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Placental Endocan Expression in Woman With Preeclampsia and its Relation With Maternal and Fetal Outcomes: A Cross-section Study

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Abstract

Objectives: This study aimed to determine placental endocan expression in women with preeclampsia (PE) and its relation to fetal and maternal outcomes.

Materials and Methods: This cross-sectional study was carried out at the Obstetrics Department/Al-Yarmouk Teaching Hospital from January 2020 to October 2020. The study included 90 pregnant inpatient women with PE. The participants were divided into 3 groups including 30 patients with severe PE, 30 non-severe PE, and 30 normotensives. After delivery, placental endocan expression was determined immunohistochemically.

Results: The study showed that endocan was expressed in 44 patients' placenta, all of them were hypertensive vs. 46 negatives for endocan ($P=0.001$), this expression correlated with adverse maternal outcomes including HELLP (haemolysis, elevated liver enzymes, and low platelets count) syndrome (9.1%), Placental abruption (13.6%) and increase rate of CS (63.6%), as well as adverse fetal outcomes ($P=0.001$). included stillbirth (13.6%), birth weight <2500 g (68.2%), Apgar score in 1 min <7 (63.6%) and in 5 minutes <7 (31.8), admission to neonatal intensive care unit (NICU) (31.8%), and (68.2%) delivered preterm.

Conclusions: This study showed a higher expression of endocan in the placenta of women with PE, and it had a positive correlation with adverse maternal and fetal outcomes.

Keywords: Immunohistochemistry, Placental endocan, Pregnancy, Preeclampsia

Introduction

Preeclampsia (PE) is an idiopathic disorder of pregnancy, defined as an elevation of blood pressure (≥140-≥90 mm Hg), ≥ 20 weeks gestation with or without proteinuria and/or multisystem damage (such as hepatic, renal, and central nervous system dysfunctions) (1,2) with a well-recognized risk factor of maternal and fetal adverse outcome (3).

Major advances have been seen in the field of PE. Although the underlying pathogenesis remains elusive (4), systematic inflammatory response and endothelial dysfunction are the primary pathophysiological causes of PE (5).

Endocan, a novel endothelial dysfunction biochemical marker, is involved in this pathophysiological mechanism, and changes in circulating endocan have been seen in women with cardiovascular diseases and hypertension (6,7).

Many studies have investigated the role of endocan in the serum of women with PE which have indicated conflicting results. Some studies have showed an increase in serum level in comparison with normal pregnancy (8-11), while there is no difference in the mentioned level in other studies (12-14).

The last meta-analysis in 2020 by Lan and Liu showed that serum endocan was significantly higher in preeclamptic women than in those with normal pregnancy and that endocan may have a role in the pathogenesis and progression of PE (15).

Meanwhile, only a few studies have investigated the role of endocan in the placenta and assessed its correlation with maternal and fetal outcomes.

This study aimed to evaluate the placental endocan expression in women with PE using immunohistochemistry and determine its relation to fetal and maternal outcomes.

Materials and Methods

This cross-sectional study was carried out at AL-Yarmouk Teaching Hospital, Baghdad, Iraq from January to October 2020.

The study included pregnant women who attended the labor ward or labor room with labor and or elevation of blood pressure and with gestational age (GA) of 26 and < 40 weeks gestation. Women with multiple pregnancies, chronic hypertension, renal disease, vascular disease, diabetes, or women with GA > 40 weeks were all excluded. Full history and examination were taken from all participants, and the blood sample was taken for blood film and there were complete blood count, liver and renal

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Key Messages

- Placental endocan expression increases in preeclampsia, and its presence is associated with adverse maternal and fetal outcomes.

function test, and coagulation profile.

This study included 90 women who were equally divided into three groups (n = 30/each): A) severe PE (Blood pressure of ≥160/110 with clinical and or biochemical indices of severe PE), B) non-severe PE (Blood pressure <160/110 with no clinical and or biochemical indices of severe PE), and C) healthy normotensive pregnant women.

Placental tissues were immediately (<30 minutes) obtained from products of healthy and PE pregnant women after delivery, either delivered vaginally or by caesarian section. Placental tissue was taken halfway between the site of insertion of the cord and the margin of the placenta and fixed with 4% paraformaldehyde solution for immunohistochemical assessment.

The expression of endocan was assessed in each case in the maternal endothelial cell (MEC), fetal endothelial cell (FEC), decidual cell (DC), syncytiotrophoblasts (STC), and cytotrophoblast (CTC) by using the Allred-like scoring system for estrogen receptor in breast cancer. The score was on a scale of 0-5 (depending on the percentage of positive cells): score zero = 0%, score 1 = <1%, score 2 = 1-10%, score 3 = 11-33%, score 4 = 34-66% and score 5 = 67%-100%).

