ORIGINAL RESEARCH

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The Relationship of Maternal Serum Amphiregulin Levels with Early-Onset Fetal Growth Restriction and Doppler Findings: A Prospective Cohort Study

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ABSTRACT Objective: This study aimed to compare the maternal blood amphiregulin (AR) levels of pregnant women with early-onset fetal growth restriction (FGR) and healthy pregnant women and to correlate them with Doppler findings to determine the association of AR with early-onset FGR. **Material and Methods:** Outpatient pregnant women who were between 18-45-years, >20 and ≤32-weeks, with no antibodies or infection markers for Toxoplasmosis, Rubella, Cytomegalovirus, hepatitis and human immunodeficiency virus conditions, with a low risk of genetic disease or malformation in first trimester screening test, with no pathologic findings in detailed ultrasonography were included in the study. Doppler measurements were evaluated. Two groups were formed as FGR and healthy control group. Delphi consensus methodology was used for FGR diagnosis. Delphi consensus criteria were fetuses with an estimated birth weight (EFW) or abdominal circumference below the 3rd percentile or reversed flow or loss of end-diastolic flow in the umbilical artery, were fetuses with EFW below 10th percentile and uterine artery pulsatility index (PI)>95th percentile or umbilical artery PI>95th percentile. For AR analyses, 4 mm of venous blood was taken and centrifuged. Serum samples were analyzed by enzyme-linked immunosorbent. **Results:** There was no statistically significant difference in serum AR levels between groups (Group-FGR, Group-C; 796.65 ng/L, 740.21 ng/L, p=0.765, respectively). There was no statistically significant association between serum AR values and umbilical artery changes, notch positivity in bilateral uterine arteries, pulsatility indices, oligohydramnios, and mode of delivery (p>0.05). **Conclusion:** Maternal serum AR levels may not predict early-onset FGR disease, and Doppler findings.

Keywords: Amphiregulin; fetal growth restriction; pulsatility index; reversed flow

Fetal growth restriction (FGR) is an estimated birth weight below the 10th percentile. However, this diagnosis also includes the structurally small-for-gestational-age (SGA). An international consensus has been established to differentiate SGA fetuses from FGR fetuses. Consensus has been reached on excluding congenital anomalies in the diagnosis of FGR and supporting the diagnosis with Doppler findings. FGR has been divided into early and late onset, and the 32nd week of gestation was defined as the cutoff.[1] Early-onset FGR was defined by an international committee of experts in 2016 as, before 32nd weeks, fetus with an estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd percentile or reversed flow or loss of end-diastolic flow in the umbilical artery. Additionally, in fetuses with EFW below 10th percentile, FGR has been defined as, uterine artery pulsatility index (UtA PI)>95th percentile or umbilical artery pulsatility index (UmA PI)>95th percentile. It has been emphasized that EFW above 10th percentile alone cannot exclude the diagnosis of FGR, therefore the importance of evaluation with Doppler findings has been emphasized.[2,3] In early-onset FGR not associated with fetal genetic abnormalities or infectious etiology, most cases are thought to result from malperfusion due to inadequate tro-

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phoblast invasion. Fetuses with early-onset FGR due to abnormal placentation have higher mortality and morbidity rates than fetuses with late-onset FGR.[4,5] Therefore, predictive biomarkers that will provide early diagnosis are essential. And descriptive studies are needed in pregnant women with FGR in which feto-maternal etiologies are excluded (genetics etc).

Amphiregulin (AR), a member of the epidermal growth factor (EGF) family, is a growth-regulating glycoprotein with prominent amino acid homology.[6] Expression of AR was found in great numbers of different textures.[7,8] In the female reproductive system, AR has effects on oocyte development, maturation and ovulation by sensing ovulatory luteinizing hormone signaling.[9] AR is the most abundant EGF receptor ligand in chorionic villi and amniotic fluid and can stimulate human chorionic gonadotropin (hCG) expression. It has also been determined that AR may be responsible for trophoblast cell proliferation and invasion in early pregnancy.[10,11] Considering that the pathophysiology of early-onset FGR is associated with inadequate trophoblast invasion, could AR deficiency have a role in early-onset FGR? We hypothesized that maternal serum AR levels of pregnant women with fetuses with early-onset FGR are lower than those of healthy pregnant women.

