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Original

Serum Bcl-2, caspase-9 and soluble FasL levels as perinatal markers in late preterm pregnancies with intrauterine growth restriction

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Intrauterine growth restriction (IUGR) is the inability of the fetus to grow and develop in the expected pattern. It occurs in about 5% of pregnancies and is associated with severe fetal mortality and morbidity. Affected infants are also highly vulnerable to diseases such as perinatal asphyxia, cerebral palsy, meconium aspiration syndrome, coagulation disorders, and immune system disorders that require long-term treatment. Apoptosis is thought to play a key role in the etiopathogenesis of IUGR. In conclusion, fetal complications are thought to be related to the severity of apoptosis in pregnancies complicated with IUGR.

The aim of the study was to test the measurability of the severity of apoptosis using Bcl-2, caspase-9, soluble Fas ligand (sFasL) markers and the maternal blood sample in addition to the diagnostic methods commonly used to diagnose IUGR; and to decrease the rates of adverse perinatal outcomes due to IUGR and to evaluate the fetal well-being status without feeling a need for invasive procedures. One hundred and fifty-nine late preterm pregnancies were included in the study. Eighty were diagnosed with IUGR and the others were the control group. During delivery, maternal and umbilical cord blood samples were taken. Bcl-2, caspase-9, sFasL marker levels in maternal and umbilical cord sera were determined using ELISA method. Bcl-2 levels were found to be significantly high in the maternal and umbilical cord sera in the IUGR group. There was also no significant difference between umbilical cord sera of the two groups in terms of sFasL and caspase-9 levels.

The results suggest that maternal serum Bcl-2 levels may also be helpful in the diagnosis of IUGR when used besides the ultrasonographic findings. Multicenter studies with large patient groups will increase knowledge in this area.

Key words: Late preterm birth, intrauterine growth restriction, Bcl-2, caspase-9, soluble Fas ligand.

Intrauterine growth restriction (IUGR) is an important, common and complex obstetric problem. There is no international consensus in terms of its definition and terminology concerning it. For this reason, the existence of IUGR is guessed based on the expected weight that a fetus should have put on in a given gestational week. Stillbirth is 8 times more common than other pregnancies when IUGR cannot be recognized antenatally.[1] In addition, IUGR is a great public health problem because the survivors who have

been diagnosed with IUGR in pregnancy are increasing pediatric morbidity in the long term. Abnormal neurological development, cerebral palsy, motor dysfunction, behavioral, low intellectual achievement, speech and cognitive delay can be observed in the short run, while low level of achievement at school, chronic disorders, metabolic diseases can be observed in these babies in the long run. This situation explained by the Barker hypothesis has been interpreted as the failure of fetal programming and the consequences of trying to keep up with the postnatal compensator growth.[2] This is true for newborns with both term and preterm growth restriction.[3]

The leading factor thought to play a key role in the IUGR etiology is increased apoptosis. It is thought that the reduction of trophoblast cell number, number of spiral arteries and luminal width in the placenta of IUGR diagnosed pregnancies may be related to apoptosis.[4] Although about 3% of late preterm labor is due to IUGR, this rate is increasing day by day due to the diagnosis of IUGR and the improvement of perinatal intensive care conditions.[5] The increase in the number of late preterm births constituting the 75% of premature deaths has made this group a focus of attention thanks to the enhancements in obstetric care and increased number of multiple pregnancies with the use of assisted reproductive techniques.[6]

There is no clinically available method for estimating placental function in vivo directly as new techniques are required for this. It is difficult to assess fetal well-being in the intrauterine life. It is important to be able to schedule the correct birth date due to the constantly changing parameters, their false positivity rates and problems that may be brought about by preterm birth. Evaluation with non-stress test (NST) is widely used in the assessment of fetal well-being. The observance of decreased short-term variability in NST is closely associated with acidosis and hypoxia.[7] Fetal distress should be considered in the case of decreased Amniotic fluid index (AFI), one of the important components of the biophysical profile, which is one of the advanced methods evaluating the fetal well-being. In the literature, an AFI of less than 5cm is associated with an abnormal 5th minute APGAR score.[8] An antenatal follow-up of the IUGR case and a Doppler ultrasound for fetal well-being are attempted to detect the birth timing. In high risk pregnancies, measurements of umbilical artery Doppler velocimetry reduce the number of perinatal deaths and even reduce the number of unnecessary obstetric interventions.[9,10] Furthermore, placental dysfunction, in which apoptosis is thought to play a role, may not always be detected by fetal biometry, biophysical profiling, or NST. It may be difficult to notice the fetuses whose findings concerning the hypoxic process are not evident and which don't have an IUGR diagnosis. In addition, the determination of fetal well-being can reduce fetal morbidity and mortality rates by directing the baby to a tertiary center while it is in the womb. On the other hand, if the fetal well-being is more likely to indicate a good prognosis, unnecessary antenatal follow-up and the costs associated there with besides the patient anxiety are removed. Therefore, in this study, we examined the levels of antiapoptotic Bcl-2 and apoptotic caspase-9 and sFasL in the maternal and umbilical serum of the group diagnosed with IUGR and late preterm control group. We aimed to decrease the neonatal mortality and morbidity rates and to enhance the fetal well-being using a noninvasive technique.

