

Research Article

Çağdaş Özgökçe*, Kazım Uçkan and Ayfer Meral



The relationship between pregnancies complicated with fetal growth restriction and umbilical cord blood endocan concentrations

<https://doi.org/10.1515/tjb-2021-0231>

Received September 25, 2021; accepted February 24, 2022;
published online March 24, 2022

Abstract

Objectives: The main etiological factor in intrauterine growth restriction (IUGR) is the impairment of the fetoplacental unit. Due to the placental endothelial disintegrity and vascular permeability disruptions, endocan has been an interesting molecule to search for associations with IUGR. The aim of this study was to investigate the umbilical cord blood endocan concentrations in IUGR pregnancies.

Methods: This cross-sectional case-control study was conducted on 50 IUGR-complicated (patients) and 50 control pregnancies. The demographics and clinical findings were recruited from records. The umbilical cord blood was studied for endocan concentrations.

Results: The patient group compared to controls had significantly more previous IUGR history, lower maternal weight gain, an earlier gestational week at delivery, and more cesarean sections ($p < 0.001$). The umbilical cord endocan concentrations were significantly higher in patients than in controls ($p < 0.001$). Oligohydramnios ($n = 38$) was significantly higher in the patients and had a significant relationship with high endocan concentrations ($p < 0.001$). Moderate and mild positive correlations were found among endocan concentration and biparietal diameter/head circumference and femur length values, respectively, while a moderate negative correlation was observed in abdominal circumference values ($p < 0.001$).

Conclusions: A significant increase in the umbilical cord blood endocan concentrations was found in IUGR pregnancies.

Keywords: Doppler velocimetry; endocan; intrauterine growth restriction; oligohydramnios; placental insufficiency.

Introduction

Fetal growth restriction (FGR), with a frequency of 5–10%, is generally described as the fetus unable to achieve its genetically-based growth potential [1]. The updated criteria to identify FGR factor in the prenatal measurements using ultrasonography and Doppler velocimetry [2].

The etiology of FGR has a broad spectrum ranging from genetic abnormalities to maternal malnutrition. The most commonly shared pathological mechanism among various etiological factors is uteroplacental perfusion impairment [3]. The uteroplacental unit is essential for proper fetal development, and angiogenesis is the primary process for placenta. Previously, the abnormal activity of a gene, which codes for the production of a vascular endothelial growth factor (VEGF-A), had been shown to be related to FGR [4].

A dermatan sulfate proteoglycan, endothelial-specific molecule-1 (ESM-1), also denoted as endocan, is produced by vascular endothelial cells in various tissues [5]. Among the various functions attributed to the endocan are cell adhesion, the enhancement of vascular permeability, the stimulation of cytokines in inflammation [6, 7], and along with the VEGF, the regulation of the hypoxia-related endothelial injury [8]. The role of endocan has been studied in a range of pathological conditions, such as hypertension (HT), pneumonia, glioma, premature preterm rupture of membranes (PPRM), endometriosis, and preeclampsia (PE) [8–17].

In normal pregnancies, maternal plasma endocan levels were found to decrease with the increased gestational age [18].

In pregnancies complicated with fetal neural tube defects (NTD), amniotic fluid endocan concentrations were

*Corresponding author: Çağdaş Özgökçe, Department of Gynecology and Obstetrics, Van Training and Research Hospital, Erdremit 65170, Turkey, E-mail: cagdasozgokce@gmail.com. <https://orcid.org/0000-0003-4960-4625>

Kazım Uçkan, Department of Obstetrics and Gynecology, Van Eğitim ve Araştırma Hastanesi, Van Training and Research Hospital, Van, Turkey. <https://orcid.org/0000-0002-5576-6789>

Ayfer Meral, Medical Biochemistry, University of Health Sciences, İzmir Bozyaka Education and Research Hospital, İzmir, Turkey. <https://orcid.org/0000-0002-8870-3725>

found to increase proportionally to the gestational age [19]. PE is one of the most researched pregnancy-related pathologies in which the endocan has been studied for its relationship [17]. In one such study, concomitant measurement of endocan in pregnancy-related compartments revealed an increase in maternal plasma while a decrease in fetal plasma and placenta [20]. Yet, in another, endocan was found to increase in the placenta, while no significant change was observed in the maternal plasma in another study [21]. As apparent from those controversial results, no consensus has been reached for the relationship between endocan and PE.

