Zeynep Kamil Med J 2021;52(4):165–169
DOI: 10.14744/zkmj.2021.15046

ORIGINAL ARTICLE

Serum endocan concentration in women with placenta accreta

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ABSTRACT

Objective: Placenta accreta was shown to be associated with abnormal attachment, invasion, and penetration of the chorionic villi to the myometrium. Endocan was shown to have a significant role in the regulation of cell adhesion, inflammation, and tumor progression. The aim of this study was to investigate serum endocan levels in pregnant women with and without placenta accreta.

Material and Methods: This study was conducted on 27 pregnant women with placenta accreta, 27 pregnant with total placenta previa, and 27 healthy pregnant women matched for gestational age. Maternal levels of serum endocan were measured with the use of an enzyme-linked immunosorbent assay kit.

Results: A significantly lower median level of endocan was detected in the group with placenta invasion compared to the other two groups (132.2 vs. 153.2 and 296.4). The differences among these three groups were statistically significant.

Conclusion: These findings suggest a possible protective role of endocan in the pathogenesis of placental invasion. It may be utilized as a biomarker for the detection of placenta accreta during early pregnancy.

Keywords: Abnormal placentation, accreta, endocan, placenta previa, placental invasion.

Cite this article as: Yayla Abide Ç, Yenidede İ, Kılıççı Ç, Bostancı E, Eser A, Dağ İ, et al. Serum endocan concentration in women with placenta accreta. Zeynep Kamil Med J 2021;52(4):165–169.

Received: September 10, 2021 **Accepted:** October 02, 2021 **Online:** December 01, 2021
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INTRODUCTION

Direct attachment of chorionic villi to the uterine wall with a partial or complete absence of decidua basalis has been defined to be placenta accreta. Placenta accreta was shown to be associated with abnormal attachment, invasion, and penetration of the chorionic villi to the myometrium. Due to the significant risk for massive peripartum hemorrhage with a great risk of morbidity, prenatal diagnosis of placenta accreta has significant importance for proper management to minimize serious maternal and neonatal complications.[1] Although ultrasonography and magnetic resonance imaging have been proposed to be well-established tools to identify cases with placenta accreta, neither method is sufficient to predict placenta accreta reliably in clinical practice.[2,3] For this reason, several investigations have been conducted to show predictive values of some biochemical and/or biological markers to improve the accuracy of antenatal diagnosis of placenta accreta.[4–7]

Endocan is a human endothelial cell-specific molecule, which was originally cloned from a human endothelial cell in a DNA library in 1996.[8] Endocan is synthesized and released into the circulation by vascular endothelium. Endocan was shown to have a significant role in the regulation of cell adhesion, inflammation, and tumor progression.[9] Endothelial activation/dysfunction was shown to result in increased levels of endocan in the circulation.[10]

To the best of our knowledge, no studies have investigated the role of endocan in placenta accreta patients. Hence, the aim of this study is to investigate serum endocan levels in pregnant women with and without placental accreta.

MATERIAL AND METHODS

A total number of 81 pregnant women, 27 pregnant women with placenta accreta, 27 pregnant with total placenta previa, and 27 healthy pregnant women matched for gestational age who had been diagnosed and treated at the Zeynep Kamil Women and Children's Health Training and Research Hospital between June 2017 and June 2018 were included in this cross-sectional study. The Ethics Committee of our hospital approved the study protocol, and all participants were given detailed instructions and signed informed consent forms before recruitment. The exclusion criteria were multiple pregnancies, premature rupture of the membrane, chorioamnionitis, medical complications including autoimmune disorders, diabetes mellitus, smoking, chronic hypertension, polyhydramnios, inflammation, and prior renal diseases, as well as treatment with aspirin, antihypertensive drugs, nonsteroidal anti-inflammatory drugs, or antibiotics.

