ABSTRACT

Background: Intrauterine growth restriction is associated with high incidence of perinatal mortality and serious long term morbidity. Ferritin is an iron storage protein and failure of serum ferritin level to decrease with advancing pregnancy points to impaired iron extraction by the feto-placental unit leading to asymmetric intrauterine growth restriction.

Aim of the study: Evaluation of serum ferritin levels at 30-32 weeks gestation as a marker and a predictor of asymmetrical intrauterine growth restriction.

Patients and Methods: Blood sample was taken from 145 high risk pregnancies at 30-32 weeks in the period from July 2014 to March 2015 for estimation of serum ferritin level by the enzyme linked fluorescent assay method. Data of 115 pregnancies were available at birth and included 85 cases appropriate weight for gestational age, 25 cases with asymmetric intrauterine growth restriction and 5 with cases symmetric intrauterine growth restriction. Serum ferritin levels were analyzed the mean ± SD, the Student t test, the χ² test and the receiver operating characteristic curve were used. Results were considered significant at p value <0.05.

Results: Serum ferritin level was significantly higher in the asymmetric intrauterine growth restriction group compared to the appropriate weight for gestational age group (18.95±8.32 vs 12.01±3.82), (p<0.001). A cut off value of serum ferritin 17.17 ng/dl was 80% sensitive, 88.2% specific, 66.7 and 93.8% positive and negative predictive values with 86.4% overall accuracy. Conclusion: Estimation of serum ferritin level at 30-32 weeks gestation in high risk pregnancy is a good biomarker which can be used with other investigations for prediction and diagnosis of asymmetric intrauterine growth restriction.

INTRODUCTION

According to ACOG guidelines, a fetus with intrauterine growth restriction (IUGR) is a fetus with an estimated weight less than the 10th percentile for gestational age (1). Intrauterine growth restriction (IUGR) is a serious Obstetric problem associated with 20 time's higher rate of perinatal mortality and serious
short or long term morbidity in half of the affected surviving infants (2). The incidence of IUGR varies from 5% in healthy mothers to 25% in high risk groups (3) and its etiology is frequently unknown. However; two types of IUGR are recognized (4); the asymmetric IUGR which represents about 80% and is caused by decrease nutrient supply to the fetus as in maternal hypertension, antiphospholipid syndrome, placental insufficiency, smoking and extreme low BMI <15; and the symmetric IUGR which represents about 20% and is caused by chromosomal abnormalities especially 21, 18 and 13, congenital anomalies and congenital infection of the fetus as toxoplasmosis and cytomegalovirus. Antenatal care, serial clinical and ultrasound examinations are essential for prediction, diagnosis and types of IUGR (5, 6); however other biochemical markers were also studied (7). Ferritin is an iron storage protein and the need of the growing fetus and placenta, the increasing maternal blood volume and red cell mass imposes a demand on maternal iron stores hence there is a decrease of serum ferritin (SF) with advancing gestation which is maximally noted between 30-32 weeks (8). The missing decrease of SF level points to decreased extraction of iron from blood of pregnant women by the feto-placental unit which can be in correlation with the development of the asymmetric IUGR (9). Previous studies reported different and conflicting results as regards the value of SF as a marker and a predictor of IUGR.

PATIENTS AND METHODS

This prospective observational study was carried out in the Obstetrics and Gynecology department of Benha University Hospital, Egypt, in the period from July 2014 to March 2015 after approval of the local ethical committee and informed consents of the participants. The study included 145 singleton pregnancies at 30-32 weeks gestation with the following inclusion criteria: 1- Presence of risk factor for IUGR as history of IUGR, malnutrition with extremely low maternal body mass index (BMI<15), toxemia of pregnancy, chronic hypertension, heart or kidney diseases and smoking. 2- No evidence of anemia or infection because both conditions affect serum ferritin level (Hb 10.5-15 g/dL, hematocrit % (HCT) 28-40, WBC 5.6-16.9 x 10^3/mm^3 and C-reactive protein (CRP) 0.4-8.1 mg/L). Cases with multiple pregnancy or congenital malformations of the fetus were excluded. Three ml venous blood sample was taken at 30-32 weeks gestation and serum separated for estimation of SF level by the enzyme linked fluorescent assay (ELFA) (Biomefieux s a rcs Lyon 673 620 390 France). Serial ultrasound examinations were done to measure the fetal biometry and to estimate the fetal weight. The biophysical profile and Doppler study of the umbilical and middle cerebral arteries blood flow were also done. Asymmetric IUGR was defined when the head circumference was between the 10th and 90th percentile and the abdominal circumference, the femur length and the estimated fetal weight were <10th percentile for gestational age and the ponderal index of the neonate (weight in grams/crown–heal length in centimeters)^3 x 100 was <2.32, while in symmetric IUGR all measurements were <10th percentile and the ponderal index was ≥2.32 and appropriate weight for gestational age (AGA) was defined as birth weight between the 10th
and 90th percentile (11). Data of 115 pregnancies were available at birth and included 85 cases AGA, 25 cases asymmetric IUGR and 5 cases symmetric IUGR which were excluded from analysis due to small number. Statistical analysis was done using SPSS version 10. Result was considered significant at p value <0.05.

RESULTS

Table 1 shows no significant differences between the asymmetric IUGR and AGA groups as regards WBC and CRP, while the Hb level, the HCT % and the SF level were significantly higher in the asymmetric IUGR group compared to the AGA group (p<0.03-0.001).

Figure 1 shows the ROC curve of the IUGR group versus the AGA group. The area under the curve was 0.792 and the best cutoff value of SF with the maximum sensitivity and specificity for prediction of asymmetric IUGR was 17.17 ng/dl.

