Pro Index | Journal of Science in Medicine and Life
Volume: 3 Issue: 8 Year: 2025
ISSN: 2992-9202 | http://journals.proindex.uz

Serum Endothelial Specific Molecule -1(EMS-1) and Uric Acid Levels in Severe Preeclampsia

Sura Adnan Abbas
Al-Elwiya Maternity Teaching Hospital

Bushra M Majeed
Al-Kindy College of Medicine, University of Bagdad, Iraq

Abstract: It is estimated that anywhere from 2% to 8% of all pregnancies are affected by the pregnancy-specific condition known as preeclampsia. Preeclampsia continues to be a prominent cause of maternal and neonatal morbidity and mortality around the world, particularly in poor socioeconomic circumstances and in third-world nations. It is thought that between 3 and 10 percent of all pregnancies are impacted with serious illness, which can have an adverse effect on multiple organ systems. Preeclampsia and the problems that might arise from it are among the major causes of maternal death around the world. The purpose of this research was to investigate the relationship between endocan and uric acid levels in severely preeclamptic women.

According to the findings of this study, women who were experiencing severe preeclampsia had higher levels of both serum uric acid and endocan (EMS-1). When it comes to predicting a negative outcome for the pregnancy, the performance of serum endocan seems to fall short.

Key points: preeclampsia, Endothelial molecule, Uric acid.

1. Introduction

After 20 weeks of pregnancy, preeclampsia is diagnosed if the mother's blood pressure is consistently high (systolic > 140 mmHg and diastolic > 90 mmHg). Thrombocytopenia (platelet count 150 000 /l), renal insufficiency (serum creatinine concentration > 1.1 mg/dl), impaired liver function (raised concentrations of liver transaminases to twice the normal), pulmonary edema, or cerebral or visual problems at presentation are all considered to be associated with new-onset hypertension. [1, 2].

In most cases, PE clears itself after birth due to placental and maternal vascular insufficiency, impacts about 3-5% of all birth. [3] The woman and fetus are at elevated risk for significant morbidity even though over 90% of cases present in the late preterm, term, or postpartum period and have poor maternal, fetal, and infant outcomes. The remaining 10% of instances manifest themselves prematurely (34 weeks), putting the infants at risk for all the complications that come with being born prematurely. Preeclamptic patients who live with the condition for a long time are at higher risk for cardiovascular and renal illness. [3]

It's important to remember that proteinuria isn't always necessary to diagnose new-onset hypertension if other indications of severe end-organ failure are present. Intrauterine growth restriction, preterm birth, and the resulting rise in neonatal morbidity are the primary causes of

concern. The most significant risk factors for adverse perinatal outcomes are uteroplacental insufficiency, placental abruption, and a small maternal age at delivery. [4]

*Email: Bushramajeed@kmc.uobaghdad.edu.iq

1.1 Classification of hypertensive disorders in pregnancy

NICE is the UK's national health and care research institute. In the United Kingdom, hypertension in pregnancy is being treated according to the guidelines outlined in CLINICAL GUIDELINE 107. The following is a list of the NICE definitions related to hypertension in pregnancy. [5]

A. Those with a systolic blood pressure of 140–149 mm Hg and a diastolic blood pressure of 90–99 mm Hg have mild hypertension.

B. Systolic blood pressure between 150 and 159 mm Hg; diastolic blood pressure between 100 and 109 mm Hg; class B hypertension.

C. Diastolic blood pressure greater than 110 mm Hg and systolic blood pressure of 160 mm Hg or higher constitutes severe hypertension, category C.

D. Chronic hypertension, which is defined as hypertension present at the booking appointment or before 20 weeks, or if the woman is already on antihypertensive medication when sent to maternity care. The underlying cause may be primary or secondary.

E. Gestational hypertension, or hypertension that develops throughout pregnancy but doesn't cause noticeable proteinuria until after 20 weeks.