The diagnosis of placenta previa was made when the lower edge of placental tissue was within 20 mm of the internal cervical os or it overlapped the cervical os at transvaginal ultrasound examination. The exact distance between the center of the internal cervical os and the leading edge of the placenta was measured by transvaginal sonography after voiding. Prenatal diagnosis of placenta accreta was mainly based on ultrasonography that showed (i) irregularly shaped placental lacunae within the placenta, (ii) thinning of the myometrium overlying the placenta, (iii) loss of retroplacental clear space, and (iv) increased vascularity of the uterine serosa/bladder interface. Placenta accreta was ultimately diagnosed at cesarean delivery if the invasion was detected between the placenta and myometrium. Pathological examinations of specimens were performed in cases of hysterectomy or segmental uterine resection.

Venous blood samples were taken from pregnant women at 24–28 weeks when the patients were admitted to the hospital for routine examination. None of the patients were in labor at the time of the sampling. Serum samples for the determination of endocan were obtained from venous blood samples by the centrifugation of clotted specimen within 30 min. The separated serum samples were stored in several small aliquots at –80°C until assayed. Serum endocan (ESM1) concentrations were measured using a commercially available enzyme-linked immunosorbent assay kit (Catalog Number: EK0752, Boster Biological Technology 3942 Valley Ave Pleasanton, CA 94566, USA). Endocan levels were detected as pg/ml.

To produce a standard curve of optical density (OD) versus endocan concentration, we added specimens, standard samples, and biotin-labeled antibodies to micropores pre-coated with the endocan antibody, and the OD values of the standard samples and specimens were then detected with a microplate spectrophotometer (Smart Microplate Reader; USCN KIT INC.) at a wavelength of 450 nm. The concentration of endocan in the samples was subsequently determined by comparing the OD value of the samples to the standard curve.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences software version 18.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the normality of the distribution of variables. Data were presented as median and interquartile ranges (25–75th quartiles). Comparison between groups was performed using a Mann-Whitney U-test or an independent samples t-test. The relationship between endocan and pregnancy variables was determined by the Spearman Rho correlation test. The independent relationship of serum endocan level with placental invasion anomaly was evaluated by multivariate analysis. The relationship between serum endocan level and placental invasion anomaly was evaluated by ROC curve analysis. Sensitivity and specificity were calculated by determining the optimal cutoff value of serum endocan level. $P<0.05$ was considered statistically significant.

RESULTS

There were significant differences among groups in terms of age and gravidity. Age and gravidity were significantly lower in the control group (Table 1, $p<0.05$).

Post-operative hemoglobin, hematocrit, and white blood cell count were significantly different among groups (Table 2, $p<0.05$).

Duration of operation and hospital stay, gestational age, and birth weight at delivery were significantly different among groups, and median serum endocan level was significantly lower in the group with accreta (Table 3, $p<0.05$).

Placental invasion was significantly positive correlated with gravidity ($r=0.311$, $p=0.005$), parity ($r=0.266$, $p=0.017$), white blood cell count ($r=0.307$, $p=0.006$), duration of operation ($r=0.819$, $p<0.001$), duration of hospital stay ($r=0.464$, $p<0.001$), on the other hand, negatively correlated with the postoperative hemoglobin ($r=–0.477$,

Table 1: Demographic characteristics of groups

	Median	25% IQR	75% IQR	p
Age (years)				0.027
Accreta	33	30	38	
Previa	32	27	38	
Control	27.5	23.75	33.75	
BMI				0.392
Accreta	25.5	23.8	30.8	
Previa	27.7	24.8	29.5	
Control	26.6	24.7	31.6	
Gravidity				0.001
Accreta	3	3	4	
Previa	3	2	4	
Control	2	2	3	
Parity				0.053
Accreta	2	1	2	
Previa	1	0	2	
Control	1	1	2	

IQR: Interquartile range; BMI: Body Mass Index.

