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Original Article

The importance of maternal ischemia modified albumin, non stress test and doppler ultrasonography in foreseeing perinatal asphyxia

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ABSTRACT

Objective: 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: Women with preeclampsia had higher IMA compared to controls. 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.

Keywords: ischemia; fetal asphyxia; preeclampsia; non stress test; doppler ultrasonography

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Introduction

The recent studies showed that ischemia modified albumin (IMA) is a biochemical marker that can make the early diagnosis of coronary artery 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 [3].

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 [4]. Preeclampsia develops in an abnormal hypoxic intrauterine environment characterized by reperfusion and oxidative stress [5]. Several lines of evidence suggest that IMA is elevated in pathologies, where hypoxia and/or oxidative stress are found [6]. To determine the prenatal asphyxia 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 [7].

In response to hypoxia resulting from placental insufficiency, fetal compensatory mechanisms redistribute blood flow toward essential fetal organs [8]. The early stage of this redistribution results in increased blood flow to the brain and is detected with increased resistance of the umbilical artery (UA) and decreased resistance of the middle cerebral artery (MCA) at Doppler examination. The cerebral/placental ratio (C/P ratio) becomes less than one. It has been called the 'brain sparing effect' and it has been suggested that the C/P ratio alone was a more precise index than others [9]. However, the relationship of serum IMA levels, as a hypoxiarelated marker, with abnormal Doppler findings has never been investigated.

The nonstress test (NST) was most useful in evaluation of abnormal ultrasound monitored variables [10].

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%. [11] . 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.

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Material and methods

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. All preeclampsia patients who accepted to participate in the study and approved the informed consent form, and all patients with similar age and body mass index as the control group, who did not meet the exclusion criteria, were included in the study. Preeclampsia diagnosis was made with hypertension (blood pressure >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 in order to ensure group homogeneity in preeclampsia group patients.

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). The analysis of the obstetric Doppler velocimetry wave forms includes resistance index (RI), pulsatility index (PI) and peak systolic/end diastolic ratios (S/D). 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 [12]. The brain sparing impact was defined by the fact that umbilical artery PI/MCA PI being over 1,08. The C/P ratio was calculated by MCA-PI/UA-PI and a ratio of <1.08 was considered abnormal [13].

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. Frozen samples were mixed thoroughly after thawing and recentrifuged before analysis. Samples with more than a trace of hemolysis were discarded. All serum samples were diluted 400-fold with 0.02 M PBS before analysis. 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) [2].

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 [14]. The classification related with APGAR score was made concerning study that Li et al. [15], 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.

Statistical analysis was performed using the SPSS version 15.0 statistical package (SPSS, Chicago, IL, USA). Normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Differences between cases and controls were tested for significance using the c2 -test (or Fischer's exact test) for categorical variables. Student's t-test was used for normally distributed variables in the analysis of continuous variables and the Mann–Whitney U-test was used for non-normally distributed variables. The data were indicated as median and range for non-normally distributed variables. Pearson and Spearman correlation coefficients were used for the analysis of correlation for continuous normally and non-normally distributed variables, respectively. A receiver operating characteristic (ROC) curve was constructed, and sensitivity and specificity were calculated based on the best cut-off. The optimal cut-off for IMA was determined from the ROC curve as the point nearest to the upper left corner. Values of $P < 0.05$ were considered to indicate a statistically significant difference.

Results

The demographic characteristics of the patients that took part in the study are all presented in Table 1. Preeclampsia group had a lower birth weight when compared with neonates in the control group.

Table 1. Comparison of demographic findings of preeclampsia group and controls.

	Preeclampsia group (n=104)	Control group (n=110)	p value
Age (years)*	28,80±5,20 (18-41)	30,40±5,4 (17-46)	0,026
Gestational age*	37,54±1,97 (34-40)	38,10±1,42 (34-41)	0,038
Gravida*	2,21±1,32 (1-7)	2,22±1,33 (1-7)	0,987
Parity *	0,80±0,80 (0-3)	0,82±0,91 (0-4)	0,868
Abortus*	0,27±0,49 (0-2)	0,35±0,73 (0-4)	0,38
IMA	16,4 ±1,93	6,73±1,62	<0,001
Birthweight (g)	2908.91 ±82.52	3328.08 ± 47.97	<0.001
C/P Ratio-PI	1.10 ±0.04	2.04± 0.18	<0.001
UA-S/D	3.6± 0.5	2.5± 1.7	0.03

**Mean ± standart deviation; IMA, ischemia-modified albümin; C/P, cerebro/placental. According to Kruskal Wallis variance analysis (the Mann-Whitney U test with Bonferroni correction as post hoc).*

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).