F. Preeclampsia, or severe proteinuria and hypertension, is diagnosed after 20 weeks of pregnancy.

G. Eclampsia, or G. Preeclampsia, is a form of convulsions.

H. Extremely high blood pressure or significant biochemical and hematological damage characterize severe preeclampsia.

I. Significant proteinuria is defined as a 24-hour urine collection result of more than 300mg protein or a urinary protein/creatinine ratio of more than 30mg/mmol.

J. Hemolysis, high liver enzymes, and low platelets (HELLP) syndrome, a condition characterized by these three symptoms. HELLP syndrome is a kind of preeclampsia that can occur with or without hypertension. [6]

1.2 Epidemiology

Preeclampsia kills the lives of about 50,000 women annually around the world. Preeclampsia occurs in 2%-10% of pregnancies, albeit this range varies widely depending on the population under study and the diagnostic criteria used. Scotland had an incidence rate of 5.8%, while Australia's rate was 14.1%. About 5% to 8% of pregnant women worldwide experience this, and it can have devastating effects on both the mother and the unborn child. Although there has been encouraging progress in reducing maternal death due to the illness, it is still one of the leading causes of maternal mortality in affluent countries. Preeclampsia largely affects fetal well-being in industrialized countries, where maternal mortality owing to the condition has been minimized, through intrauterine growth restriction, preterm birth, low birth weight, and perinatal death. At the time of antenatal booking, a risk assessment can be made based on the analysis of risk factors and the underlying evidence base, allowing for the development of an appropriate monitoring routine to detect preeclampsia during the remainder of the pregnancy. Clinicians may benefit from being aware of the most significant population-level risk factors for preeclampsia, which include advanced maternal age, family history, obesity, a lack of previous pregnancies, a high number of pregnancies, pregnancy following assisted reproductive technology, and diabetes mellitus. A model that can predict individual PE risk must be developed if we are to see an increase in PE screening. [7, 8]

In regions with high rates of maternal mortality, eclampsia, rather than preeclampsia, is the leading cause of death. Preeclampsia during labor and delivery increased by 25%, but eclampsia reduced by 22% according to the United States National Hospital Discharge Survey. [9]

Renal failure, stroke, cardiac malfunction or stoppage, coagulopathy, and liver failure are among examples of the severe morbidity associated with preeclampsia and eclampsia. Preeclampsia was the second highest cause of obstetric critical care unit admissions in a study of hospitals managed by Health Care America Corporation; behind only obstetric hemorrhage. [10,11]

1.3 Pathophysiology

The placenta is the site of the disease's first pathogenesis in PE. It is possible for the condition to exhibit itself in the absence of fetal tissue (molar pregnancy), and it will only disappear when the placenta has been delivered. Although the exact cause of preeclampsia is unknown, it is known that both maternal and fetal/placental factors play a role in the disease's pathogenesis. [13, 14]

Defective trophoblastic invasion, a key event in the pathophysiology, can result from abnormal interactions between fetal trophoblasts and maternal cells. 13% of the cytotrophoblast cells travel through the decidua's spiral arteries but stop short of the myometrium. Additionally, spiral artery remodeling and decreased placental perfusion are thought to contribute to oxidative stress and the release of inflammatory substances into the maternal circulation.[15]

Shallow placentation results in a defective placenta and spiral arteries do not mature into big arterial channels. In addition to atherosclerosis, this may contribute to inadequate placental perfusion, which is hypothesized to be what sets off preeclampsia. Changes in agent synthesis in the placenta as a result of decreased perfusion lead to activated and damaged endothelial cells. Endothelial dysfunction and cell injury from ejected microvilli are caused by trophoblast products, which in turn contribute to this disease. Increased sensitivity to otherwise normal endogenous pressures is a hallmark of endothelial dysfunction. This causes the coagulation cascade to be activated and leads to an increase in vascular permeability. Poor placental perfusion and endothelial dysfunction are two potential causes of preeclampsia. [16, 17]

