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Maternal Serum and Fetal Cord Blood C-Reactive Protein Levels but not Procalcitonin Levels Are Increased in Idiopathic Intrauterine Growth Restriction

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Background: The aim of the present study was to compare procalcitonin and CRP levels in maternal serum and fetal cord blood samples of patients with idiopathic intrauterine growth restriction (IUGR) *vs.* a control group of appropriate for gestational age (AGA) infants.

Material/Methods: The present prospective study included 43 patients: 27 patients with idiopathic IUGR (IUGR group) and 26 AGA infants at similar gestational ages (control group). Maternal serum and fetal cord blood samples were collected from the control group and IUGR group at time of delivery. Procalcitonin and CRP levels were analyzed in maternal blood. Procalcitonin and CRP levels were analyzed in fetal cord blood.

Results: The median value of CRP levels in maternal blood was 47.5 mg/dl in the IUGR group and 15.255 mg/dl in the AGA group (p=0.001). The mdian CRP level in cord blood was 36.4 mg/dl (range, 17.3–47.2) in the IUGR group and 10.1 mg/dl (range, 4.07–16.5) in the control group, and the difference was statistically significant (p=0.001). The median maternal serum procalcitonin level was 0.05 µg/l in the IUGR group and 0.04 µg/l in the AGA group, and the difference was not statistically significant (p=0.435). The median procalcitonin value in fetal cord blood was 0.06 µg/l in the IUGR group and 0.04 µg/l in the AGA group, and the difference was not statistically significant (p=0.741).

Conclusions: Maternal serum and fetal cord CRP levels were higher in the IUGR group; however, there was no difference in procalcitonin, which is another inflammatory indicator, between the groups.

MeSH Keywords: C-Reactive Protein • Calcitonin • Fetal Growth Retardation

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Background

Intrauterine growth restriction is a serious problem that causes perinatal mortality and morbidity [1–3]. Intrauterine growth restriction is also known as fetal growth restriction (FGR). The causes for IUGR include hypertensive diseases during pregnancy, genetic disorders, infections, maternal malnutrition, toxins, and drug use [4]. However, there is no known cause in 70% of these patients and this condition is defined as idiopathic IUGR [5]. Idiopathic IUGR usually presents with placental failure [6].

Procalcitonin is a calcitonin-progenitor polypeptide acting in calcium homeostasis. It is produced in parafollicular C cells of the thyroid gland, as well as in neuroendocrine cells of the lungs and intestines [7]. It is also used as an indicator for inflammation in the body [8]. Increasing inflammatory cytokines in the maternal blood negatively affect fetal development [9]. Therefore, we hypothesized that levels of procalcitonin, an inflammatory marker, are increased in patients with IUGR.

Procalcitonin has been studied in many inflammatory processes. There are studies indicating elevated procalcitonin levels in preeclampsia [10–12]. However, to the best of our knowledge, the present study is the first to evaluate procalcitonin levels in IUGR. At present, there is no diagnostic marker for IUGR. The inflammatory process is considered to be active in IUGR. Therefore, the aim of the present study was to assess procalcitonin levels in maternal blood and cord blood of patients with IUGR and to compare the results with a control group.

Therefore, this prospective, single-center study compared procalcitonin and CRP levels in maternal serum and fetal cord blood samples from pregnancies associated with idiopathic IUGR *vs.* appropriate for gestational age (AGA) births.

Material and Methods

This prospective study was carried out at the Obstetrics Clinic of Ondokuz Mayis University on 27 patients with idiopathic IUGR as the patient group and 26 appropriate for gestational age (AGA) infants as the control group. The study was approved by our Local Ethics Committee approval (no. B.30.2.ODM.0.20.08/213-315), and written informed consent was obtained from all women who participated in the study. All authors and the study protocol complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. IUGR was diagnosed in infants with predicted fetal body weight below the 10th percentile according to the gestational week through ultrasonographic measurements. Gestational age was calculated from the first day of the last menstruation and was confirmed by the first fetal ultrasound measurements.

The causes of termination of pregnancy before 38 weeks by caesarean section were events that required termination of pregnancy prematurely due to maternal conditions such as maternal lumbar discopathy or maternal cardiac diseases. Patients at gestational week 36 weeks and over were included in the study because steroids that are administrated for lung maturation can change the inflammation levels in earlier weeks.

