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**Ischemia modified albumin levels in intrauterine growth restriction: levels are increased in fetal cord blood but not in maternal blood**

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**ABSTRACT**

**Objectives:** In this study, our aim was to determine the differences between intrauterine growth restriction (IUGR) and normal birth weight fetuses in terms of ischemia modified albumin (IMA) levels. For this purpose, we measured ischemia modified albumin levels in the cord blood of fetuses and the mothers.

**Material and methods:** This study is a prospective study conducted at University of Health Sciences Tepecik Training and Research Hospital between January 2018 and December 2019. According to the inclusion/exclusion criteria, 227 patients were included in the study. Participants were divided into two groups according to the presence (patient group) or absence (control group) of intrauterine growth restriction (IUGR). In addition to routine parameters recorded during pregnancy, the IMA levels and Doppler USG findings of all participants were recorded.

**Results:** The mean cord blood serum IMA levels of the patient group were significantly elevated compared to controls ( $p = 0.038$ ). Whereas mean maternal blood serum IMA levels were similar among groups ( $p = 0.453$ ). The cord blood and mother blood serum IMA levels were not significantly different with regard to the presence or absence of perinatal asphyxia.

**Conclusions:** In the literature, studies evaluating IMA levels in the cord and maternal blood of IUGR fetuses are limited. In IUGR patients, IMA level is expected to increase and in our study, IMA levels were significantly increased but the presence of oxidative stress has not been found to affect IMA levels.

**Key words:** ischemia modified albumin (IMA); oxidative stress; intrauterine growth restriction (IUGR); cord blood; asphyxia

## INTRODUCTION

Ischemia Modified Albumin (IMA) is a non-specific ischemia marker that is associated with insufficient oxygenation, elevated anaerobic metabolism and free oxygen radicals [1]. The clinical utility of IMA has been demonstrated in the identification of acute coronary syndrome [2, 3]. It was a marker that received significant interest by researchers and clinicians as it was believed to show ischemia in its early stages; that is before necrosis occurred. In addition, it has been explored in diseases such as diabetes mellitus, trauma, heart failure and pulmonary embolism [4, 5]. The interesting results put forth in these studies and the fact that IMA measurement is very cheap has attracted the attention of various other specialties, including perinatologists and gynecologists, for its use as a marker of ischemia [6].

Although there are various opinions about the approach to the delivery of low birth weight infants and when infants with intrauterine growth restriction (IUGR) should be delivered [7, 8], each case is multifactorial and should be an individual decision based on many factors. The current problem with timing is to prevent intrauterine fetal loss while also allowing sufficient time for fetal lung development. The hypoxic environment in which fetuses with intrauterine growth retardation are situated can lead to growth retardation and negative effects on brain development. Early detection of hypoxia is critical when considering the possibility of preventing such problems. Several markers reflecting the oxidative stress of the fetus, such as prolidase activity, total free sulfhydryl and various parameters in the oxidative stress index have been studied for this purpose [9]. In addition to well-established markers, some researchers have investigated whether IMA can be used to determine intrauterine hypoxia [6, 10, 11]. Moreover, studies have been conducted previously on the

measurement of IMA in conditions such as preeclampsia, preterm delivery, and recurrent miscarriages [12–14]. Most studies in the field were performed by the measurement of IMA levels in cord blood; however, the levels of this marker in maternal blood may also be important for fetal development. On the other hand, it is apparent that the number of patients included in these studies and the number of studies themselves are insufficient to reach any clear conclusion as to how IMA levels change in such conditions [6].

In this study, our aim was to ascertain whether IMA levels could be regarded as a marker that could identify the optimal birth time in fetuses with IUGR. For this purpose, we measured and compared IMA levels in the cord blood and maternal circulation of all patients who accepted to participate in the study, and we evaluated results according to birth weight.

