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Serial measurement of soluble endoglin for risk assessment at the diagnosis of fetal growth restriction

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Abstract

Aim: In this study, we aimed to investigate the soluble endoglin (sEng) levels in pregnant women with fetal growth restriction (FGR) and to examine the possible relation of the sEng levels with the time remaining to delivery and maternal and fetal complications.

Methods: A total of 42 pregnant women diagnosed with FGR were retrospectively reviewed. Using the maternal blood samples it is at the collected 24-37 gestational weeks, the sEng levels were measured. Fetal biometry measurements, umbilical artery, uterine artery, middle cerebral artery Doppler indices were documented.

Results: Of all patients, 17 (40%) were diagnosed with early-onset FGR, while 25 (60%) were diagnosed with late-onset FGR. Abnormal Doppler findings were present in 25 (60%) patients. Of 42 newborns, 18 (42%) were hospitalised in the neonatal unit. The mean sEng level calculated by taking the average of the first and second blood samples was 63.24 ± 49.83 ng/mL. There was no statistically significant difference in the mean sEng levels between those who gave birth within four, three, and two weeks after the diagnosis of FGR and those who did not. There was a positive significant correlation between the mean sEng levels and systolic blood pressure ($r = 0.319$, $P = .04$).

Conclusions: We did not find a statistically significant relationship between the sEng level and the time remaining to the time of delivery in pregnant women with FGR. We found no statistically significant difference in sEng level between the groups in pregnant women with fetuses with FGR with or without maternal and fetal complications.

1 | INTRODUCTION

Fetal growth restriction (FGR) is one of the leading causes of fetal and neonatal morbidity and mortality. Preeclampsia is also an important cause of fetal, neonatal, and maternal morbidity and mortality. Decreased fetal growth and FGR can be caused by maternal factors (eg, hypertension, preeclampsia and maternal malnutrition), fetal factors (chromosomal abnormalities and multiple fetuses), or placental factors, but most cases are because of placental dysfunction.[1] Maternal malnutrition and hypertension may be among the causes leading to the development of placental insufficiency, but nearly 60% of cases are idiopathic, where there is a physiological deficiency in the remodelling of the uterus and placental spiral arteries, which reduces uteroplacental perfusion.[1] Early-onset FGR (<32 gestational week) is more severely associated with the phenotype impairment of placental perfusion causing chronic fetal hypoxia, followed by in utero fetal cardiovascular adaptation.[1] Late-onset FGR (>32 weeks of gestation) is the more common form (80% of FGRs) that usually leads to a lower degree of fetal hemodynamic adaptation with a milder placental insufficiency.[1]

Abnormal placentation is defined as a condition that occurs in the absence of trophoblastic invasion of spiral arterioles into the myometrial strips.[2] Placental insufficiency results from abnormal placental growth and this failure in the vascular alterations are considered to be the main pathology in FGR and preeclampsia.[3] Reduced uteroplacental perfusion is the leading cause of FGR in a healthy fetus.[4] Placental abruption, FGR, and preeclampsia are diseases associated with placental dysfunction. Angiogenic factors decrease and anti-angiogenic factors increase in conditions, such as FGR, preeclampsia, unexplained fetal death and twin-twin transfusion syndrome. The disruption in the delicate equilibrium between these angiogenic and anti-angiogenic factors is the most important triggering factor in the underlying mechanism of placental dysfunction and endothelial damage. Demonstrating the imbalance between angiogenic and anti-angiogenic factors as the cause of placental dysfunction in the pathophysiology is useful in establishing early diagnosis and prognosis.[5]