Despite the growing body of evidence on the role of endocan in endothelial function, angiogenesis, and vascular permeability, to the best of our knowledge, there are only two studies in which increased concentrations of endocan in maternal circulation had been associated with FGR [22, 23].

We hypothesized that the fetal circulation would be better represented in the umbilical cord blood due to its inherent structural proximity to the fetus than the maternal plasma. Therefore, we aimed to investigate the relationship between endocan and FGR complicated pregnancies by analyzing its levels in the umbilical cord blood.

Materials and methods

This case-control study was conducted in the Department of Obstetrics and Gynecology in 2020 at Van Training and Research Hospital, Health Sciences University, Van, Turkey. The volunteering participants provided signed informed consent to the study protocol that was in agreement with the Declaration of Helsinki and approved by the Institutional Ethics Committee (Number: 2020/15, Date: 06.08.2020).

Case and control groups

The women aged between 18 and 35 years and followed up in the outpatient clinics of obstetrics were assessed for recruitment in the study. The case group consisted of pregnancies complicated with FGR. The FGR was defined using the following criteria: an abdominal circumference (AC) and an estimated fetal weight (FW) below 3rd centile, absence of umbilical artery (UA) end-diastolic flow (EDF), and an AC/estimated FW below 10th centile combined with a pulsatility index (PI) greater than 95th centile. The presence of at least one parameter before the 32nd gestational week has been accepted for FGR [2, 24]. The pregnancies without FGR were involved in the control group.

The exclusion criteria were the presence of multiple pregnancy, major developmental or chromosomal anomalies, maternal malnutrition, smoking, alcohol use, known infectious disease, previous FGR pregnancy, and detection of placental or umbilical cord anomalies.

Clinical evaluation

The demographics and clinical data were recorded from the medical files. The maternal factors included age, body mass index (BMI), gravidity/parity. The pregnancy-related factors consisted of the method of delivery, weight gain, and complications such as gestational diabetes, PE.

The results of USG investigations involving fetal biometry (biparietal diameter [BPD], femur length [FL], abdominal circumference [AC], head circumference [HC]), amniotic fluid volume (AFV), and Doppler velocimetry consisting of end-diastolic flow (EDF), resistive index (RI), pulsatility index (PI), systolic/diastolic velocity ratio (S/D), middle cerebral artery (MCA), ductus venosus (DV) were noted. The fetal biometry was evaluated by comparing the actual and the corresponding gestational week for that measurement.

The physical examination of the newborns, including gender, weight, height, and APGAR score evaluation, was performed by a neonatologist. The Rohrer's ponderal index (RPI) was calculated using the formula: $RPI = \text{weight (g)} / \text{length (cm)}^3 \times 100$.

Endocan quantification

Umbilical cord blood was collected immediately after clamping during delivery. The plasma aliquots separated by centrifugation at 1,000 g for 15 min were stored at -80°C until the testing date. Enzyme-linked immunosorbent assay (ELISA) was used to quantify the endocan concentration via commercially available "Human Endocan ELISA kit" (human ESM-1) according to the manufacturer's recommendations (Bioassay Technology Laboratory, Shanghai, China). The measurements were carried out using Bio-Tek ELx 800 (Biotek Instruments Inc, Winooski, Vermont/USA).

Statistical analysis

A priori power analysis using the G*Power software (Version 3.1.9.7 for Windows) indicated that 45 pregnancies in each of the cases and the control groups were required to achieve an 80% power with a 95% confidence interval and a 0.7 effect magnitude. Statistical analyses were performed using Jamovi Project (2020), Jamovi (V.1.6.7), and JASP (V.0.14). Descriptive statistics for continuous variables were expressed as mean $\pm$ standard deviation (SD), and median (range). The number of cases and percentages were used to express categorical variables. Data distribution was assessed by a histogram, q-q graphics, and Kolmogorov-Smirnov test, while variance homogeneity was controlled by the Levene test. Mann-Whitney-U, Kruskal-Wallis H, and Dwass-Steel-Critchlow-Fligner tests were used to compare variables between groups. Categorical variables were compared using Pearson Chi-Square, Fisher's Exact, and Fisher Freeman Halton test. A p-value below 0.05 was considered statistically significant.