Table 2. Relationship between IMA and umblical artery doppler flow, brain sparing effect, NST and Apgar score in patients with preeclampsia and healthy controls.

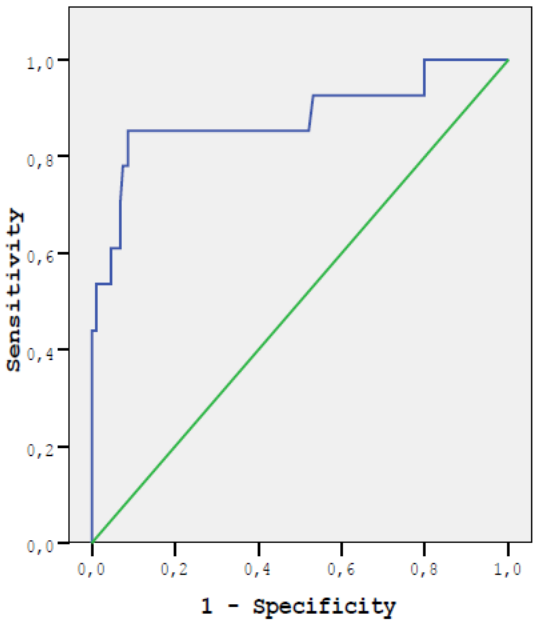
	Preeclampsia group		P value	Control group		P value
	Umblical artery S/D<2 (n=69)	Umblical artery S/D≥2 (n=35)		Umblical artery S/D<2 (n=99)	Umblical artery S/D≥2 (n=11)	
IMA (IU/ml)	11.83±1.33	19.62±1.56	<0.001	10.28±1.57	18.09±2.13	<0.001
	Negative brain sparing impact (n=69)	Positive brain sparing impact (n=35)		Negative brain sparing impact (n=102)	Positive brain sparing impact (n=8)	
IMA (IU/ml)	9.16±1.99	25.59±2.48	<0.001	6.72± 1.53	16.37±1.97	<0.001
	NST good (n=58)	NST poor (n=46)		NST good (n=94)	NST poor (n=16)	
IMA (IU/ml)	10.69±1.92	20.72±1.15	<0.001	7.42±1.94	9.72 ±2.19	<0.001
	5th min Apgar score>6 (n=74)	5th min Apgar score<6 (n=30)		5th min Apgar score>6 (n=105)	5th min Apgar score<6 (n=5)	
IMA (IU/ml)	9.44±1.70	18.41±1.72	<0.001	6.28±1.57	10.09±1.68	<0.001

Mean ± standart deviation, IMA: Ischemia modified albumin, According to Kruskal Wallis variance analysis (the Mann-Whitney U test with Bonferroni correction as post hoc).

According to the C/P ratio-PI, umblical arter S/D indices and NST, the maternal blood IMA levels were significantly increased in cases with abnormal test results. (p<0,001) Table 2. The serum IMA levels were also higher in newborns with low APGAR scores as compared to healthy controls, and a statistical significant difference was observed.

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%.

Figure 1. ROC curve of IMA



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) [16]. 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 [17].

In addition to cardiac pathologies, usage of IMA has been expanded over time including the assessment of mesenteric ischemia [18], muscle ischemia [19], 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 [20,21].

Obstetricians could not remain unresponsive to the introduction of IMA utilization into literature. 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 [22].

Elevated IMA levels were demonstrated in women with recurrent pregnancy loss (RPL), gestational DM, intrauterine growth retardation (IUGR), and preeclampsia [23,25].

Poor placental perfusion characterizes preeclampsia because of vasospasm of uterine spiral arteries, which forms hypoxia and oxidative stress. 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 [26]. 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 [27]. 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. In literature, Kagan et al showed it. [28] 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. [29] 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 [30].

Papageorghiou et al. [31] 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. Papageorghiou et al. stated that poor placental perfusion caused hypoxia, which lead to pregnancy induced hypertension.

Previously, an imbalance between oxidative stress markers and antioxidant capacity has been shown in fetuses with IUGR resulting in increased oxidative stress index [32]. 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 normotensive 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.

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