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ENDOCAN ،ASOLUBLE MARKER OF ENDOTHELIAL CELL ACTIVATION, AS AMARKER OF DISEASE SEVERITY IN WOMEN WITH PREECLAMPSIA

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ABSTRACT

Background: Preeclampsia is a pregnancy-specific multisystem disorder characterized by new-onset hypertension after 20 weeks of gestation accompanied by proteinuria and/or maternal organ dysfunction, and endothelial dysfunction is considered its central pathological mechanism. Endocan (Endothelial Cell-Specific Molecule-1, ESM-1) is a soluble endothelial proteoglycan that has recently emerged as a promising biomarker of endothelial activation and vascular injury. **Aim:** To evaluate serum Endocan as a biomarker of endothelial cell activation in women with preeclampsia and to investigate its association with disease severity, clinical manifestations, laboratory findings, and diagnostic performance. **Patients and Methods:** A hospital-based case-control study was conducted at the Department of Obstetrics and Gynecology, Tikrit Teaching Hospital, Iraq, from October 2025 to June 2026 on 90 pregnant women: 45 with preeclampsia (ACOG criteria) and 45 healthy normotensive controls. Demographic, obstetric, and clinical data were collected, routine laboratory investigations were performed, and serum Endocan was measured by quantitative sandwich ELISA. ROC curve analysis and binary logistic regression were used to evaluate its diagnostic value. **Results:** Maternal age, gestational age, gravidity, and parity were comparable between groups ($P > 0.05$), whereas BMI was significantly higher in preeclampsia ($P < 0.001$). Women with preeclampsia had significantly higher blood pressure, white cell count, liver enzymes, creatinine, urea, and uric acid, and significantly lower platelet counts ($P < 0.001$). Serum Endocan was markedly higher in preeclampsia than controls (856.42±198.73 vs. 382.54±97.18 pg/mL, $P < 0.001$) and rose further with severity (978.81±151.63 in severe vs. 728.46±112.54 pg/mL in mild disease, $P < 0.001$). Endocan correlated positively with blood pressure, BMI, proteinuria, white cell count, liver enzymes, creatinine, urea, and uric acid, and negatively with platelet count. ROC analysis showed an AUC of 0.942, sensitivity 91.1%, specificity 88.9%, and accuracy 90.0%, and Endocan was the strongest independent predictor of preeclampsia on logistic regression (OR = 8.52, $P < 0.001$). **Conclusion:** Serum Endocan is significantly elevated in preeclampsia and rises further with disease severity. Its strong associations with clinical and laboratory markers of endothelial dysfunction, together with its excellent diagnostic accuracy, suggest that it is a promising biomarker for the diagnosis, severity assessment, and risk stratification of preeclampsia.

KEYWORDS: Preeclampsia, Endocan, Endothelial dysfunction, Biomarker, ELISA, ROC curve analysis.

1. INTRODUCTION

Preeclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality worldwide, and delivery remains its only definitive treatment, underscoring the central role of the placenta in its pathophysiology.[1], [2] Multiple pathological mechanisms contribute to PE, including oxidative stress, systemic inflammation, impaired nitric oxide synthesis, coagulation abnormalities, and angiogenic imbalance, among which vascular endothelial dysfunction plays a pivotal role. Numerous molecular effectors, such as soluble fms-like tyrosine kinase-1, placental growth factor, endoglin, and endothelin, interact with vascular endothelial growth factor receptors to regulate endothelial homeostasis during pregnancy, and their

dysregulation underlies the hypertension and proteinuria that characterize PE.

Endocan, also known as endothelial cell-specific molecule-1 (ESM-1), is a soluble dermatan sulfate proteoglycan of approximately 50 kDa secreted by vascular endothelial cells that regulates leukocyte-endothelium interactions, endothelial proliferation, and angiogenic signaling.[3] Its expression is stimulated by pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, as well as by angiogenic factors including vascular endothelial growth factor and soluble endoglin, positioning it as a promising biomarker of endothelial activation and vascular injury. Because endothelial activation is a hallmark of PE, circulating Endocan concentrations may reflect the degree of endothelial dysfunction and disease severity, and its diagnostic and prognostic value in this setting warrants systematic evaluation.