Material and Methods

The study protocol was approved by the Institutional Ethics Committee of our university hospital and performed in accordance with the Declaration of Helsinki (Number: 2016- 06/09).

The study was a prospective study dating from 1st July 2016 to 1st December 2017. The study included 159 pregnant women who gave birth between the 34th and 37th gestational weeks. Of these, 80 were patients and 79 were controls.

First, informed consent was obtained from all participants. Patients with preeclampsia or those with HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome, those with pre-pregnancy diabetes mellitus or chronic hypertension, those with suspected fetal anomaly or aneuploidy, those with intrauterine dead fetuses and multiple pregnancies were excluded.

The IUGR criteria were based on estimated fetal weight <10 percentile or regression in the developmental curve of the abdominal circumference as indicated in the DIGITAT study.[11] In the groups divided according to this, maternal demographic qualities (maternal age, gravida, parity, weight during pregnancy, weight gain during pregnancy, presence of systemic disease, smoking status) and clinic measurements (fasting blood sugar, Oral Glucose Tolerance Test (OGTT) results, NST type (reactive or nonreactive), ultrasound measurements (biparietal diameter, abdominal circumference, femur length, amniotic fluid index) made during the last week of gestation before birth and Doppler ultrasound findings (umbilical artery, median cerebral artery) were recorded. Moreover, the newborn gender, type of delivery (vaginal or cesarean), 1st and 5th APGAR scores, umbilical cord blood gas findings (pH, pO_2, pCO_2) and neonatal intensive care need information were recorded. The height and weight of each newborn that was included in the study were evaluated by calculating the percentages in the Fenton curve.[12] All parameters were compared between the groups and the existence of a possible relationship between these parameters was investigated.

Ten cc of blood from the maternal and umbilical cord at the time of birth was taken from the patient and control group and centrifuged for 15 minutes at 2500 rpm. The blood serums were kept in Eppendorf tubes and stored at -86°C until studied. In this study, sFasL, Bcl-2, caspase-9 levels were determined as ng / mL for Bcl-2 and pg / mL for sFasL using tests belonging to Elabscience company (Houston, Texas, USA) and conforming to the prospectus of the tests.

Statistical package program IBM SPSS® version 22.0 (IBM Corp., NY, USA, 2015) was used for statistical analysis. The mean ± SD, median (min-max) and percentage were used for descriptive statistics. In the evaluation of numerical data, Kolmogorov-Simirnov test was performed first, and when the parametric test assumptions were fulfilled, the significance test of the difference between the two means was performed in independent groups, and the Mann-Whitney-U test was performed when the parametric test assumptions could not be met. In analyzing the relations among the data, Pearson correlation analysis was performed. In the analysis of proportional data, Chi-square and Fisher exact Chi-square were applied. The level of error was taken as 0.05.

Results

According to the obtained data, the demographic data are summarized in Table I. The age of the mothers in the control group was 31.6 ± 6.2 years, while those in the IUGR group were found to be 28.3 ± 6.2 years. There was significant age difference between the groups ($p < 0.05$, Table I). Study groups were classified according to gestational week. The biggest share was formed by those whose week of gestation ranged from 36 weeks to 36 weeks and 6 days. The maternal weight before pregnancy was found to be significantly lower in the IUGR group and the mean was 61.7 ± 13.7 ($p < 0,05$). It was also found that the mothers in the IUGR group put on an average of 10 kilograms during pregnancy and this was found to be significantly lower than the control group did ($p < 0.05$). The number of births and pregnancies in the control group was found to be significantly higher than that of the IUGR group ($p < 0,05$). It was determined that the individuals in the IUGR group had their first pregnancies, which was significant ($p < 0.05$). In addition, the smoking rate in pregnancies in the IUGR group was about 6 times higher than the control group (Table I).