Soluble endoglin (sEng), a soluble coreceptor of transforming growth factor-beta 1 (TGF-β1) and transforming growth factor-beta 3 (TGF-β3), is an anti-angiogenic protein and inhibits angiogenesis by antagonising the effect of TGF-β. Endoglin (Eng) inhibits nitric oxide synthesis mediated by TGF-β in endothelial cells by antagonising the effect of TGF-β1. Abnormal Engexpression plays a role in several vascular diseases such as telangiectasia, preeclampsia, systemic sclerosis, endometriosis, and tumour angiogenesis.[6-8] Similar to the level of sFlt-1, the level of sEng has been shown to increase in the placentas of preeclamptic pregnant.[9] In addition, the sEng levels increase in the maternal blood weeks before the appearance of clinical signs of preeclampsia.[9] The combination of Eng with sFlt-1 has strengthened endothelial dysfunction with more severe clinical sings of preeclampsia, including glomerular endotheliosis, HELLP syndrome, cerebral oedema and eclampsia.[10] However, it is still unclear that these findings are related to sEng level in FGR.

In the present study, we aimed to investigate the sEng levels in the pregnant women with FGR and to examine the possible relation of the sEng levels with the time remaining to delivery and maternal and fetal complications.

What's known

Endoglin is primarily expressed on endothelial cells and induces pro-angiogenic proliferation and migration of these cells, it has also been demonstrated, erythroid precursors, syncytiotrophoblast, and stromal cells. Soluble endoglin (sEng) inhibits TGFβ1 binding to its receptor, disordering signalling and preventing stimulation of endothelial nitric oxide synthase and vessel dilatation and is known to be elevated in preeclampsia, fetal growth restriction and severe placental disease.

What's new

In this study, we did not find a statistically significant relationship between the sEng level and the time remaining to the time of delivery in pregnant women with FGR. We found no statistically significant difference in sEng level between the groups in pregnant women with fetuses with FGR with or without maternal and fetal complications.

2 | MATERIALS AND METHODS

This single-centre, retrospective study was conducted at Akdeniz University, Faculty of Medicine, Department of Obstetrics and Gynecology from August 2018 to January 2020. A total of 42 pregnant women with FGR who participated in the study of "To investigate the prognostic value of serial soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) (sFlt-1/PlGF) ratio measurements in predicting the timing of delivery and maternal-fetal complications in singleton pregnancies with fetal growth restriction (FGR)" with the Project No TTU-2019-4143 were included. We included pregnant women referred for FGR from 24 + 0 to 36 + 0 weeks of gestation. Multiple pregnancies and pregnant women having a fetus with major congenital anomalies were excluded from the study. Prior to the study, all patients were informed about the nature of the study and a written informed consent was obtained. The study protocol was approved by the Akdeniz University, Faculty of Medicine, Clinical Research and Ethics Committee (26/08/2020-657). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Fetal growth restriction was defined as the sonographic estimated fetal weight (EFW) below the 10th percentile.[11] Early-onset FGR was defined as that diagnosed at 24-32 weeks of gestation, while late-onset FGR was defined as that diagnosed >32 weeks of gestation. Abnormal Doppler findings included end-diastolic flow loss, inverse flow, or umbilical artery Doppler indices above the 95th percentile of pulsatility index (PI), uterine artery Doppler indices above the 95th percentile of PI, and middle cerebral artery (MCA) Doppler indices below the 5th percentile of PI. Fetal Medicine Barcelona calculator application (Spanish v2017 calculator) was used for Doppler calculation.[12] Preeclampsia was diagnosed according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy criteria[13] and defined as a systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg arising after 20 weeks of gestation and proteinuria (≥300 mg on a 24-hour urine collection). The patients who were at 24th–34th weeks of gestation and expected delivery because of fetal distress within one week were administered corticosteroid for fetal lung maturation (two doses of betamethasone 12 mg/day, q.o.d.). The pregnant women expected delivery because of fetal distress within one week, before the 32nd weeks of gestation were given magnesium sulphate treatment for fetal neuroprotection (magnesium sulphate loading dose of 4.5 g, followed by 1 g/hour maintenance treatment over 24 hours).