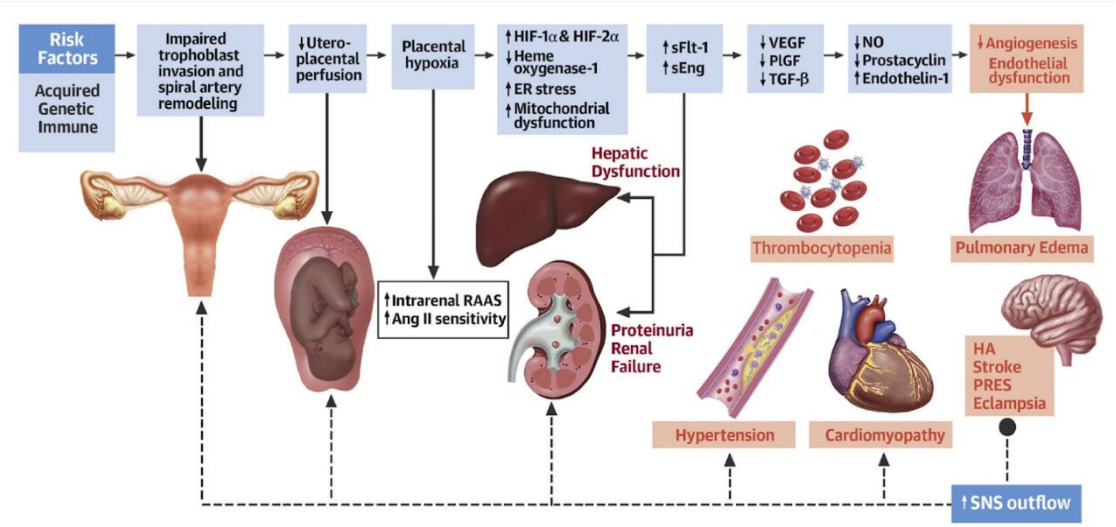

Figure 1: Pathogenesis of preeclampsia**.** [18]

2. Patients and Methods.

2.1 Study Design and data collection time

From January 1, 2022, through October 1, 2022, researchers at Al-Elwiya Maternity Teaching Hospital, Baghdad analyzed data from a control case study.

The study protocol was authorized by the Iraqi Board of Medical Specialization's Scientific Council of Obstetrics and Gynecology Specialization and the Al-Elwiya Maternity Teaching Hospital.

2.2 Study patients and sample size

The study included (90 pregnant women) in 3rd trimester (after 28 weeks) had been equally divided into 2 subgroups:

GROUP I: Included 45 pregnant were normotensives (uncomplicated pregnancy)

GROUP II: Among the group were 45 pregnant women who had presented with severe preeclampsia (defined as systolic blood pressure of 160 mmHg or higher or diastolic blood pressure of 110 mmHg or higher, on at least two occasions at least 4 hours apart, when the patient is on bed rest with proteinuria).

The inclusion criteria for severe preeclamptic women are:

- Singleton fetus
- Gestational age 3rd trimester 28-40 weeks
- Protein in urine 300mg or more.

Exclusion criteria for severe preeclamptic women are:

- Multiple pregnancies
- Diabetes mellitus
- Active infection
- Women in Labor
- Renal disease
- Cardiovascular disease

2.3 Sample Collection and Data

Each participant's blood was tested for a variety of parameters including complete blood count, liver function, renal function, uric acid, and endocan.(EMS-1)

On the day of diagnosis, around 5 mL of venous blood was collected from each pregnant lady with severe preeclampsia or uncomplicated pregnancy and placed into a gel tube (the yellow tube) to assess the endocan level. Separated serum was frozen at 80 degrees Celsius until analysis could be performed. Additionally, 5 mL of midstream urine was tested for albumin concentration using a dipstick. Enzyme-linked immunosorbent assay (EL-ISA), an enzymatic diagnostic kit measuring uric acid, was used to determine the serum endocan level.

2.4 Methods

- The patients' ages ranged from 18 to 40.
- The study's purpose was explained to all participants.
- Everyone who took part was well into their third trimester of pregnancy.

All patients who participated in our study gave their verbal consent after we explained the study's purpose in great detail.

- A complete history, physical examination, blood pressure reading, abdominal exam, obstetric exam, laboratory investigation, and sonographic examination were performed on all participants.

