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Role of Inflammation Markers and Osteopontin in the Prediction of Fetal Stress

Fetal Distresde Osteopontin ve Enflamasyon Markerlarının Rolü

Betül Tokgöz Çakır, Hande Esra Koca, Elif Akkaş Yılmaz, Tuncay Küçüközkan

Department of Obstetrics and Gynecology, University of Health Sciences Türkiye, Dr. Sami Ulus Women's and Children's Health Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Objective: To determine the possible association between acute fetal stress during labor and maternal blood levels of osteopontin (OPN), white blood cells, sedimentation, and C-reactive protein (CRP).

Methods: The study included women with a term pregnancy (37 weeks or more) who had a cesarean section during the active phase of labor. The study included 30 term pregnancies who underwent cesarean section for fetal distress and 30 pregnant women who underwent cesarean section for other indications (prior uterine surgery, head-pelvis incompatibility, large baby, non-progressing plot) as a control group. The levels of OPN and other inflammatory markers (leukocytes, sedimentation, CRP) in the maternal venous blood of 60 pregnant women were compared, and whether there was a significant association between the groups was investigated.

Results: OPN levels in the fetal stress group were higher than those in the control group, and the difference was statistically significant (p=0.008). There was no statistically significant difference in white blood cell, blood sedimentation, and CRP levels between the two groups (p>0.005).

Conclusion: Placental inflammation plays a role in the etiology of fetal stress, and OPN may be released because of fetal stress. The increase in OPN in maternal blood during labor may be an important marker for predicting fetal stress.

Keywords: CRP, C-section, fetal distress, leukocyte count, osteopontin

ÖZ

Amaç: Doğum sırasında akut fetal stres ile anne kanındaki osteopontin (OPN), beyaz kan hücreleri, sedimantasyon ve C-reaktif protein (CRP) seviyeleri arasındaki olası ilişkiyi belirlemektir.

Yöntemler: Çalışmaya term gebeliği (37 hafta ve üzeri) olan ve doğumun aktif fazında sezaryen olan kadınlar dahil edildi. Çalışmaya fetal distres nedeniyle sezaryen uygulanan 30 term gebelik ve diğer endikasyonlar (geçirilmiş uterin cerrahi, baş-pelvis uyumsuzluğu, büyük bebek, ilerlemeyen eylem) nedeniyle sezaryen yapılan 30 gebe kontrol grubu olarak alındı. Altmış gebenin maternal venöz kanında OPN ve diğer inflamatuar belirteçlerin (lökosit sayısı, sedimantasyon, CRP) düzeyleri karşılaştırıldı ve gruplar arasında anlamlı bir ilişki olup olmadığı araştırıldı.

Bulgular: Fetal stres grubunda OPN düzeyleri kontrol grubuna göre daha yüksekti ve aradaki fark istatistiksel olarak anlamlıydı (p=0,008). İki grup arasında lökosit sayısı, sedimentasyon ve CRP düzeylerinde istatistiksel olarak anlamlı fark yoktu (p>0,005).

Sonuç: Plasental inflamasyon fetal stresin etiyolojisinde rol oynar ve fetal stres nedeniyle OPN salınabilir. Doğum sırasında anne kanındaki OPN artışı, fetal stresi tahmin etmede önemli bir belirteç olabilir.

Anahtar Sözcükler: CRP, sezaryen, fetal distres, lökosit sayısı, osteopontin

Address for Correspondence/Yazışma Adresi: Betül Tokgöz Çakır, MD, Department of Obstetrics and Gynecology, University of Health Sciences Türkiye, Dr. Sami Ulus Women's and Children's Health Training and Research Hospital, Ankara, Türkiye
E-mail / E-posta: btltkgz@gmail.com
ORCID ID: orcid.org/0000-0003-0202-4981

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INTRODUCTION

Fetal distress is a pathophysiologic condition in which fetal oxygen is not available in sufficient quantity (1). Fetal hypoxia can lead to permanent fetal damage or death if not corrected or if emergency delivery is not performed. When a clinical diagnosis of fetal distress is made, physicians aim for rapid delivery because they cannot clearly determine the severity of hypoxia (2). There are antepartum and intrapartum markers of fetal distress, such as abnormal fetal heart rate (recurrent late decelerations, wavy baseline bradycardia), decreased blood oxygen pressure (pO_2) in fetal blood, meconium staining of amniotic fluid, lactate increase in fetal scalp, and low pH (3-5). The diagnosis of postpartum fetal distress was based on low pH in cord blood, worsening Apgar score (6,7), and other parameters (8,9). The negative predictive value of the tests used for antepartum assessment (fetal movements, fetal heart rate, fetal respiration, and amniotic fluid) is 99.8%, whereas the positive predictive value ranges from 10% to 40% (6). This means that the fetus is not always under stress when the test is positive.

