THE IMPORTANCE OF MATERNAL ISCHEMIA MODIFIED ALBUMIN, NON STRESS TEST AND DOPPLER ULTRASONOGRAPHY IN FORESEEING PERINATAL ASPHYXIA

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Abstract

Background: The aim of this study is to evaluate the importance of ischemia changed albumin, in foreseeing fetal asphyxia and comparing it between normal and preeclamptic pregnant. Method: We planned our study as a prospective case-controlled study between May 2011 and June 2013. We recruited 104 pregnant women complicated by preeclampsia and 110 healthy pregnant women in the study. Doppler ultrasonography, non-stress test and fetal biometric measurements were performed. Venous blood samples taken to measure ischemia modified albumin (IMA). The presence of fetal hypoxia/acidosis was analyzed by conducting post-natal cord blood gas examination and 1.-5. minutes APGAR scoring. Results: IMA levels in the preeclamptic group were found statistically high (p<0,0001). The correlations between umbilical artery doppler systolic/diastolic (S/D) ratio, brain sparing effect, non stress test and IMA analyzed. We have found IMA statistically high when S/D ratio is above 2 standard deviations (preeclampsia; 11.83±1.33 vs 19.62±1.56 p<0.001, control; 10.28±1.57 vs 18.09±2.13 p<0.001) or brain sparing effect started (preeclampsia; 25.59±2.48 vs 9.16±1.99 p<0.001, control; 16.37±1.97 vs 6.72± 1.53 p<0.001) or abnormal NST findings occurred (preeclampsia; 10.69±1.92 vs 20.72±1.15 p<0.001, control; 7,42±1,94 vs 9,72±2,19 p<0.001). Conclusions: Maternal IMA levels are found high in preeclamptic pregnant women and it can be used as a biomarker for determining fetal wellbeing. What's already known about this topic? Hypertensive disease of pregnancy is the most frequently complication of pregnancy, being 5-10%. It is the most important reason for perinatal morbidity and mortality. Preeclampsia develops in an abnormal hypoxic intrauterine environment characterized by reperfusion and oxidative stress. To determine the fetal wellbeing, various tests were suggested, yet many of them provided a few benefits. What does this article add? The detected elevations in serum concentrations of IMA propose that measurements of this biomarker may be useful in assessing fetal hypoxia and predicting pregnancies which preeclampsia may develop

ABSTRACT

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Conclusions: Maternal IMA levels are found high in preeclamptic pregnant women and it can be used as a biomarker for determining fetal wellbeing.

What's already known about this topic?

Hypertensive disease of pregnancy is the most frequently complication of pregnancy, being 5-10%. It is the most important reason for perinatal morbidity and mortality. Preeclampsia develops in an abnormal hypoxic intrauterine environment characterized by reperfusion and oxidative stress. To determine the fetal wellbeing, various tests were suggested, yet many of them provided a few benefits.

What does this article add?

The detected elevations in serum concentrations of IMA propose that measurements of this biomarker may be useful in assessing fetal hypoxia and predicting pregnancies which preeclampsia may develop

INTRODUCTION

The recent studies showed that ischemia modified albumin (IMA) is a biochemical marker that can make the early diagnosis of coronary artery illness and cerebrovascular illness (1).

When tissue ischemia occurs, there can be changes in some albumin molecules. Within a few minutes and a few hour duration, ischemia decreases the dependency of albumin on substances like cobalt (2). The discovery of this characteristic paved the way for the development of a new test. Through this test, the amount of ischemia-modified albumin can also be measured by measuring the amount of decrease in metal binding. In acute ischemic cases, metal binding capacity in the N terminus region of albumin and a new variant metabolic protein comes into existence. Hypertensive disease of pregnancy is one of the most frequently seen complications of pregnancy, being 5-10% and it is the most important reason for maternal and perinatal morbidity and mortality (3). Preeclampsia develops in an abnormal hypoxic intrauterine environment characterized by reperfusion and oxidative stress. Several lines of evidence suggest that IMA is elevated in pathologies, where hypoxia and/or oxidative stress are found (4). To determine the prenatal hypoxic brain injury resulting as a result of the preeclampsia, various biochemical and biophysical tests were suggested, yet many of them provided a limited number of benefits. The decrease of diastolic blood flow in the umbilical artery and the decrease of resistance in cerebral vessels could be an indicator of placental insufficiency in preeclampsia cases (5).

The most common method used in the prediction of fetal wellbeing is a non-stress test (NST). There are many studies in the literature conducted to predict the fetal wellbeing of NST.