Results

The study was completed with 50 FGR-complicated (cases) and 50 control pregnancies (controls). No significant

differences in maternal age, gravidity, parity, and BMI were observed between the study groups ($p > 0.05$). The median value of maternal weight gain (14 kg) in cases compared to that of controls (15 kg) was significantly lower ($p=0.040$) (Table 1). Significantly more oligohydramnios was observed in the cases ($n=38$, 76%) than controls ($n=4$, 8%) ($p<0.001$). PE and gestational diabetes were found in 18 (36%) and 6 (12%) of the cases, respectively.

The fetal biometry results indicated that the median gestational weeks for the BPD, HC, FL, and AC in cases were significantly earlier than those in the controls ($p \leq 0.001$). It was observed that the median gestational weeks for the BPD, HC, and FL (38, 37, and 35 weeks, respectively) in cases were later than that for the AC (32 weeks) in the cases. The Doppler velocimetry showed reduced EDF and MCA, and increased RI, PI, and S/D in only 31 newborns in the case group (62%) ($p<0.001$) (Table 2).

The cesarean section was used for delivery in significantly more cases than controls (11 vs. 2, $p=0.007$). The

Table 1: Demographic and clinical characteristics in patients and controls.

	Cases (n = 50)	Controls (n = 50)	p- Value
Maternal factors			
Age, years ^a	24 [18–35]	25 [18–35]	0.704
Gravidity ^a	2 [1–5]	3 [1–5]	0.124
Parity ^a	1 [0–3]	1 [0–4]	0.062
BMI, kg/m ^{2a}	23 [20–30]	23 [21–29]	0.303
Pregnancy factors			
Weight gain in pregnancy, kg ^a	14 [12–18]	15 [12–18]	0.040
Amniotic fluid volume ^b			
Adequate	12 (24)	46 (92)	<0.001
Oligohydramnios	38 (76)	4 (8)	
Neonatal features			
Delivery method ^b			
Normal spontaneous vaginal	39 (78)	48 (96)	0.007
Cesarean section	11 (22)	2 (4)	
Gender ^b			
Male	23 (46)	24 (48)	0.841
Female	27 (54)	26 (52)	
Birth weight, g ^a	2,295 [1,600–2,490]	3,430 [2,890–4,020]	<0.001
Birth length, cm ^a	48 [45–49]	50 [48–50]	<0.001
APGAR score ^b			
<8	37 (74)	8 (16)	<0.001
≥8	13 (26)	42 (84)	
Rohrer's ponderal index (RPI) ^b			
<2.32	42 (84)	2 (4)	<0.001
≥2.32	8 (16)	48 (96)	

^aMedian [min–max]. ^bn (%), BMI, body mass index. Bold p-values indicate statistically significant differences.

Table 2: Fetal biometry and Doppler velocimetry findings.

	Cases (n = 50)	Controls (n = 50)	p- Value
Fetal biometry (gestational week)			
Biparietal diameter ^a	38 [31–40]	39 [37–40]	0.001
Head circumference ^a	37 [31–39]	38 [37–39]	<0.001
Femur length ^a	35 [26–37]	38 [36–40]	<0.001
Abdominal circumference ^a	32 [28–36]	38 [37–40]	<0.001
Doppler velocimetry			
End-diastolic flow (EDF)^b			
Normal	19 (38)	50 (100)	<0.001
Reduced/Absent	31 (62)	0 (0)	
Resistive index (RI)^b			
Normal	19 (38)	50 (100)	<0.001
Increased	31 (62)		
Pulsatility index (PI)^b			
Normal	19 (38)	50 (100)	<0.001
Increased	31 (62)	0 (0)	
Systolic/diastolic velocity ratio (S/D)^b			
Normal	19 (38)	50 (100)	<0.001
Increased	31 (62)	0 (0)	
Middle cerebral artery (MCA)^b			
Normal	19 (38)	50 (100)	<0.001
Reduced	31 (62)	0 (0)	
Ductus venosus (DV)^b			
Normal	48 (96)	50 (100)	0.495
Inverse A wave	2 (4)	0 (0)	

^aThe length values were converted to corresponding gestational week and presented as median [min–max]. ^bn (%), bold p-values indicate statistically significant differences.

gender distribution of the neonates in the patients and controls was similar ($p=0.841$). The median birth height (48 vs. 50 cm) and weight (2,295 vs. 3,430 g) in the case group were significantly lower than those in the controls ($p<0.001$). The grouping based on the APGAR scores revealed that there were more newborn babies with the APGAR score <8 in the cases than the controls (37 vs. 8, $p<0.001$) (Table 1). There were significantly more neonates with RPI<2.32 ($n=42$) in the cases than the controls ($n=8$) ($p<0.001$).