The body's first response to the immunological phase is the innate, non-specific response that precedes the specific immune response. The acute phase response is a systemic response to local or systemic disturbances of homeostasis due to infection, tissue damage, trauma or surgery, neoplastic growth, or immunologic disturbances (10). When tissue is damaged, the tissue itself triggers a series of responses. Pro-inflammatory cytokines are released, and the vascular system and inflammatory cells are activated. These reactions are in turn associated with the production of additional cytokines and other inflammatory mediators, which are distributed in the extracellular fluid and enter the bloodstream (11). The most important of these acute-phase reactors are the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and ferritin. While ESR and CRP are most commonly used, fibrinogen and ferritin are rarely used (11).

Osteopontin (OPN) is a phosphorylated and glycosylated protein found in various biological fluids (12,13). It is found in the epithelial cells of the bile duct, pancreas, lung, sweat glands, placenta, gastrointestinal tract, urinary tract, breast, and reproductive system. Because OPN is released from the epithelium at the sites of contact between the embryo and uterus during pregnancy, it is believed to be able to communicate between the placenta and uterine tissue to support pregnancy (14,15).

The purpose of this study was to determine if there is a relationship between fetal stress, OPN, white blood cell (WBC) count, sedimentation, and CRP levels measured in maternal venous blood during active labor.

MATERIALS AND METHODS

This prospective cross-sectional study included pregnant women who underwent cesarean section for fetal distress and indications other than fetal distress. The study was conducted at Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Türkiye, according to the principles of the Declaration of Helsinki. Institutional Review Board approval was obtained before the start of the study, and mothers provided signed informed consent [Ankara Etlik Zübeyde Hanım Gynecology Traning and Research Hospital Ethics Committee; (approval number: 2017/7, date: 13.09.2017)].

Sixty pregnant women with a gestational age of 37 weeks participated in the study. Of these, 30 were delivered by cesarean section when signs of fetal distress were present. The other 30 cases were pregnancies delivered by cesarean section for reasons other than fetal distress (previous uterine surgery, head-pelvis incompatibility, large baby, and breech presentation). Cesarean section was performed during active labor in all patients. Fetal distress was confirmed by fetal meconium staining, an APGAR score of 6, acidotic cord blood, or the need for neonatal intensive care.

The levels of OPN and other inflammatory markers (leukocytes, sedimentation, CRP) in the venous blood of pregnant women were compared, and whether there was a significant association between these markers and fetal distress was investigated. Women between the ages of 20 and 40 years who had a singleton pregnancy participated in the study. Pregnant women with obstetric complications (gestational diabetes, preeclampsia/eclampsia) or chronic systemic diseases (thyroid dysfunction, diabetes, hypertension, chronic kidney/heart disease) were excluded from the study. In total, 15 mL of venous blood from the patients was divided into three equal parts. Two venous blood samples were collected in EDTA tubes for the measurement of CRP and OPN, and one venous blood sample was collected for the measurement of blood sedimentation. Serum was separated by centrifugation and stored at -80 °C until analysis. Plasma concentrations of OPN and CRP were measured using ELISA. At the end of the ELISA study, the CRP and OPN levels of each serum sample were calculated using the optical density values of known calibrators.

Serum OPN levels in participants' samples were analyzed using the Elabsiciens Human OPN ELISA Kit from Atlas Biotechnology Laboratory. At the hospital, leukocyte dissection and laser and total leukocyte electrical impedance measurements were performed using the Beckman Coulter LH 780 automated blood counter. Western blotting was used to measure blood sedimentation. The birth dates of pregnant women (cesarean indication, week of gestation) were obtained from delivery room records, and the results were recorded by the researchers along with the values of OPN, CRP, leukocytes, and blood sedimentation.