## **MATERIAL AND METHODS**

### **Study Group**

This is a prospective study conducted at University of Health Sciences Tepecik Training and Research Hospital from January 2018 to December 2019. The criteria for inclusion in the study were to give birth between the age of 18–40 years, accepting to participate in the study and to attend all pregnancy control evaluations at our hospital. The exclusion criteria were:

- Multiple pregnancies (7 individuals excluded)
- Fetal malformation or chromosomal anomaly (3 individuals excluded)
- Delivery with complications (dystocia, cord prolapse, placental abruption) (6 individuals excluded)
- Neonatal complications (11 individuals excluded)
- Gestational diabetes mellitus (16 individuals excluded)
- Preeclampsia (21 individuals excluded)
- Recurrent pregnancy loss (3 individuals excluded)

During the study period, a total of 294 women who met the inclusion criteria in our hospital delivered. According to the above-mentioned reasons, 67 were excluded. As a result, a final group of 227 individuals were included in the study and were divided into two groups according to fetal birth weight. Those with low birth weight comprised the patient group ( $n = 76$ ), while those with normal birth weight formed the control group ( $n = 151$ ). In addition, patients were divided into groups according to the presence/absence of asphyxia and the effect of oxidative stress was evaluated.

Fetuses with an expected fetal weight below the 10<sup>th</sup> percentile threshold according to gestational age were accepted to have IUGR when gestational age could be determined accurately and there were no signs of constitutionally small stature (regarding maternal and paternal characteristics). Perinatal asphyxia was defined as the occurrence of asphyxia in the newborn after birth and diagnosis was made according to the criteria of American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) [13, 15]: (i) metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH less than 7 and base deficit of 12 mmol/L or more, (ii) persistence of an Apgar score of 0–3 for longer than 5 minute, (iii) neonatal neurologic sequelae (*e.g.*, seizures, coma, hypotonia), and (iv) multiple organ involvement (*e.g.*, kidney, lungs, liver, heart, intestines).

### **Ethical**

Permission for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Tepecik Training and Research Hospital. During the conduct of the study, the Helsinki Declaration and Good Clinical Practices Guide were followed. Written and oral consent was obtained from all mothers who participated in the study.

### **Measurements**

All routine data obtained to assess gestational health (including maternal age, gestational age, gravida, parity, birth weight, fetus gender, type of delivery, history of fetal death) were recorded for the study. Blood samples from the umbilical vein (after clamping of the cord) were drawn into serum separator tubes immediately after delivery.

The cerebroplacental ratio (CPR) was determined by the measurement of umbilical and middle cerebral artery pulsatility indexes (PI) via Doppler. The middle cerebral artery (MCA) PI values were calculated via measurements performed at the portion of the artery that passes close to the sphenoid wing, while the umbilical artery (UA) PI values were calculated from measurements performed at the free loop. During measurements, the insonation angle was kept lower than 30° and values were recorded when fetal movements were absent. The cerebroplacental ratio (CPR) was defined as the ratio between middle cerebral artery (MCA) PI and umbilical artery (UA) PI. All results obtained with this procedure were converted into multiples of the median (MoM), with corrections performed according to gestational age reference ranges [16].

Cesarean sections were carried out with the following protocol: The patients did not receive premedication therapy. In the operating room, Patients were placed supine before.

Then, oxygen (3L/min) and intravenous colloidal solution (20 ml/kg/hour) were given to the patients through a face mask. After three minutes in this state, baseline measurements (Oxy-, Deoxy-, Total-Hb Concentrations, Tissue Oxygenation Index, Mean Blood Pressure, and Heart Rate) were recorded. Later, the patients were placed in the lateral position and lumbar puncture was performed at the L3/L4 interval. Hyperbaric 0.5% bupivacaine was used in all patients by adjusting the individual dosage by the anesthesiologist. After the injection, the patients were placed in the supine position. If anesthesia-related hypotension was observed (MBP < 80% of baseline value or systolic blood pressure < 90 mmHg), ephedrine was given to the patient by the anesthesiologist.