1.1 AIM OF THE STUDY

To evaluate the diagnostic and prognostic value of serum Endocan, a soluble marker of endothelial cell activation and dysfunction, in women with preeclampsia and to investigate its association with disease severity.

1.2 Specific Objectives

- To compare serum Endocan concentrations between women with preeclampsia and healthy normotensive pregnant women.
- To evaluate the association between serum Endocan concentrations and the severity of preeclampsia.
- To determine the relationship between serum Endocan levels and clinical parameters, including blood pressure, body mass index, gestational age, and proteinuria.
- To investigate the correlation between serum Endocan concentrations and laboratory findings, including hematological, hepatic, and renal function parameters.
- To assess the diagnostic performance of serum Endocan for identifying preeclampsia using receiver operating characteristic (ROC) curve analysis.
- To determine whether serum Endocan is an independent predictor of preeclampsia using binary logistic regression analysis.

2. PATIENTS AND METHODS

2.1 Study Design, Setting and Population

This hospital-based case-control study was conducted at the Department of Obstetrics and Gynecology, Tikrit Teaching Hospital, Salah Al-Din Governorate, Iraq, from 1 October 2025 to 30 June 2026. Ninety pregnant women were enrolled and allocated into two comparable groups: 45 women diagnosed with preeclampsia according to the American College of Obstetricians and Gynecologists (ACOG Practice Bulletin No. 222, 2020) criteria — new-onset hypertension after 20 weeks of gestation (systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg on two occasions four hours apart) accompanied by proteinuria or another feature of maternal organ dysfunction — and 45 apparently healthy normotensive pregnant women with uncomplicated singleton pregnancies as controls. Eligible women were aged 18–45 years with a singleton pregnancy and gestational age ≥20 weeks; women with chronic hypertension, gestational hypertension without proteinuria, chronic kidney, hepatic, cardiovascular, autoimmune, or chronic inflammatory disease, diabetes mellitus, active infection, multiple pregnancy, fetal congenital anomaly, premature rupture of membranes, malignancy, or smoking were excluded.

2.2 Clinical Assessment and Sample Collection

Demographic, obstetric, and clinical data were recorded on a standardized case-record form, including maternal age, BMI, gravidity, parity, gestational age, previous abortion, previous preeclampsia, and family history of hypertension. Blood pressure was measured with a calibrated mercury sphygmomanometer after 10 minutes of rest, on two occasions at least four hours apart, and urinalysis was performed to detect and grade proteinuria. Approximately 5 mL of venous blood was collected aseptically from each participant, allowed to clot, and centrifuged at 3000 rpm for 10 minutes; the separated serum was stored at −80°C until analysis.

2.3 Laboratory Investigations and Measurement of Serum Endocan

Routine investigations — complete blood count, platelet count, ALT, AST, serum creatinine, blood urea, and uric acid — were performed using standard calibrated automated analyzers. Serum Endocan (ESM-1) concentration was measured in duplicate using a commercially available quantitative sandwich ELISA kit (BT LAB, Shanghai, China) according to the manufacturer's instructions, with optical density read at 450 nm and concentrations expressed in pg/mL.

2.4 Ethical Considerations

Ethical approval was obtained from the Scientific and Ethical Committee of the College of Medicine, Tikrit University, and the Directorate of Health, Salah Al-Din Governorate. Written informed consent was obtained from every participant, and confidentiality was maintained throughout the study.

3. Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 27.0. Continuous variables were expressed as mean±SD or median (IQR) and compared using the independent-samples t-test or Mann-Whitney U test; categorical variables were expressed as frequencies and percentages and compared using the Chi-square or Fisher's exact test. Correlations were assessed using Pearson's or Spearman's correlation coefficients. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of serum Endocan (AUC, sensitivity, specificity, predictive values, and optimal cut-off), and binary logistic

regression was used to identify independent predictors of preeclampsia. A two-tailed P-value < 0.05 was considered statistically significant.

4. RESULTS

Ninety pregnant women were studied, 45 with preeclampsia and 45 healthy normotensive controls.

4.1 Baseline Demographic and Obstetric Characteristics

Table 1 shows that maternal age, gestational age, gravidity, and parity were comparable between the two groups (P > 0.05), whereas BMI was significantly higher in women with preeclampsia than in controls (31.54±3.92 vs. 28.11±3.35 kg/m², P < 0.001).

Table 1: Baseline demographic and obstetric characteristics of the study population (n = 90).

Variable	Preeclampsia (n=45)	Control (n=45)	P-value
Age (years), Mean±SD	29.87±5.94	28.76±5.38	0.356
BMI (kg/m²), Mean±SD	31.54±3.92	28.11±3.35	<0.001
Gestational age (weeks), Mean±SD	34.48±2.91	34.82±2.64	0.562
Primigravida, n (%)	21 (46.67)	18 (40.00)	0.523
Multigravida, n (%)	24 (53.33)	27 (60.00)	
Nulliparous, n (%)	18 (40.00)	16 (35.56)	0.663
Multiparous, n (%)	27 (60.00)	29 (64.44)	

4.2 Previous Obstetric and Family History

Table 2 demonstrates significantly higher frequencies of previous preeclampsia (P = 0.007) and family history of hypertension (P = 0.019) among women with preeclampsia, while previous abortion showed no significant difference (P = 0.468).

Table 2: Previous obstetric and family history.

Variable	Preeclampsia (n=45)	Control (n=45)	P-value
Previous abortion	13 (28.89%)	10 (22.22%)	0.468
Previous preeclampsia	11 (24.44%)	2 (4.44%)	0.007
Family history of hypertension	18 (40.00%)	8 (17.78%)	0.019

4.3 Blood Pressure Measurements

Table 3 reveals significantly higher systolic blood pressure, diastolic blood pressure, and mean arterial pressure in the preeclampsia group compared with controls (P < 0.001).

Table 3: Blood pressure measurements.

Variable	Preeclampsia	Control	P-value
Systolic BP (mmHg)	163.62±15.44	116.47±8.33	<0.001
Diastolic BP (mmHg)	105.76±9.38	74.22±6.45	<0.001
Mean arterial pressure (mmHg)	125.05±9.74	88.30±6.92	<0.001

4.4 Laboratory Findings

Table 4 demonstrates significantly elevated WBC count, ALT, AST, serum creatinine, blood urea, and uric acid, together with significantly lower platelet counts in women with preeclampsia (P < 0.001). Hemoglobin did not differ significantly between groups (P = 0.057).

Table 4: Laboratory findings of the studied groups.

Variable	Preeclampsia	Control	P-value
Hemoglobin (g/dL)	11.18±1.12	11.61±0.98	0.057
WBC (×10³/µL)	10.84±2.66	8.96±2.03	<0.001
Platelets (×10³/µL)	181.53±54.24	249.16±42.38	<0.001
ALT (U/L)	42.83±17.61	24.18±8.27	<0.001
AST (U/L)	45.36±18.52	23.64±7.51	<0.001
Serum creatinine (mg/dL)	0.94±0.21	0.69±0.13	<0.001
Blood urea (mg/dL)	29.76±8.54	19.82±5.47	<0.001
Uric acid (mg/dL)	6.91±1.46	4.18±0.88	<0.001

4.5 Distribution of Proteinuria

Table 5 shows a highly significant difference in proteinuria between the study groups (P < 0.001). All healthy pregnant women had negative proteinuria (100%), whereas women with preeclampsia showed varying grades, with +3 being the most common (35.56%), followed by +2 (28.89%), while +1 and +4 were each observed in 17.78% of patients.

