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Maternal serum vasohibin-1 and vasohibin-2 concentrations in pregnant women diagnosed with late fetal growth restriction or small for gestational age fetus

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ABSTRACT

Aims: Vasohibin-1, a member of the vasohibin family, is an inhibitor of angiogenesis, while vasohibin-2 stimulates angiogenesis. Placental expressions of vasohibins and their relationship with preeclampsia have been investigated, but their effects on intrauterine fetal growth are unknown. In this context, we aimed to investigate the concentrations of vasohibin-1 and 2 in the serum of pregnant women diagnosed with late fetal growth restriction (FGR) or small for gestational age (SGA) in the third trimester.

Methods: This prospective non-interventional cohort study was conducted on 81 pregnant women, 26 of whom were diagnosed with late FGR, 28 were diagnosed with SGA, and 27 were healthy controls. The groups were compared in terms of serum vasohibin-1 and 2 concentrations in the third trimester.

Results: The groups were similar in terms of demographic characteristics and gestational age at blood sampling for vasohibin 1 and 2 ($p<0.05$). The median vasohibin 1 concentration was determined to be 1227.41 ng/mL in the late FGR group, 1311.15 ng/mL in the SGA group, and 1391.38 ng/mL in the control group ($p=0.139$). The median vasohibin 2 concentration was determined to be 11.24 ng/mL in the late FGR group, 11.86 ng/mL in the SGA group, and 14.34 ng/mL in the control group ($p=0.198$).

Conclusion: Serum vasohibin-1 and 2 concentrations were found to be similar in pregnant women diagnosed with late FGR and SGA and in pregnant women with appropriate-for-gestational-age (AGA) fetuses. Vasohibin-1 and 2 are involved in the regulation of placental angiogenesis, but their roles in intrauterine fetal growth remain unclear.

Keywords: Fetal growth restriction, pregnancy, small for gestational age, vasohibin-1, vasohibin-2

INTRODUCTION

Fetal growth depends on many factors, including the genetic background of the fetus, maternal characteristics, the structure of the placenta, and nutrient supply.[1] In some pregnancies, due to maternal and fetal diseases or placental disorders, the fetus cannot reach its potential growth curve and falls further behind in gestational age. A fetus that is smaller than the gestational age calculated from the last menstrual date confirmed by crown rump length (CRL) measurement in the first trimester is either a fetus with fetal growth restriction (FGR) or a fetus that is small for gestational age (SGA). Although differential diagnosis is not always possible with a single examination, it is important to distinguish FGR from SGA fetuses for clinical management, as fetuses with FGR are at high risk for adverse perinatal outcomes.[2]

FGR is divided into two groups according to the initial gestational week. If FGR started before the 32nd week of gestation in the absence of any fetal congenital anomaly, it is called early FGR; if it started on the 32nd week of gestation or later, it is called late FGR.[3] For the diagnosis of early FGR, three solitary parameters have been defined: fetal abdominal circumference (AC)<3rd , estimated fetal weight (EFW)<3rd percentile, and absent end-diastolic flow in the umbilical artery. In addition, four contributory parameters have been defined: AC or EFW<10th percentile and a pulsatility index (PI)>95th percentile in either the umbilical or uterine artery. For the diagnosis of late FGR, AC or EFW<3rd percentile have been defined as solitary parameters, while the following contributory parameters have been defined: EFW or AC<10th percentile, AC or EFW crossing centiles by >two quartiles on growth charts, and cerebroplacental ratio <5th percentile or umbilical artery PI>95th percentile.[3]

If the fetal AC or EFW measurement is between the 3rd and 10th percentiles but has normal uteroplacental and

fetoplacental circulation, the fetus is considered SGA. SGA involves structurally small, mostly healthy fetuses, who are at lower risk of adverse perinatal outcomes.[4]

Vasohibin-1 and vasohibin-2, two members of the vasohibin family, are the proteins responsible for the regulation of angiogenesis.[5] The human vasohibin-1 gene is located on chromosome 14q24.3, and its 44 kDa protein is post-translationally processed into vasohibin-1A and vasohibin-1 B isoforms.[6] The gene for human vasohibin-2 is located on chromosome 1q32.3, and its protein is composed of 355 amino acid residues.[7] It has been determined that vasohibin-1 and 2 are highly conserved among different species.[8]