There was no significant difference between the groups in terms of fasting blood sugar (FBS), OGTT and gestational hypertension (GHT) (Table II). However, the incidence of non-reactive NST was significantly higher in the patients with IUGR than in the control group ($p < 0.05$; Table II). When the groups were examined in terms of AFI, it was found that there was significantly decreased AFI in the IUGR group ($p < 0.05$, Table II). While vaginal delivery rate was 11% (n=9) in the patient group, it was 24% (n=19) in the control group. There was no difference between groups in terms of fetal sex (Table II). There was no significant difference between the patient group and the control group in terms of 1st - and 5th -minute Apgar scores, cord blood pH, pO_2 and pCO_2 (Table II). Doppler ultrasound

findings (Umbilical artery (UA) systolic/diastolic (S/D) ratio, fetal middle cerebral artery (MCA), UA resistive index (RI)) were not significantly different between the groups (Table II). However, among the infants in the group, the duration of IUGR patients' hospital stay in the intensive care unit was significantly longer of the that of the other group ($p < 0.05$; Table II).

When the maternal serum Bcl-2 levels of the IUGR and the control group were compared, that of the IUGR group was significantly higher ($p < 0.05$; Fig. 1). When the umbilical cord serum Bcl-2 levels of the IUGR and the control group were compared, it was found that the levels of the IUGR group were also significantly higher ($p < 0.05$; Fig. 1). When the relationship between maternal and umbilical cord serum Bcl-2 levels was examined in IUGR group, there was a significant, similar directional and mild ($r = 0.24$) relationship between them ($p < 0.05$; Fig. 2). When the relationship between maternal and umbilical cord serum Bcl-2 levels was examined in the control group, there was a meaningful, same-directional and moderate correlation ($r = 0.55$) ($p < 0.05$; Fig. 2)

When the caspase-9 levels were compared in maternal sera of IUGR and control group, there was no significant difference between them. When the Caspase-9 levels were also compared in the umbilical cord sera of both groups, it was seen that the difference between the two groups was not significant. When the relation between maternal and umbilical cord serum Caspase-9 levels was examined in IUGR group pregnancies, there was a meaningful, same directional and moderate relation ($r = 0.44$) ($p < 0.05$). When the relationship between the maternal and umbilical cord serum Caspase-9 levels was examined in the control group, there was a significant, same directional and weak ($r = 0.36$) relationship between them ($p < 0.05$; Fig. 3).

When the sFasL levels were compared in maternal sera of IUGR and control group, there was no significant difference between them. When the sFasL levels were also compared in the umbilical cord sera of both groups, it was

Table I. Demographic Data of Study Groups.

	IUGR (n=80)	Control (n=79)
Age (years)	28.3 ± 6.2[a]	31.6 ± 6.2
Maternal weight before pregnancy (kilograms)	61.7 ± 13.7[b]	67 ± 14.7
The weight gain in pregnancy (kilograms)	10.3 ± 5.2[c]	13.3 ± 7.1
Gestational week		
34 weeks-34 weeks 6 days	18 (22.5%)	6 (7.5%)
35 weeks-35 weeks 6 days	12 (15%)	12 (15%)
36 hafta-36 weeks 6 day	50 (62.5%)	61 (77.2%)
Obstetric history		
Gravidity	2 (1-12)	3 (1-8)
Parity	1 (0-5)	2 (0-7)
Systemic disease		
No	66 (82.5%)	66 (83.5%)
Yes	14 (%17.5%)	13 (16.5%)
Smoking		
No	70 (92.1%)	76 (98.7%)
Yes	6 (7.9%)[d]	1 (1.3%)

Findings are suitably presented using mean ± SD, median (min-max) or percentage.
a, b, c, d: $p<0.05$.

Table II. Clinical Data of Study Groups.