The median umbilical cord endocan concentration in cases (617.5 ng/mL) was significantly higher than in the controls (147 ng/mL) ($p<0.001$). The endocan levels were not correlated with the birth weight and height in both groups ($p > 0.05$). No significant impact of gender and the APGAR groups on the endocan concentrations was seen among the cases ($p=0.231$ and $p=0.274$). Endocan concentrations did not significantly associate with gender, the APGAR and RPI groups, and oligohydramnios in the control group ($p > 0.05$). Significantly higher median concentrations of endocan were found in cases with RPI<2.32 than those with RPI≥2.32 (854.5

Table 3: Endocan levels in the cases and the controls and subgroup analyses of endocan levels within and between the groups.

	Cases (n = 50)		Controls (n = 50)		p ^c
	Endocan concentration, ng/L ^a	CV, %	Endocan concentration, ng/L ^a	CV, %	
	617.5 [178–1824]	75.6	147 [120–176]	11.6	<0.001
Gender^a			Gender^a		
Male (n = 23)	258 [178–1824]	89.2	Male (n = 24)	144.5 [120–176]	<0.001
Female (n = 27)	746 [179–1759]	65.8	Female (n = 26)	150.5 [123–174]	<0.001
p ^b	0.231			0.299	
APGAR score^a			APGAR score^a		
<8 (n = 37)	746 [179–1824]	70.4	<8 (n = 8)	146 [120–171]	<0.001
≥8 (n = 13)	258 [178–1,647]	90.1	≥8 (n = 42)	147 [122–176]	<0.001
p ^b	0.274			0.606	
Rohrer's ponderal index (RPI)^a			Rohrer's ponderal index (RPI)^a		
<2.32 (n = 42)	854.5 [178–1824]	64.6	<2.32 (n = 2)	149.5 [137–162]	0.002
≥2.32 (n = 8)	187 [179–198]	3.3	≥2.32 (n = 48)	147 [120–176]	<0.001
p ^b	<0.001			0.94	
Pre-eclampsia^a			Pre-eclampsia^a		
Present (n = 18)	1,500.5 [1,089–1824]	72	Present (n = 0)	–	
Absent (n = 32)	201 [178–1,055]	14.3	Absent (n = 50)	147 [120–176]	<0.001
p ^b	<0.001			NA	
Oligohydramnios^a			Oligohydramnios^a		
Absent (n = 12)	190 [178–198]	3.5	Absent (n = 46)	145.5 [120–176]	<0.001
Present (n = 38)	1,046.5 [180–1824]	57.5	Present (n = 4)	162.5 [135–169]	<0.001
p ^b	<0.001			0.308	

^aMedian [min-max]. CV, coefficient of variation (%); NA, not applicable. p^b: for intragroup analysis, p^c: for intergroup analysis. Bold p-values indicate statistically significant differences.

vs. 187 ng/mL, $p < 0.001$). The median endocan concentrations in preeclamptic (1,500.5 ng/L) and oligohydramniotic (1,046.5 ng/L) cases were significantly higher than those in the cases without PE (147 ng/L) and oligohydramnios (162.5 ng/L) ($p < 0.001$) (Table 3).

Inter-group analyses revealed that there were significant differences in endocan levels between the cases and controls according to sex, the APGAR and RPI groups, PE, and oligohydramnios ($p < 0.05$). The endocan levels of the controls in each subgrouping were significantly lower than those of the cases (Table 3).

No significant correlations were observed between the endocan and fetal biometry values in the controls ($p > 0.05$). The endocan concentration in the cases had moderate positive correlations with fetal BPD ($r = 0.594$, $p < 0.001$) and HC ($r = 0.552$, $p < 0.001$), mild positive correlation with FL ($r = 0.332$, $p = 0.019$), and a moderate negative correlation with AC ($r = -0.406$, $p < 0.003$). No significant relationships between Doppler velocimetry in the cases and the endocan concentrations were found ($p > 0.05$).

Discussion

In the current study, which represents the first example of research on the relationship between umbilical cord

endocan levels and FGR, we found a significant 4.2 fold increase in the median endocan levels in pregnancies complicated with FGR compared to those without.