- Following a brief period of rest, the patient's blood pressure was taken using a mercury sphygmomanometer.
- All cases were investigated by sending a complete blood count, liver function test, kidney function test, albumin urine test, and uric acid and Endocan serum measurements.
- Every woman who took part in the study was given a thorough questionnaire to fill out about their health and medical history, current conditions, and medications. After at least 10 minutes of resting with the correct sized cuff, blood pressure was taken with the patient lying on their left side using a mercury sphygmomanometer.

2.5 Adverse pregnancy outcome.

Included maternal and fetal morbidity, or one or more serious CNS, cardiorespiratory, hepatic, renal, and haematological morbidities as:

Maternal outcome

- Placenta abruption
- Eclamptic fit
- Immanent eclampsia
- HELLP Syndrome
- CNS manifestations
- Renal problem

Fetal outcome:

- Intrauterine death
- Low birth weight: less than 2500g
- Preterm
- Admission to Neonatal Care Unit.

3. Results

3.1 Patient's characteristics.

There were a total of 90 individuals participating in this trial; 45 had normal pregnancies with no complications, and 45 had severe preeclampsia.

Table 1 displays the results showing that there was no statistically significant difference between women experiencing an uncomplicated pregnancy and those with severe PE throughout their third trimester.

Table 1: Comparing patients who have severe preeclampsia to those who have an uncomplicated pregnancy regarding their clinical characteristics.

Clinical Characteristics	Uncomplicated pregnancy NO. 45(%)	Severe Preeclampsia NO.45 (%)
Maternal age (years)		
18-25 years	20 (44.4%)	15(33.3%)
25-34 years	8(17%)	19 (42.2%)
≥35	7(15.5%)	11(24.4%)
Gestational age (weeks)		
28-31w+6d	4(8.8%)	8(17%)

32 – 36w+6d	17(37.7%)	12(27%)
≥37 weeks	24(53.3%)	25(56%)
Parity		
Prim parity	18(40%)	10 (22%)
Multiparity	27(60%)	35(78%)

3.2 *Blood pressure*

The calculated Mean ± SE values for systolic and diastolic pressure in severe preeclampsia patients and healthy control groups as depicted in Table 2 and Figure 2. The consequences revealed significant differences in systolic and diastolic pressure ($p<0.001$) between study groups.

Table 2: Average systolic and diastolic pressure values of uncomplicated pregnancy and severe preeclampsia.

Parameter	Mean ± S. E	
	Uncomplicated pregnancy 45	**Severe Preeclampsia 45**
SBP (mmHg)	12.8±1.56	15.6±2.02
DBP (mmHg)	7.3±1.01	9.9±0.96
P-value	0.0001	0.0001

