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VIA MEDICA

Elabela levels in pregnancies with intrauterine growth retardation

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ABSTRACT

Objectives: The aim of our study is to examine maternal serum Elabela levels in pregnancy with intrauterine growth retardation (IUGR). IUGR is one of the most important causes of perinatal mortality and morbidity. IUGR is also related future comorobidities such as diabetes mellitus, hyperlipidemia, hypertension and coronary artery disease.

Material and methods: Fifty pregnancies diagnosed as IUGR (Group 1) and fifty healthy pregnancies (Group 2) enrolled into the study. Obstetric and demographic characteristics of the patients, serum elabela levels, ultrasound parameters, cord pH value and APGAR scores of the newborns were recorded. In the study, which was planned as a prospective case-control study, an independent t test was used for the evaluation of continuous data and the Mann Whitney U test was used for the statistical evaluation of ordinal data. $p < 0.05$ was considered significant.

Results: The mean gestational age of the cases at delivery was 36.35 ± 1.29 in Group 1 and 38.16 ± 0.94 weeks in Group 2 ($p < 0.05$). Mean serum Elabela levels were 15.05 ± 9.03 in Group 1 and 8.96 ± 4.33 ng/mL in Group 2 ($p < 0.0001$). Mean newborn weights were 2498.20 ± 465.92 in Group 1 and 3179.44 ± 387.99 gr. in Group 2 ($p < 0.0001$). Systolic and diastolic blood pressure measurements taken on the day of delivery were higher in Group 1, and diastolic blood pressure was 77.0 ± 9.53 in Group 1 and 72.60 ± 13.37 mmHg in Group 2 ($p < 0.05$). Bilateral uterine artery Pulsatile Index (PI) and umbilical artery PI value were significantly higher in Group 1 ($p < 0.05$), and middle cerebral artery PI and cerebroplacental ratio were significantly lower in Group 1 compared to Group 2 ($p < 0.05$). Although the cord pH value, 1st and 5th minute APGAR scores were lower in Group 1 compared to Group 2, no statistically significant difference was found ($p > 0.05$).

Conlusions: In our study, it was found that serum Elabela levels increased significantly in pregnancies complicated by IUGR compared to the control group.

Key words: pregnancy; intrauterine growth retardation; Elabela

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INTRODUCTION

Normal fetal growth depends on maternal, fetal, placental, and external factors as well as genetic growth potential. Disruption in one or more of these factors may affect fetal growth and lead to intrauterine growth retardation (IUGR) [1]. IUGR, which is often defined as birth weight below the 10th percentile, remains to be one of the important causes of perinatal mortality and morbidity in modern obstetric practice [2]. Perinatal mortality rate in infants with IUGR increases 10–20 times compared to that in normal infants [3]. IUGR is also closely related to postnatal morbidities, such as insecure fetal condition, perinatal asphyxia, need for prolonged stay in the neonatal intensive care unit after delivery, and hypoglycemia. In addition, there is an increased

risk of coronary artery disease, type 2 diabetes mellitus, hyperlipidemia, psychiatric diseases, and hypertension in fetuses with IUGR at later ages [4].

In recent years, Doppler ultrasonography has become a popular imaging method in the antenatal diagnosis of IUGR, because it is both non-invasive and easily applicable. Owing to this method, the presence and severity of fetal hypoxemia can be accurately determined and a significant reduction in mortality and morbidity can be achieved with timely intervention [5]. In addition, fetal biophysical profile (BFP), nonstress test (NST), and arterial and venous Doppler ultrasonography appear to be synergistically effective in detecting fetal risk in early-onset IUGR and prolonging pregnancy safely [6].

Elabela is a placental peptide hormone that was recently discovered to be the endogenous ligand for apelin (APJ), a receptor bound to G-protein. The APJ receptor is widely expressed in several tissues of the human body. Apelin is another endogenous ligand of the APJ receptor that is of the same origin as that of Elabela. Elabela and apelin have a series of similar functions. Elabela-APJ system also plays an important role in fetal cardiovascular development. In addition, this system has shown to have important biological effects, such as embryonic development, skeletal development, angiogenesis, and vascular morphogenesis. Theoretically, Elabela could play a role in preventing preeclampsia by lowering the blood pressure and proteinuria levels during pregnancy. Also, the deficiency of Elabela may cause developmental defects in the embryo and various morbidities in pregnant women. Several studies to date have, therefore, investigated the relationship between Elabela levels during pregnancy and the development of preeclampsia, gestational diabetes mellitus, and obesity [7, 8]. However, according to our knowledge, the association between serum Elabela levels and IUGR in pregnant women has been studied in only one study.