Primary outcome measures, levels of maternal OPN, and other inflammatory markers will be the success rate in predicting fetal distress; secondary outcomes will be age, gestational week, and birth weight of women who underwent cesarean section for fetal distress and women who underwent cesarean section outside this indication.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 20). Frequency tables were used to interpret the results. Variables were examined using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov test/Shapiro-Wilk test) to determine whether or not they were normally distributed. Descriptive analyses were performed using means and standard deviations for normally distributed variables, and medians and quartiles (Q1-Q3) were used for numerical data that were not normally distributed. The Mann-Whitney U test and Student's t-test were performed to compare

parametric variables in the two groups with and without normal distribution, respectively. The levels of OPN and other inflammatory markers (leukocytes, sedimentation, CRP) in the venous blood of pregnant women were compared, and whether there was a significant association between these markers and fetal distress was investigated. The statistical significance level was set at 0.05 for all analyses.

RESULTS

A total of 60 pregnant women were included in the study. Thirty pregnant women underwent cesarean section with the indication of fetal distress and 30 pregnant women underwent cesarean section without the indication of fetal distress. Cesarean indications included 2 (6%) head-pelvis incompatibility, 4 (14%) non-progressive measures, 3 (10%) breech presentation, 3 (10%) large infants, and 18 (60%) old cesarean sections. The characteristics of the patients and their dates of birth are shown in Table 1. Between the two groups, the WBC count, blood sedimentation (p=0.07), and CRP (p=0.85) levels were not statistically significant (p>0.005). There was a significant difference in OPN levels between the two groups (p=0.006) (Table 2).

DISCUSSION

Currently, efforts are being made worldwide to reduce the number of births by cesarean section. Fetal distress and failure of labor to progress are the most common indications for cesarean section, unless the uterus has been previously operated on (16,17). Previous studies have identified several biomarkers to predict fetal distress, including fetal heart rate patterns, umbilical artery pH, and lactate levels. There are studies suggesting that fetal complications are more common in pregnant women with non-reactive NST results; therefore, NST should be routinely performed as a valuable diagnostic test in the prenatal period (18). In addition to NST, biophysical scores (fetal movements, fetal heart rate, fetal respiration, amniotic fluid, and NST), modified biophysical scores (amniotic fluid and NST), and various Doppler parameters (umbilical artery, fetal cerebral artery, ductus venosus) are used to assess fetal well-being. Numerous studies in the literature question the reliability of these tests. However, a test with high positive and negative predictive values that could be an alternative to these tests has not yet been found.

ESR, CRP, and WBC count are commonly used markers of inflammation. In this study, we measured maternal serum OPN levels in addition to these markers. We hypothesized that they might increase in maternal serum because of possible inflammation of the placenta during fetal stress. OPN plays an important role in inflammation, biomineralization, cell viability, and wound healing. In addition, OPN is also known to be released from the placenta. OPN is thought to increase inflammation in acute and chronic inflammatory diseases by contributing to the proliferation of macrophages and T cells in areas of inflammation (19).

In our study, we found that blood sedimentation, CRP, and WBC levels, which are known to increase during normal pregnancy (20,21), did not increase more in maternal blood during fetal distress. In their studies evaluating the diagnostic value of chorioamnionitis, Amirabi et al. (22) examined 71 pregnant women with early rupture of membranes for CRP, ESR, and WBC but emphasized that the diagnostic value of ESR was minimal. In contrast to these studies, Nowak et al. (23), in their work with 80 pregnant women, considered that CRP is the most reliable indicator of histological chorioamnionitis and that it may be able to diagnose intrauterine infection earlier than WBC or ESH. However, in our study, no significant association was found between CRP levels and fetal distress. These parameters, whose levels increased in chorioamnionitis, did not increase in acute fetal distress during the active phase. In contrast to chorioamnionitis, it can be assumed that fetal distress is not only of placental origin, but that both fetal and maternal causes contribute to this condition.

Numerous studies have been conducted in the literature using various biomarkers to predict fetal distress. Bligh et al. (24) found in their study of 438 pregnant women that low placental growth factor was associated with low birth weight, cesarean section due to fetal

Table 1. Patients' characteristics

Variable	Fetal distress (n=30)	Control group (n=30)	p-value
Maternal age median (Q1-Q3)	26 (25-30.2)	29.5 (24-33)	0.32
BMI (kg/m^2) median (Q1-Q3)	28.4 (26.3-31)	28.1 (26-29.9)	0.56
Birth week (week) median (Q1-Q3)	39.5 (38-41)	39 (38-39)	0.07
Birth weight (gram) (mean ± SD)	3,336±458	3,273±414	0.57

Data are presented as median (Q1-Q3) or mean ± standart deviation. A p-value of <0.05 indicates a significant difference. BMI: Body mass index, SD: Standard deviation.