Measurement of IMA was performed spectrophotometrically according to the method described by Bar-Or et al. [17]. According to this method, 200  $\mu$ L patient blood serum was mixed with 50  $\mu$ L of 0.1% cobalt chloride (Sigma, St. Louis, MO, USA) and incubated for 10 minutes. After the incubation step, 50  $\mu$ L of dithiothreitol (DTT) solution in water (1.5 mg/mL) (Sigma, St. Louis, MO, USA) is added. After 2 minutes, 1 mL of 0.9% NaCl is added. The absorbance of the sample is measured with a spectrophotometer set at 470 nm. A sample without DTT addition is used as the blank for each measurement. All results were reported in absorbance units (AbsU).

Fetal and maternal IMA measurements were performed at > 37 weeks of gestation.

### **Statistical analysis**

Power analysis was performed with G-Power. Accordingly, the total minimum number of people to attend was calculated as 46 for each group. SPSS version 22.0 (IBM Corporation, Armonk, New York, US) was used for statistics and calculations. Differences between cases and controls were tested for significance using the chi-square test for categorical variables. The normally distributed variables were evaluated using Shapiro–Wilk ( $n < 30$ ) tests. Independent T-test was used if the data showed normal distribution for continuous variables (data were presented as mean  $\pm$  standard deviation) and Mann–Whitney U test if the data did not show normal distribution (data were presented as median  $\pm$  min, max).  $p < 0.05$  was accepted as statistically significant.

## **RESULTS**

Seventy-six (33.5%) of the 227 neonates had IUGR. Gestational ages and birth weights were lower in the IUGR group compared to the newborns in the control group. However, no differences were found in maternal age between these groups. In terms of IMA,

the mean cord blood serum IMA levels of the patient group were significantly elevated compared to those from uncomplicated pregnancies ( $p = 0.038$ ). However, mean maternal blood serum IMA levels were similar ( $p = 0.453$ ). (Tab. 1).

Thirty (13.2%) newborns were diagnosed with perinatal asphyxia. In these cases, mean birth weight was significantly lower than the controls. Oligohydramnios before delivery was more common in those with perinatal asphyxia. The cord blood and maternal blood serum IMA levels were not significantly different in newborns with perinatal asphyxia compared to healthy controls. (Tab. 2).

We also investigated Doppler findings of 76 fetuses with fetal growth retardation were compared according to the presence/absence of asphyxia. The mean C/P ratio was statistically similar between the groups. The PI values of the middle cerebral artery and the umbilical artery were also similar when those with and without asphyxia were compared. (Tab. 3)

## **DISCUSSION**

In our study, IMA levels in the maternal blood of IUGR fetuses were found to be similar to IMA levels in the blood samples of mothers with normal fetuses. IMA concentrations were found to be higher in the cord blood samples of the IUGR group. On the other hand, it was observed that IMA levels were similar when the groups were separated according to the presence of asphyxia.

In recent years, there has been an opinion that IMA levels in cord blood are a reliable indicator of intrauterine ischemia and hypoxia [18]. Guvendag Guven et al. [19] compared IMA levels with the cord blood of 20 IUGR fetuses and 20 controls. The IMA levels of those with IUGR were reported to be lower in addition to significant alterations in other important parameters. They also found a strong positive correlation between umbilical artery PI and IMA levels. However, the low number of samples raises concerns about the reliability of the findings of this study. In another case-control study, Gugliucci et al. [18] showed that IMA levels would increase by 3-fold in a fetus that experienced oxidative stress and hypoxia compared to healthy controls. However, the number of patients in this study is also very low. In another study, which included a relatively higher number of patients (57 IUGR and 110 fetuses with normal birth weight), Iakovou et al. [10] did not find a significant difference between the two groups in terms of IMA levels. However, in this study, IUGR patients were not separated according to the presence or absence of asphyxia. In our study involving 257 fetuses, although IMA levels were higher in the cord blood IUGR group, IMA levels in the cord blood of fetuses who experienced oxidative stress were similar. This suggests that IMA



may be elevated in cord blood due to another reason. In this respect, the pathophysiology underlying the elevation of IMA in this condition requires elucidation.