Archival plasma samples were collected from the antecubital vein on the day of diagnosis of FGR, at the time of conduct of Project No. Plasma from maternal blood samples was first collected when FGR (estimated fetal weight ≤10th percentile) was diagnosed (first sample) and then at one week after the diagnosis (second sample). TTU-2019-4143 and centrifuged at +4°C at 4000 rpm for 5 minutes and stored at −80°C and the second plasma samples collected one week later were obtained. First and second samples were measured and the average of both samples was calculated, and the mean sEng was estimated. Using these samples, maternal sEng levels were analysed using the enzyme-linked immunosorbent assay (ELISA) kit (Catalog No. E0316Hu; Bioassay Technology Laboratory). The lower detection limit of the kit was 0.50 pg/mL, and the upper detection limit was 200 00 pg/mL. According to the statement of the manufacturer; intra-assay coefficient of variation (CV) of sEng kits was below 8%, while the inter-assay CV was below 10%. The sEng levels were analysed in the first and second samples separately and combined, and the average levels were recoded.

Blood pressure measurements during follow-up, fetal biometry measurements using ultrasound, umbilical artery, uterine artery, and MCA Doppler indices were documented. Postnatal data of pregnant women were also noted. Doppler abnormality was defined as at least one of the following: UA pulsatility index (PI) >95th percentile, absent or reversed diastolic flow, mean UtA PI >95th percentile, and fetal MCA PI <5th percentile. Adverse perinatal outcomes were defined as preeclampsia, stillbirth, placental abruption, neonatal unit admission and neonatal death.

2.1 | Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp.). Descriptive data were presented in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Normality assumption was checked using the Shapiro-Wilk test, skewness-kurtosis values and q-q plot graphs. The Fisher's exact test was used to analyse categorical variables. The independent samples *t* test was performed to analyse the significant difference between the normally distributed numerical data of the two groups. The Mann-Whitney *U* test was used, when the normal distribution assumption was unmet. The Spearman correlation analysis was carried out to examine the relationship between the numerical variables. A $P < .05$ was considered statistically significant.

3 | RESULTS

A total of 42 pregnant women with FGR were included in this study. Corticosteroid treatment for fetal lung maturation and magnesium sulphate for fetal neuroprotection were administered to 11 (26%) and 4 (9.5%) of the patients, respectively. Of all patients, 17 (40%) were diagnosed with early-onset FGR, while 25 (60%) were diagnosed with late-onset FGR. Abnormal Doppler findings were present in 25 (60%) patients. During follow-up, preeclampsia developed as a maternal hypertensive complication in six patients (14%). After the first blood sample collection, 23 (55%) of the patients gave birth within four weeks, 20 (48%) within three weeks, and 11 (26%) within two weeks. Of 42 newborns, 18 (42%) were hospitalised in the neonatal unit. The overall perinatal survival rate was 97%.

TABLE 1 Maternal characteristics of the patients

Variable	FGR (n = 42)
Maternal age	28.14 ± 6.17
Height	160.81 ± 6.04
Body weight	66.38 ± 10.7
BMI	25.73 ± 4.36
Nulliparous	
No	24
Yes	18
Smoking status	
No	40
Yes	2
Alcohol use	
No	42
Yes	0
History of preeclampsia	
No	41
Yes	1
History of FGR	
No	39
Yes	3
Trombophilia	
No	39
Yes	3
Low-dose acetylsalicylic acid	
No	34
Yes	8
Low-dose heparin	
No	38
Yes	4
Mean systolic blood pressure	107.67 ± 19.2
Mean diastolic blood pressure	70.24 ± 11.37

The mean sEng level was 63.59 ± 50.86 ng/mL in the first blood samples and 62.89 ± 49.38 ng/mL in the second blood samples. The mean sEng level calculated by taking the average of the first and second blood samples was 63.24 ± 49.83 ng/mL. Maternal characteristics of the patients are summarised in Table 1. Maternal and fetal outcomes are shown in Table 2.