Vasohibin-1 is dominantly expressed in endothelial cells in vitro, and its mRNA expression is induced by stimulations with certain angiogenic factors, such as the VEGF/VEGFR2 pathway, and FGF-2 via PKC-d pathway activation.[9] Vasohibin-1 has been found to inhibit the migration and proliferation of endothelial cells in cultures and exhibits feedback anti-angiogenic activity in vivo.[5] The endogenous expressions of vasohibin-2 in endothelial cells have been observed to be very low and independent of VEGF induction. However, vasohibin-2 is mainly expressed in mononuclear cells mobilized from bone marrow to stimulate angiogenesis.[10] Both vasohibin-1 and 2 proteins have been detected in the endothelial cells of developing organs of embryos and have been observed to be widely expressed in endothelial cells of embryonic organs in mid-gestation. It has been shown that from late pregnancy until birth, the expression of these proteins continues to a certain degree to meet the increased angiogenesis demand.[10]

In a study published in 2014, the role of the vasohibin family on angiogenesis in the placenta was evaluated. Wild-type, vasohibin-1$^{(-/-)}$, and vasohibin-2$^{(-/-)}$ mice models were used in the study to explore the function of vasohibins. They showed that the fetal vascular area was higher in the vasohibin-1$^{(-/-)}$ mice and lower in the vasohibin-2$^{(-/-)}$ mice relative to the wild-type mice.[11]

In light of all the above information, we aimed to investigate maternal serum vasohibin-1 and 2 concentrations in pregnant women diagnosed with FGR and SGA in the third trimester. We hypothesized that the concentration of vasohibin-1, an angiogenesis inhibitor, would be higher and that the concentration of vasohibin-2, which stimulates angiogenesis, would be lower in the FGR group compared to the SGA and control groups.

METHODS

The Local Ethics Committee of Ümraniye Training and Research Hospital, İstanbul, Turkiye, approved this study (Date: 16/03/2023, Decision No: 80). The study protocol followed the guidelines set by the Declaration of Helsinki, and informed written consent was obtained from all the participants. This prospective non-interventional cohort study included 81 pregnant women aged between 18 and 45 years who applied to the Gynecology and Obstetrics Clinic of Ümraniye Training and Research Hospital, İstanbul, Turkiye, between April 2022 and June 2022 and were followed up and delivered in our hospital. In the pregnancy follow-ups, 26 pregnant women were diagnosed with late FGR after 32 weeks of gestation and included in the late FGR group, 28 pregnant women were diagnosed with SGA and included in the SGA group, and 27 healthy pregnant women had AGA fetuses in the third trimester and formed the control group. The three groups were formed by matching maternal age, BMI, and gestational week at blood sampling.

Gestational age was calculated according to the last menstrual period and confirmed by fetal CRL measured in the first trimester. Serial fetal biometric measurements and percentiles of the participants were recorded during antenatal follow-ups until birth. Late FGR and SGA groups were created using the Delphi procedure reported in 2016 and the criteria reported in the ISUOG Application Guide published in 2020. Accordingly, pregnant women who did not have congenital anomalies and whose fetal EC or EFW values were below the 3rd percentile at or after the 32nd week of gestation were diagnosed with late FGR. Pregnant women whose fetal AC or EFW values were between the 3rd and 10th percentiles according to gestational age but whose umbilical artery Doppler values were normal were diagnosed with SGA.[3,12]

Multiple pregnancies, those who conceived via in vitro fertilization, and those with any pregestational disease were not included in the study. Pregnant women who had congenital uterine anomalies, were using any anticoagulant drugs, or were smokers were not included in the study. Pregnant women with known chromosomal or structural abnormalities in themselves, their partners, or their fetuses were not included in the study. Pregnant women who were categorized into the high-risk group in fetal chromosomal anomaly screening tests were not included in the study. In addition, those who were diagnosed with FGR and additionally developed gestational hypertension or preeclampsia were not included in the study.

Participants' age, BMI, and obstetric histories were recorded. Fetal biometric and umbilical artery Doppler velocimetry measurements were performed by the same obstetrician on the same ultrasound device (Hitachi Aloka F37 Ultrasound Device).