In light of all these data, the aim was to compare the maternal blood AR levels of pregnant women with early-onset FGR and healthy pregnant women and to correlate them with Doppler findings to determine the association of AR with early-onset FGR.

MATERIAL AND METHODS

The study adhered to the ethical guidelines outlined in the Declaration of Helsinki. Written and signed informed consent was obtained from all participants. Approval was obtained from Başakşehir Çam and Sakura City Hospital Ethics Committee (date: December 27, 2023, no: 2023-667).

DESIGN OF THE STUDY

All cases were selected prospectively from outpatient pregnant women between December 2023 and May 2024, 18-45 years, >20 and ≤32-weeks. Gestational week was determined according to the date of last menstrual period and confirmed with first trimester crown rump length. Pregnant women with no pathology detected in Toxoplasmosis, Rubella, Cytomegalovirus, hepatitis, and human immunodeficiency virus results in blood samples taken at the first visit were included in the study. Pregnant women with a low risk of genetic disease or malformation in the first trimester screening test (nuchal translucency ultrasound & blood sample-pregnancy associated plasma protein A) and no pathologic findings in detailed ultrasonography (level II ultrasound) were included in the study. Obstetric and ultrasonographic examinations of all pregnant women were performed by the same physician (GB) and the same ultrasonography device (Hitachi, Tokyo, Japan and C253 transducer/curvilinear probe) was used. Fetal biometric measurements, percentiles and Doppler findings were evaluated. In Doppler measurements; UmA PI, bilateral UtA PI, ductus venosus PI, middle cerebral artery PI, resistance increase/end diastolic flow loss/reverse flow parameters in UmA and notch positivity in bilateral UtA were evaluated. Delphi consensus methodology was used for FGR diagnosis.[2]

Two groups were formed as FGR and control group (Group C). The group C was selected from healthy pregnant women with a gestational week between 20 and 32-weeks, whose last menstrual period and fetal development parameters were compatible. Approximately 4 mm of venous blood was taken for biochemical and hematological analyses from all pregnant women included in the study. Samples were placed in a tube prepared with ethylenediaminetetraacetic acid and centrifuged (2,600 x g, 10 min, 4˚C) to remove blood and serum. Serum samples were frozen at -80˚C until analysis. Serum samples were analyzed by enzyme-linked immunosorbent assay (ELISA) using human AREG Elisa kit (BT Lab, Shanghai, PRC). AR values of Group FGR and Group C were compared. Differences in laboratory values or Doppler findings between the two groups were analyzed. The relationship between AR values and the diagnosis of FGR and Doppler findings was investigated.

Exclusion criteria were multiple pregnancies, smoking during pregnancy, became pregnant after in vitro fertilization, maternal chronic disease, history

of autoimmune diseases, and the presence of fetal genetic or structural anomalies.

STATISTICAL ANALYSIS

To evaluate the distribution of the data, the Shapiro-Wilk test was used. Variables with normal distribution are shown as mean±standard deviation values and independent sample t-test was used to compare two independent groups. Variables that were not comply with normal distribution are shown with median (minimum-maximum) values and Mann-Whitney U test was used for comparisons between two independent groups. Categorical variables are given as frequencies (n) and percentages (%), and Pearson's chi-square test and Fisher's exact test were used for comparisons. Statistical analyzes were performed in IBM SPSS Statistics 22.0 program (IBM Corp., Armonk, NY, USA). The significance level was taken as a p value of 0.05.

RESULTS

The study included 36 pregnant women with FGR and 36 healthy women. One patient in the healthy group was excluded from the study due to nonconformity in the blood sample. The study was completed with 71 patients in total.