The FGR etiology consists of materno-fetal factors and uteroplacental inadequacies [1]. The endothelial disintegrity and dysangiogenesis have been established as important causes of uteroplacental perfusion deficiency, leading to fetal growth restriction [3]. The biochemical responses to FGR have been researched by investigating various molecules like ischemia-modified albumin, plasminogen activator inhibitor-1, and growth-arrest specific protein 6 [25–27]. One of those molecules is endocan, which has been investigated for its relationship with PE. As there are studies that associated the increased maternal blood [12, 18] and fetal [20] endocan concentrations with PE; there are also others with decreased levels of maternal blood [17, 28] and placental [21] endocan levels. In a recent meta-analysis, maternal endocan concentrations in PE pregnancies were concluded to be higher than those in normal pregnancies [14]. Although the current study was not designed for investigating the relationship between PE and endocan levels, we observed that significantly higher mean umbilical cord endocan concentrations were present in the cases (1,500.5 ng/L) that also had PE ($n = 18$) when compared to those (201 ng/dL) in cases without PE ($n = 32$) ($p < 0.001$). The inconsistent results regarding the endocan levels in PE

pregnancies led to the speculations related to the sampling compartment of the endocan. While some researchers suggested that the origin of higher levels of endocan was primarily maternal endothelial cells [18, 20], some studies demonstrated high expressions of endocan in placental decidual cells of hypertensive women [8, 21]. Recently, the regulation of endocan was significantly found to be different between maternal plasma and amniotic fluid [19].

Recently, significantly high umbilical cord blood endocan concentrations had been associated with neonatal pneumonia [15]. Our results indicated a 7-fold more umbilical cord endocan levels than the results reported for neonatal pneumonia. The significant difference in the quantity of endocan between the two studies might potentially be the reflection of different etiologic backgrounds in two separate pathologies [15]. The investigations on the endocan levels in FGR pregnancies are extremely limited [22, 23]. In one of those studies, maternal plasma endocan concentrations were 1.4-fold more than those in normal pregnancies [23]. In the other one, maternations were pronouncedly higher in fetal endothelial cells compared to the maternal ones in hypertensive pregnl plasma endocan concentrations were 1.8-fold more in the FGR group than those of the normals [22]. Here, the difference in umbilical cord endocan concentrations between the FGR pregnancies and controls was 4.2-fold, which was markedly higher than those in the previous results [22, 23]. As one of the critical variables between those studies and ours was the compartment of endocan sampling, we suspected that fluctuations in the levels of endocan in FGR pregnancy could become more detectable in the umbilical cord. Supportedly, Chew et al. found that endocan expressions were pronouncedly higher in fetal endothelial cells compared to the maternal ones in hypertensive pregnancies [8].

In a former study, increased maternal serum endocan concentrations in pregnancies complicated with PPRM pregnancies have been demonstrated [10]. In the current study, the oligohydramnios, which was significantly present in more cases than the controls ($p < 0.001$), had been found to have a significant relationship with the high umbilical cord endocan concentrations ($p < 0.001$). In the present study, we found that the endocan concentrations were significantly higher in the cases than in the controls. Besides, inter-group analyses confirmed that there were significant differences between the cases and controls based on each subgroup. This finding can be regarded as evidence that FGR was the only factor causing higher endocan levels. Due to the limitation inherent to the design of the current study, no causal relationships could be interpreted for that observation; however, for future studies, the potential etiological factors for oligohydramnios, such as the disintegration of the amniotic membrane, increased

permeability of the placental vasculature and subacute leakage of amniotic fluid might be tested along with the endocan levels in oligohydramniotic pregnancies.

The fetal biometry revealed that the mean BPD, HC, FL, and AC in the cases were significantly earlier than those in the controls ($p \leq 0.001$). Furthermore, in the cases, the mean BPD, HC, and FL (38, 37, and 35 weeks, respectively) were later than that for the AC (32 weeks). Type II IUGR was characterized by less affected HC and FL and more affected AC. The marked difference in the mean AC compared to the BPD, HC, and FL in cases could be attributed to the asymmetrical FGR. In the cases, moderate positive and mild positive correlations were found with mean BPD/HC ($r = 0.594/0.552$, $p < 0.001$) and FL ($r = 0.332$, $p = 0.019$), respectively, while a moderate negative correlation was present between endocan concentration and mean AC ($r = -0.406$, $p = 0.003$). Lower AC in FGR had been related to a reduction in glycogen storage and liver size besides abdominal adipose tissue depletion [1]. There are still so many unknowns regarding the role of endocan in pregnancy, so it would be safe to conclude that glucose and fat metabolism might be more related to endocan than the skeletal system in FGR pregnancies as per the results of the current study. To differentiate the type of FGR and to confirm or dismiss the fetal biometry results, the RPI was calculated. When previously reported cut-off values [29] were considered, 84% of the IUGR newborns were found to be below 2.32, which was significantly different from that of the controls ($p < 0.001$). Further analysis indicated significantly higher endocan concentrations in cases with $RPI < 2.32$ compared to cases with $RPI > 2.32$ ($p < 0.001$). As the lower RPI reflects asymmetrical FGR, the presence of more newborns with $RPI < 2.32$ might indicate more asymmetrical IUGR in our patients. Additionally, the increased endocan concentrations in the umbilical cord might be more related to asymmetrical IUGR.

