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THE EFFECT OF PREOPERATIVE ANXIETY ON FETAL CORD BLOOD TUMOR NECROSIS FACTOR-ALPHA, INTERLEUKIN-6, AND NEONATAL OUTCOMES IN PREGNANT WOMEN

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SUMMARY

Backgrounds: *In this study, we aimed to investigate the relationship in pregnant women who undergo elective cesarean section between the preoperative anxiety (POA) levels and neonatal results and TNF-α, IL-6 and IL-8 levels, the pro-inflammatory cytokines in cord blood.*

Subjects and methods: *Sixty-six volunteer patients, aged 18 to 40, who underwent elective cesarean surgery were included in the study. Trait Anxiety Inventory (TAI) was evaluated at the anesthesia outpatient clinic and State Anxiety Inventory (SAI) was determined one hour before cesarean section. Plasma levels of TNF-α, IL-6 and IL-8 in the umbilical cord blood were determined using the ELISA method. Fetal cord blood gas, birth weight, and APGAR scores at the 1st and 5th minutes after birth were recorded.*

Results: *The mean preoperative maternal SAI and TAI scores were 46.6±10.9 and 41.4±7.8, respectively. There was a significant correlation between POA and fetal birth weight and fetal cord blood TNF-α, IL-6 and IL-8 parameters. The inflammatory marker levels in the cord blood of fetuses in the high anxiety groups were significantly higher ($p<0.001$). Fetal birth weight was significantly lower in the high anxiety groups ($p<0.05$), whereas there was no significant difference in cord blood gas values.*

Conclusions: *Our results show that an increase in the levels of TNF-α, IL-6, and IL-8 cytokines in fetal cord blood in pregnant women with high anxiety levels and this situation causes negative effects on the newborn.*

Key words: *birth outcomes - fetal cord blood - interleukin-6 - preoperative anxiety - tumor necrosis factor-alpha*

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INTRODUCTION

Preoperative anxiety (POA) is a common problem that causes negative physiological responses in preoperative patients and is more commonly encountered in pregnant patients who are about to deliver a baby via cesarean section (Akildiz et al. 2017, Badner et al. 1990). Patients with indications for elective cesarean surgery may exhibit anxiety symptoms such as high levels of tension, anxiety and even panic attacks in the preoperative period (Van den Bergh et al. 2005). These symptoms cause neuroendocrine system activation resulting in increased heart rate, blood pressure and cardiac stimulation due to high catecholamine discharge in patients (Akildiz et al. 2017, Van den Bergh et al. 2005).

Prenatal maternal stress has been shown to cause several negative clinical outcomes, such as preterm birth, low birth weight, low APGAR scores, and cognitive and behavioral problems (Van den Bergh et al. 2005, Pimenta et al. 2016, Ding et al. 2014). Autonomic stress response triggered by maternal anxiety may cause negative neonatal outcomes due to uterine artery vasoconstriction (Ding et al. 2014). In addition, various studies have reported that maternal anxiety affects fetal brain circulation, causing some physical disorders and epigenetic changes (Entringer et al. 2013).

The biological mechanism responsible for the negative consequences of maternal anxiety has not been clearly demonstrated (Van den Hove et al. 2006). Cytokines are thought to be one of the possible mechanisms (Glover et al. 2014). In experimental and clinical studies, cytokines have been shown to produce neurochemical, neuroendocrine, and neuroimmune changes by sending signals to the brain (Glover et al. 2014). Physical or psychological stress can also cause negative consequences as a result of triggered neuroinflammation and cytokine expression (Zavala 1997, Coussons-Read et al. 2012). In addition, anxiolytic benzodiazepines were shown to protect against this stress-induced immunosuppression (Zavala 1997).

Tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) are the most researched cytokines in neuropsychiatric disorders and have been shown to be associated with psychosocial stress (Coussons-Read et al. 2012). The negative effects of TNF-α elevation on embryological and adult neurogenesis have been demonstrated by in vitro studies (Van den Hove et al. 2006, Coussons-Read et al. 2012, Thorngren-Jerneck &

Herbst 2001). The awareness of the clinical significance of cytokines has increased in perinatal medicine and has been an area of interest for researchers.

The relationship between psychiatric disorders experienced during pregnancy and the fetus has been demonstrated in many studies (Van den Bergh et al. 2005, Pimenta et al. 2016, Ding et al. 2014, Entringer et al. 2013, Glover et al. 2014). However, studies on the effect of POA prior to cesarean section on neuroimmunological marker levels regarding the fetus are limited. In this study, we investigated the relationship in pregnant women who undergo elective cesarean section between the POA levels and birth results and TNF-α, IL-6 and IL-8 levels, the pro-inflammatory cytokines in cord blood.