	IUGR (n=80)	Control (n=79)
FBS	86.7 ± 25.9	88.9 ± 26.3
OGTT		
No	49 (62%)	49 (57.7%)
Normal	25 (31.7%)	29 (34.1%)
Impaired glucose tolerance	1 (1.3%)	3 (3.5%)
GDM	4 (5%)	4 (4.7%)
GHT		
No	64 (82%)	71 (89.9%)
Yes	14 (18%)	8 (10.1%)
NST		
Non-reactive	44 (55%)[a]	11 (14%)
Reactive	36 (45%)	68 (86%)
AFI		
<5 cm	44 (55.7%)[b]	9 (11.4%)
5-20 cm	35 (44.3%)	68 (86.1%)
>20 cm	0%	2 (2.5%)
Doppler ultrasound findings		
UA S/D	3.201 ± 1.49	2.426 ± 0.51
UA RI	0.7333 ± 0.12	0.8111 ± 0.1
MCA RI	0.65 ± 0.11	0.571 ± 0.1
Neonatal gender		
Female	40 (50%)	37 (46.8%)
Male	40 (50%)	42 (53.2%)
Vaginal birth	9 (11%)	19 (24%)
APGAR score		
1st minute	7.2 ± 1.7	7.6 ± 1.5
5th minute	8.6 ± 1.5	8.9 ± 1.2
Umbilical cord blood gas		
pH	7.3 ± 0.1	7.3 ± 0.1
pO_2	30.4 ± 9.5	31.7 ± 10.4
pCO_2	42 ± 8.1	43 ± 7.3
Neonatal intensive care need (day)	4.4 ± 8.5[c]	2.6 ± 4.7

Findings were presented using the suitable appropriate mean ± SD or percentage. FBS fasting blood sugar, AFI amniotic fluid index, GDM Gastrointestinal diabetes mellitus, GHT gestational hypertension, MCA middle cerebral artery, NST non-stress test, RI resistance index, OGTT oral glucose tolerance test, UA umbilical artery. a, b, c: p <0.05.

seen that the difference between the two groups was not significant. When the relation between maternal and umbilical cord serum sFasL levels was examined in control group pregnancies, there was not a significant relation (r = 0.05; p< 0.05; Fig. 4). When the relationship between the maternal and umbilical cord serum sFasL levels was examined in the control group, there was and weak (r = 0.35) relationship between them (p <0.05).

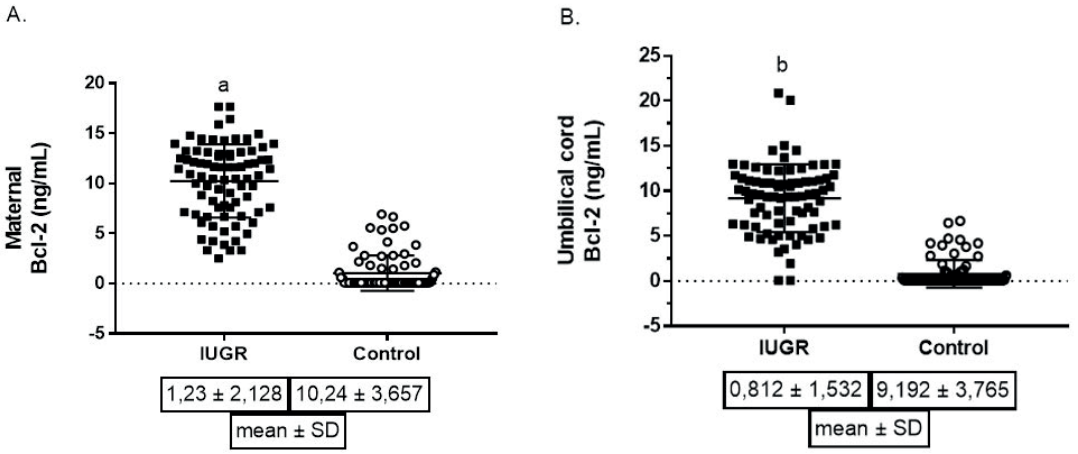

Fig. 1. Comparison of Bcl-2 Levels of Maternal and Umbilical Cord Blood between Study Groups. Horizontal lines and whiskers are in average and interquartile range, respectively. Mean ± SD's are below figure. a, b: p <0,05.

