

Maternal Serum Ischemia Modified Albumin Level Does Not Change In The Presence of Intrauterine Growth Restriction

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ABSTRACT

Maternal vascular hypoperfusion is the most common cause of fetal growth restriction. Maternal oxidative status features are identifiable on placental pathology, and antepartum diagnostic methods are rapidly evolving. The current study was constructed to determine the maternal oxidative status by measuring serum ischemia modified albumin (IMA) levels in pregnancies complicated with idiopathic intrauterine growth restriction (IUGR).

The current study was designed as a descriptive and cohort trial. A total of 87 pregnant women; 45 healthy controls and 42 pregnancies complicated with idiopathic IUGR were included to the study population. Maternal serum IMA concentration was measured prior to the administration of any medication. The perinatal outcomes of patients were also recorded.

Maternal serum IMA concentration in pregnancies complicated by idiopathic IUGR was higher than in healthy controls.

There was no significant difference between the groups (0.54 ± 0.04 versus 0.55 ± 0.06 ABSU, $p: 0.314$).

IUGR is a significant pregnancy complication. Elevated oxidative stress which leads to an ischemic microenvironment is associated with IUGR. Maternal serum IMA which is a possible marker for oxidative stress is not increase in pregnancies complicated with idiopathic IUGR.

Keywords: Intrauterine growth restriction, Ischemia modified albumin, Oxidative stress

Introduction

Intrauterine growth restriction (IUGR) is described as an estimated fetal weight (EFW) below 10 percentile with respect to the gestational week and appears in 7-15% of all pregnancies in the world (1,2). However, IUGR is one of the most widespread reasons for perinatal and postnatal morbidity and mortality (3). The etiology for IUGR can be summarized into two groups: Fetal causes and maternal causes. The most frequent maternal cause for IUGR is preeclampsia. Preeclampsia establishes hypoxic

and oxidative conditions for the fetus which can lead to IUGR (4). Other hypoxic and oxidative conditions like anemia, smoking, and hypertension can also give rise to IUGR (5). However, these factors are present in only 30% of all cases of IUGR. In 70% of cases, the cause of IUGR is identified as 'idiopathic', with placental insufficiency being the most common cause (6). Obstetricians use the doppler ultrasound in order to diagnose and follow-up IUGR pregnancies. Changes in the pulsatility index and resistance index of the umbilical artery during doppler ultrasound screening are the first sign for the

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fetuses' decreasing blood flow (7). Other parameters such as the APGAR score, fetal monitoring or amniotic fluid index are used to determine fetal hypoxia (5). Thus, there is any single method enabling the diagnosis of fetal hypoxia and oxidative stress on it's own. Ischemia modified albumin (IMA) is a new biomarker showing ischemia and oxidative stress (8,9). In previous studies, it has been found that IMA increases in the maternal serum and cord blood of fetuses (10,11). In this context, the present study was constructed to determine the maternal oxidative status by measuring serum IMA levels in pregnancies complicated with idiopathic IUGR.

Materials and Methods

This descriptive cohort study was planned at the Department of Obstetrics and Gynecology, Yuzuncu Yil University, spanning from January 2016 to July 2017. The Local Ethics Committee of Yuzuncu Yil University approved the study protocol. Every patient provided informed consent. A sample of 40 cases per group is required for a 2-tailed test of proportions with an alpha of 0.05 and a power of 0.80. A total of 95 pregnant women; 49 healthy pregnancies as group 1 and 46 pregnancies complicated with idiopathic IUGR as group 2 were enrolled to the study. 4 patients in group 1 and 4 patients in group 2 who had incomplete data excluded to the study. All participants were in their third trimester of pregnancy. IUGR is defined as an estimate of fetal weight less than 10th percentile for gestational age on serial fetal ultrasound scans. Gestational week was determined by the first day of the last menstrual period and confirmed by measurements taken during the first trimester ultrasonography. The patients who had preeclampsia- eclampsia, preterm rupture of membranes, gestational diabetes mellitus, renovascular disorders, sickle-cell anemia, Type 1 diabetes mellitus, collagen-vascular diseases, hereditary or acquired thrombophilia, congenital anomalies and multiple pregnancies were excluded to the study population. The study's control group consisted of pregnant women with similar gestational age, who had clinically uncomplicated pregnancies.