The aim of this study is to investigate the possible relationship between Elabela levels during pregnancy and IUGR.

MATERIAL AND METHODS

This single center prospective case-control study was conducted on pregnant women who presented to the gynecology and obstetrics department for antenatal examination between 2017 and 2018. Before starting the study, approval was obtained from the local ethics committee (*Ethics Committee approval no:* 2018.09.06-14-15). Informed consent was obtained from all the study participants.

Patient selection

A total of 100 cases, including 50 cases (Group 1) diagnosed with IUGR and followed up in the Gynecology and Obstetrics Clinic, and 50 cases with normal fetal development (Group 2), were included in the study.

Determination of gestational age was made according to the last menstrual period and confirmed by ultrasonography in the first trimester. The antenatal diagnosis of IUGR was based on the fetal abdominal circumference below the 10th percentile at the 3rd trimester. Umbilical artery pulsatility index (PI), Middle Cerebral Artery (MCA) PI or cerebro-placental ratio (CPR) values were used in Doppler ultrasonography in order to differentiate the fetuses with IUGR from small for gestational age fetuses. The IUGR group (Group 1) was thereby composed of the patients with abnormal Doppler ultrasonography parameters mentioned above. (Umbilical Artery PI > 95th percentile, Cerebroplacental Ratio and MCA PI <5th percentile were considered abnormal).

Patients were excluded from the study if they had a severe physical disease, pregestational diabetes, liver and kidney failure, any endocrine disorder, hematological disease, received medical treatment for any reason in the last three months, chronic inflammation or infection, patients under 19 and over 35 years old, patients with BMI < 19 and > 30, small for gestational age fetuses, multiple pregnancies, congenital anomalies, fetuses with risk of genetic screening tests (> 1/250) and if they were smokers and drugs and alcohol abusers.

Biochemical and coagulation parameters, complete urinalysis, complete blood counts, systolic and diastolic arterial blood pressure values of the cases included in the study were recorded on the day of delivery.

Sampling and evaluation

Ten milliliters of venous blood samples were collected from all pregnant women included in the study to determine Elabela levels. The blood samples were centrifuged in the laboratory of Biochemistry Department at FU and stored at −80°C. Serum Elabela levels were analyzed using human Elabela enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Sunred Biological Technology Co., Ltd, catalog no: 201-12-8569, China), according to the instruction manual. Absorbances were read spectrophotometrically at 450 nm in an ELISA microplate reader (Thermo Scientific, Multiskan FC, USA). The results were given in ng/mL. The kit sensitivity was 0.118 ng/mL, the measurement range was 0.15–40 ng/mL.

The measurement process of Elabela levels was performed on the condition that the laboratory technician was unaware of the results and the patient group.

Statistical evaluation

SPSS 21.0 program (IBM, Armonk, NY, USA) was used for statistical analysis of the data. The Kolmogorov-Smirnov test was used for normality analysis of continuous variables. An independent sample t-test was used for comparison of normally distributed continuous variables, and the Mann-

-Whitney U test was used to compare continuous variables without normal distribution. The Fischer's exact test was used to compare proportional distributions of 2×2 nominal variables, while a chi-square test was used for $n \times n$ variables. The level of statistical significance was set at a p-value of 0.05.

RESULTS

Body mass index (BMI), number of pregnancies, parity, abortion, and curettage numbers were similar between Group 1 and Group 2. Body mass index (BMI), number of pregnancies, parity, abortion and curettage numbers were similar between Group 1 and Group 2, and no statistical difference was found between both groups. The values are shown in Table 1. However, the gestational week at which delivery took place was found to be significantly different between both groups and the delivery occurred earlier in Group 1. (Gestational Age at birth is 36.35 ± 1.29 for Group 1 and 38.16 ± 0.94 for Group 2.). The results are shown in Table 1.