EVALUATION OF DESCRIPTIVE STATISTICS

There was a significant difference between the age of pregnant women with FGR (31.33±6.45) and the control group (27.11±5.23) (p=0.004). There was no statistical difference in parity or gestational week (p=0.369, p=0.699, respectively). When Group FGR and Group C were compared, there was a significant difference in body mass index (BMI) values (31.05±4.63 and 27.86±4.11, p=0.003, respectively). There was no significant difference in the number of abortions between groups (p=0.567) (Table 1). Of the

TABLE 1: Comparison of demographic data, amphiregulin values, Doppler findings and laboratory parameters between groups.

	Group	n	X̄±SD/Median (minimum-maximum)	t/Z	p value
Amphiregulin**	FGR	36	796.65 (21.74-2663.26)	-0.299	0.765
	Control	35	740.21 (360.76-4628.75)		
Albumin**	FGR	36	32 (21-39)	-4.542	<0.001
	Control	35	36 (30-41)		
Age*	FGR	36	31.33±6.45	3.023	0.004
	Control	35	27.11±5.23		
Body mass index*	FGR	35	31.05±4.63	3.043	0.003
	Control	35	27.86±4.11		
Protein/Creatinine in spot urine**	FGR	36	648 (82-12813)	-4.163	<0.001
	Control	35	130 (64-250)		
Pregnancy week**	FGR	36	29 (21-32)	-0.387	0.699
	Control	35	29 (21-32)		
Parity**	FGR	36	0.5 (0-5)	-0.898	0.369
	Control	35	0 (0-4)		
Abort**	FGR	36	0 (0-7)	-0.572	0.567
	Control	35	0 (0-3)		
Middle cerebral artery PI**	FGR	36	1.41 (0.85-2.59)	-0.776	0.438
	Control	35	1.5 (0.52-45505)		
Ductus venosus PI**	FGR	36	0.64 (0.29-1.83)	-1.622	0.105
	Control	35	0.53 (0.21-1.42)		
Umbilical artery PI**	FGR	36	1.53 (0.75-2.59)	-5.2	<0.001
	Control	35	0.98 (0.49-2.2)		
Bilateral uterine artery PI**	FGR	36	1.87 (0.81-2.89)	-6.234	<0.001
	Control	35	0.91 (0.6-1.76)		

p<0.05, *Independent sample t-test; **Mann-Whitney U test; FGR: Fetal growth restriction; PI: Pulsatility index; SD: Standard deviation.

36 patients diagnosed with FGR, 29 of them also had a diagnosis of preeclampsia (PE).

COMPARISON OF LABORATORY PARAMETERS BETWEEN GROUPS

Albumin values were statistically significantly lower in the FGR group compared to the control group (32 vs. 36, p<0.001). Protein/creatinine ratio in spot urine was significantly higher in the FGR group (648 vs. 130, p<0.001) (Table 1).

There was no statistically significant difference in serum AR levels between groups (Group FGR, Group C; 796.65 ng/L, 740.21 ng/L, p=0.765, respectively) (Table 1). Within the FGR group, the mean serum AR values of patients with a diagnosis of FGR accompanied by PE and patients with a diagnosis of FGR alone were similar (FGR+PE, FGR; 943 vs 877, respectively).

COMPARISON OF THE DOPPLER FINDINGS BETWEEN GROUPS

There was a statistically significant difference between the groups regarding UmA PI and bilateral UtA PI values (p<0.05). UmA PI and bilateral UtA PI values of the FGR group participants were higher than the control group participants. No significant difference was observed between the groups in terms of middle cerebral artery PI and ductus venosus PI measurements (p>0.05) (Table 1).