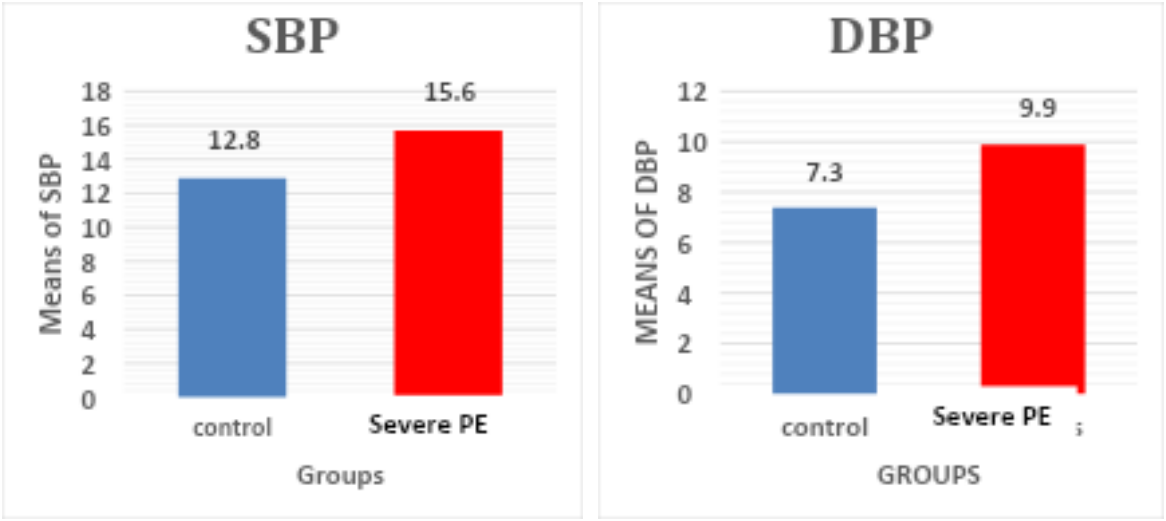

Figure 2. Systolic and Diastolic pressure of uncomplicated pregnancy and severe preeclamptic women

3.3 *Endothelial Cell-Specific Molecule 1 (Endocan) and Uric acid*

To assess Uric acid and ESM1, all obtained data were analyzed statistically and presented Mean ± SE. The p values were also included to verify differences in levels of study parameters between patients and control. The results specified the existence of a significant increase ($p<0.001$) in serum levels of uric acid and ESM-1 (Endocan) for patients with severe preeclampsia when compared with uncomplicated pregnancy. As seen in Table 3 , figures 3and 4.

Table 3. Uric acid and endocan in uncomplicated pregnant women and severe preeclampsia

Marker	Uncomplicated pregnancy	Preeclampsia	p. value
Endocan	30.98±1.83	72.28±2.59	0.0001
Uric acid (µmol/L)	244.58 ± 3.41	342.40±9.44	0.0001

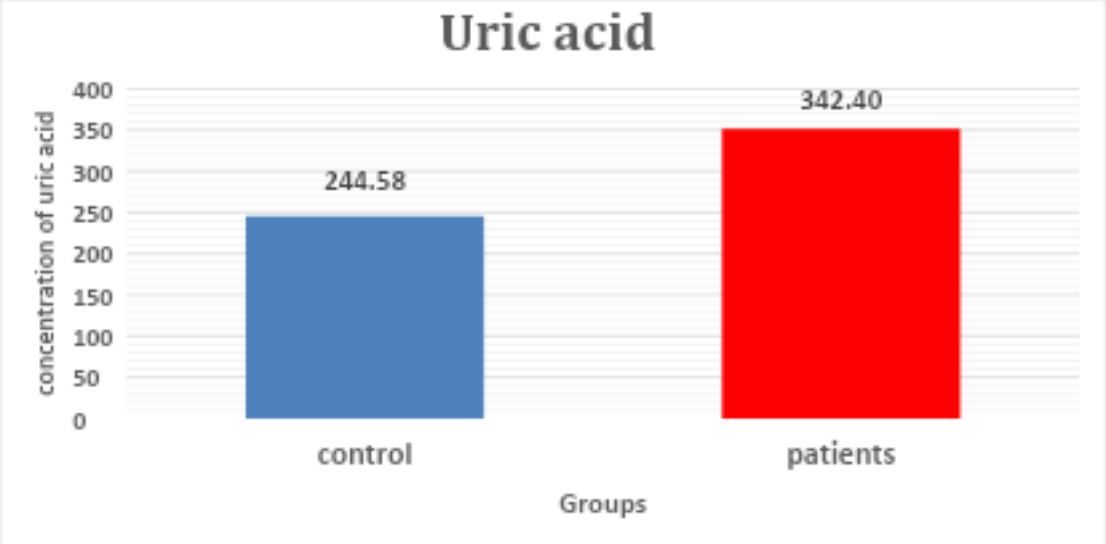

Figure 3. Uric acid of severe preeclampsia comparison with Uncomplicated pregnancy