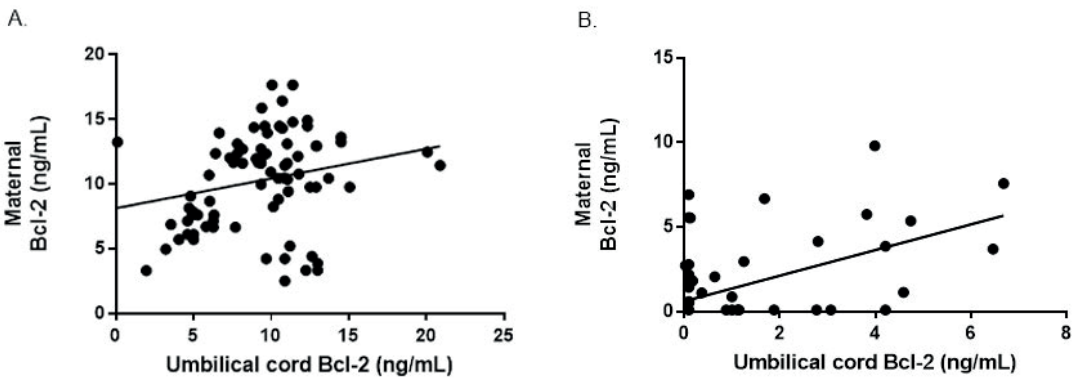

Fig. 2. Correlation of Bcl-2 Levels between Maternal and Umbilical Cord Sera. A. Correlation of Bcl-2 Levels Between Maternal and Umbilical Cord Sera in the IUGR Group (r =0.24, p <0.05). B. Correlation of Bcl-2 Levels between Maternal and Umbilical Cord Sera in the Control Group (r =0.55, p <0.001).

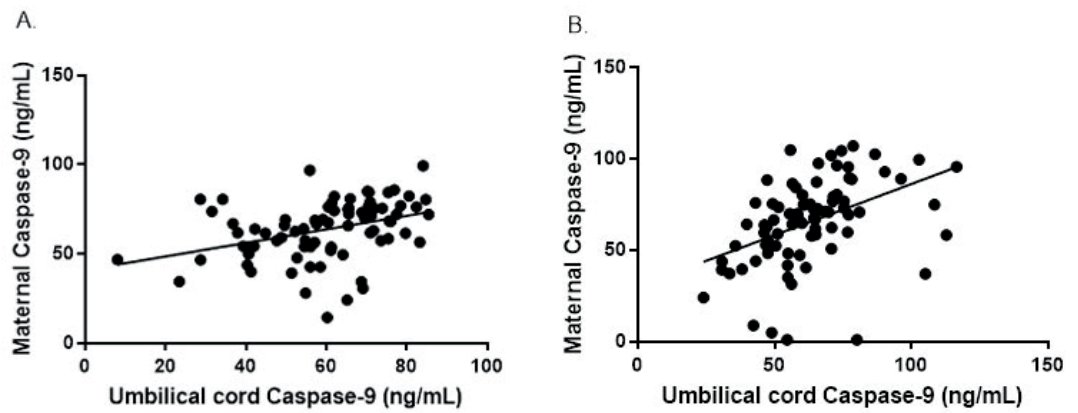

Fig. 3. Correlation of Caspase-9 Levels between Maternal and Umbilical Cord Sera. A. Correlation of Bcl-2 Levels between Maternal and Umbilical Cord Sera in the IUGR Group (r =0.36, p <0.05). B. Correlation of Bcl-2 Levels between Maternal and Umbilical Cord Sera in the Control Group (r =0.44, p <0.001).