Each pregnant woman underwent a clinical examination and fetal assessment through obstetric ultrasound. We recorded clinical information like maternal age, gravidity, parity, gestational age, and body mass index (BMI). Following the diagnosis of IUGR, maternal serum samples were collected for IMA. The samples were promptly centrifuged at 1800 g for 10 minutes, separating plasma and serum. The serum samples were then stored at -80°C until the

analysis day. The control group's maternal serum samples were obtained during the routine prenatal care visit in the third trimester of gestation. Maternal serum samples were collected prior to the administration of any medication. Subsequently, these individuals were monitored until the time of delivery. IUGR patients were administered intramuscular betamethasone (two doses of 12mg at 24-hour intervals) for fetal lung maturation before reaching 34 weeks of gestation, following our clinic protocol. The method and timing of delivery were determined individually for each case. Cesarean section performed exclusively for obstetric indications.

We presented descriptive statistics for the studied variables in terms of mean and standard deviation. We used the Student's t-test to compare continuous variables between the two groups. The association between categorical variables was evaluated with the Chi-Square test. We considered a significance level of 5%. All statistics computed with the SPSS software (IBM SPSS Statistics for Windows, Version 22.0, released 2013, IBM Corp., Armonk, NY).

Results

A total of 87 pregnant women; 45 healthy controls (Group 1) and 42 pregnancies complicated with idiopathic IUGR (Group 2) were included to the study population (Figure 1). The clinical characteristics, obstetric outcomes and maternal serum IMA levels were demonstrated in Table 1. Group 1 and group 2 exhibited no significant difference with respect to maternal age, BMI, gravidity, parity, gestational week at sampling and route of delivery (vaginal or cesarean section) (Table 1). The group 2 had poor perinatal outcomes than group 1. Gestational week at delivery, birthweight, Apgar scores were significantly lower in group 2 (p: 0.001, p: 0.001, p: 0.001, p: 0.001, p: 0.001, respectively). NICU admission rate was significantly higher in group 2 (p: 0.001). Maternal serum IMA concentration in pregnancies complicated by idiopathic IUGR was higher than in healthy controls. However, there was no significant difference between the groups (0.54 ± 0.04 versus 0.55 ± 0.06 ABSU, p: 0.314) (Figure 1).

Discussion

The present study presented the possible association between increased OS and the development of idiopathic IUGR. We found high maternal serum IMA concentrations in pregnancies complicated by idiopathic IUGR. However, there were no significant

Table 1: The Clinical Characteristics, Laboratory Parameters and Obstetric Outcomes of The Patients

Table 1	Control group (n: 45)	Study group (n: 42)	p
Maternal age (years)	27.0±5.7	26.0±4.2	0.337*
Gravidity	2.9±1.3	2.7±1.7	0.737*
Parity	1.7±1.3	1.6±1.5	0.593*
BMI (kg/m ²)	27.6±3.9	26.5±3.4	0.175*
Gestational age at sampling (weeks)	36.6±2.9	35.6±2.3	0.063*
Vaginal delivery	17 (37.8%)	9 (21.4%)	0.096#
Cesarean-section	28 (62.2%)	33 (78.6%)	0.096#
Gestational age at delivery (weeks)	38.7±0.9	36.2±2.2	0.001*
Birthweight (g)	3240±366	2075±554	0.001*
Apgar, 1. Minute	7.3±0.9	6.0±1.5	0.001*
Apgar, 5. Minutes	8.9±0.7	7.8±1.5	0.001*
NICU admission	0	16 (38.1%)	0.001#
Maternal serum IMA (ABSU)	0.54±0.04	0.55±0.06	0.314*

*Student's t-test was used to compare continuous variables.

Chi-square test was used to compare categorical variables.

BMI: Body mass index; NICU: Neonatal intensive care unit; IMA: Ischemia Modified Albumin; ABSU: Absorbance units