Approximately 5 mL of blood samples were drawn at any time of the day during the third trimester to investigate serum vasohibin-1 and 2 concentrations in the participants. Blood samples were placed in biochemistry tubes and kept at room temperature for about 20 minutes before centrifugation at 3000 rpm for 10 minutes. After centrifugation, the supernatant was separated and stored at –80 degrees. Serum vasohibin-1 concentrations were measured with the Human Vasohibin-1 ELISA Kit (Bioassay Technology Laboratory, 202 5/F 2 Bldg, 501 Changsheng S Rd, Nanhu Dist, Jiaxing, Zhejiang, China, Catalog No: E6395Hu) using the enzyme-linked immunosorbent assay method.

Serum vasohibin-2 concentrations were measured with the Human Tubulinyl-Tyr carboxypeptidase 2 ELISA Kit (Bioassay Technology Laboratory, 202 5/F 2 Bldg, 501 Changsheng S Rd, Nanhu Dist, Jiaxing, Zhejiang, China, Catalog No: E7212Hu) using the enzyme-linked immunosorbent assay method. For the vasohibin-1 ELISA kit used in the study, the inter-measurement value was 20–7000 ng/L, and the sensitivity was determined to

The late FGR, SGA, and control groups were compared in terms of maternal serum vasohibin-1 and 2 concentrations as the primary outcome of the study.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to check whether the distribution of the data was normally distributed. Descriptive statistical methods (mean, standard deviation, median, IQR, frequency, ratio) were used when evaluating the study data. An independent t-test was used to compare pairs of groups with parametric distribution, while one-way ANOVA was used for comparisons of more than two groups. The Mann–Whitney U test was used to compare pairs of groups with non-parametric distribution, while the Kruskal–Wallis test was used for comparisons of more than two groups. Significant differences resulting from more than two group comparisons were examined using the Tamhane and Tukey tests. Statistical significance was evaluated at $p<0.05$ for all values.

RESULTS

When the late FGR, SGA, and control groups were compared in terms of demographic characteristics, the groups were similar in terms of age, BMI, and parity (p=0.397, p=0.899, p=0.158, respectively). While the gestational week at which ultrasonographic examination was performed was similar in the three groups, fetal biparietal diameter, abdominal circumference, femur length measurement and estimated fetal weight were significantly lower in the late FGR group compared to the other two groups (p=0.981, p=0.005, p=0.001, p=0.009, p=0.001, respectively) (Table 1).

Table 1. Comparison of groups in terms of demographic ve ultrasonographic features

		LateFGR group =26	SGA group n=28	Control group n=27	p-value
Age (Years) Median (IQR)		29.5 (7)	30.5 (11)	29 (9)	0.397*
BMI (kg/m²) Median (IQR)		30.2 (4)	30.4 (3.2)	30.8 (2.2)	0.899*
Parity	Nulliparous n (%)	15 (57.7)	9 (32.1)	11 (40.7)	0.158**
	Multiparous n (%)	11 (42.3)	19 (67.9)	16 (59.3)	
Gestational week at which ultrasonographic evaluation was performed		34.5 (5)	35 (5.5)	35 (5)	0.981*
Biparietal diameter (mm) Median (IQR)		76.5 (14)	82.5 (9.5)	85 (11)	0.005*
Abdominal circumference (mm)Median (IQR)		268 (52)	294.5 (36)	310 (46)	0.001*
Femur length (mm) Median (IQR)		61 (12)	65.5 (9)	67 (9)	0.009*
EstimatedFetal Weight (g) Median (IQR)		1719 (945)	2243 (763.5)	2539 (1029)	0.001*

* Kuruskal Wallis test, ** chi-square test, FGR: fetal growth restriction, SGA: small for gestational age

When the three groups were evaluated in terms of perinatal outcomes, the gestational age at birth was significantly lower in the FGR group than in the other groups, while the number of participants who gave birth by cesarean section was higher (p=0.000, p=0.025, respectively). Newborn weight and height and first- and fifth-minute Apgar scores were significantly lower in the late FGR group, and admission to the neonatal intensive care unit was significantly higher than in the other two groups (p=0.000, for all) (Table 2).