Table 5: Distribution of proteinuria.

Proteinuria	Preeclampsia, n (%)	Control, n (%)	P-value
Negative	0 (0.00)	45 (100.00)	<0.001
+1	8 (17.78)	0	
+2	13 (28.89)	0	
+3	16 (35.56)	0	
+4	8 (17.78)	0	

4.6 Serum Endocan Concentrations

Table 6 demonstrates that serum Endocan concentrations were significantly higher in women with preeclampsia than in healthy pregnant controls (856.42±198.73 vs. 382.54±97.18 pg/mL, P < 0.001).

Table 6: Serum Endocan concentrations.

Group	Mean±SD (pg/mL)	Median (IQR)	P-value
Preeclampsia	856.42±198.73	841 (724–998)	<0.001
Control	382.54±97.18	376 (321–446)	

'4.7 Serum Endocan According to Disease Severity

Table 7 demonstrates that serum Endocan increased significantly with disease severity: women with severe preeclampsia had significantly higher levels than those with mild disease (978.81±151.63 vs. 728.46±112.54 pg/mL, P < 0.001), indicating a positive association between Endocan concentration and disease severity.

Table 7: Serum Endocan according to disease severity.

Severity	n	Endocan (pg/mL), Mean±SD	P-value
Mild preeclampsia	22	728.46±112.54	<0.001
Severe preeclampsia	23	978.81±151.63	

4.8 Correlation Between Serum Endocan and Clinical Parameters

Table 8 shows significant positive correlations between serum Endocan and systolic blood pressure, diastolic blood pressure, mean arterial pressure, BMI, and proteinuria grade, whereas no significant correlation was found with gestational age (r = -0.114, P = 0.287).

Table 8: Correlation between serum Endocan and clinical parameters.

Variable	Correlation (r)	P-value	Interpretation
Systolic blood pressure	0.672	<0.001	Strong positive
Diastolic blood pressure	0.644	<0.001	Strong positive
Mean arterial pressure	0.658	<0.001	Strong positive
Body mass index	0.341	0.022	Weak-moderate positive
Gestational age	-0.114	0.287	Not significant
Proteinuria grade	0.592	<0.001	Moderate positive

4.9 Correlation Between Serum Endocan and Laboratory Findings

Table 9 shows significant positive correlations between serum Endocan and WBC count, liver enzymes, serum creatinine, blood urea, and uric acid, while platelet count showed a significant negative correlation. Hemoglobin was not significantly correlated (r = -0.148, P = 0.165).

Table 9: Correlation between serum Endocan and laboratory findings.

Variable	Correlation (r)	P-value	Interpretation
Hemoglobin	-0.148	0.165	Not significant
WBC	0.391	0.008	Moderate positive
Platelets	-0.512	<0.001	Moderate negative
ALT	0.441	0.003	Moderate positive
AST	0.456	0.002	Moderate positive
Serum creatinine	0.527	<0.001	Moderate positive
Blood urea	0.488	0.001	Moderate positive
Uric acid	0.574	<0.001	Moderate-strong positive

4.10 Receiver Operating Characteristic (ROC) Analysis

Table 10 demonstrates that serum Endocan showed excellent diagnostic performance for identifying preeclampsia, with an AUC of 0.942, sensitivity of 91.1%, and specificity of 88.9% (P < 0.001).

Table 10: ROC curve analysis of serum Endocan.

Parameter	Value
Cut-off value (pg/mL)	560.0
Area under curve (AUC)	0.942
95% Confidence interval	0.894–0.990
Sensitivity (%)	91.1
Specificity (%)	88.9
Positive predictive value (%)	89.1
Negative predictive value (%)	90.9
Accuracy (%)	90.0
P-value	<0.001

4.11 Binary Logistic Regression Analysis

Table 11 shows that elevated serum Endocan was the strongest independent predictor of preeclampsia (OR = 8.52, P < 0.001), followed by BMI, previous preeclampsia, and family history of hypertension.