The strengths of the present study need to be expressed. First, the design of the current study presented us with the option to evaluate the relationship between endocan levels and both the intrauterine and neonatal periods. Secondly, the demographic and clinical features of the cases and controls were similar to allow minimizing the ascertainment bias. However, the current results need to be interpreted considering the limitations of the study. First, this was a single-center study with a small size of study group, so the results could not be generalized and extrapolated for larger populations. Second, it would have been better to measure the endocan concentrations concomitantly in all compartments of the materno-fetoplacental unit. Third, the presence of pregnancy-related complications, such as PE and gestational diabetes in the case group should be taken into account as the pathogenetic factors inherent to those

conditions could be the reason for increased endocan levels. Last but not least, the current study design did not allow us to control for all the maternal and fetal comorbid and chronic pathologies that might interfere with the results.

In conclusion, the current results of the first study, in which the umbilical cord blood levels of endocan were significantly increased in FGR pregnancies, providing valuable data for future and larger studies that would be designed to delineate the exact relationship between endocan and FGR.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interest: Authors state no conflict of interest..

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study protocol was in agreement with the Declaration of Helsinki and approved by the Institutional Ethics Committee (Number: 2020/15, Date: 06.08.2020).

References

- Nardoza LM, Caetano AC, Zamarian AC, Mazzola JB, Silva CP, Marcal VM, et al. Fetal growth restriction: current knowledge. *Arch Gynecol Obstet* 2017;295:1061–77.
- Gordijn SJ, Beune IM, Ganzevoort W. Building consensus and standards in fetal growth restriction studies. *Best Pract Res Clin Obstet Gynaecol* 2018;49:117–26.
- Krishna U, Bhalerao S. Placental insufficiency and fetal growth restriction. *J Obstet Gynaecol India* 2011;61:505–11.
- Szentpéteri I, Rab A, Kornya L, Kovács P, Joó JG. Gene expression patterns of vascular endothelial growth factor (VEGF-A) in human placenta from pregnancies with intrauterine growth restriction. *J Matern Fetal Neonat Med* 2013;26:984–9.
- Balta S, Mikhailidis DP, Demirkol S, Ozturk C, Celik T, Iyiso A. Endocan: a novel inflammatory indicator in cardiovascular disease? *Atherosclerosis* 2015;243:339–43.
- Kali A, Shetty KS. Endocan: a novel circulating proteoglycan. *Indian J Pharmacol* 2014;46:579.
- Lee W, Ku S-K, Kim S-W, Bae J-S. Endocan elicits severe vascular inflammatory responses in vitro and in vivo. *J Cell Physiol* 2014; 229:620–30.
- Chew BS, Ghazali R, Othman H, Ismail NA, Othman AS, Laim NM, et al. Endocan expression in placenta of women with hypertension. *J Obstet Gynaecol Res* 2019;45:345–51.
- Zhao T, Kecheng Y, Zhao X, Hu X, Zhu J, Wang Y, et al. The higher serum endocan levels may be a risk factor for the onset of cardiovascular disease. *Medicine (Baltim)* 2018;97:e13407.
- Ovayolu A, Ovayolu G, Karaman E, Yuce T, Turgut A, Bostancieri N. Maternal serum endocan concentrations are elevated in patients with preterm premature rupture of membranes. *J Perinat Med* 2019;47:510–5.
- Adekola H, Romero R, Chaemsaitong P, Korzeniewski SJ, Dong Z, Yeo L, et al. Endocan, a putative endothelial cell marker, is elevated in preeclampsia, decreased in acute pyelonephritis, and unchanged in other obstetrical syndromes. *J Matern Fetal Neonat Med* 2015;28:1621–32.