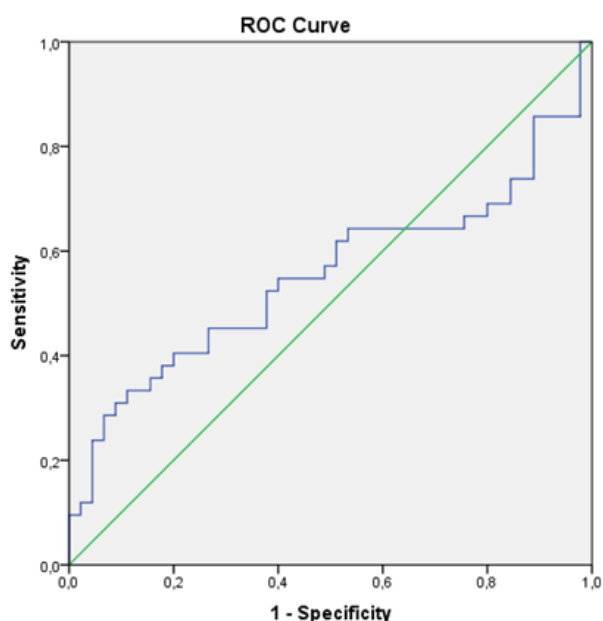


Fig. 1. The ROC analysis of maternal serum IMA levels of the patients

difference between healthy controls and idiopathic IUGR group in the third trimester of gestation.

Currently, objective clinical evidence indicates a significant association between elevated uteroplacental oxidative stress and the development of placenta-related disorders such as intrauterine growth restriction (IUGR) during pregnancy (12-15). Oxidative stress hinders the transfer of crucial neutral amino acids necessary for fetal development through the human

placenta. Additionally, it impedes the accumulation of glucose in syncytiotrophoblasts (16). Placental insufficiency can lead to the emergence of free ROS in the environment, causing oxidative stress. This is due to the balancing effect of potential antioxidant mechanisms. ROS act as second messengers in various intracellular signaling pathways to maintain homeostasis. Conversely, they have the potential to hinder the activity of diverse biological molecules such as DNA, proteins, and lipids, and may even precipitate cellular death (17). Biri et al. investigated the concentrations of malondialdehyde and xanthine oxidase in maternal plasma and placental tissue. These molecules are important in lipid peroxidation, while glutathione peroxidase plays a crucial role in antioxidant defense. This study revealed significantly elevated levels of OS markers and superoxide dismutase in pregnancies with IUGR fetuses (18). 8-Hydroxy-20-deoxyguanosine is a hydroxylated product of deoxyguanosine that forms during DNA damage in the presence of oxidative stress. Takagi et al. reported a significant elevation in the placental concentrations of this molecule in cases of IUGR and IUGR with preeclampsia (13). IUGR is defined by hindered fetal growth and impaired transport of nutrients across the placenta. IUGR is caused by a chronic ischemic-hypoxic microenvironment that disrupts the vascular system. As discussing above, there have been several biomarkers for oxidative stress in pregnancy, such as IMA. Gursoy et al. recently

conducted a study which demonstrated elevated cord blood IMA levels in cases of intrauterine hypoxia and birth asphyxia (19). Karadeniz et al. demonstrated an increase in IMA levels in IUGR fetuses and suggested its potential as a marker for perinatal hypoxia and IUGR detection (20). Guvendag-Guven ES et al. also demonstrated a positive correlation between abnormal Doppler blood flow and OS markers, including cord blood IMA (21). However, there are confusing results in the literature. In contrast to these studies, Lacovidou et al. found no significant differences in IMA levels between IUGR and AGA fetuses (22). In our study, maternal serum IMA levels were higher in idiopathic IUGR group, however there was no significant difference between the groups, similar with Lacovidou et al.'s study.

There are several limitations in our study. Firstly, our sample size was relatively small, which limited the comprehensiveness of our data. Second, serum IMA levels were not measured in these pregnant women prior to pregnancy. So, the pre-conceptional status of OS was unknown. Third, although the patients in both groups had similar gestational ages; maternal serum IMA levels may change throughout pregnancy as a possible manifestation of placental development. Hence, even a small variance in gestational weeks could potentially influence the outcomes and data obtained. To minimize this confounding variable, we recruited only pregnant women in their third trimester of gestation to the study. Fourth, the other studies evaluated cord blood and maternal serum IMA levels both, we only focused on maternal serum IMA levels in the present study. We chose this design to find possible confounding factors in maternal circulation among IUGR cases.

To summarize, considering that IUGR is a significant pregnancy complication, it is probable that it is linked to various pathophysiological mechanisms. Hypoxia and factors that elevate OS, leading to an ischemic microenvironment, such as placental insufficiency, are associated with IUGR. Maternal serum IMA which is a biomarker for OS is increased among pregnancies complicated by IUGR in above mentioned studies. However, our study showed that maternal serum IMA levels are similar in pregnancies with and without idiopathic IUGR. Designing follow-up studies in the early stages of gestation are recommended to assess the correlation between maternal serum IMA concentration and the development of IUGR in high-risk pregnancies. Additional research involving larger sample sizes is required to establish conclusive evidence on this subject.

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