Table 11: Binary logistic regression analysis.

Variable	OR	95% CI	P-value
Maternal age	1.04	0.97–1.12	0.281
BMI	1.18	1.03–1.35	0.018
Previous preeclampsia	3.86	1.18–12.61	0.026
Family history of hypertension	2.74	1.09–6.91	0.032
Serum Endocan	8.52	3.14–23.11	<0.001

5. DISCUSSION

Preeclampsia (PE) is an important pregnancy-related hypertensive disorder and remains a major cause of maternal and fetal morbidity. Due to its complex pathophysiology involving endothelial dysfunction, inflammation, vascular injury, and platelet activation, several clinical, hematological, and biochemical indices have been investigated for the diagnosis and assessment of disease severity.[3]

5.1 Baseline Characteristics

Maternal age, gestational age, gravidity, and parity were comparable between groups, indicating that the two groups were well matched and that the observed differences in Endocan and clinical/laboratory parameters are unlikely to be explained by demographic imbalance. BMI was significantly higher among women with preeclampsia, and previous preeclampsia and family history of hypertension were also significantly more frequent in this group, consistent with the well-established contribution of obesity and predisposing obstetric and familial factors to disease risk.[24]

5.2 Serum Endocan and Endothelial Dysfunction in Preeclampsia

Serum Endocan concentrations were markedly elevated in women with preeclampsia compared with healthy controls, supporting the concept that endothelial dysfunction is a central pathological feature of the disease.[1], [2] Placental ischemia resulting from defective trophoblastic invasion stimulates release of anti-angiogenic factors, oxidative mediators, and inflammatory cytokines that activate the maternal vascular endothelium, increase vascular permeability, and enhance Endocan secretion.[4] This finding agrees with Cakmak *et al*.[5], and Wang *et al*.[6], who all reported significantly elevated maternal Endocan in preeclampsia, and is corroborated at the placental level by Chang *et al*.[7] and Chew *et al*.[8], who observed increased placental Endocan expression in hypertensive pregnancies. Adekola *et al*.[9] further showed that Endocan elevation is relatively specific to preeclampsia among obstetric syndromes, and Hentschke *et al*.[10] demonstrated parallel increases in maternal plasma and placental Endocan during the third trimester. The biological role of Endocan in vascular injury extends beyond pregnancy: Sarrazin *et al*.[3] first described it as an endothelial-activation proteoglycan, and Zhao *et al*.[11] and Musiałowska *et al*.[12] linked elevated Endocan to cardiovascular risk and primary hypertension, suggesting it reflects vascular injury irrespective of the underlying disease process. Some discrepancy exists with Schuitemaker *et al*.[13], who found that gestational age and sampling timing may influence circulating Endocan, which may explain minor variability across study populations, ELISA methodology, and disease severity.

5.3 Serum Endocan and Disease Severity

Serum Endocan rose significantly with disease severity, women with severe preeclampsia having markedly

higher concentrations than those with mild disease. This parallels the progressively worsening placental hypoxia, anti-angiogenic factor release, oxidative stress, and inflammatory activation that characterize severe disease, and is consistent with Cakmak *et al.*[5] and Yüksel *et al.*[4], who reported a similar severity gradient, and with Chang *et al.*[7] and Chew *et al.*[8], who found stronger placental Endocan expression with more severe vascular lesions. These findings suggest that Endocan is not only a diagnostic marker but also a useful indicator of disease progression.