SUBJECTS AND METHODS

Study population and ethics

This prospective observational study was carried out between February 1 and May 15, 2020 in the Medical Faculty Hospital of Bozok University (a tertiary medical center in Turkey).

Sixty-six volunteer patients, aged 18 to 40, who gave written informed consents and underwent elective cesarean surgery were included in the study. Patients with a known psychiatric or neurological disease, drug users, patients who did not have the mental competence to understand the survey questions or were illiterate, patients scheduled to undergo an emergency cesarean operation, urgent patients, patients with fetal anomaly, fetal growth retardation, meconium aspiration or congenital anomaly were not included in the study. Ethics committee approval of this study was given by the local ethics committee (reference number: KAEK-189_2019.10.30_08, date: September 30, 2019) and recorded at clinicaltrials.gov with the following code: NCT04226573.

Procedures

Anxiety levels in patients who were referred to an anesthesia outpatient clinic due to elective cesarean section were evaluated using the Trait Anxiety Inventory (TAI). Preoperative instantaneous anxiety level was determined using the State Anxiety Inventory (SAI) scale one hour before cesarean section. Maternal demographic and medical data were recorded for prenatal evaluation. The gestational week was calculated based on the ultrasound imaging performed during the first trimester by the obstetrics department. Following delivery, cord blood gas, birth weight, and APGAR scores at the 1st and 5th minutes were recorded. The health status of the newborns was evaluated using the 10-point APGAR score, which evaluates five parameters (heart rate, respiratory effort, muscle tone, reflex irritability and color) with a score from 0 to 2. A total score of 7 or higher suggests that the newborn is in good health, while a total score of 4 to 6 means the newborn needs medical attention, and scores of 3 or lower indicate a critical condition (Thorngren-Jerneck & Herbst 2001).

Preoperative anxiety assessment

The TAI scale (20 items) determines how the individual feels, regardless of the situation and conditions the individual is in. The SAI scale (20 items) determines how the individual feels at a certain time and under certain conditions. Both scales are scored between 20 and 80 points, where higher scores indicate a higher level of anxiety. The SAI and TAI are widely used to assess anxiety in pregnancy, and their validity and reliability have been demonstrated (Nast et al. 2013). In the evaluation of the scale scores, 40 points was considered the threshold value, as is common in the literature (Bayrak & Sancak 2020), scores below 40 were classified as 'low to moderate' anxiety, and scores above 40 were classified as 'high' anxiety. Psychiatry consultation was requested for patients who exhibited high anxiety.

Analysis of TNF-α, IL-6 and IL-8 assays of cord blood

Immediately after birth, a 5 mL blood sample was taken from the umbilical cord. Blood was centrifuged for 5 minutes and serums were stored at -80°C until patient samples were completed. Plasma levels of TNF-α, IL-6 and IL-8 in the cord blood were determined using anti-human TNF-α and IL-6 enzyme-linked immunosorbent assay (ELISA) kits (Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's recommendations. Measurements of the ELISA kits were carried out using an ELISA microplate reader (SPECTROstar Nano; BMG LABTECH, Ortenberg, Germany). All samples were subjected to repeated trials.

Statistical Analysis

Data were analyzed using SPSS v.20.0 (SPSS Inc., Chicago, IL, USA) software. Data were expressed as mean±standard deviation. Variable distribution normality was tested using the Kolmogorov-Smirnov test. Variables that exhibited normal distribution among the maternal anxiety groups were compared using the independent samples t-test, those without normal distribution were evaluated using the Mann-Whitney U test, and categorical variables using the chi-square test. Correlations between cord blood cytokine levels and other variables were analyzed using the Spearman's correlation test for non-normally distributed variables and the Pearson distribution for normally distributed variables. A multivariate linear regression model was used to identify independent predictors (SAI, TAI, smoking history) of fetal birth weight. The results were considered statistically significant at $p<0.05$.

RESULTS

Of the 80 pregnant women who underwent caesarean section with spinal anesthesia, 14 were excluded from the study because of missing questionnaire results and extreme measurement values. A total of 66 pregnant women were included in the study. Maternal-neonatal characteristics and inflammatory marker levels according to the state and trait anxiety levels of the study population are shown in Table 1.

Maternal characteristics

The mean age of the patients was 30.4±6.2 years, and the mean TAI and SAI scores were 41.4±7.8 and 46.6±10.9, respectively. Table 1 provides detailed information on the differences between women with and without high anxiety. There was no statistically significant difference between the TAI groups and between the SAI groups in terms of gestational age, gravidity, parity, education level, work status, smoking history, anesthesia history (p>0.05) (Table 1).