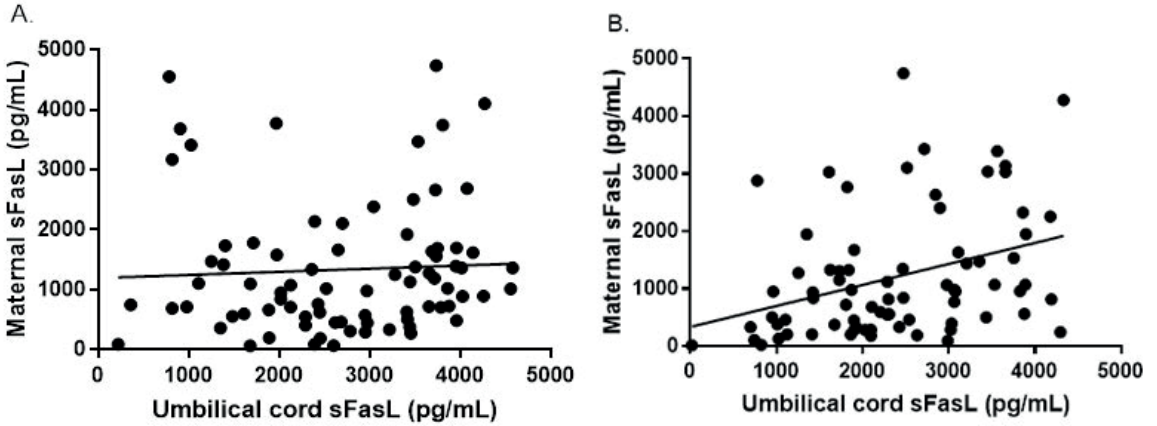

Fig. 4. Correlation of sFasL Levels between Maternal and Umbilical Cord Blood. A. Correlation of Bcl-2 Levels between the Umbilical Cord and Maternal Blood in the IUGR Group ($r = 0.05$; $p > 0.05$). B. Correlation of sFasL Levels between Umbilical Cord and Maternal Blood in Control Group ($r = 0.35$, $p < 0.05$).

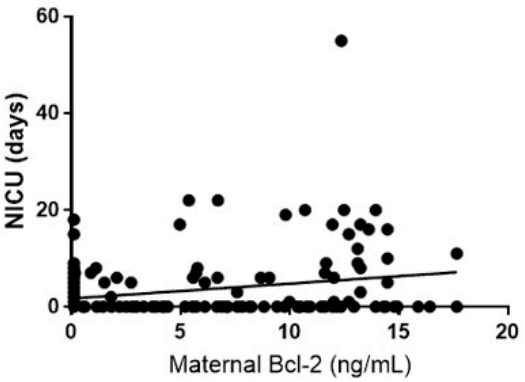

Fig. 5. Correlation between Maternal Bcl-2 levels and the Duration of NICU stay. (NICU: neonatal intensive care unit) ($r = 0.24$, $p < 0.05$).

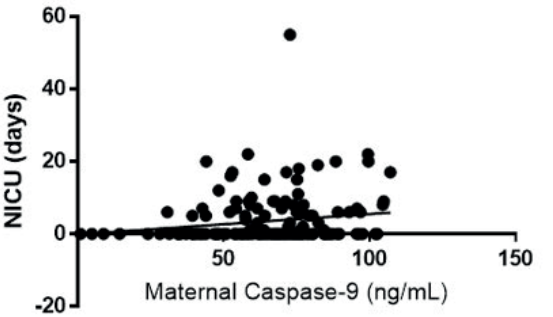

Fig. 6. Correlation between Maternal Caspase-9 Levels and Duration of NICU Stay. (NICU: neonatal intensive care unit) ($r = 0.17$, $p < 0.05$).

When the correlation between maternal serum Bcl-2 levels and the neonatal hospital stay time was examined in the study groups, it was seen that the relationship was significant, same directional and mild ($r=0.24$) ($p < 0.05$; Fig. 5). Similarly, when the correlation between maternal serum caspase-9 levels and the duration of neonatal intensive care unit stay was examined, the relation between them was significant, same directional but very slightly related ($r = 0.17$) ($p < 0.05$; Fig. 6).

Discussion

Inactivation of maternal immune system cells against fetal tissues (trophoblasts) during pregnancy through maternal apoptosis is one of the important mechanisms for proper placentation and the continuity of normal pregnancy. Exaggerated observation of this physiological apoptotic process leads to placental dysfunction. If adequate placental support is not provided, the growth potential of the fetus becomes restricted and IUGR is observed. Based on this, it is considered that apoptosis has the leading role in the etiology of IUGR. However, apart from this, fetuses that have no obvious hypoxic findings but are in the hypoxic process can be hardly recognized.

Most commonly, there are placenta rooted trophoblast invasion inadequacy and high

resistance flow in maternal spiral arterioles in the etiology of IUGR. This in turn leads to oxidative stress due to hypoperfusion.[13] Dysfunction of syncytiotrophoblasts is blamed in IUGR-related placental insufficiency.[14] However, the pathology that is thought to play a key role in the etiology of IUGR is increased apoptosis. Apoptosis is a physiological process in placental development.[15] The amount of apoptosis gradually increases in pregnancy until the 40th week.[16] In the case of IUGR, it is thought that this physiological process progresses to the pathological direction with decreasing number of trophoblast cells, number of spiral arteries and luminal width.[4]