- Cakmak M, Yilmaz H, Baglar E, Darcin T, Inan O, Aktas A, et al. Serum levels of endocan correlate with the presence and severity of pre-eclampsia. *Clin Exp Hypertens* 2016;38:137–42.
- Tanriverdi T, Kemerdere R, Inal B, Yuksel O, Emre H, Ahmedov M, et al. Serum endocan levels before and after surgery on low-grade gliomas. *Surg Neurol Int* 2017;8:32.
- Lan X, Liu Z. Circulating endocan and preeclampsia: a meta-analysis. *Biosci Rep* 2020;40:BSR20193219.
- Yıldırım E, Turkler C, Demir E, Tuten A, Akcay A. Umbilical arterial endocan levels can predict early neonatal pneumonia: a prospective case-control study. *Early Hum Dev* 2020;142: 104952.
- Güralp O, Acikgöz S, Tüten N, Ekmekci H, Schild-Suhren M, Malik E, et al. Evaluation of serum endocan levels in endometriosis: a case-control study. *Clin Ter* 2020;171: e517–22.
- Lopes AC dos S, Martins SR, Dusse LM, Pinheiro M de B, Alpoim PN. Are endocan plasma levels altered in preeclampsia? *Rev Bras Ginecol Obstet/RBGO Gynecol Obstet* 2021;43:232–4.
- Schuitmaker JH, Cremers TI, Van Pampus MG, Scherjon SA, Faas MM. Changes in endothelial cell-specific molecule 1 plasma levels during preeclamptic pregnancies compared to healthy pregnancies. *Pregnancy Hypertens* 2018;12:58–64.
- Ovayolu A, Ovayolu G, Yuce T, Ozek MA, Dogan I, Bostancieri N. Amniotic fluid concentrations of soluble endoglin and endothelial cell-specific molecule-1 in pregnancies complicated with neural tube defects. *J Perinat Med* 2020;48: 132–8.
- Hentschke MR, Lucas LS, Mistry HD, Pinheiro da Costa BE, Polide-Figueiredo CE. Endocan-1 concentrations in maternal and fetal plasma and placenta in pre-eclampsia in the third trimester of pregnancy. *Cytokine* 2015;74:152–6.
- Chang X, Bian Y, Wu Y, Huang Y, Wang K, Duan T. Endocan of the maternal placenta tissue is increased in pre-eclampsia. *Int J Clin Exp Pathol* 2015;8:14733–40.
- Kucukbas GN, Kara O, Yüce D, Uygur D. Maternal plasma endocan levels in intrauterine growth restriction. *J Matern Fetal Neonat Med* 2020;14:1–6.
- Szpera-Gozdziewicz A, Kosicka K, Gozdziwicz T, Krzyscin M, Wirstlein P, Siemiatkowska A, et al. Maternal serum endocan concentration in pregnancies complicated by intrauterine growth restriction. *Reprod Sci* 2019;26:370–6.
- American College of Obstetricians and Gynecologists. Intrauterine growth restriction. Practice Bulletin-Clinical Guidance 2020-ACOG No: 12. Available from: <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/09/updated-guidance-regarding-fetal-growth-restriction>.
- Andiç E, Karaman E, Kulusarı A, Çokluk E. Association of cord blood ischemia-modified albumin level with abnormal foetal Doppler parameters in intrauterine growth-restricted fetuses. *J Matern Fetal Neonat Med* 2021;34:1–6.
- Seferovic MD, Gupta MB. Increased umbilical cord PAI-1 levels in placental insufficiency are associated with fetal hypoxia and angiogenesis. *Dis Markers* 2016;2016:1–13.

27. Lindqvist PG, Balogh I, Dahlbäck B. Umbilical cord plasma levels of growth-arrest specific protein 6 in intrauterine growth restriction. *Acta Obstet Gynecol Scand* 2010;89:22–6.
28. Szpera-Goździewicz A, Kosicka K, Goździewicz T, Krzyścin M, Wirstlein P, Siemiątkowska A, et al. Serum endocan concentration and its correlation with severity of hypertensive disorders in pregnancy. *J Matern Fetal Neonat Med* 2020;33:2313–9.
29. Owa JA, Adebami OJ. Looking for the best indicator fetal malnutrition: an overview. *Internet J Nutr Wellness* 2006;3: 1–5.