Newborn features

Gestational age of the newborns were similar between the anxiety groups (p>0.05). There was a significant correlation between maternal anxiety and fetal birth weight and fetal cord blood TNF-α, IL-6 and IL-8 parameters (Table 2). Fetal birth weight was significantly correlated by TAI and SAI (p=0.02 and p=0.03, respectively). There was no significant relationship between TAI scores and APGAR scores (p=0.13), whereas a significant relationship was detected between SAI scores and APGAR scores at the 1st (p=0.001) and 5th minutes (p=0.004) scores. No significant correlation was found between fetal cord blood gas values and maternal anxiety groups. In addition, the birth weight of fetuses of smoker mothers was lower (p=0.05). In addition, in multivariate regression analysis, fetal birth weight was not affected from SAI and smoking (respectively: p=0.239, beta = -156; p=0.61, beta = 215). On the other hand, only TAI variable (p=0.026, beta = -300) was found to have a significant effect on fetal birth weight.

Table 1. Characteristics of the mother and the newborn according to maternal anxiety groups

	Low-intermediate state anxiety (SAI) (*n*=22)	High state anxiety (SAI) (*n*=44)	*p*	Low-intermediate trait anxiety (TAI) (*n*=36)	High trait anxiety (TAI) (*n*=30)	*p*
Maternal characteristics						
Maternal age (mean±SD; years)	30.00±6.06	30.83±6.44	0.59‡	30.27±5.15	30.43±6.72	0.92‡
Gravidity (mean±SD)	3.24±1.4	3.08±1.3	0.73*	3.36±0.27	3.18±0.22	0.44*
Parity (mean±SD)	1.74±1.02	1.52±0.6	0.39*	1.95±0.24	1.64±0.14	0.34*
Education level n (%)			0.19*			0.16*
Primary school	14 (63.6)	33 (75)		23 (63.9)	24 (76.7)	
High school	3 (13.6)	6 (13.6)		7 (19.4)	2 (6.7)	
University	5 (22.7)	5 (11.4)		6 (16.7)	4 (13.3)	
Smoking history n (%)	5 (22.7)	12 (27.3)	0.69**	7 (19.4)	10 (33.3)	0.19**
Work status n (%)			0.51**			0.72**
Housewife	17 (77.3)	37 (84.1)		30 (83.3)	24 (80.0)	
Employee	5 (22.7)	7 (15.9)		6 (16.7)	6 (20.0)	
Anesthesia history n (%)	17 (77.3)	35 (79.5)	0.83**	29 (80.6)	23 (76.7)	0.70**
Newborn characteristics						
Gestational age (mean±SD; weeks)	38.45±1.0	37.89±0.8	0.53*	38.18±0.19	38.11±0.15	0.88*
Fetal birth weight (mean±SD; grams)	3302±381	3078±438	0.03‡	3361±414	3120±404	0.02‡
APGAR score 1st (mean±SD)	8.34±0.9	7.94±0.9	0.001*	8.32±0.8	7.98±0.9	0.13*
APGAR score 5th (mean±SD)	9.48±0.6	9.11±0.6	0.004*	9.45±0.5	9.16±0.7	0.13*
pH value (mean±SD)	7.33±0.04	7.32±0.06	0.54*	7.31±0.6	7.33±0.5	0.13*
$PaCO_2$ level (mmHg) (mean±SD)	42.44±5.39	43.01±8.64	0.26*	44.13±7.4	42.08±7.2	0.55*
HCO_{-3} level (mmol/L) (mean±SD)	21.73±2.08	21.18±2.69	0.35‡	21.73±2.06	21.36±2.55	0.55‡
Lactate level (mmol/L) (mean±SD)	2.45±0.99	2.24±0.73	0.95*	2.30±0.80	2.35±0.89	0.79*
Basal inflammatory markers						
TNF-α (mean±SD; pg/ml)	27.90±9.30	39.29±8.19	<0.001‡	26.55±10.20	36.34±9.07	<0.001‡
IL-6 (mean±SD; pg/ml)	2.08±0.80	2.66±0.77	0.002‡	2.01±0.77	2.50±0.82	0.01‡
IL-8 (mean±SD; pg/ml)	11.38±3.00	12.55±2.90	0.01‡	10.74±3.24	12.50±2.71	0.02‡

*Mann-Whitney U test; **chi-square test; ‡independent samples t-test; HCO_{-3} - bicarbonate; IL-6 - interleukin 6; IL-8 - interleukin 8; ml - milliliters; $PaCO_2$, - partial carbon dioxide; pg - pictograms; TNF-α - tumor necrosis factor alpha