The staining intensity of endocan expression, using an Olympus BX41 microscope at 40× magnification, was scored on a scale of 0–3: negative = 0, weak = 1, moderate = 2, and strong = 3. The total score was calculated by the percentage of positive cells plus the intensity of endocan expression to produce a total score of 0-8. A score of 0-2 was considered negative, while 3-8 as positive (Figure 1).

Data Analysis

The statistical analysis was done by SPSS version 23. The presence of the studied variables was checked using tables (frequency, relative frequency, mean, and standard deviation) and graphs, accordingly. The statistical significance of associations between related categorical data was tested using chi-square test parametric statistical tests like 2 sample *t* tests used to find the statistical significance of differences between 2 independent numerical variables. *P* value < 0.05 was considered significant.

Results

This study included 90 women as sample size who had been divided into three groups: thirty subjects had severe PE, thirty subjects had non-severe PE, and thirty subjects were normotensives. Placental specimens were taken after delivery and sent for immunohistochemistry.

No significant difference was seen regarding mean weeks of gestation and BMI among the studied group. The mean GA of the severe PE group was 32.00 ± 3.216, significantly lower than the non-sever PE group 36.83±1.683 and the control group. Regarding proteinuria among the studied groups, there was a significant difference (P = 0.001) as seen in Table 1. The distribution of complications among the study groups is shown in Table 2.

Endocan Expression in Placental Cells

The expression of endocan was seen in approximately all cell types and all cases in the placenta of women with PE and with high expression. However, it was variable in the normotensive group. In severe preeclampsia, endocan was expressed in MEC (30/30; 100%), FEC (29/30; 97 %), CTC (30/30; 100%), STC (29/30; 97%) and DC (29/30; 97%). In non-severe preeclampsia group, endocan was expressed in MEC (28/30; 93.3%), FEC (23/30; 76.6), CTC (22/30; 73.33%), STC(26/30; 68.67%), DC (23/30; 76.6%). In normotensive women, endocan expression was low: (MEC 19/30; 63.3%). (FEC 11/30; 36.6%), CTC (22/30; 73.33%), STC (23/30; 76.67%), DC (7/30; 23.3%). The difference in expression was significant in MEC, FEC, DC (P = 0.001), and CTC (P = 0.008), and it was also expressed in STC but did not reach statistical significance.

Endocan expression showed strong expression in 66.7% of FEC, CTC and STC. It showed expression in DC 76.7% and 70% in MEC of the placenta of the hypertensive group. On the contrary, normotensive women did not strongly express endocan (Table 3, Figure 2).

Endocan and Maternal Demography

There was no significant difference between maternal age and endocan expression in MEC (P = 0.466), FEC (P = 0.566), DC (P = 0.117), and CTC (P = 0.649). There

Table 1. Demographic Criteria of the Studied Groups

Variables	Severe PE (n=30)	Non-severe PE (n=30)	Normotensive (n=30)	*P* Value
Maternal age (y), Mean ± SD	28.13±5.61	26.50±5.63	25.07±4.81	0.09
GA* (wk), Mean ± SD	32.00±3.21	36.83±1.68	37.63±1.29	<0.001
BMI (kg/m^2), Mean ± SD	28.85±3.82	30.12±4.42	28.20±2.66	0.13
Proteinuria (g/L), No. (%)				
Yes	30 (68.2)	14 (31.8)	0 (0.0)	<0.001
No	0 (0.0)	16 (34.8)	30 (65.2)	

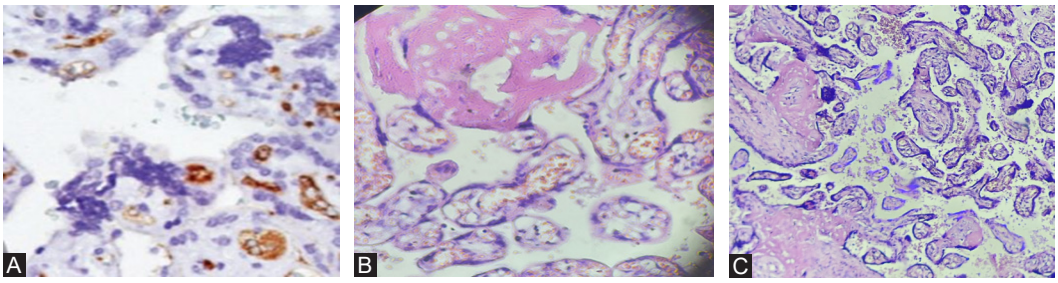

Figure 1. Endocan Expression. (A) Normal Placental Tissue, (B, C) Placental Tissue Positive Endocan Expression (brown Spots).

was also no significant difference in endocan expression between primigravida and multigravida in MEC ($P=0.690$), DC ($P=0.508$), CTC ($P=0.813$), and also no significant difference in endocan expression in MEC ($P=0.97$), DC ($P=.803$), and CTC ($P=0.728$) regarding BMI.