There was no statistically significant difference in the mean sEng levels between those who gave birth within 4, 3 and 2 weeks after the diagnosis of FGR and those who did not. The sEng levels in patients who delivered within 2, 3 and 4 weeks in pregnancies with fetal growth restriction are presented in Table 3. Median (P50), 25th

TABLE 2 Maternal and fetal outcomes

Maternal and fetal outcomes	FGR (n = 42)
Gestational age at the time of FGR diagnosis	31.73 ± 3.16
EFW at the time of FGR diagnosis	1536.79 ± 520.19
EFW percentile at the time of FGR diagnosis	4.57 ± 2.05
Abnormal Doppler findings at the time of FGR diagnosis	
No	17
Yes	25
Time from FGR diagnosis to delivery (day)	30.4 ± 20.72
Gestational age at the time of delivery (week)	36.19 ± 3.11
Birth weight	2091.02 ± 683.66
Birth percentile	5.79 ± 14.48
Type of delivery	
Vaginal delivery	5
C/S	37
5. min APGAR score <7	4
Admission to neonatal unit	
No	24
Yes	18
Corticosteroid used for fetal maturation	
No	31
Yes	11
Magnesium sulphate used for fetal neuroprotection	
No	38
Yes	4
Maternal hypertensive complications	
No	36
Yes	6
1. sEng (ng/mL)	63.59 ± 50.86
2. sEng (ng/mL)	62.89 ± 49.38
Mean 1. and 2. sEng (ng/mL)	63.24 ± 49.83

percentile (P25) and 75th percentile (P75) of the data are presented in Tables 3 and 4.

The patients with FGR were divided into two groups as those with and without preeclampsia. There was no statistically significant difference in the mean sEng levels between the FGR groups with and without preeclampsia ($P = .495$). In addition, the patients with FGR were divided into two groups as those with and without abnormal Doppler findings. There was no statistically significant difference between the mean sEng levels in the FGR group with abnormal Doppler findings and in the FGR group without abnormal Doppler findings ($P = .617$). There was no statistically significant difference between the mean sEng levels in the early-onset FGR and late-onset FGR ($P = .337$). There was no statistically significant difference between the patients whose infants were hospitalised in the neonatal unit and the patients whose infants were not hospitalised in the neonatal unit ($P = .839$). Table 4 shows sEng levels in the early-late fetal growth restriction (FGR), who did develop preeclampsia-who did not develop preeclampsia, who were hospitalised in the neonatal unit-who were not hospitalised in the neonatal unit, who did have abnormal Doppler findings-who did not have abnormal Doppler findings.

According to the correlation analysis, we found a positive and significant correlation between the mean sEng levels and systolic blood pressure ($r = 0.319$, $P = .04$).

4 | DISCUSSION

In the present study, we found no statistically significant relationship between the mean sEng level and the time remaining to delivery in pregnant women with FGR. There was also no statistically significant difference in the mean sEng level between the groups in pregnant women diagnosed with FGR with or without maternal and fetal complications. On the other hand, we found a positive and significant correlation between the mean sEng levels and systolic blood pressure.

In a large-scale, case-control, prospective study, Aswold et al[14] collected serum samples from 26 000 pregnant women at 10th and 23rd weeks of gestation. In the control group, the sEng levels remained stable at 6 ng/mL until 26th week of gestation, followed by a rapid increase. The sEng level in pregnant women with small for gestational age (SGA) was similar to the control group until the 16th gestational week, while the sEng level in the SGA group was consistently higher than the control group afterwards. In this study, the women with high sEng (highest third) at the second sampling had nearly 3.5-fold increased risk for SGA. Similarly, in previous studies, pregnant women with SGA had higher sEng levels.[9,15] Zamarian et al[16] examined the sEng levels in 66 pregnant women at 24th–41st weeks of gestation who were diagnosed with FGR and 64 healthy pregnant women as the control group. The sEng levels were significantly higher in the FGR group, compared with the control group.

