agreement with our results, Salem *et al.*,  $(2019)^{[24]}$  reported a significant negative correlation between serum ferritin level and fetal weight at birth (r =-0.453; p=0.009) and a significant positive correlation between serum ferritin level and development of IUGR (r= 0.183; p=0.001).

On the other hand, Vazirinejad *et al.*, (2007) <sup>[25]</sup> reported Significant positive correlations between the mother's ferritin concentration and the baby's birth weight. Of note, in their study, blood samples for ferritin were collected just before delivery during the last 24 hours of pregnancy, a period at which fetal growth would have been completed.

In harmony with our findings, Salem *et al.*, (2019) <sup>[26]</sup> reported that the best ferritin cutoff level, between mothers with asymmetric IUGR neonates and those with AGA, was >18.2 ng/mL. This cutoff had a sensitivity of 59.38% and a specificity of 90.62%. AUC at 0.896 showed an accuracy of 76.8%, thus serum ferritin was found a good predictor for predicting babies with IUGR.

However, Akkurt *et al.*, (2017) <sup>[27]</sup> reported that a maternal serum ferritin cutoff of 48 ng/ml was found to be optimal for distinguishing between IUGR and AGA with a sensitivity of 67.7%, specificity of 92%, PPV of 84%, NPV of 82%. The difference from our results may be explained as they assessed serum ferritin level at 34 -36 weeks while we evaluated it at 30-32 weeks and as there was differences in the kits.

#### 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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## Declarations

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# Conflict of interest: Nil

**Ethical approval:** The study was approved from the ethics committee of Faculty of Medicine, Tanta University.

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