Table 2. Examination of the values taken from maternal venous blood according to cesarean status

Variable (n=60)	Cesarean birth		p-value
	Fetal stres (n=30)	Control (n=30)	
Sedimentation (mm/h); median (Q1-Q3)	27 (20-40)	30 (24.7-48.5)	p=0.07
CRP (mg/dL); median (Q1-Q3)	8.6 (4.7-12.7)	7.9 (4.9-13.1)	p=0.85
WBC (mcL); (mean **±** SD)	14.3±4.1	12.6±4	p=0.11
OPN (ng/mL); median (Q1-Q3)	21.9 (20.8-23.3)	20.3 (18.3-22.3)	**p=0.006**

Data are presented as median (Q1-Q3) or mean **±** standart deviation. A p-value of <0.05 indicates a significant difference. Statistically significant p values are in bold. CRP: C-reactive protein, WBC: White blood cell, OPN: Osteopontin.

risk, and poor neonatal outcome. Knight et al. (25) distinguished between weeks of gestation and SLC9B1 methylation in venous blood samples from pregnant women and found that the fetal burden could be estimated. In our study, we found that OPN levels were elevated in the blood of pregnant women who underwent cesarean section for fetal distress before term. Considering the functions of OPN, this situation can be explained by the increased expression of OPN in the placenta during fetal distress.

Plasma OPN concentrations increase in patients with preeclampsia and endothelial damage (26). A study in mice has shown that OPN is required for the initiation of inflammation (27). OPN is known to play a role in biomineralization, inflammation, dystrophic calcification, wound healing, granulomatous formation, fibrosis, nitric oxide regulation, tumor metastasis, and maintenance of cell viability (28).

In their studies of human and mouse placentas, Gabinskaya et al. (29) demonstrated that OPN and fibronectin are expressed in functioning placental compartments. Thus, we can conclude that OPN expression increased in the functional placenta during acute fetal distress and was significantly higher in our study. However, an increase in other inflammatory markers (WBC, ESR, CRP) might be required for chronic inflammatory processes. Therefore, we hypothesized that although OPN levels were higher in the fetal distress group than in the control group, no significant changes were observed in other parameters.

OPN is critical to successful pregnancy. It was observed that the expression levels of natural decidual cells (dNK) and OPN were low, especially in women with repeated pregnancy loss (30). At the same time, OPN levels in cord blood were also measured, and OPN was found to play a physiological role in fetal growth and development (31).

Study Limitations

A limitation of the study is that only a few patients participated in the study, and a larger population is needed on this topic. Because of technical and financial difficulties, we could not measure OPN levels in cord blood. More accurate information can be obtained from OPN measurements from cord blood and maternal blood. We believe that further studies on the functions of OPN during pregnancy are needed.

In our study, we found that OPN was significantly higher in the venous blood of pregnant women who developed fetal distress than in the control group. We believe that OPN may be a useful biomarker for predicting fetal distress.

CONCLUSION

Placental inflammation plays a role in the etiology of fetal distress, and OPN may be released because of fetal distress. We hypothesize that the increase in OPN in maternal blood during labor may be an important marker for predicting fetal distress. Further research on this topic is needed because the mechanisms contributing to the increase in OPN during fetal distress are not yet known; therefore, this increase may be used in predicting fetal distress in the clinical setting.

Ethics

Ethics Committee Approval: Institutional Review Board approval was obtained before the start of the study [Ankara Etlik Zübeyde Hanım Gynecology Traning and Research Hospital Ethics Committee; (approval number: 2017/7, date: 13.09.2017)].

Informed Consent: Mothers provided signed informed consent.

Author Contributions

Concept: B.T.Ç., H.E.K., E.A.Y., T.K., Design: B.T.Ç., H.E.K., E.A.Y., T.K., Data Collection or Processing: B.T.Ç., H.E.K., E.A.Y., T.K., Analysis or Interpretation: B.T.Ç., H.E.K., E.A.Y., T.K., Literature Search: B.T.Ç., H.E.K., E.A.Y., T.K., Writing: B.T.Ç., H.E.K., E.A.Y., T.K.

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