The average age of the patients was 27.86 ± 4.94 in Group 1 and 28.12 ± 3.86 in Group 2, and no statistically significant difference was observed between the two groups

($p > 0.05$, Mann Whitney U test). Umbilical cord pH**, 1st and 5th minute APGAR scores * Although it was lower in Group 1 compared to Group 2, no statistically significant difference was found ($p > 0.05$, **independent t test, *Mann Whitney U test). While there was no significant difference between Group 1 and Group 2 between the systolic arterial blood pressure values on the day of delivery, diastolic arterial blood pressure values were significantly higher in Group 1. (77.00 ± 9.53 for Group 1 and 72.60 ± 13.37 for Group 2, $p < 0.05$, Mann Whitney U test). Fetal weight in Group 1 2498.20 ± 465.92 g and 3179.44 ± 387.99g in Group 2 and there is a statistically significant difference in Group 1 ($p < 0.0001$, independent t test) (Fig. 1 and 2).

Serum Elabela values were 15.05 ± 9.03 ng/mL for Group 1 and 8.96 ± 4.33 ng/mL for Group 2, and the values were statistically significantly higher in Group 1 ($p < 0.0001$, Mann Whitney U test).

Elabela levels, maternal age, fetal weight, the 1-minute and 5-minute appearance, pulse, grimace, activity, and respiration (APGAR) scores, cord pH value, and systolic and diastolic blood pressure values of both the groups are shown in Table 2.

Table 1. Obstetric and demographic characteristics of the patients

Parameters	Group 1 (n = 50)		Group 2 (n = 50)		p value
	Mean ±	SD	Mean ±	SD	
Gestational age [weeks]	36.35	1.29	38.16	0.94	*< 0.05**
Gravida [number]	2.46	1.69	2.32	1.46	NS*
Parity [number]	1.13	1.32	1.43	1.67	NS*
Abortus [number]	0.30	0.70	0.03	0.18	NS*
Curettage [number]	0.06	0.18	0.01	0.10	NS*
BMI [kg/m²]	24.1	1.10	23.7	1.04	NS**

* — Mann Whitney U test, ** — independent t test; BMI — body mass index; mean ± SD — mean ± standard deviation; NS — not nignificant
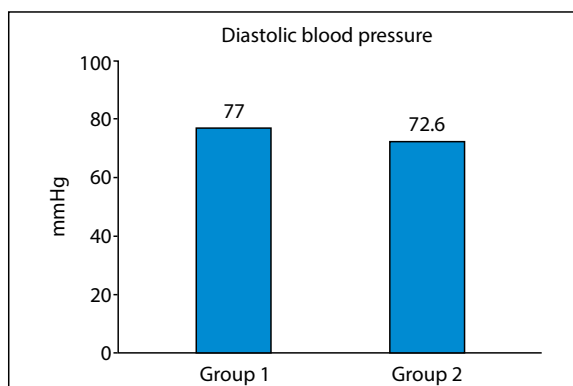

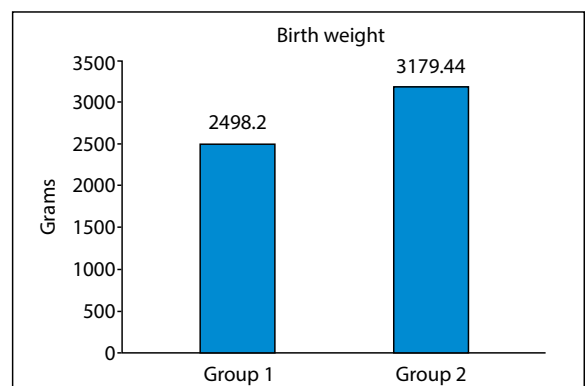**Figure 1.** Diastolic blood pressure in Group 1 and Group 2

Figure 2. Birth weight in Group 1 and Group 2

Table 2. Distribution of maternal and neonatal parameters by groups

Parameters	Group 1 (n = 50)		Group 2 (n = 50)		p value
	Mean ±	SD	Mean ±	SD	
Maternal age [years]	27.86	4.94	28.12	3.86	NS*
Elabela [ng/mL]	15.05	9.03	8.96	4.33	< 0.0001**
NB weight [g]	2498.20	465.92	3179.44	387.99	< 0.0001**
APGAR 1	7.12	1.10	7.36	0.78	NS*
APGAR 5	8.84	1.09	9.16	0.68	NS*
Cord pH	7.30	0.07	7.32	0.04	NS*
Systolic BP [mmHg]	116.80	10.96	113.80	7.80	NS**
Diastolic BP [mmHg]	77.00	9.53	72.60	13.37	< 0.05**