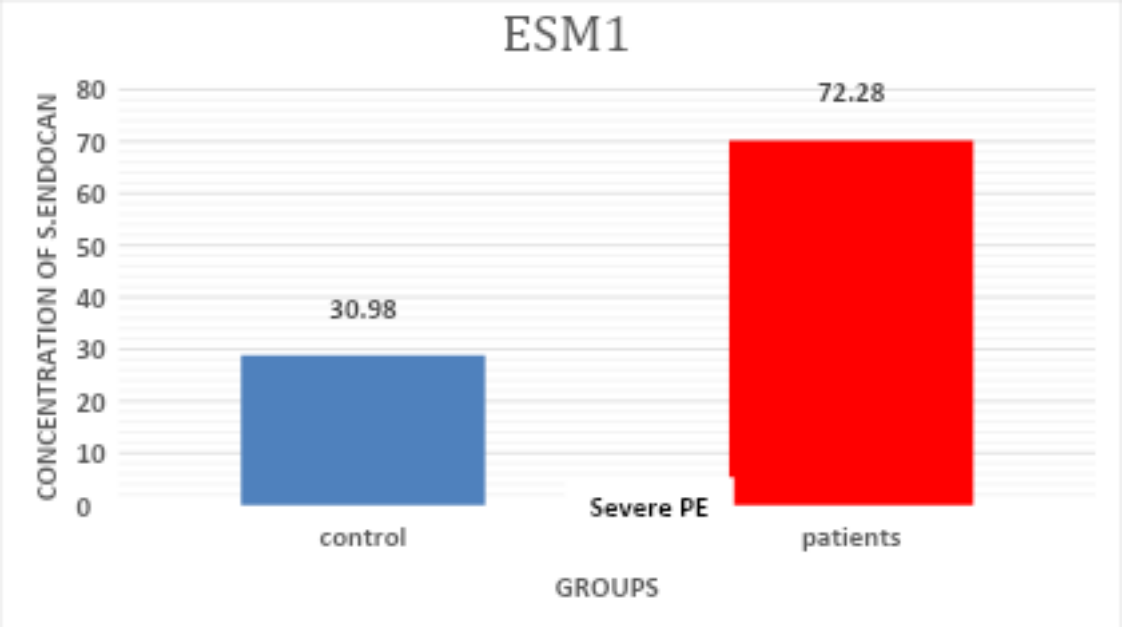

Figure 4. ESM1of severe preeclampsia comparison with Uncomplicated pregnancy.

3.4 Complications of severe preeclampsia

From the total of 90 cases enrolled in the study, with the intention of the occurrence of pregnancy outcome, 45 women with severe preeclampsia developed adverse maternal and fetal complications during live birth, 100% of 45 uncomplicated pregnancies.

Table 4 shows maternal and Fetal complications, preterm (13.3%), low birth weight (17.7%), IUFD (8.8%), Eclamptic fit (13.3%), Placenta abruption(20%), Immanent eclampsia(15.5%), Admission to NCU(11.1%).

Table 4. Complications in women with severe preeclampsia

complications	NO (%)
Placenta abruption	**9(20%)**
Eclamptic fit	**6(13.3%)**
Immanent eclampsia	**7(15.5%)**

Low birth weight	**8(17.7%)**
IUFD*	**4(8.8%)**
Preterm	**6(13.3%)**
Admission to NCU	**5 (11.1%)**
HELLP syndrome	**Zero**
Maternal mortality	**Zero**

*IUFD: Intrauterine Fetal Demise

Table 5. Effect of severe preeclampsia on the mode of delivery

Mode of delivery	Uncomplicated pregnancy	severe preeclampsia
LSCS		
Preterm	2 (4.4%)	12 (26.6%)
Term	17 (37.7%)	20 (44.4%)
Vaginal delivery		
Preterm	2 (4.4%)	3 (6.6%)
Term	24 (53.3%)	10 (22.2%)

3.5 Correlations

The Pearson correlation analysis was used to investigate the nature of the relationships between all of the factors in this investigation involving the chemical analysis and the physical measurements. Table 6 contains a presentation of the combined findings. The analysis showed that there was a positive correlation between the levels of Endocan (EMS-1) and the levels of uric acid in patients with severe preeclampsia at the 0.001 and 0.002 level, and the analysis also showed that there was a negative correlation at the 0.01 level between the levels of uric acid and the levels of ESM-1.