By looking at the post-natal normal and abnormal umbilical artery gas values of the reactive NST patterns, the sensitivity, specificity, positive and negative predictive values were found to be respectively 79%, 85%, 68%, 91%.6,7. The search for new tests continues to increase these values. This study determines the use of IMA in predicting the prenatal fetal asphyxia in normal and preeclamptic pregnancies and to evaluate the correlations between IMA, NST and fetal Doppler ultrasonography findings.

MATERIALS AND METHOD

After receiving approval from Ethics Committee of Dokuz Eylul University, Faculty of Medicine, (Approval date: 14.02. 2011, Number: 2013/03-05) we planned our study as a prospective case-controlled study between May 2011 and June 2013. Informed consent forms were received from all pregnant participants. 104 pregnant women complicated by preeclampsia, 110 healthy pregnant women were recruited in the study. Preeclampsia diagnosis was made with hypertension (TA >140/90) and with the identification of 300 mg or more proteinuria in 24-hour urine. In severe cases of the disease there may be red blood cell breakdown, a low blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath because of fluid in the lungs, or visual disturbances. The patient group we included in the study was in the class of mild preeclampsia, and we did not include the patients with these findings in the study.

Singleton pregnancies between 34-42 weeks of gestational with a normal fetal anatomy were included. Exclusion criteria were as follows; chorioamnionitis, abnormal fetal karyotype, smoking, alcohol or drug abuse. All patients were undergoing prenatal doppler ultrasonography and fetal biometric measurement, and they were assigned to our clinic for normal vaginal birth during the 34-42 weeks of gestational or emergency or planned cesarean section (C/S). All of the Doppler measurements were taken by using Voluson 730 (GE Medical Systems, USA) with a 3.5-MHz convex transabdominal probe by only one researcher (FA). Doppler measurements were received from the umbilical artery (UA) and middle cerebral artery (MCA). Then, systole/diastole ratio (S/D), pulsatility index (PI) and resistance index (RI) were calculated. A decrease below 2 standard deviations (SD) in MCA PI, an increase above 2 standard deviations in S/D ratio in umbilical artery, was accepted as an abnormal doppler finding. The brain sparing impact was defined by the fact that umbilical artery PI/MCA PI being over 1,08.

Among all the patients included in the study, when the cervical dilatation reached 5 cm in patients who are expected to have normal vaginal delivery, maternal venous blood samples were taken into non-heparinized tubes and centrifuged for IMA measurement. After the samples had been left for 30 minutes of coagulation, it was centrifuged for 10 minutes in 3500 rpm. Following the centrifuge, the samples were kept in -80 oC. Measurement of IMA level was made with a commercial enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (CusoBio Biotech, China). The absorbance was measured at 450 nm using a microplate reader. IMA concentrations in the sample were determined by drawing a standard graph of the standards in 6 different dilutions. The IMA results were expressed in IU per milliliter (IU/ml).

30-minute cardiotocography monitorization of all the patients was recorded before delivery. The NST data was divided into 2, being normal and abnormal. The cardiotocography whose heart rate is between 120-160 beats per minute, beat to beat variability between 5-25 and where there is no deceleration were accepted to be normal.

The presence of fetal hypoxia/acidosis was analyzed by conducting post-natal umbilical cord blood gas examination and 1-5 minutes of APGAR scoring. The classification for cord blood gas was made as; pH [?] 7,0 , base excess (BE) [?]16 severe acidosis; pH: 7,01-7,15, BE:15,9-10 moderated acidosis. The classification related with APGAR score was made concerning study that Li et al. (29), carried out respecting APGAR scoring and its effect on the neonatal, postnata mortality velocities and 5th minute Apgar score was accepted as: 7-10; high, 4-6; low, 1-3; very low.

Because the primary purpose of the power analysis evaluation was to predict fetal hypoxia, the groups were divided into 2, those whose 5th minute APGAR score is less than 6 and those over 6. The mean IMA level of the group 1 is 14,15 IU/ml standard deviation value is 1,54, while the IMA level of group 2 is 8,24 IU/ml and standard deviation value is 1,64. Because of the strength analysis evaluation made considering these data, the power of the study was determined as 100%.

Independent t-test was used in the average's comparison of independent samples, in defining statistical methods (average, standard deviation, median, minimum and maximum) serum IMA level, and the correlation of this value with NST and Doppler ultrasonography, the comparisons among control and patient groups.Area under the curve (AUC)() was calculated according to the pH value of fetal cord blood. SPSS version 15.0 was used for statistical analyzes. The value $p < 0,05$ was accepted as statistically significant.