In pregnancies with IUGR, if the fetal percentile curve is regressed, the Doppler findings deteriorate, and fetal hypoxia is observed, the pregnancy may have to end before pregnancies without complications. The fact that late preterm births constitute 75% of premature births and medicolegal concerns in the obstetrics have attracted attention to the late preterm group.[6] Late preterm babies may have some developmental deficiencies even if they have the same physical conditions as term babies.[17] Late preterm infants need more hospitalization after birth than term babies. While problems such as hypothermia, hypoglycemia, difficulty in feeding, hyperbilirubinemia, respiratory distress, and sepsis are short-term problems of late preterm infants, they are threatened by decreased cognitive abilities and behavioral problems in the long term.[18,19]

Apoptosis is a physiological pathway for the destruction of cells. The amount of apoptosis is important for body balancing. It is responsible for the loss of some cells during normal development and during the destruction of various cell types in the adult organism. For this reason, apoptotic markers are used in order to determine the association of apoptosis with diseases. It is thought that apoptosis in pathological levels plays an important role in pregnancies complicated by IUGR, preeclampsia and HELLP. In a study by Karakus et al.[20] in which similarly developed HELLP syndrome, preeclamptic pregnancies and control groups were compared, it was shown that M30 levels and apoptosis increased in the HELLP syndrome.

Interaction of proapoptotic and antiapoptotic regulators is important for controlling apoptosis, and their expression in the villous trophoblast has been the subject of an important study.[21] Bcl-2, one of the antiapoptotic markers used to determine apoptosis status, has been used in many studies.[22] Bcl-2 is an anti-apoptotic protein released from the trophoblast layer of the placental villus and it protects this key layer of placental villus from apoptosis. To date, the information available in the literature has shown the expression of the Bcl-2 protein in syncytiotrophoblast cells, which are abundant in early placenta, less in preterm placenta and least in term placenta.[23] In the literature, although an increased placental apoptosis[24] is usually reported in pregnancies diagnosed with IUGR, decreased apoptosis[25] has also been reported. Ischihara et al.[24] demonstrated increased placental apoptosis using Fas antigen and Bcl-2 in pregnancies diagnosed with IUGR and preeclampsia. On the other hand, interestingly, in their study in which caspase-3 and BCL-2 levels were examined in placental tissue to show placental apoptosis in preeclempsia, IUGR and HELLP syndrome, Cali et al.[26] reported that there was no significant difference in Bcl-2 levels between the healthy and ill group at the same gestational week. In a study in which Aban et al.[27] showed the increase of placental apoptosis using M30 and caspase-3 level, it was reported that there were increased nuclear factor kappa beta and reduced Bcl-2 expression in pregnancies complicated by IUGR and preeclampsia. In a study by Stepan et al.[28] in which placental apoptosis was aimed to be shown using apoptotic mediators Nix and BNip3 in pregnancies diagnosed with HELLP, preeclempsia and IUGR, it was reported that there was decreased apoptosis in the study groups, suggesting that this may be due to tolerance development against chronic hypoxia. In our study, in accordance with the literature, it was seen that Bcl-2 increased. The fact that Bcl-2 was high in late preterm pregnancies may also indicate the presence of an immature placenta due to increased apoptosis. The elevated level of antiapoptotic Bcl-2 may also be due to chronic hypoxia tolerance just as reported by Stepan et al.[28], the high level of Bcl-2 in our patients might stem from this. One of the most important

findings of the study is that the level of Bcl-2 in the maternal blood level is related to the Bcl-2 level in the umbilical cord. This suggests that Bcl-2, which is maternally diagnosed, can help in the diagnosis of IUGR.

In a study investigating the role of apoptosis and oxidative stress in the pathogenesis of preeclampsia, caspase-9 levels were found high in the placenta of preeclamptic pregnancies.[29] In our study, Caspase-9 levels were not significantly different when compared among maternal sera. In addition, there was no significant difference in umbilical cord sera, which was not compatible with the literature. Besides, a same directional relation was found between levels of umbilical cord and maternal serum in both the IUGR group and control group.