Table 2. Correlation between preoperative anxiety levels, fetal birth weight and umbilical cord blood inflammatory cytokine levels

		TNF-α level	IL-8 level	IL-6 level	Birth weight	SAI score
IL-8 level	*r*	0.232				
	p	0.061				
IL-6 level	*r*	0.485**	0.158			
	p	*<0.001*	0.206			
Birth weight	*r*	-0.354**	-0.140	-0.281*		
	p	*0.004*	0.262	*0.022*		
SAI score	*r*	0.576**	0.441**	0.424**	-0.328**	
	p	*<0.001*	*<0.001*	*<0.001*	*0.007*	
TAI score	*r*	0.505**	0.360**	0.297*	-0.394**	0.523**
	p	*<0.001*	*0.003*	*0.016*	*0.001*	*<0.001*

IL-6, interleukin-6; IL-8, interleukin 8; SAI, state anxiety inventory; TAI, trait anxiety inventory; Significant p values are written in bold; *Significantly correlated at p<0.05 level (two-tailed); **Significantly correlated at p<0.01 level (two-tailed).

Basal inflammatory markers

The average IL-6, IL-8, TNF-α concentrations in the fetal cord blood of the high anxiety SAI and TAI groups are given in Table 1. The inflammatory marker levels in the cord blood of fetuses in the high anxiety groups were significantly higher, with the most affected parameter being the TNF-α level (p<0.001). In analyzing to cytokine levels, SAI anxiety levels were correlated with TNI-α (p=0.000, r=0.576), IL-6 (p=0.000, r=0.424), IL-8 (p=0.000, r=0.441), and fetal birth weight (p=0.007, r=-0.328) and TAI anxiety levels were correlated with TNF-α (p=0.000, r=0.505), IL-6 (p=0.016, r=0.297), IL-8 (p=0.013, r=0.360), and fetal birth weight (p=0.001, r=-0.394) (Table 2). In addition, regardless of maternal anxiety levels, no statistically significant difference was observed between fetal cord cytokine levels and fetal sex and maternal smoking status (p>0.05).

DISCUSSION

While many studies have shown that maternal anxiety during pregnancy is an important factor in fetal development and can cause negative perinatal outcomes (Ding et al. 2014), others have suggested that maternal anxiety is not associated with negative perinatal outcomes (Thorngren-Jerneck & Herbst 2001), leaving the issue unclear.

Previous studies have generally focused on the neonatal outcomes of chronic maternal anxiety (Hosseini et al. 2009) and studies investigating the effect of preoperative instantaneous anxiety on cytokine levels and birth outcomes are limited. With this observational study, we found that maternal POA level in cesarean delivery had a significant relationship with fetal cord blood inflammatory marker levels, birth weight and APGAR scores. Our results support the findings of previous studies on immune change with maternal anxiety.

Preoperative anxiety in pregnant women who undergo elective cesarean delivery are observed at a high level depending on surgical or anesthetic procedures (Akildiz 2017). Consistent with previous studies (Beilin et al.1996), we found that pregnant women had a high anxiety level (SAI ≥40 in 66.7% of the patients) in the preoperative period.

It is important that the pregnant individual's immune, endocrine and nervous system be in a sensitive balance for the continuity of maternal and fetus health during normal pregnancy, disruption of this balance may cause negative effects on the fetus (Coussons-Read et al. 2010). Elective cesarean delivery can affect this balance as a strong source of stress, causing an excessive immune response in both mothers and newborns (Coussons-Read et al. 2010). It has been shown that there is a link between maternal anxiety and cytokines (TNF-α, IL-6, IL-8) and central nervous system development. It is assumed that stress-induced neurochemicals affect the inflammatory markers by crossing the placental and fetal blood-brain barrier (Van den Hove et al. 2006, Coussons-Read et al. 2010, Beilin et al. 1996). Apart from this mechanism, maternal stress hormones (glucocorticoids) also cause negative results on feto-placental function (Ghaemmaghami et al. 2014) and may lead to a decrease in uterine blood flow (Ding et al. 2014).