Exclusion criteria were: gestational and pre-gestational diabetes, hypertension, multiple pregnancy, fetal abnormalities including trisomies, thyroid diseases, drug use during pregnancy (smoking, alcohol, or illegal drugs) premature membrane rupture, autoimmune disease, systemic lupus erythematosus, fever at least 37.5°C, elevated white blood cells before delivery, suspicion of infectious diseases, and receiving antibiotic therapy.

After diagnosis of IUGR through obstetric ultrasound scan, were recorded patient age, gravidity, parity, gestational week, and body mass index (BMI). Doppler ultrasound scan of the umbilical artery was performed for all patients, and diastolic flow was classified as present or absent. Amniotic fluid index was calculated on 4 quadrants for amniotic fluid measurement. If the amniotic fluid index was below 50 in 4 quadrants, the case was evaluated as oligohydramnios.

Collection and storage of serum samples

Maternal blood was collected from the mother and cord blood was collected from the newborn after birth, then the samples were centrifuged. Serum samples obtained were placed into Eppendorf tubes and stored at –80°C. Serum samples were stored at –40°C, –20°C, and at 2–8°C, then the samples were kept at room temperature and analysis was performed.

Procalcitonin and CRP measurement

Procalcitonin measurement was performed by electrochemiluminescence (ECLIA) method through original Roche diagnostic kits on a Roche Cobas E601 hormone device. This method uses a procalcitonin-specific monoclonal antibody, a biotin-labeled procalcitonin-specific monoclonal antibody, and a ruthenium complex.

CRP measurement was performed by immunoturbidimetric method using original Roche diagnostic kits on a Roche Cobas C501 device. We used human-originated CRP agglutinate with latex particles coated with monoclonal anti-CRP antibodies. The aggregates were analyzed turbidimetrically.

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Table 1. Demographic criteria.

	Patient group (IUGR) Median (IQR)	Control group (AGA) Median (IQR)	P value
Age (year)	31 (27–34)	28.5 (24.7–32)	0.095
BMI (kg/m^2)	28.4±3.1	28.3±2.7	0.05
Pregnancy period (days)	258 (255–262)	266 (265–271)	0.4
Birth weight (grams)	2100 (2000–2440)	3230 (3000–3545)	0.001**
Gender	15 (55.6%)/12 (44.4%) boy/girl	14 (53.8%)/12 (46.2%) boy/girl	

Table 2. Test results.

	Patient (IUGR) Median (IQR)	Control (AGA) Median (IQR)	P value
Apgar score 1st min.	8 (7.2–9.1)	9 (8.25–9.25)	0.033*
Diastolic flow loss	4/27	0/26	0.298
Number of the patients with Oligohydramnios	4/27	0/26	0.02
CRP mg/dL	47.5 (25–60)	15.25 (8–22.45)	0.001**
Serum Procalcitonin (µg/L)	0.05 (0.02–0.07)	0.04 (0.02–0.06)	0.435
Cord Procalcitonin (µg/L)	0.06 (0.02–0.07)	0.04 (0.03–0.08)	0.741
CRP/Procalcitonin (mg/dL/µg/L)	853.3 (527.8–2200)	312.7 (163.3–870)	0.004*
Cord CRP mg/dL	36.4 (17.3–47.2)	10.1 (4.07–16.5)	0.001**
Cord CRP/procalcitonin (mg/dL/µg/L)	735.0 (274.6–1126.3)	178.5 (104.1–419.8)	0.001**

Alpha significance level p<0.05; IQR – interquartile range.

Statistical analysis

Statistical analysis of the data was performed using SPSS 15 for Windows. Definitive statistical data were presented as median, interquartile range (IQR), and percent (%). Skewness and kurtosis values of normal distribution were detected by Kolmogorov-Smirnov test (with Lilliefors significance correction), Shapiro-Wilk tests, and histogram distribution graphs. Comparison of independent groups that did not meet normal distribution criteria for numeric variables was performed through Mann Whitney U test, whereas Spearman correlation analysis, which is used for non-parametric tests, was performed for correlation analysis. The alpha significance level was accepted as p<0.05.

Results

There were no significant differences detected between the groups in terms of age, BMI, sex of the infant, and pregnancy period (p=0.095, p>0.05, p>0.05). The median birth weight was 2100 g in the IUGR group and 3230 g in the AGA group, and the difference was statistically significant (p=0.001) (Table 1).