Table 1: Comparison between the asymmetric IUGR and AGA groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Asymmetric IUGR n=25</th>
<th>AGA n=85</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (gm)</td>
<td>2024.0 ± 220.38</td>
<td>2915.3 ± 263.9</td>
<td>15.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White blood cells(×10^3)</td>
<td>8.53 ± 1.8</td>
<td>7.76 ± 1.92</td>
<td>1.8</td>
<td>0.08</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>5.04 ± 1.63</td>
<td>4.69 ± 1.32</td>
<td>1.1</td>
<td>0.30</td>
</tr>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>11.7 ± 0.98</td>
<td>11.27 ± 0.71</td>
<td>2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>34.9 ± 2.7</td>
<td>33.2 ± 2.8</td>
<td>2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum ferritin (ng/dl)</td>
<td>18.95 ± 8.32</td>
<td>12.01 ± 3.82</td>
<td>5.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 1: Receiver operating characteristic curve of serum ferritin level at 30-32 weeks gestation in the asymmetric IUGR group versus the AGA group. AUC=0.792, P<0.001, Cutoff value=17.17 ng/dl

Table 2 shows that 80% (20/25) in the IUGR group had SF level >17.17 ng/dl compared to 11.8% (10/85) in the AGA group (p<0.001). The test predicts asymmetric IUGR with 80% sensitivity, 88.2% specificity, 66.7 and 93.8% positive and negative predictive values and 86.4% overall accuracy.

Table (2): Validity of serum ferritin level at 30-32 weeks gestation for prediction of asymmetric IUGR.

<table>
<thead>
<tr>
<th>Group SF</th>
<th>IUGR n %</th>
<th>AGA n %</th>
<th>χ²</th>
<th>P value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive value +</th>
<th>Predictive value -</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;17.17 ng/dl</td>
<td>20 80</td>
<td>10 11.8</td>
<td>45.35</td>
<td>&lt;0.001</td>
<td>80.0%</td>
<td>88.2%</td>
<td>66.7%</td>
<td>93.8%</td>
<td>86.4%</td>
</tr>
<tr>
<td>&lt;17.17 ng/dl</td>
<td>5 20</td>
<td>75 88.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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DISCUSSION

In the present study, SF level at 30-32 weeks gestation was significantly higher in the asymmetric IUGR group (18.95 ± 8.32) compared to the AGA group (12.01 ± 3.82) (p<0.001) and also the hemoglobin concentration and the hematocrit % (p<0.03-0.01). A cut off level of SF >17.17 ng/dl predicts asymmetric IUGR with 80% sensitivity, 88.2% specificity, 66.7% and 93.8% positive and negative predictive values and overall accuracy 86.4%. This result agreed with a previous study (12) which reported that among 480 infants, 370 were AGA, 58 had asymmetric fetal growth retardation (FGR) and 52 had symmetric FGR. Mothers of asymmetric FGR infants had higher mean ferritin levels than mothers of AGA infants at 25 weeks (38.0 versus 20.2 ng/L, P<0.01) and at 36 weeks' gestation (21.0 versus 13.3 ng/L, P<0.01), whereas mothers of symmetric-FGR infants had significantly lower ferritin levels at 36 weeks (8.3 µg/L). In the present study 5 cases of symmetric IUGR had significantly lower SF level (5.76 ± 1.94 ng/dl) compared AGA (p<0.001). In another study (13) 63 mothers and their 90 pre-term neonates had elevated maternal ferritin that was related to an increased risk of IUGR. In another prospective study, Milasinovic et al., (14) included 220 healthy pregnant women between 30-32 gestational weeks, 8.1% of women delivered at full term and had low birth weight babies for gestational age without anemia and the value of ferritin, hemoglobin, hematocrit and erythrocyte count was significantly higher in this group than in mothers with normal weight newborns (p<0.005). The authors reported also that ROC curve analysis showed that the pregnant women with the ferritin level above 13.6 µg/L, and with erythrocyte count >3.76X10/L, hemoglobin >117 g/L and hematocrit >32.9%, in the period of 30-32 weeks of gestation had a significantly higher probability of having a low birth weight newborn for gestational age (p<0.05). In a systematic review and meta-analysis (7) a total of 53 studies that included 39,974 women and evaluated 37 novel biomarkers the authors concluded that none of the biomarkers were sufficiently accurate to recommend their use as predictors of IUGR in routine clinical practice and that the use of biomarkers in combination with biophysical parameters and maternal characteristics could be more useful. In a recent study Ozgu et al. (15) found that in 94 pregnant who underwent amniocentesis between 16-22 weeks, 7.5% delivered a baby below the 10 th percentile for gestational age and maternal blood ferritin levels were higher than patients who were appropriate for gestational age (P=0.03), the authors concluded also that there is not enough clinical evidence to recommend maternal serum ferritin measurement as a screening test for IUGR in routine practice.

CONCLUSIONS:

Estimation of serum ferritin levels at 30-32 weeks gestation in high risk pregnancy is a good biomarker which can be used with other investigations for prediction and diagnosis of asymmetric intrauterine growth restriction.

Conflict of interest: The author declare no conflict of interest.
REFERENCES


Serum Ferritin

quantitative estimation of Ferritin in maternal serum during weeks 18-22 of pregnancy. The study included pregnant women in the Department of Obstetrics and Gynecology at the University of Alexandria. The study was conducted from July 2015 to March 2016. The study aimed to measure the Ferritin level in maternal serum during weeks 18-22 of pregnancy and correlate it with the growth of the fetus. The results showed a significant correlation between Ferritin levels and fetal growth. The study concluded that the measurement of Ferritin levels in maternal serum during weeks 18-22 of pregnancy can predict fetal growth and early intervention can prevent complications.