Table 2. Comparison of the groups in terms of perinatal outcomes

		Late FGR group n=26	SGA group n=28	Control group n=27	p-value
		Mean± SD	Mean± SD	Mean± SD	
Gestational age at birth (week) Median (IQR)		37 (3)	39 (2.5)	38 (3)	0.000*
Mode of delivery	Vaginal Birth n (%)	5 (19.2)	14 (50)	14 (51.9)	0.025**
	Cesarean Section n (%)	21 (80.8)	14 (50)	13 (48.1)	
Birth weight (g) mean± SD		2039 ± 575	2664 ± 474	3286 ± 370	0.000***
Birth height (cm) Median (IQR)		45 (3)	48 (3.7)	50 (3)	0.000*
1st minute apgar score Median (IQR)		8 (1)	8 (1)	9 (1)	0.000*
5th minute apgar score Median (IQR)		9 (0)	(1)[9]	10 (0)	0.000*
NICU admission n (%)		14 (53.8)	4 (14.3)	1(3.7)	0.000**

Kuruskal Wallis test, **chi-square test, *** One-way ANOVA test, FGR: fetal growth restriction, SGA: small for gestational age, NICU: neonatal intensive care unit

The three groups were similar in terms of gestational age at which blood was drawn (p=0.981). The three groups were also similar in terms of maternal serum vasohibin-1 and 2 concentrations (p=0.139, p=0.198, respectively). The highest serum vasohibin 1 concentration was detected in the control group, followed by the SGA and late FGR groups (1391.38 ng/mL, 1311.15 ng/mL, 1227.41 ng/mL, respectively) (Figure 1). The highest serum vasohibin 2 concentration was detected in the control group, followed by the SGA and late FGR groups (14.34 ng/mL, 11.86 ng/mL, 11.24 ng/mL, respectively) (Figure 2) (Table 3).

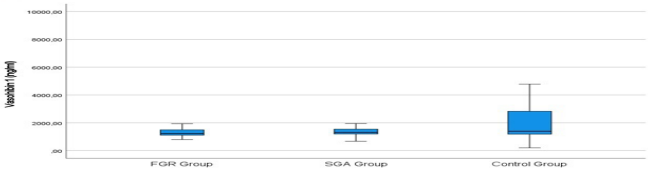

Figure 1. Box plot of serum vasohibin 1 concentrations of FGR, SGA, and control groups

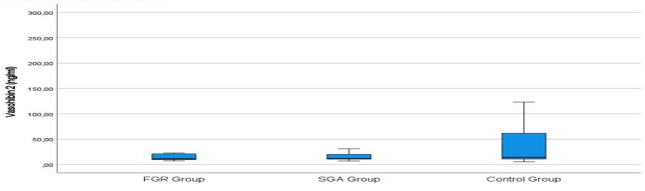

Figure 2. Box plot of serum vasohibin 2 concentrations of FGR, SGA, and control groups

Table 3. Comparison of the groups in terms of maternal serum vasohibin-1 and vasohibin-2 concentrations

	Late FGR Group n=26	SGA Group n=28	Control Group n=27	p-value
Gestational age at blood sampling (weeks) Median (IQR)	34.5 (5)	35 (5.5)	35 (5)	0.981
Vasohibin-1 concentration (ng/mL) Median (IQR)	1227.41 (386.29)	1311.15 (354.03)	1391.38 (2235.63)	0.139
Vasohibin-2 concentration (ng/mL) Median (IQR)	11.24 (11.59)	11.86 (9.39)W	14.34 (52.73)	0.198

Kruskal Wallis Test, FGR: fetal growth restriction, SGA: small for gestational age

DISCUSSION

In this study, the relationships between fetal growth and maternal serum vasohibin-1 and 2 concentrations taken in the third trimester were investigated. Serum vasohibin 1 and 2 concentrations were found to be similar in pregnant women whose pregnancies were complicated by late FGR, pregnant women diagnosed with SGA, and pregnant women with AGA fetuses.