There are a limited number of studies looking at IMA levels in samples taken from the maternal blood in cases where developmental problems are observed. Although it has been noted that in many clinical situations IMA is higher than in normal pregnancies, no studies have analyzed IMA in the maternal blood of IUGR fetuses. In our study, maternal IMA levels were similar in mothers with IUGR fetuses compared to mothers that had fetuses with normal development. In addition, IMA concentrations of the mothers bearing fetuses exposed to oxidative stress according to Doppler USG were found to be similar to those bearing fetuses without exposure to oxidative stress. In a study by Rossi and colleagues [11] which was comprised of 65 normal and 16 small-for-gestational-age (SGA) fetuses at different periods of pregnancy, the IMA/albumin ratio was investigated. Interestingly, while the IMA/albumin ratio was found to be higher in mothers who had SGA fetuses in the first and second trimester, the IMA/albumin ratio was similar two weeks after termination of pregnancy. Thus, the authors suggested that IMA may be useful in predicting oxidative stress in the early stages of pregnancy but may lose its sensitivity thereafter. In several studies, it was emphasized that IMA increased physiologically during pregnancy [20, 21].

Although our study reached some important findings, we should note that there are several limitations. First, some parameters that were likely to affect IMA levels were not similar in both groups. IMA levels might be affected by various factors, which may lead to unreliable results and conclusions. For instance, the gestational age was higher in the control group, which may have marginally affected results. In addition, being a tertiary center may have affected the high-risk pregnancies rates and the prevalence of neonatal asphyxia. We also did not look at other oxidative stress parameters which may have been useful in determining the levels of oxidative stress. Finally, we could not analyze the long-term results of our patients due to insufficient records and patients not attending long-term follow-up studies.

However, our study also has some strengths to be mentioned. Firstly, we analyzed patients regarding the presence/absence of oxidative stress. Secondly, we included a relatively high number of patients compared to other studies in a prospective fashion. Thirdly, we measured IMA in maternal blood which is absent in the majority of studies in this field. In addition, we excluded patients with clinical conditions that are known to affect IMA levels and our study group was homogeneous in terms of other confounding factors.

## **CONCLUSIONS**

In the literature, studies evaluating IMA levels in the cord blood and maternal blood with IUGR fetuses are quite limited. Although the common opinion is that IMA levels will increase in patients with IUGR, we found that IMA levels are elevated in IUGR's and do not change compared to normal pregnancies in the presence of oxidative stress. Further studies in larger groups are needed to establish clear evidence on the subject and to determine the pathophysiologic mechanism by which IMA levels are altered.

**Table 1.** Clinical and demographic features of the study group

	<b>IUGR Group (n = 76)</b>	<b>Control Group (n = 151)</b>	<b>p</b>
Fetus gender; n (%)			
Female	49 (64.5)	74 (49.0)	0.019
Male	27 (35.5)	77 (51.0)	
Maternal age; years (mean $\pm$ SD)	26.0 $\pm$ 5.9	27.2 $\pm$ 6.4	0.165
Gravida (median, min–max)	2 (1–7)	2 (1–10)	0.044
Parity (mean $\pm$ SD)	1.7 (0-6)	2.2 (0-10)	0.002
Birth weight; g (mean $\pm$ SD)	2322 $\pm$ 546	3288 $\pm$ 376	< 0.001
Gestational age; weeks (mean $\pm$ SD)	37.4 $\pm$ 2.1	38.9 $\pm$ 1.1	< 0.001
History of fetus mortality; n (%)	0 (0.0)	3 (2.0)	0.292
History of abortion; n (%)			
0	60 (78.9)	128 (84.8)	
1	10 (13.2)	14 (9.3)	0.400
2	2 (2.6)	6 (4.0)	
$\geq$ 3	4 (5.3)	3 (2.0)	
Amniotic fluid index (AFI); mm (mean $\pm$ SD)	79.5 $\pm$ 29.7	99.9 $\pm$ 16.9	< 0.001
Oligohydramnios; n (%)	15 (19.7)	2 (1.3)	< 0.001
Asphyxia; n (%)	27 (35.5)	3 (2.0)	< 0.001
IMA level in cord blood (AbsU) (mean $\pm$ SD)	0.6 $\pm$ 0.4	0.5 $\pm$ 0.3	0.038
IMA level in maternal blood (AbsU) (mean $\pm$ SD)	0.4 $\pm$ 0.1	0.4 $\pm$ 0.2	0.453
Apgar (1 min) (mean $\pm$ SD)	6.9 $\pm$ 0.7	7.3 $\pm$ 0.6	< 0.001