* — Mann Whitney U test; ** — independent t test; APGAR — appearance, pulse, grimace, activity, and respiration (APGAR) Score; BP— blood pressure; mean ± SD — mean ± standard deviation; NB — Newborn; NS — not nignificant
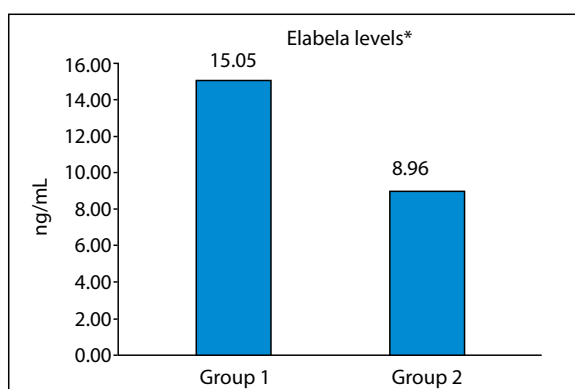
Figure 3. Serum Elabela levels in Group 1 and Group 2

Elabela levels were significantly higher in Group 1, and the p value was < 0.0001. Elabela levels of both groups are shown in Figure 3.

The cases were also examined in terms of doppler ultrasonography parameters, and all of the umbilical artery, Middle Cerebral Artery (MCA), bilateral uterine artery Pulsatility Index (PI) values and cerebroplacental ratio (CPR) measurements were found to be significantly different in Group 1 compared to Group 2 (p < 0.05, Mann Whitney U test). Doppler ultrasonography parameters are shown in Table 3.

DISCUSSION

Fetuses with IUGR are at high risk in terms of poor perinatal outcomes and long-term risks compared to fetuses with normal growth. The best results are obtained with the combined use of fetal biometry, biophysical profile, NST, and arterial and venous Doppler ultrasonography in follow-ups to confirm fetal well-being. The use of these tests alone has limited value in the management of IUGR. The timing of delivery in a fetus with preterm IUGR is very critical and still controversial. Gestational age is an independent factor for neonatal outcomes, and delayed delivery may increase the risk of stillbirths [9].

Studies have found that APJ or Elabela deficiency manifests as vascular defects in animals [10–12]. In contrast, apelin-deficient mice are viable and fertile; however, they show delayed retinal and cardiac vascularizations at birth [12, 13]. Consistent with this finding, Cekmez et al. showed that preterm neonates with retinopathy had lower cord blood apelin levels than preterm neonates without retinopathy [14]. The APJ receptor is highly expressed in both the endothelial precursor cells (angioblasts) and endothelial cells of the developing vasculature in the animal embryos [15, 16].

The placenta of preeclamptic women is characterized by weak trophoblastic invasion and endothelial vasospasm.

Table 3. Doppler ultrasonography parameters of the cases.

Doppler parameters	Group 1 (n = 50)		Group 2 (n = 50)		p value
	Mean ±	SD	Mean ±	SD	
Right Ut. A. PI	1.32	0.44	0.91	0.37	< 0.05*
Left Ut. A. PI	1.12	0.32	0.75	0.17	< 0.05*
MCA PI	1.37	0.17	1.56	0.28	< 0.05*
Umbilical A. PI	1.17	0.07	0.80	0.11	< 0.05*
CPR	0.91	0.19	1.90	0.28	< 0.05*

* — Mann Whitney U test; CPR — cerebroplacental ratio; MCA PI — middle cerebral artery pulsatile index; Mean ± SD — mean ± standard deviation; Umbilical A. PI — umbilical artery pulsatile index; Ut. A. PI — uterine artery pulsatile index

These defects are considered to be the driving forces of the development of preeclampsia [17]. Proper invasion of the spiral arteries by trophoblasts during implantation relies on a good balance between placental angiogenic and antiangiogenic factors. To date, the development of preeclampsia has been associated with the elevation of two placental antiangiogenic factors, soluble Fms-like tyrosine kinase 1 (sFlt1 or sVEGFR-1) and endoglin. Indeed, application of these factors to pregnant rats reproduces preeclampsia-like symptoms [18]. Apelin controls the vascular tone in the placenta. Therefore, several studies have investigated placental APJ and apelin expression in patients with preeclampsia. Among all available studies, some studies used control and preeclampsia patient groups that did not match in terms of age, gestational age, or BMI [19, 20], or included a very small number of patients [21]. These limitations may lead to potential bias, as apelin levels can vary based on these factors [21, 22].