Table 6. Correlation between variables and adverse pregnancy outcomes in severely preeclamptic women

Adverse pregnancy outcome	Endocan level	Uric acid level
	P value	P value
Intrauterine fetal death	0.678(negative)	0.773 (negative)
Placenta abruption	0.001(positive)	0.001(positive)
Eclamptic fit	0.002(positive)	0.001(positive)
Immanent eclampsia	0.675(negative)	0.876(negative)
Preterm birth	0.532(negative)	0.001(positive)
Low birth weight	0.03(negative)	0.001(positive)
Admission to NCU	0.01(negative)	0.001(positive)

3.6 ROC Curve

It is reasonable to state that the hypothesis AUC result is significant; this is because all of the factors that were evaluated had some validity in terms of predicting whether or not the test value is greater than the table value (0.5).

This study showed the values of systolic and diastolic pressure had been a powerful diagnostic tool between healthy and patients [AUC=0.956, S.E=0.019, 95%cl=0.918 to 0.994 and P-value=0.0001] (Figure 5A.), [AUC=0.999, S.E=0.002, 95%cl=0.995 to 1.000 and P-value=0.0001] (Figure 5B) respectively. As well, ESM1 was found to be a better predictor for severe preeclampsia than Uric acid [AUC=.0.961, S. E=0.018, 95%cl=0.936 to 0.999 and P-value=0.0001] (Figure 5D) [AUC=.0.929, S.E=0.030, 95%cl=0.870 to 0.988 and P-value=0.0001] (Figure 5C) Straight.

Table 7. Area under the ROC Curve for each investigated biomarker.

Parameters	AUC	S. E	95% Confidence Interval	P-value
SBP (mmHg)	0.956	0.019	0.918 to 0.994	0.0001
DBP (mmHg)	.9990	.0020	0.995 to 1.000	0.0001
Uric acid (µmol/L)	.9290	.0300	0.870 to 0.988	0.0001
ESM1 (pg/ml)	0.961	0.016	0.936 to 0.999	0.0001