It has been reported that acute and chronic (continuous) stress triggers cytokine release in pregnant women, and negative results are most common in pregnant women with chronic anxiety (Hosseini et al. 2009). In a study of 560 newborns exposed to constant maternal stress (economic distress, social pressure, poor housing conditions), increased IL-8 and TNF-α levels were detected in fetal cord blood (Wright et al. 2010). In another study, it was reported that low birth weight due to high anxiety was increased towards the last trimester (Hosseini et al. 2009). On contrary, a significant relationship was noted between both anxiety groups and cytokine levels in our study, with the SAI level being higher. Andersson et al. reported that there was no relationship between fetal cord blood cytokine levels and SAI levels but a significant relationship with TAI

levels (Andersson et al. 2016). The authors also stated that IL-1β, IL-4, IL-5, IL-6 and IL-8 cytokines were associated with maternal anxiety (related to Th2 humoral immunity), but there was no significant relationship between IL-12 and TNF- α and maternal anxiety. In another study, Konuk et al. reported a significant increase in TNF-α and IL-6 levels in pregnant women with anxiety disorders compared to healthy controls (Konuk et al. 2007).

Although there are studies in the literature stating that there is no relationship between maternal anxiety and APGAR scores (Andersson et al. 2004), others report that maternal anxiety causes low APGAR scores (Ding et al. 2014). In our study, we observed that the APGAR scores of the newborns of the mothers with a high preoperative SAI scores were low, whereas APGAR scores in mothers with a high TAI score did not decrease. The reason for this negative clinical situation may be that the pregnant women have a higher SAI average than the TAI average and that pregnant women are more sensitive to stress in the preoperative period (Hosseini et al. 2009).

In a comprehensive meta-analysis, it was shown that maternal anxiety is associated with an increased risk of preterm delivery and low birth weight (Coussons-Read et al. 2012). Sjöström et al. found that SAI detected in late pregnancy causes lower birth weight than TAI (Sjöström et al. 1997). Similarly, in our study, low birth weights were observed in both high anxiety groups. Studies have shown that smoking causes low birth weight and shorter gestational age (Hosseini et al. 2009). Our findings suggested that smoking was higher in pregnant women with a high anxiety level and a significant relationship was observed between smoking and low birth weight in simple analysis. However, in the multiple regression analysis in which the factors affecting fetal birth weight were investigated, only TAI was found to be a significant risk factor and smoking was not found as a significant risk factor. This may be due to the small number of pregnant smoking subgroups.

Another important observation in our study was the negative relationship between fetal cord blood cytokine levels and birth weight. The mechanism underlying this negative result is currently unclear (Van den Hove et al. 2007), however, high maternal anxiety-induced increases in hypothalamic pituitary adrenal (HPA) axis activity, increases in stress hormones (cortisol and catecholamines) (Ghaemmaghami et al. 2014) and decreases in placental 11β-HSD2 mRNA activity (O'Donnell et al. 2012) have been reported as potential mechanisms. Although the relationship between prenatal stress and high inflammatory markers with negative birth outcomes such as low birth weight and preterm birth has been demonstrated in various studies (Loomans et al. 2013), there are also studies reporting that such a relationship does not exist (Andersson et al. 2004). It was stated that the reason for this discrepancy could be sample size, socioeconomic status, ethnic origin, timing of prenatal anxiety evaluation, and the type of scale used (Ding et al. 2015). Results in the literature in this field vary and still lack a consensus.

In evaluating our findings, an average APGAR score above 7 and an average birth weight of 3,182 g indicate that the newborns are in good health. In line with these results, we can say that maternal anxiety causes excessive immune response but does not cause negative consequences that will clinically distress the fetus.

In our study, there was no significant difference between the anxiety groups regarding fetal cord blood gas parameters. It was reported that maternal anxiety caused lower fetal cord blood pH values and more frequent neonatal hypoglycemia (Horsch et al. 2019). Our results also established no significant relationship between the anxiety groups and the mother's employment status, education level, anesthesia experience, fetal gender, or gestational age. Based on these results, we can say that high maternal anxiety is a risk factor for an increase in fetal cord blood cytokine levels.

Evidence in the literature suggests that anxiolytic benzodiazepine-derived drugs can protect the individual from stress-induced immunosuppression (Zavala 1997). As premedication, midazolam has been shown to significantly reduce POA levels without causing any adverse effects on newborns (Bansal & Joon 2017). Accordingly, the successful treatment of POA before cesarean delivery can prevent the immune response and negative clinical results in the fetus (Ding et al. 2014). However, this assumption needs to be confirmed in random, case-control studies with larger sample sizes.

CONCLUSIONS

In conclusion, our results show that an increase in the levels of TNF-α, IL-6, and IL-8 cytokines in fetal cord blood in pregnant women with high anxiety levels and this situation causes negative effects on the newborn. For this reason, the identification of pregnant women with high anxiety levels in the preoperative period and providing them with psychiatric support may contribute to the prevention of negative birth results to the fetus.

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Contribution of individual authors:

All the authors have significantly contributed to the manuscript, and they have all approved its final version.

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