As mentioned earlier, pregnant mice carrying Elabela-deficient embryos show features of placental insufficiency of vascular origin and preeclampsia (hypertension, proteinuria, and glomerular endotheliosis). In addition, subcutaneous injection of Elabela to Elabela-null mice between E11 and E19 has prevented the development of maternal hypertension and proteinuria [23]. This reveals the primary role of Elabela in preeclampsia. Three studies recently measured circulating Elabela levels in preeclamptic women to evaluate whether Elabela is involved in the etiology of preeclampsia in humans. These studies revealed no difference in circulating Elabela levels between preeclampsia and control patients, except for a group of women with late-onset preeclampsia [7, 24, 25].

To date, these studies do not support the hypothesis that human preeclampsia is characterized by an early deficiency in circulating Elabela levels. In two studies using the same ELISA kit, very different Elabela levels were found in samples collected over a similar time period. Further studies are needed to establish guidelines for the adequate measurement of Elabela as well as determining the relative variation of specific Elabela isoforms.

Current literature highlights the critical role of Elabela/apelin (APJ) axis in fetal and placental development. While Elabela appears to have specific roles in early fetal development, particularly for the cardiovascular system formation, apelin function emerges afterwards to control fetal angiogenesis and energy homeostasis. Similarly, Elabela is essential for the early placental development (contributing to trophoblastic invasion and angiogenic sprouting process) [7, 23]. On the other hand, apelin regulates constitutive functions, such as placental vessel tone and nutrient exchange. Both hormones act through a common receptor expressed on multiple cell types in the fetus and placenta throughout the pregnancy [19].

PE and IUGR cause abnormal placentation, and results in adverse pregnancy outcomes [26]. Both diseases have heterogeneous etiology and risk factors are similar [27, 28]. More importantly, the histopathological features of PE and IUGR are similar [29]. The two diseases sometimes coexist. This may be due to the similarity of the pathophysiological mechanism. Further studies are needed in this area.

In the literature, there is only one study examining the maternal serum Elabela levels in cases with IUGR fetuses. In the study by Behram et al., serum Elabela levels were found to be significantly lower in IUGR cases compared to the healthy control group [30]. In the study, measurement of serum Elabela levels was performed at the 30th gestational week in both groups due to matching the gestational age. The IUGR group gave birth two weeks after the measurement, and the pregnancy continued for another 8 weeks in the control group. In addition, IUGR cases included in the study were cases with EFW below the 3rd percentile. Although these cases are more homogeneous, they are all in high-risk in terms of adverse perinatal outcomes [31]. It is possible that some patients gave birth in the second trimester due to impaired placental adaptation. In our study, cases with fetal AC measurement below the 10th percentile in the third trimester were accepted as IUGR. In our study group, different mechanisms may have been activated in terms of pregnancy adaptation and increased Elabela levels. In addition, serum Elabela levels were measured on the day of delivery in our study. The difference in Elabela levels between the two studies may also be related to this.

In addition, the results of various studies comparing preeclampsia and Elabela levels at similar weeks of gestation show conflicting results. In the study of Deniz et al, maternal serum Elabela levels were found to be significantly lower in preeclampsia and severe preeclampsia cases compared to the control group, while Elabela levels were found to be higher in preeclampsia cases in the study of Panaitescu et al. [7, 32]. No significant difference was found in the study of Pritchard et al. [25]. These results may also be a result of the complex nature of placental pathology. Similar conflicting results are likely to occur in IUGR cases.

Studies in the current literature have shown that the uterine artery PI is increased, and the middle cerebral artery PI and CPR values are decreased in pregnancies with growth retardations [33, 34]. The results of our study also support these studies.

To our knowledge, there are only few studies in the literature evaluating the diastolic arterial blood pressure in pregnancies with intrauterine growth retardations and comparing them with normal pregnancies. However,

in our study, a significant difference was found between both the groups.

CONCLUSIONS

In our study, Elabela levels were found to be 15.05 in pregnancies with IUGR. The differences in the control group were found to be significant. In this respect, we consider that placental Elabela levels increase in cases of IUGR, and this may be a protective mechanism. Comprehensive studies are needed in this area.

Conflicts of interest

All authors declare no conflict of interest.

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