Table 2: Hematological findings of groups

	Median	25% IQR	75% IQR	p
Pre-operative hemoglobin (g/dL)				0.881
Accreta	11.1	10.4	12.3	
Previa	11.6	10.7	12.5	
Control	11.4	10.8	12.2	
Pre-operative hematocrit (%)				0.441
Accreta	33.9	31.5	37	
Previa	34.4	32.2	36.2	
Control	35	32.5	37.5	
Post-operative hemoglobin (g/dL)				<0.001
Accreta	8.7	7.6	9.8	
Previa	9.9	9.1	10.8	
Control	10.3	9.1	10.8	
Post-operative hematocrit (%)				<0.001
Accreta	26.3	22.8	29	
Previa	29.2	27.5	32	
Control	32	29.7	33.6	
White blood cell count (×1000/mm^3)				0.033
Accreta	11.8	9.5	13.6	
Previa	10.5	9.1	11.5	
Control	9.9	8.4	11.02	
Platelet (/mm^3)				0.655
Accreta	199.500	180.000	246.000	
Previa	190.000	168.000	240.000	
Control	195.500	169.000	232.000	

IQR: Interquartile range.

p<0.001), HCT (r=–0.524, p<0.001), gestational age at delivery (r=–0.605, p<0.001), birth weight (r=–0.471, p<0.001), and serum endocan levels (r=–0.285, p<0.01).

In multivariate analysis, serum endocan level (beta coefficient = –0.265, p=0.014) was found to be significantly associated with placental invasion anomaly after adjustment for gravidity and parity.

Serum endocan level was a significant predictor for placental invasion with an optimal cutoff value of 184 with 63% sensitivity and 63% specificity (Fig. 1).

DISCUSSION

We hypothesized that endocan as an endothelial cell marker would have a value in predicting placenta accreta. In contrast to general expectations, we found significantly lower serum endocan levels in cases with placenta accreta compared to cases with placenta previa and otherwise uncomplicated pregnancies. Our study is the first study that investigates the expression of endocan in women with placenta accreta. Endocan is a soluble proteoglycan that is secreted from the vascular endothelium. Endocan was proposed to have a role in organ-specific inflammation and endothelium-dependent pathological disorders.[10]

In a previous study on pregnant women with preeclampsia, it was found that plasma endocan levels decreased during pregnancy and increased in early- and late-onset preeclampsia. The author of the study proposed the possible source of endocan to be the maternal endothelial cells but not the placenta.[11]

Preeclampsia is a serious condition, unique for human pregnancies, characterized by generalized maternal systemic inflammatory response associated with generalized dysfunction of endothelial cells.[12] Irregularities in the process of placentation and trophoblast invasion during the development of the placenta have been shown to result in poor placental perfusion and hypertension in the early stages of pregnancy,[13] on the other hand, a recent study on placenta accreta pathophysiology has shown angiogenic and growth factors to be significantly altered at the placental invasion site which resulted in the hyperinvasive trophoblast and placenta accreta.[14] It seems that opposite pathophysiological processes occur during the development of preeclampsia and placenta accreta.

Endocan is a member of the proteoglycan family, and it was reported to be involved in a wide range of diseases including obesity and diabetes. A previous study on pregnant women with gestational diabetes showed that endocan expression is increased in the human placenta from obese women with ges-

Table 3: Duration of operation, duration of hospital stay, gestational age at delivery, birth weight, and endocan levels of the groups

	Median	25% IQR	75% IQR	p
Duration of operation (min)				<0.001
Accreta	90	60	90	
Previa	40	30	55	
Control	30	30	30	
Duration of hospital stay (days)				<0.001
Accreta	3.1	2	4	
Previa	2	2	3	
Control	2	2	3	
Gestational age at delivery (weeks)				<0.001
Accreta	35	34	36	
Previa	37	35	37	
Control	39	38	39	
Birth weight (g)				<0.001
Accreta	2600	2060	2995	
Previa	2901	2620	3260	
Control	3330	3037	3560	
Endocan levels (pg/ml)				<0.001
Accreta	132.1	45.5	259.2	
Previa	153.2	96.9	276.3	
Control	296.4	249.1	546.3	