There was a statistically significant difference between the groups regarding UmA changes and notch positivity in bilateral UtA (p<0.05). The rate of increased resistance (n=12, 33.3%), loss of diastolic flow (n=11, 30.6%) and presence of reversed flow (n=4, 11.1%) were higher in the FGR group compared to the control group, while the rate of normal umbilical artery (n=9, 25%) was lower. The rate of notch positivity in bilateral UtA was higher in the FGR group compared to the control group (66.7% vs. 8.6%, respectively) (Table 2).

COMPARISON OF AR VALUES WITH OTHER PARAMETERS

In all participants, there was no statistically significant association between serum AR values and umbilical artery changes, notch positivity in bilateral uterine arteries, presence of oligohydramnios, and mode of delivery (p>0.05) (Table 3). There was no statistically significant correlation between AR values and the presence of oligohydramnios in the FGR group (p>0.05) (Table 4).

DISCUSSION

Within the scope of this study, serum AR levels of patients with FGR were similar to those of healthy pregnant women. Although not statistically significant, the mean AR values were higher in the FGR group. Since the participants included in the study

TABLE 2: Comparison of groups in terms of umbilical artery changes or notch positivity in bilateral uterine arteries.

			Group		
			FGR	C	p value
Umbilical artery changes**	Normal	n	9	33	<0.001
		%	25.0	94.3	
	Resistance increase	n	12	2	
		%	33.3	5.7	
	Diastolic flow loss	n	11	0	
		%	30.6	0.0	
	Presence of reverse current	n	4	0	
		%	11.1	0.0	
Notch in bilateral uterine artery*	Absent	n	12	32	<0.001
		%	33.3	91.4	
	Positive	n	24	3	
		%	66.7	8.6	

p<0.05, *Pearson's chi-square test; **Fisher's exact test; FGR: Fetal growth restriction.

TABLE 3: Examination of amphiregulin values in terms of umbilical artery changes, notch positivity in bilateral uterine arteries, amniotic fluid index, and mode of delivery.

		n	Median (minimum-maximum)	p value
Umbilical artery changes**	Normal	42	764.84 (21.74-4628.75)	0.81
	Resistance increase	14	838.82 (432.91-3115.65)	
	Diastolic flow loss	11	716.21 (514.56-1299.25)	
	Presence of reverse flow	4	774.32 (670.74-967.58)	
Notch in bilateral uterine artery*	Absent	44	756 (360.76-4393.61)	0.631
	Positive	27	810.14 (21.74-4628.75)	
Birth type*	Vaginal	11	656.84 (463.29-3815.97)	0.064
	Cesarean section	48	819.79 (21.74-4628.75)	

p<0.05, *Mann-Whitney U test; **Kruskal-Wallis H test.

TABLE 4: Examination of amphiregulin values of participants in the fetal growth restriction group according to amniotic fluid index.

	Amniotic Fluid Index	n	Median (minimum-maximum)	Z	p value
Amphiregulin	Oligohydramnios	12	831.79 (514.56-2126.32)	-0.705	0.481
	Normal	24	757.27 (21.74-2663.26)		

p<0.05; Mann-Whitney U test.

were prospectively selected in accordance with the Delphi procedure of the international consensus of fetal medicine experts, patients in the FGR group had higher UmA PI or UtA PI values. Additionally, they had umbilical artery changes such as a loss of end-diastolic flow or the presence of reverse flow. The FGR group had lower serum albumin values, higher protein/creatinine ratio in spot urine and high notch positivity in bilateral uterine arteries. These results were consistent with the fact that 29 of the FGR group patients also had a PE diagnosis. AR values were not predictive for oligohydramnios, Doppler changes, PI values, notch positivity, or FGR diagnosis.