Table 2. Distribution of Studied Cases According to Complications

Variables	Severe PE	Non-Severe PE
HELLP	4 (15.00)	0 (0.00)
Placental abruption	5 (16.60)	1 (3.30)
Visual disturbance	1 (3.30)	0 (0.00)
Stillbirth	5 (16.60)	2 (6.60)
Premature Delivery	29 (96.60)	13 (43.30)

Data presented as n (%).

Endocan Expression and Maternal Outcomes

There was no significant difference in maternal outcomes regarding visual complications ($P=0.304$) (Table 5). But it significantly affected maternal development of HELLP ($P=0.036$) and mode of delivery ($P=0.003$)

Endocan Expression and Fetal Outcomes

Endocan expression significantly affected prematurity, stillbirth, admission to neonatal intensive care unit (NICU), and Apgar score at 5 minutes ($P=0.001$) (Table 6).

Discussion

In the current study, there were comparable values regarding maternal age and BMI, but it showed that the mean GA and birth weight were lower in the PE than in the normotensive women ($P=0.001$). These results were

Table 3. Intensity of Endocan Expression in Maternal Endothelial Cells, Fetal Endothelial Cells, Syncytiotrophoblasts, and Cytotrophoblasts and Decidual Cells

Variables	Severe PE				Non-Severe PE				Control			
	N	WP	MP	SP	N	WP	MP	SP	N	WP	MP	SP
MEC	0.00	3.30	26.70	70.00	6.70	10.00	50.00	33.30	36.70	40.00	23.30	0.00
FEC	3.30	3.30	26.70	66.70	23.30	13.30	36.70	26.70	63.30	23.30	13.30	0.00
CTC	0.00	3.30	30.00	66.70	26.70	6.70	43.30	23.30	26.70	63.30	10.00	0.00
STC	3.30	3.30	26.70	66.70	13.30	16.70	43.30	26.70	23.30	70.00	6.70	0.00
DC	3.30	3.30	16.70	76.70	23.30	13.30	36.70	26.70	76.70	16.70	6.70	0.00

Data presented as percentages.

MEC, maternal endothelial cell; FEC, fetal endothelial cells; STC, syncytiotrophoblasts; DC, decidual cells; CTC, cytotrophoblasts; PE, preeclampsia; N, negative; WP, weak positive; MP, moderate positive; SP, Strong positive.

Table 4. Endocan Expression and Maternal Demography

	MEC		FEC		DC		CTC	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Maternal age*	26.70±5.60	25.50±4.60	26.35±5.40	27.07±5.60	27.20±5.70	25.30±4.70	27.00±5.40	26.00±5.60
P value	0.46		0.56		0.11		0.64	
BMI*	29.30±3.90	27.50±2.70	29.60±4.10	27.80±2.60	29.10±4.00	28.90±3.30	29.00±3.60	29.00±4.40
P value	0.09		0.01		0.80		0.72	
Prime gravida**	31 (40.30)	6 (46.20)	31 (49.20)	6 (22.20)	24 (40.70)	13(41.90)	30 (40.50)	7 (44.00)
Multigravida**	46 (59.70)	7 (53.80)	32 (50.90)	21 (77.80)	35 (59.30)	18 (58.10)	44 (59.50)	9 (56.00)
P value	0.69		0.01		0.90		0.81	

*All data are expressed as mean ± SD. ** Data are expressed as n (%).

MEC, maternal endothelial cell; FEC, fetal endothelial cells; STC, syncytiotrophoblasts; DC, decidual cells; CTC, cytotrophoblasts.

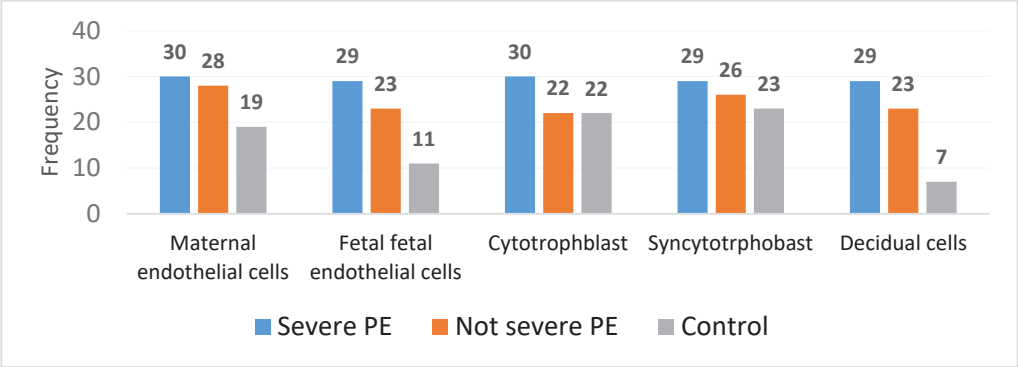

Figure 2. Endocan Expression Positive Rates.