In a study examining the significance of Fas and FasL expression in preeclamptic pregnancies, both Fas and sFasL serum levels were significantly higher in preeclamptic pregnancies than in healthy pregnancies and placental tissue was not significantly different between normal and preeclamptic pregnancies in terms of Fas and FasL levels.[30] In our study, sFasL levels between the IUGR and the control group did not differ significantly between both maternal and umbilical cord blood and this was in accordance with the literature. In the control group, maternal and umbilical cord blood sFasL levels showed poor correlation in the same direction, while no correlation was observed in the IUGR group, which can be explained by the fact that the different mechanisms and the development of IUGR may distort the balance in different ways, and sFasL may have been affected from this.

Because maternal diabetes is associated with increased placental apoptosis, it can be alleged that systemic diseases affect human placenta.[31] However, in our study, there was no difference between groups in terms of chronic diseases, FBS and OGTT, which was contradictory to the literature. This may be because of the small sample size.

The most common test used to determine fetal well-being is NST. Because the actual rate of fetal distress in the presence of nonreactive NST is 40%, further tests are needed to understand the actual fetal distress. Contraction stress testing, biophysical profile, ultrasound (amniotic fluid index, fetal movements and tonus) should be performed. In 2013, aiming at examining the perinatal and obstetric outcomes of low-risk pregnancies pre-diagnosed with nonreactive NST, Aktulay et al.[32] determined the increases in primary cesarean rates. In our study, in conformity with the literature, the NST of the IUGR group was significantly more non-reactive compared to that of the control group.

Doppler ultrasound is used to understand fetal well-being for the antenatal follow-up of IUGR status and to schedule the delivery.[33] Interestingly, the Doppler ultrasound parameters of the IUGR group did not differ significantly from the control group in our study. Fetal distress should be considered in the case of decreased AFI, one of the important components of the biophysical profile, which is one of the advanced methods evaluating the fetal well-being. The fact that AFI is below 5cm in the literature is associated with an abnormal 5th minute APGAR score.[34] In our study, in accordance with the literature, AFI was significantly <5 cm in the IUGR group, whereas there was no significant difference in the 5th minute APGAR score between the two groups, which was incompatible with the literature. This result may be due to the fact that the newborns in our study were met by pediatricians at our tertiary center during birth correctly and effectively.

However much pediatric intensive care conditions are better in a tertiary health care institution than in a secondary one, some additional problems caused by the restricted growth of these infants will persist. For this reason, in investigating the correlation between the length of NICU stay and the maternal marker levels, we demonstrated the severity of the disease with a noninvasive technique for the mother and fetus. This study has shown that the severity of IUGR can be predicted antenatally with Bcl-2 checked from the maternal blood.

Intrauterine growth restriction is an entity which has not yet fully been understood both in terms of its cause and mechanism of development. The parts of the antenatal

follow-up applied during the diagnosis are not always enough to enlighten the whole situation. In some cases, misdiagnosis is made and unnecessary antenatal follow-up burden on the physician and patient anxiety emerge. This can be explained through the fact that the accuracy rates of antenatal follow-up methods are not 100%. On the contrary, the inability to make the correct diagnosis may lead to negative perinatal and neonatal outcomes. For this reason, diagnosis with higher accuracy is needed using additional diagnostic tools. For this, we used apoptotic and antiapoptotic markers in our study.

As a result of our study, we showed that maternal Bcl-2 could be used as a marker to confirm the diagnosis of IUGR as an additional method. Interestingly, the fact that caspase-9 levels are in the same direction between maternal and umbilical cord blood in both groups suggests that caspase-9 may not play an active role in the etiology. We also found out that the disruption in the correlation of the sFasL levels in the maternal and umbilical cord blood may be associated with IUGR.

According to the investigations we made, apoptotic and antiapoptotic markers have not been studied in the literature in late preterm cases. In this study, we showed that looking at the Bcl-2 level in the maternal serum can be used as an additional method in the future to confirm the IUGR diagnosis. In addition, the results make us think that Bcl-2 may be used as a marker to assess fetal well-being regardless of IUGR. With this information, we believe that new results will be achieved to reduce the perinatal mortality rates in studies with wider patient groups at earlier gestational weeks. To our knowleage, apoptotic and antiapoptotic markers had not previously been studied in the literature in late preterm infants. In this study, we showed that Bcl-2 from the maternal serum can be used as an additional method in the future for the confirmation of IUGR diagnosis. In addition, the results suggest that Bcl-2 may be used as a marker to assess fetal well-being regardless of IUGR. With this information, we believe new results will be achieved that will reduce perinatal mortality rates through studies with wider patient groups.

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