IQR: Interquartile range.

tational diabetes mellitus, and in response to pro-inflammatory stimuli.[15] Consistently, preeclampsia is associated with intravascular inflammation and endothelial dysfunction. Therefore, it is expected to see high levels of endocan concentrations in these cases which are associated with increased vascular inflammation.[16] In another study, the authors aimed to evaluate the endocan levels in the umbilical cord blood regarding the delivery mode, serum endocan levels were found to be significantly lower in patients who underwent an elective cesarean section with the general anesthesia compared to cases with vaginal or elective cesarean section delivery with spinal anesthesia. The authors of this study indicated a possible change of serum endocan levels based on the delivery mode.[17]

Placenta previa was not found to be associated with fetal growth restriction.[18] These data were also pointed in an older study.[19]

All these data show us that placental pathologies associated with preeclampsia and placental invasion anomalies have opposite mechanisms, which lead to, altered serum markers.

An opposite relationship between placenta previa and preeclampsia has been shown in a previous study, authors of the

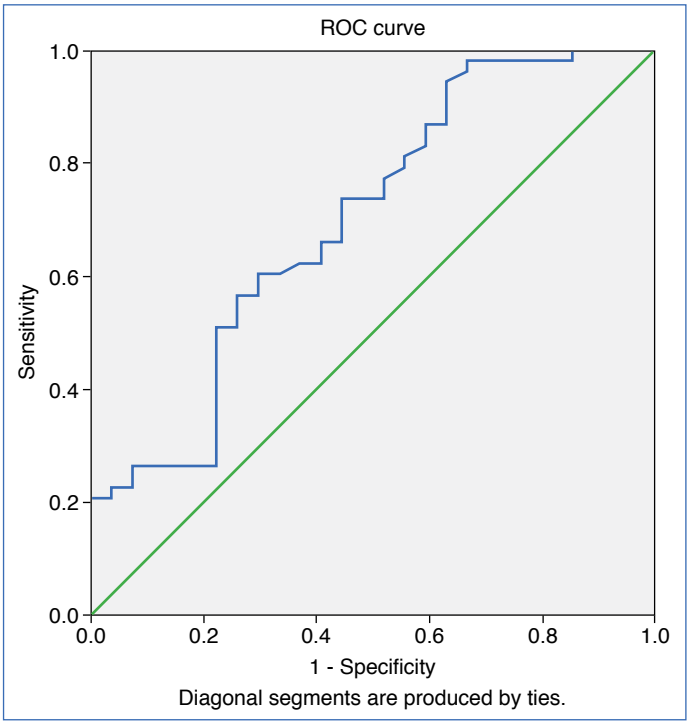

Figure 1: Receiver operating characteristic curve.

study concluded that PP is associated with a significant reduction in the incidence of gestational hypertension – preeclampsia and various types of PE.[20]

CONCLUSION

In contrast to the elevated concentration of endocan in preeclampsia, our data analysis revealed decreased serum endocan levels in cases with placenta accreta. These findings suggest a possible protective role of endocan in the pathogenesis of placental invasion. Hence, endocan may be used as a predictive biomarker for placenta invasion anomalies but our findings must be supported by future studies.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 10.03.2017, number: 49).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ; Design – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ; Supervision – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ; Resource – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ; Materials – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ; Data Collection and/or Processing – ÇYA, İD, İY, EÖ; Analysis and/or Interpretation – EB, EÖ, ÇK, AE; Literature Search – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ; Writing – EÖ, ÇYA; Critical Reviews – ÇYA, İY, ÇK, EB, AE, İD, ÖT, EÖ.

Conflict of Interest: The authors have no conflict of interest to declare.

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

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