in agreement with Yuksel et al. results on serum endocan concentration in PE women (12) and they were attributed to the early intervention due to severity of the disease. The current study showed a significant increase in endocan expression in maternal placental tissue of PE versus the control group. The results were in agreement with Chang et al results, who first demonstrated that endocan localized in the human placentas and endocan placenta levels were elevated with the progression of pregnancy, suggesting its important role in placental growth. They also found a significant increase in placenta endocan level of patients with PE compared with the normotensive full-term controls, but they found that maternal serum endocan concentration was just slightly higher in PE but with no significance (16).

Our results also were in agreement with Chew et al results which showed high endocan expression in fetal and maternal tissue and positively correlated with adverse pregnancy outcomes (7).

The current study found endocan expression in all placental cell types (MEC, FEC, DC, STC, CTC), and this expression was statistically significant ($p < 0.05$), STC also showed an endocan expression, but this did not reach statistical significance ($P=0.075$). These results again were in agreement with Chew et al. results which showed statistically significant endocan expression in MEC ($P=0.003$), FEC ($P=0.001$), and DC ($P<0.001$) with more statistically non-significant expression in STC and CTC (7).

This study showed that endocan is strongly correlated with adverse maternal outcomes regarding HELLP development ($P=0.036$), placental abruption ($P=0.01$), and mode of delivery ($P=0.003$). It was also associated with adverse fetal outcomes regarding significant effects in stillbirth, LBW, prematurity, admission to NICU, and Apgar score at 5 min ($P<0.05$). Chew et a lresults showed no significant association with adverse maternal complications but a significant association with negative fetal outcome (7). Endocan expression in placental (MEC, FEC, DC, CTC) showed no relation with age, BMI, or parity, and no similar studies to compare with due to limitations in placental endocan studies.

Table 5. Comparison between Placental Endocan Expression and Maternal

	Endocan Expression		*P* Value
	Positive	Negative	
HELLP syndrome	4 (9.10)	0 (0.00)	0.03
Placental abruption	6 (13.60)	0 (0.00)	0.01
Visual disturbance	1 (2.30)	0 (0.00)	0.30
Mode of delivery			
Vaginal delivery	16 (36.40)	31 (67.40)	<0.001
Cesarean delivery	28 (63.60)	15 (32.60)	

Data presented as n (%).
HELLP: haemolysis, elevated liver enzymes, and low platelets count syndrome

Table 6. Placental Endocan Expression and Fetal Outcomes

	Endocan Expression		*P* Value
	Positive	Negative	
Still Birth	6 (13.60)	1 (2.20)	0.04
Birth weight (g)			
<2500	30 (68.20)	7 (15.20)	<0.001
>2500	14 (31.80)	39 (84.80)	
Apgar score in 1 min			
<7	28 (63.60)	22 (47.80)	0.13
>7	16 (36.40)	24 (52.20)	
Apgar in 5 min			
<7	14 (31.80)	2 (4.30)	<0.001
>7	30 (68.20)	44 (95.70)	
Admission to NICU	14 (31.80)	1 (2.20)	<0.001
Prematurity			
Preterm	30 (68.20)	12 (26.10)	<0.001
Full term	14 (31.80)	34 (73.90)	

Data presented as n (%).

Limitations

The reason for these conflicting data among the studies may be due to differences in the sample size and lack of standardization of the assays used to determine endocan, controversies in methodological approaches, or the fact

that PE is a multifactorial disorder.

Conclusions

Endocan was expressed strongly in the placenta of the woman with PE, and its expression may be related to adverse maternal and fetal outcomes. This expression did not show to be affected by maternal age, BMI, and parity.

Authors' Contribution

Conceptualization: Fadia Alizzi.
Methodology: Fadia Alizzi.
Formal analysis: Shatha J Kadhim.
Data curation: Shatha J Kadhim.
Writing–original draft: Fadia Alizzi.
Writing–review and editing: Fadia Alizzi.
Supervision: Fadia Alizzi.
Project administration: Fadia Alizzi.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The protocol of the study was approved by the Scientific Council of the Iraqi Board of Obstetrics and Gynecology and the written informed consent was obtained from all individuals.

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