RESULTS

The demographic attributes of the patients that took part in the study are all presented in Table 1.

Examining the average maternal blood ischemia modified albumin level in pregnant diagnosed with preeclampsia and healthy pregnant included in the study, there is a statistically significant difference was determined between both groups (p<0,001).

The distribution of the relation between IMA and S/D rates got because of the artery Doppler measurements is seen in Table 2. The relation between umbilical artery S/D rates and IMA was separately examined in the preeclamptic pregnant and control group. Statistically significant differences were determined (p<0,001).

It is seen that the brain sparing effect got with the rating of umbilical artery pulsatility index and middle cerebral artery pulsatility index has a correlation with the IMA in the study's population (p<0,001). The correlation between brain sparing effect and IMA level was separately analyzed in the preeclampsia group and control group. Statistically significant difference was determined in both groups (p<0,001) and it is shown in Table 2.

The correlation between non stress test and IMA was investigated in the entire patient group. Statistically significant differences were determined (p<0,001). The correlation between NST and IMA was separately analyzed in preeclampsia and control groups. The average IMA level in preeclampsia patients was 10,69 IU/ml +-1,92 in the presence of normal NST while the average IMA level was 20,72 IU/ml +-1,15 in the presence of abnormal NST and statistically significant differences were determined among them (p<0,001) (Table 2).

The correlation between 5th minute APGAR score and IMA level was showed. The average IMA level was 8,24 IU/ml +-1,64 in patients whose APGAR score was 6 or more, it was 14,15 IU/ml +-1,54 in patients whose APGAR score was less than 6. Statistically significant differences were determined (p<0,001). The correlation between APGAR score and IMA was separately evaluated in preeclamptic pregnant and control group patients (p<0,001). The IMA level was 6,28 IU/ml +-1,57 when the 5th minute APGAR score was determined as 6 or higher in the control group while it was e than 7,15. A statistically significant difference was determined between IMA level and pH (p<0,001). The correlation between IMA level and pH value of cord blood was studied in preeclampsia and control groups. The average IMA level was 10,17 IU/ml +-1,64 when the pH value in preeclampsia group was determined to be higher than 7,15 while it was 22,48 IU/ml +-1,86 when the pH value was determined to be equal or lower than 7,15 (p<0,001). For the control patients, the IMA level was 7,28 IU/ml +-1,57 when the pH value was higher than 7,15 and IMA level was 19,09 IU/ml +-0,125 when it was committed to be equal or lower than 7,15 (p<0,001).

In the ROC curve drawn in terms of the role of IMA in predicting fetal hypoxia (Figure 1), the part below the curve was significantly high (AUC=0,880; p<0,001), for this reason it was evaluated as a high diagnostic value. When the cut-off value is taken 18 IU/ml, sensitivity was 85,3%, specificity was 91% while positive predictive value was 70% and negative predictive value was 96%.

DISCUSSION

To our current knowledge, this is the first study in the literature to evaluate fetal well being with IMA. IMA was first used in 2000 as a finding in early diagnosis of myocardial ischemia (MI) (6-8). In this regard, albumin cobalt binding (ACB) assay has been approved by Food and Drug Administration as an early marker of acute coronary syndrome (ACS) among low-risk patient groups (9). In addition to cardiac pathologies, usage of IMA has been expanded over time including the assessment of mesenteric ischemia (10), muscle ischemia (11), and peripheral vascular events. Extended clinical applications soon emerged to cover diagnostic workup for conditions such as hypercholesterolemia, type 2 diabetes mellitus (DM), and pulmonary thromboembolism. Furthermore, studies have been conducted to investigate effect of surgical interventions on IMA (12,13).

Obstetricians could not remain unresponsive to the spectacular introduction of IMA utilization into liter-

ature. Ischemia modified albumin levels are higher in pregnant women compared to nonpregnant women. Two theories are thought about it; These are the relative intrauterine hypoxic environment in the early placentation stage and reactive oxygen species formed due to increased oxygenation after the first trimester (14).

Elevated IMA levels were demonstrated in women with recurrent pregnancy loss (RPL), gestational DM, intrauterine growth retardation (IUGR), and preeclampsia (15-18).