The median Apgar score was 8 in the IUGR group and 9 in the AGA group. There was no significant difference between the groups in first-minute Apgar scores (p=0.033). Diastolic flow loss is detected in 4 patients in the IUGR group, and this was not statistically significant between groups (0.298). There were 4 patients with oligohydroaminosis in the patient group only, and this was statistically significant (p=0.02). The median value of CRP level in maternal blood was 47.5 mg/dl in the IUGR group and 15.255 mg/dl in the AGA group (p=0.001). CRP level in the cord blood was 36.4 mg/dl (17.3-47.2) in the IUGR group and 10.1 mg/dl (4.07-16.5) in the control group, and the difference was statistically significant (p=0.001). The median maternal serum procalcitonin level was 0.05 µg/l in the IUGR group and 0.04 µg/l in the AGA group, and the difference was not statistically significant (p=0.435). The median procalcitonin value in fetal cord blood was 0.06 µg/l in the IUGR group and 0.04 µg/l in the AGA group, and the difference was not statistically significant (p=0.741). The CRP/procalcitonin ratio was 853.3

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Table 3. IUGR group, results of Spearman correlation analysis.

	Serum Procalcitonin (µg/L)	Pregnancy period (days)	Newborn weight (gram)	Apgar score	CRP (mg/dL)	Cord Procalcitonin (µg/L)	CRP/ Procalcitonin (mg/dL/µg/L)
Serum Procalcitonin (µg/L)	–	r: –0.078 p=0.699	r: –0.436 p=0.023*	r: 0.237 p=0.234	r: –0.279 p=0.159	r: –0.014 p=0.946	r: –0.814 p=0.001*
Pregnancy period (days)	r: –0.078 p=0.699	–	r: 0.738 p=0.001*	r: 0.195 p=0.331	r: 0.105 p=0.603	r: 0.063 p=0.755	r: 0.125 p=0.535
Newborn weight (gram)	r: –0.436 p=0.023*	r: 0.738 p=0.001*	–	r: 0.391 p=0.044*	r: 0.324 p=0.100	r: –0.011 p=0.957	r: 0.452 p=0.018*
Apgar score	r: 0.237 p=0.234	r: 0.195 p=0.331	r: 0.391 p=0.044*	–	r: 0.402 p=0.037*	r: –0.169 p=0.401	r: 0.054 p=0.790
CRP (mg/dL)	r: –0.279 p=0.159	r: 0.195 p=0.331	r: 0.324 p=0.100	r: 0.402 p=0.037*	–	r: 0.063 p=0.756	r: 0.717 p=0.001*
Cord Procalcitonin (µg/L)	r: –0.014 p=0.946	r: 0.063 p=0.755	r: –0.011 p=0.957	r: –0.169 p=0.401	r: 0.063 p=0.756	–	r: –0.008 p=0.970
CRP/Procalcitonin (mg/dL/µg/L)	r: –0.814 p=0.001*	r: 0.125 p=0.535	r: 0.452 p=0.018*	r: 0.054 p=0.790	r: 0.717 p=0.001*	r: –0.008 p=0.970	–
Oligohydramnios	r: –0.050 p=0.806	r: 0.067 p=0.739	r: 0.104 p=0.607	r: 0.073 p=0.718	r: 0.057 p=0.777	r: –0.281 p=0.156	r: 0.121 p=0.548
Diastolic flow loss	r: –0.124 p=0.537	r: 0.218 p=0.274	r: 0.264 p=0.184	r: 0.004 p=0.986	r: 0.309 p=0.116	r: 0.409 p=0.034*	r: 0.289 p=0.143
Cord CRP mg/dL	r: –0.247 p=0.213	r: 0.116 p=0.565	r: 0.333 p=0.090	r: 0.350 p=0.073	r: 0.851 p=0.01*	r: 0.05 p=0.803	
Cord CRP/Procalcitonin (mg/dL/µg/L)	r: –0.092 p=0.650	r: 0.139 p=0.489	r: 0.240 p=0.228	r: 0.342 p=0.080	r: 0.462 p=0.015*	r: 0.526 p=0.005*	

* Weakly significant at 0.05 level; * strongly significant at 0.01 level.

mg/dl in the IUGR group and 312.7 mg/dl in the control group, and the difference was statistically significant (p=0.004). The CRP/procalcitonin ratio in cord blood was 735 mg/dl (range, 274.6–1126.3) in the IUGR group and 178.5 mg/dl (range, 104.1–419.8) in the control group, and the difference was statistically significant (p=0.001) (Table 2).