IMA — Ischemia modified albumin; IUGR — intrauterine growth restriction; SD — standard deviation

**Table 2.** Comparison of the clinical features of the neonates with perinatal asphyxia and non-asphyxia neonates

	<b>Asphyxia Present (n = 30)</b>	<b>Asphyxia Absent (n = 197)</b>	<b>p</b>
Fetal gender; n (%)			
Female	13 (43.3)	110 (55.8)	0.139
Male	17 (56.7)	87 (44.2)	
Maternal age; years (mean ± SD)	26.0 ± 6.0	27.0 ± 6.3	0.417
Gravida (mean ± SD)	1.8 (1–9)	2.5 (1–10)	0.020
Parity (mean ± SD)	1.4 (0–7)	2.1 (0–10)	0.008
Birth weight; g (mean ± SD)	2017 ± 683	3107 ± 486	< 0.001
Gestational age; weeks (mean ± SD)	37.9 ± 2.1	38.4 ± 1.6	0.087
History of mortal fetus; n (%)	0 (0.0)	3 (1.5)	0.652
History of abortion; n (%)			0.688
0	25 (83.3)	163 (82.7)	
1	4 (13.3)	20 (10.2)	
2	0 (0)	8 (4.1)	
≥ 3	1 (3.3)	6 (3.0)	
Amniotic fluid index (AFI); mm (mean ± SD)	76.0 ± 31.4	95.7 ± 21.5	< 0.001
Oligohydramnios; n (%)	7 (23.3)	10 (5.1)	0.003
IMA level in cord blood (AbsU) (mean ± SD)	0.6 ± 0.4	0.6 ± 0.4	0.925
IMA level in maternal blood (AbsU) (mean ± SD)	0.4 ± 0.1	0.4 ± 0.2	0.181
Apgar (1 min) (mean ± SD)	6.4 ± 1.3	7.3 ± 0.4	< 0.001

IMA — Ischemia modified albumin; SD — standard deviation

**Table 3.** Distribution of antenatal Doppler findings in 76 newborns with intrauterine growth restriction and comparison with asphyxia and non-asphyxia pregnancies

	<b>Asphyxia Present</b>	<b>Asphyxia Absent</b>	<b>p</b>
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	(n = 27)	(n = 49)	
MCA-PI (mean ± SD)	1.1 ± 0.4	1.2 ± 0.3	0.426
MCA-S/D (mean ± SD)	3.4 ± 1.2	3.7 ± 0.9	0.272
UA-PI (mean ± SD)	0.9 ± 0.2	0.9 ± 0.3	0.445
UA-S/D (mean ± SD)	3.02 ± 1.1	2.90 ± 0.8	0.592
UA-S/D end-diastolic current loss; n (%)	3 (11.1)	3 (6.1)	0.851
C/P Ratio (mean ± SD)	1.2 ± 0.5	1.4 ± 0.5	0.333
C/P Ratio n (%)			0.747
Normal	17 (62.9)	29 (59.1)	
Abnormal	10 (37.1)	20 (40.9)	

UA — umbilical artery; MCA — middle cerebral artery; PI — pulsatility index; C/P ratio — cerebro-placental ratio; SD — standard deviation

### **Conflict of interest**

The authors have no conflicts of interest to declare.

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