The increase in the sEng level in preeclamptic pregnant women was also shown in the study of Reddy et al.[17] Similarly, in a retrospective study, Stepan et al[18] found significantly higher sEng concentrations in the maternal blood in the preeclampsia group, compared with the control group. In the FGR group, the maternal sEng level was also significantly higher than the control group. In our study, the mean sEng level was significantly higher in the FGR group, consistent with the literature. In the study conducted by Laskowska et al,[19] serum Eng levels were compared between the control group, FGR group, preeclampsia group, and preeclampsia group associated with FGR. Serum Eng levels of pregnant women in the FGR group was significantly higher than the control group. The highest sEng level was found in the FGR group with preeclampsia, indicating a statistically significantly higher level than the control group and the FGR group. The sEng level in the preeclampsia group was also significantly higher than the control group. Serum Eng levels were found to be higher in pregnant women with HELLP syndrome and eclamptic pregnant women. Furthermore, the authors found a positive correlation between the systolic blood pressure and sEng levels in FGR and preeclampsia groups. In all groups, there was also a positive correlation

TABLE 3 First, second and mean of first and second measurements of sEng and delivery within 2, 3 and 4 weeks among pregnancies with fetal growth restriction (FGR)

	1.sEng			2.sEng			Mean 1. and 2. sEng		
	Median (P25-P75)			Median (P25-P75)			Median (P25-P75)		
	No	Yes	*P*-value	No	Yes	*P*-value	No	Yes	*P*-value
Giving birth within 2 weeks after diagnosis	37.93 (28.53-80.98)	32.19 (28.85-84.01)	.637	35.06 (26.29-95.18)	43.99 (21.35-84.65)	.864	33.87 (28.69-83.22)	38.25 (25.18-84.33)	.898
Giving birth within 3 weeks after diagnosis	36.42 (28.53-69.35)	38.25 (29.17-142.93)	.669	32.84 (25.34-66.63)	45.51 (29.01-137.59)	.332	33.23 (26.78-69.82)	41.20 (29.80-140.26)	.378
Giving birth within 4 weeks after diagnosis	37.93 (28.53-73.01)	32.19 (28.85-142.69)	.899	34.43 (26.29-85.45)	39.53 (23.11-135.36)	.84	33.87 (28.69-78.68)	38.25 (26.78-139.27)	.87

Note: Mann-Whitney *U* test use, Median: P50, P25: Percentile 25, P75: Percentile 75

TABLE 4 sEng levels in the early-late fetal growth restriction (FGR), who did develop preeclampsia-who did not develop preeclampsia, who were hospitalised in the neonatal unit-who were not hospitalised in the neonatal unit, and who did have abnormal Doppler findings-who did not have abnormal Doppler findings

	Preeclampsia			Abnormal Doppler Value			Neonatal Unit			Onset of FGR		
	Median (P25-P75)			Median (P25-P75)			Median (P25-P75)			Median (P25-P75)		
	Yes (n = 6)	No (n = 36)	*P*-value	Yes (n = 25)	No (n = 17)	*P*-value	Yes (n = 18)	No (n = 24)	*P*-value	Early (n = 17)	Late (n = 25)	*P*-value
1. sEng	62.89 (30.44-142.69)	34.11 (28.69-77.00)	.506	44.31 (29.80-79.23)	30.92 (26.14-84.01)	.505	35.62 (28.85-79.23)	39.61 (29.17-82.50)	.77	50.69 (33.31-79.23)	30.92 (26.77-84.01)	.265
2. sEng	55.95 (30.44-139.82)	35.55 (25.82-85.05)	.577	43.99 (27.25-76.84)	30.44 (26.29-95.18)	.818	34.75 (26.29-76.84)	41.76 (26.14-90.32)	.731	36.66 (30.44-85.45)	31.24 (25.34-84.65)	.473
Mean 1. and 2. sEng	59.42 (30.44-141.26)	33.51 (27.73-80.95)	.495	40.80 (29.89-78.04)	30.44 (26.54-84.33)	.617	36.06 (25.18-78.04)	38.65 (29.00-83.77)	.839	43.68 (31.48-78.68)	30.12 (26.54-84.33)	.337