Correlation results in the IUGR group are presented in Table 3. A negative correlation was detected between serum procalcitonin and birth weight (r: –0.436, p=0.023). A positive correlation was detected between Apgar score and CRP level (r: 0.402, p=0.037). A positive correlation was found between diastolic flow loss and procalcitonin level of cord blood by Doppler scan of the umbilical artery (r: 0.409 p=0.034).

Discussion

Intrauterine growth restriction is defined as fetal weight below 10% according to the population at the same gestational age. IUGR is an untreatable pathology in intrauterine life except for delivery at a suitable time after diagnosis. However, this condition has many effects on fetal life and later. These effects include bronchopulmonary dysplasia, cerebral palsy, cardiac, metabolic, and renal diseases [13–16].

We found no detectable causes of IUGR in 70% of the patients. Previous studies indicated that increasing inflammation can cause IUGR during pregnancy. Levels of IL-6, IL1 beta, and TNF alpha were reported to be higher in amniotic fluid and cord blood of small for gestational age (SGA) infants [17,18]. Placental mRNA levels of IL-8, IL-6, interferon-g, and TNF alpha were reported to be higher in infants with IUGR [19,20]. Inflammatory cytokine levels in the serum were found to be higher in mothers of infants with IUGR compared with normal pregnant women; inflammatory cytokines were higher in the patients with IUGR and placental failure [21]. Ernst et al. showed that maternal CRP levels in early pregnancy are associated with lower birth weight and increased risk of neonatal complications [22].

Fat tissue-secreted hsCRP and the increase in fat tissue is an aseptic inflammatory process [23,24]. Boutsikou et al. found that serum CRP levels were similar in IUGR and AGA fetuses [25].

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Although IUGR patients has less fat tissue, CRP levels were reported to be similar to those in the control group. Such results were considered as higher CRP levels in the patients with IUGR according to the fat tissue quantity. The above study results are different from those of our study. Boutsikou et al. included patients with preeclampsia, hypertension, or other IUGR reasons, but we included only idiopathic IUGR patients. Thus, inflammation may be more important in idiopathic IUGR than in preeclampsia or hypertensive disorders.

We detected significantly higher CRP levels in blood samples of pregnant women whose infants were diagnosed with IUGR. However, despite higher procalcitonin levels in maternal serum and cord blood in the IUGR group, the difference was not statistically significant. CRP levels gradually increase during pregnancy and peak at birth; CRP cannot pass the placental barrier and affect the fetus [26–28]. In contrast to CRP, no difference was shown in procalcitonin levels between pregnant and non-pregnant women [29]. It was demonstrated that procalcitonin was not associated with gestational week or birth [30]. Ruiz Gonzalez et al. showed that serum CRP and procalcitonin levels were not different between IUGR and AGA neonates [31]. We therefore assessed procalcitonin levels in patients with IUGR and combined this analysis with procalcitonin levels. In fact, procalcitonin, as an inflammatory marker, was higher in pregnant women with preeclampsia than in normal pregnant women [32,33]. However, there is no relevant study about IUGR in the literature.

Procalcitonin levels are significantly higher in people with bacterial infections [34]; it increases and decreases more rapidly than does the erythrocyte sedimentation rate and CRP. The half-life is 25–30 h [35]. Although CRP is significantly higher in IUGR patients due to such increase and decrease, procalcitonin may not be significant.

The present study has some limitations. It was performed in a single center, with a small study population, and compared only 2 biomarkers that are usually associated with inflammation. There were no clinical details provided for the women or infants that could have affected the levels of these markers, such as acute or chronic infection or inflammatory diseases, prolonged labor, method of delivery, and medications used.

Conclusions

To the best of our knowledge, this is the first study assessing procalcitonin levels in patients with IUGR. However, we believe that similar studies in larger patient populations are needed. Our results indicated that increased levels of CRP contribute to the inflammatory process in idiopathic IUGR. Similar results were not found for procalcitonin, which is a less affected marker in pregnancy-associated cases. Therefore, prospective studies of IUGR in larger patient populations are needed.

Conflict of interest

None.

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