Several studies in the literature investigated the predictive or therapeutic effects of serum AR levels on colorectal cancer, acute lung injury, and brain injury.[12-14] There have also been studies examining the effects of AR during pregnancy. In 1995, Lysiak et al. reported that AR expression was absent in placental tissue after the 18th week of gestation in a study using immunohistochemical staining. They also observed an increase in trophoblast proliferation in the existence of exogenous AR.[6] In a study in 2019, AR was also detected in placentas of term pregnant women and it was reported that AR contributes to trophoblast invasion by affecting the MMP9/TIMP-1 ratio.[15] Another study by Fukami et al. found that AR was expressed in syncytiotrophoblasts at all gestational weeks and played an important role in β-hCG release.[16] Unlike these studies, Ramadan et al. examined the relationship between AR and FGR and associated clinical outcomes with AR, in the 3rd trimester. Ramadan et al. determined that serum AR levels of women with fetal growth retardation were upward of healthy pregnant women. However, they stated that it could not be determined whether this increase resulted from compensatory mechanisms since placental tissue was not evaluated.[17] As difference from this study, our study compared the serum AR levels of pregnant women with early-onset FGR between 20-32 weeks with healthy pregnant women. And the AR levels of pregnant women with early-onset FGR were similar to those of healthy pregnant women. This result suggests that in the study of Ramadan et al., compensatory effect may have been observed.[17]

Güler et al. compared serum AR levels between >20-weeks pregnant women with severe PE, healthy pregnant women and non-pregnant control group and found that serum AR levels decreased in pregnant women with severe PE.[18] In this study, the presence

of FGR was not evaluated in patients included in the severe PE group. In addition, the gestational weeks of the participants varied between 25 and 38 weeks. AR levels may have been affected by different trimesters of pregnancy. In our study, it was observed that AR levels of pregnant women with FGR accompanied by PE disease and pregnant women with FGR alone had close mean values, with higher mean values in FGR+PE patients. Additionally, it observed that there was no decrease in AR mean value or overall distribution of patients with FGR+PE compared to the control group.

Consequently, our study is the first study in the literature to analyze the relationship between early-onset FGR and maternal serum AR. The diagnosis of FGR was clearly established by excluding fetal genetic or structural anomalies and applying Delphi criteria. The low AR level in patients with early-onset FGR, which we hypothesized, was not detected in blood samples taken from 20 to 32 weeks pregnant women. The reason for this is that the effect of compensatory mechanisms may have started in our study, too. Determination of AR levels before 20 weeks of gestation, when trophoblastic remodeling mainly occurs, may provide different results.

LIMITATIONS OF THE STUDY

Although the mean AR values of patients diagnosed with FGR or FGR+PE in our study were close to each other and the general distribution was similar, further studies are needed to determine whether the patients diagnosed with PE in our FGR study group affected our study results. In addition, AR expression in the placenta was not investigated in our study. It may be useful to investigate placental AR expression levels in pregnant women with early-onset FGR to elucidate various compensatory mechanisms. There was a significant difference between the two groups in both age and body mass index (BMI) parameters. Study groups consisting of participants with similar age and BMI parameters to exclude known or unknown effects on FGR will increase the power of the study.

CONCLUSION

Maternal serum AR levels may not play a predictive role for early-onset FGR disease and Doppler findings in the UmA, UtA, ductus venosus, middle cerebral artery. In terms of the association between AR and FGR, large population studies stratifying different trimester periods, including placental tissue examinations and excluding patients with PE are needed.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Handan Turhan Karakuş, Serkan Özbey, Mustafa Can Sivas;* ***Design:*** *Handan Turhan Karakuş, Serkan Özbey, Gökhan Bayanmelek;* ***Control/Supervision:*** *Mustafa Can Sivas;* ***Data Collection and/or Processing:*** *Serkan Özbey, Handan Turhan Karakuş;* ***Analysis and/or Interpretation:*** *Serkan Özbey, Handan Turhan Karakuş, Mustafa Can Sivas;* ***Literature Review:*** *Mustafa Can Sivas, Handan Turhan Karakuş;* ***Writing the Article:*** *Handan Turhan Karakuş, Mustafa Can Sivas;* ***Critical Review:*** *Gökhan Bayanmelek, Mustafa Can Sivas;* ***Materials:*** *Serkan Özbey.*

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