Fetal growth during pregnancy is a dynamic process that is dependent on multiple factors.[13] It has been established that some disorders in the early stages of placental development are associated with adverse pregnancy outcomes, such as fetal growth retardation or preeclampsia.[14,15] In addition to known classical theories such as inappropriate trophoblast migration or insufficient remodeling in the spiral arteries, many molecules that may be related to fetal growth restriction have been investigated in recent years.[16]

The placenta is a multifaceted, transient organ with a very high rate of angiogenesis, organized in a way that allows nutrient intake, waste removal, and gas exchange for the fetus.[17] Placental angiogenesis is regulated by many factors, including the vascular endothelial growth factor (VEGF)/ VEGF receptor system, angiopoietin/TIE receptor system, platelet-derived growth factor (PDGF)/PDGF receptor system, and transforming growth factor ß (TGF- ß)/ TGF- ß receptor system.[18] Among them, the VEGF family is considered the most important factor for promoting angiogenesis in the placenta.[19]

Vasohibin-1 was isolated as a negative feedback regulator of angiogenesis induced in endothelial cells by angiogenesis stimulators, such as VEGF and fibroblast growth factor 2 (FGF-2).[20] Subsequently, a gene homologous to vasohibin-1 was identified and named vasohibin-2.[21] Studies have shown that vasohibin-1, expressed in the termination zone of endothelial cells, inhibits angiogenesis, while vasohibin-2, secreted predominantly from mononuclear cells, promotes angiogenesis at the sprouting front.[10]

Suenaga et al.[11] used a mouse model to demonstrate the role of vasohibins in the placenta. They showed that the placental vascular area in mice with vasohibin-1 gene knockdown was increased compared to the wild type. On the contrary, it was shown that in mice with vasohibin-2 gene knockdown, the vascular area was decreased compared to the wild type. Moreover, vasohibin-2 also plays a role in regulating cell fusion for syncytiotrophoblast formation. In this study, researchers also performed immunohistochemical analysis to determine the localization of vasohibin proteins in the term human placenta. It has been shown that the vasohibin-1 protein is highly expressed in endothelial cells of the villous body, while the vasohibin-2 protein is selectively expressed only in trophoblasts.

Farina et al.[22] investigated various gene expressions in chorionic villus samples taken for fetal karyotype at the 11th week of gestation from pregnant women who developed preeclampsia in the advanced gestational week. It was shown that vasohibin-1 gene expression increased 2.3 times in the group that developed preeclampsia compared to the normal healthy group that did not develop preeclampsia.In 2021, Liang et al.[23] investigated the relationship between preeclampsia and vasohibin-1. In this study, vasohibin-1 expression in placental tissue and vasohibin-1 concentration in the serum of pregnant women who developed preeclampsia during pregnancy were evaluated and compared with normotensive healthy controls. Both serum vasohibin-1 concentration and expression of vasohibin-1 in placental tissue were found to be significantly higher in preeclamptic pregnant women than in normotensive controls. The authors suggested that vasohibin-1 could be used as a biomarker for preeclampsia.

At the beginning of our study, we assumed that the vasohibin 1 concentration in the late FGR group would be higher than in the SGA and control groups, similar to what was observed in preeclamptic pregnant women in Liang et al.'s[23] study. In contrast, we found the lowest serum vasohibin 1 concentration in the late FGR group. Additionally, at the beginning of our study, we expected vasohibin-2 concentration to be lower in the late FGR group than in the SGA and control groups. Consistent with this, we detected the lowest vasohibin-2 concentration in the late FGR group, although the finding was not statistically significant.

To the best of our knowledge, this is the first study to examine maternal serum vasohibin-1 and 2 concentrations in the third trimester in pregnant women diagnosed with late FGR and SGA.

Limitations

The small number of participants and the fact that serum vasohibin-1 and 2 concentrations were evaluated only once in the third trimester are important limitations of this single-center study.

CONCLUSION

In this study, it was determined that serum vasohibin-1 and 2 concentrations were similar in the third trimester in pregnant women diagnosed with late FGR and SGA and in pregnant women with AGA fetuses. Vasohibin-1 and 2 are involved in the regulation of placental angiogenesis, but their roles in intrauterine fetal growth remain unclear. This preliminary study provides a foundation for future studies aimed at examining the roles of vasohibin-1 and 2 molecules in intrauterine fetal growth.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 16.03.2022, Decision No: 80).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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