Poor placental perfusion characterizes preeclampsia because of vasospasm of uterine spiral arteries, which forms hypoxia and oxidative stress (19,20). Yet, the etiology is still unknown. Some theories that are under consideration are abnormal trophoblast invasion, coagulation abnormalities, vascular endothelial damage, cardiovascular maladaptation, immunologic factors and genetic predisposition (21). Evidence is accumulating that lipid peroxides and free radicals may be important in the pathogenesis of preeclampsia. Superoxide ions may be cytotoxic to the cell by changing the characteristics of the cellular membrane and producing membrane lipid peroxidation (20,21). It formed serum IMA in response to hypoxia or free radical injury to N terminus (asp-ala-his-lys) of albumin. IMA is a marker of cardiac ischemia, but IMA levels may be elevated in other conditions such as scleroderma, end stage renal disease, vascular disorders, and any event that is associated with hypoxia (8,9,22,23). In literature, Kagan et al showed it. (24) for the first time that in preeclamptic pregnant women albumin binding to cobalt and copper is corrupted. With these data, our hypothesis in this study was to predict preeclampsia and fetal wellbeing with the measurement of the IMA levels which increases in conditions related to hypoxia.

Gafsou et al. (25) evaluated the serum IMA levels of 22 non-pregnant women, 19 healthy pregnant women and 20 preeclamptic women. Just like our study data, they found IMA was significantly higher in preeclamptic patients and the elevated levels continue even after delivery. The authors claimed IMA can be used as a marker in first trimester to predict the patients who will develop preeclampsia. We can say that poor placental perfusion may cause hypoxia and oxidative stress, which may lead to preeclampsia and elevation of IMA levels.

In another study, it was found that ischemia modified albumin levels measured at the 12th gestational week were higher in small gestational age babies compared to babies with normal birth weight, and the authors emphasized that this may be because of defective placentation (25-29).

Papageoghiour et al. (26) declared that IMA can be an early marker of preeclampsia. At 11-12 weeks of gestation they measured the IMA levels and conducted the women who developed preeclampsia. They found a positive correlation with elevated IMA levels and preeclampsia. Papageoghiour et al. stated that poor placental perfusion caused hypoxia, which lead to pregnancy induced hypertension. Ustun Y et al.(21) in his study observed that IMA had 80% sensitivity and 77.8% specificity for preeclampsia.

Previously, an imbalance between oxidative stress markers and antioxidant capacity has been shown in fetuses with IUGR resulting in increased oxidative stress index (27). IMA, as a marker of oxidative stress, has also been evaluated in two studies in IUGR fetuses. In another study IMA in cord blood of IUGR fetuses with abnormal Doppler indices (a decrease of >2 SD in middle cerebral artery pulsatility indices or an elevation of >2 SD umbilical artery pulsatility indices) performed in the last six hours prior to delivery at between 33 and 41 weeks' gestation, were found to be significantly elevated and needed intensive care unit submission compared to SGA fetuses with normal Doppler measurements (n = 20). Besides, antioxidant markers were found to be significantly lower in IUGR group.

The outcomes of our study showed a correlation between increased systolic/diastolic umbilical artery flow, brain sparing impact, and maternal IMA (18).

IMA has been also evaluated in cord blood of neonates from complicated deliveries (28). The cord blood IMA levels in neonates from complicated deliveries (n = 14) was significantly higher (50%) than cord blood from uncomplicated deliveries (n = 12) classified by normal or low Apgar scores.

Our study results showed the elevated levels of maternal IMA in preeclampsia when compared to normoten-

sive pregnant women. Also, when we observe the outcomes of the study, we can tell that IMA may be a predictive value for evaluating the fetal well being. Non-stress test, umbilical artery doppler flow and middle cerebral artery doppler flow are the methods to assess the fetal well being. The outcomes of our study showed a correlation between elevated maternal IMA results and poor NST, increased systolic/diastolic umbilical artery flow, brain sparing impact and poor Apgar scores. When the cut-off value for IMA is taken 18 IU/ml, sensitivity is 85.3%, specificity is 91% for fetal well-being while positive predictive value is 70% and negative predictive value is 96% for fetal wellbeing. We can claim that IMA is a good predictive value for estimating fetal hypoxia.

In conclusion, the detected elevations in serum concentrations of IMA propose that measurements of this biomarker may be useful in assessing fetal hypoxia and predicting pregnancies which preeclampsia may develop.

Disclosure

Authors declare no financial relationship with any organization. Authors have full control of all primary data. We got written informed consent from the patients for publication. Copies of the written consents are available for review by the Editor-in-Chief of this journal on request.

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