Note: Mann-Whitney *U* test use, Median: P50, P25: Percentile 25, P75: Percentile 75.

between the sEng level and diastolic blood pressure. In our study, the mean sEng level in the FGR group with preeclampsia was found to be significantly higher than in the FGR group without preeclampsia; however, the difference did not reach statistical significance. Similarly, in our study, we found a positive and significant correlation between the mean sEng levels and systolic blood pressure, but not diastolic blood pressure. In a study by Toft et al,[20] the expression of placental Eng was significantly higher in the pregnant women diagnosed with FGR with SGA and preeclampsia, compared with the preeclampsia and FGR groups. Additionally, Masuyama et al[21] and Purwosunu et al[22] found the increased Eng levels in the placentas of preeclamptic pregnant women with a positive correlation between the systolic blood pressure and Eng and Eng mRNA levels.

Furthermore, Nanjo et al[23] examined maternal serum angiogenic marker profiles within one week prior to delivery in 165 women with singleton pregnancies with gestational hypertension, preeclampsia, and/or FGR with distinct clinical conditions. The sEng level in the preeclampsia group was found to be significantly higher than the term controls. The values in pregnant women with preeclampsia and diagnosed with FGR were comparable to those in the preeclampsia group. However, the sEng level in the FGR group was significantly higher than the control group. In the group with preeclampsia and FGR coexistence, the sEng level was significantly higher than the group with those with preeclampsia or FGR only. On the other hand, in a study conducted by Jeyabalan et al,[24] higher sEng levels were found in the preeclampsia group, compared with normal pregnant women; however, there was no significant difference in the sEng levels between pregnant women diagnosed with FGR and healthy pregnant women.

Currently, there is no effective antenatal treatment for FGR, so delivery of the fetus is the only viable option for a severely affected pregnancy.[25] However, here in the management of pregnancy complicated with FGR; It is necessary to establish a good balance between organ development below its potential because of conical hypoxia, the need for intensive care after early postpartum and the risks of morbidity because of intensive care. Early recognition of FGR and close follow-up with Doppler, NST and biochemical markers and good planning of delivery time seem to be the most important factors in reducing fetal mortality and morbidity.

Although we found no significant correlation between the sEng levels and time remaining to delivery, we found a positive significant correlation between the mean sEng levels and systolic blood pressure. We believe that these findings would provide a contribution to the body of knowledge in the literature. Nonetheless, the relatively low sample size, particularly those with preeclampsia and FGR coexistence, and retrospective nature of the study are the main limitations.

5 | CONCLUSIONS

In conclusion, we did not find a statistically significant relationship between the sEng level and the time remaining to the time of delivery in pregnant women with FGR. We found no statistically significant difference in sEng level between the groups in pregnant women with fetuses with FGR with or without maternal and fetal complications.

Further large-scale, prospective studies are warranted to gain a better understanding of the role of sEng in this patient population and to elucidate the relation of sEng levels with maternal and fetal complications and delivery time.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Akdeniz University, Faculty of Medicine, Clinical Research and Ethics Committee (26/08/2020-657). The study was conducted in accordance with the principles of the Declaration of Helsinki.

DISCLOSURES

The authors have declared no disclosures.

AUTHORS' CONTRIBUTIONS

MED designed the study, collected data, interpreted the data and wrote the manuscript and contributed to revision of the manuscript. AD designed the study, interpreted the data and wrote the manuscript and contributed to revision of the manuscript. IM design the study and contributed to revision of the manuscript. CS contributed to revision of the manuscript. SO and IOK made the biochemical analysis. HK contributed to revision of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Raw data of the study are available upon request to the corresponding author.

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