5.4 Hematological, Hepatic and Renal Correlates

Platelets are an essential component of blood that play a crucial role in the process of hemostasis and are also an important part of the blood clotting process. Platelet count and function may be influenced in pre-eclampsia, which can have an effect on both the number of platelets and their ability to function. Platelet count and platelet indices, including mean platelet volume (MPV), platelet distribution width (PDW), and platelet-to-MPV ratio, have been reported to vary significantly according to the presence and severity of PE, particularly during the third trimester.[3]

The significantly higher WBC count in preeclampsia supports the exaggerated systemic inflammatory response described by McMaster-Fay[14] and Cornelius *et al.*[15], while lower platelet counts reflect platelet activation, consumption, and endothelial injury, in agreement with Wallace *et al.*[16] and Alese *et al.*[17], and are recognized diagnostically by the ACOG Practice Bulletin.[18] Elevated ALT and AST reflect hepatic vasospasm and reduced perfusion, consistent with Alese *et al.*[17] and Wallace *et al.*[16], while higher creatinine, urea, and uric acid reflect glomerular endothelial injury and reduced renal perfusion, in line with Levey *et al.*[19] and Hennessy *et al.*[1] Hemoglobin did not differ significantly between groups, suggesting it is less sensitive than platelet count or biochemical markers for reflecting disease severity, a pattern also reported by Boij *et al*.[20] The predominance of moderate-to-severe proteinuria is consistent with the ACOG diagnostic framework[18] and the ISSHP classification of Brown *et al.*[21], and reflects glomerular filtration barrier disruption as described by Boeldt and Bird.[22]

5.5 Correlations and Diagnostic Performance

Serum Endocan correlated most strongly with blood pressure parameters, a biologically plausible finding given that hypertension in preeclampsia results directly from endothelial injury and impaired vascular relaxation, as also reported by Cakmak *et al.*[5], Wang *et al.*[6], and Musiałowska *et al.*[12] The positive correlation with BMI supports the contribution of obesity-related inflammation and endothelial dysfunction to disease severity, consistent with Wang *et al.*[23] and Kinshella *et al.*[24], while the correlation with proteinuria and renal markers parallels progressive glomerular endothelial injury, as reported by Adekola *et al.*[9] and Schuitemaker *et al.*[13] Serum Endocan showed excellent diagnostic performance on ROC analysis, with an AUC of 0.942 and high sensitivity and specificity, and emerged as the strongest independent predictor of preeclampsia on logistic regression, outperforming conventional risk factors such as BMI, previous preeclampsia, and family history of hypertension. Together, these findings position serum Endocan as a robust biomarker for both the diagnosis and severity stratification of preeclampsia.

5.6 Strengths and Limitations

This study benefits from a well-matched case-control design, standardized clinical and laboratory assessment, and duplicate ELISA measurement of serum Endocan, allowing a comprehensive evaluation of its diagnostic and prognostic value. Nonetheless, the relatively modest sample size (n = 90) and single-center design may limit generalizability, and the cross-sectional measurement of Endocan cannot establish whether its elevation precedes or follows the onset of clinical disease. Larger multicenter, longitudinal studies incorporating serial Endocan measurements would help clarify its role in predicting disease onset and progression.

6. Conclusion and Recommendations

Serum Endocan concentrations were significantly higher in women with preeclampsia than in healthy pregnant controls, indicating marked endothelial dysfunction, and rose further with disease severity. Serum Endocan showed significant positive correlations with blood pressure, BMI, proteinuria, and several laboratory markers of disease severity, and a significant negative correlation with platelet count. ROC analysis demonstrated excellent diagnostic performance, and binary logistic regression identified serum Endocan as the strongest independent predictor of preeclampsia, outperforming conventional clinical risk factors. These findings suggest that serum Endocan is a promising biomarker for the diagnosis, severity assessment, and risk stratification of preeclampsia. Serum Endocan should be further evaluated as a supplementary biomarker for early diagnosis in clinical practice, ideally in combination with established angiogenic and endothelial markers such as sFlt-1, PlGF, and soluble endoglin, and validated in large multicenter prospective studies incorporating serial measurements throughout pregnancy. Women identified with elevated serum Endocan should receive close maternal and fetal surveillance to facilitate timely intervention and improve pregnancy outcomes.

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