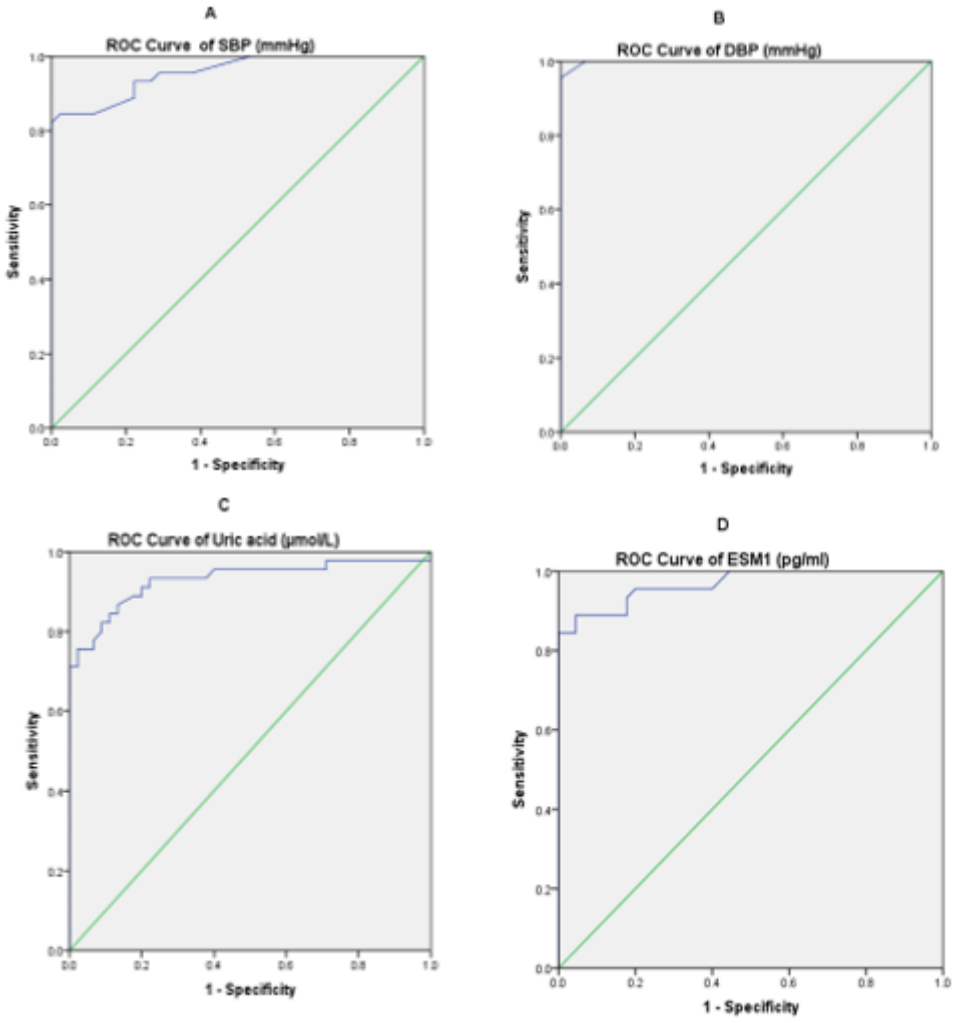

Figure 5. The receiver's operating characteristic curves, which indicate the area under the curve (AUC) between sensitivity and specificity for the researched parameters

3.8 Statistical analysis

In order to conduct the statistical analysis, we made use of the Statistical Package for Social Sciences version 20.0 for Windows computer program (IBM SPSS Statistic software, IBM Corporation, New York, United States). The data were evaluated with descriptive statistics generated by the SPSS software and then subjected to the t-test methodology.

A p-value that was either equal to or greater than 0.05 was regarded as statistically insignificant, whilst a p-value that was either equal to or less than 0.01 was regarded as highly significant statistically. The forms and standard curves that were given for each variable were drawn with the help of the Excel 2016 application. The cut-off point of the sensitivity and specificity of the measures was determined with the use of a ROC Curve.

4. Discussion

PE is arguably the most distinctive pregnancy complication linked with endothelial injury and dysfunction. It also continues to be a significant direct cause of maternal morbidity and mortality around the world [19,]

Endocan is an innovative marker for inflammation, but the relevance of its role in preeclampsia is still a mystery [20],maternai uric acid had important role in prognosis of pre-eclampsia. [3]

When compared to women who were pregnant without any complications, those who were diagnosed with severe preeclampsia had significantly greater levels of endocan-1 in their maternal plasma.

According to the findings of Adekola et al., the median maternal plasma endocan concentration was greater in PE compared to uncomplicated pregnancy. This finding is consistent with the findings of our investigation. [21]Joost et al. observed that Endocan -1 is a predictive marker for the development of severe preeclampsia, which is a conclusion that is similar to our findings. [22] Additionally, Muzaffer Camak and colleagues discovered that the serum endocan concertation level was considerably higher in women who were diagnosed with severe preeclampsia compared to normotensive controls[23] Xia Lan recently conducted a study in which she discovered that women who are diagnosed with preeclampsia had a greater circulating amount of endocan than women who are pregnant without any complications. This correlates with the findings of that study. [24]The findings of our investigation contradict the findings of Yuksel et al., who found that there was no significant difference in the amount of maternal plasma Endocan between PE and an uncomplicated pregnancy. [25]Ana Cristina and colleagues discovered that there was no correlation between the amount of endocan and the prevalence of severe PE in Brazilian pregnant women. [26]HZ Way and colleagues discovered that there was no significant difference in serum endocan levels between normal pregnant women and women with severe preeclampsia. They also discovered that there was no significant difference in serum endocan levels between women with moderate and severe preeclampsia. [27] Gokce et al. discovered that an endocan plasma level, a patient with PE, and the control group (uncomplicated pregnancy) did not differ significantly from one another in any way that was statistically significant. [28]

According to the findings of this research, the concentration of endocan in the serum of women who experienced eclamptic fit, imminent eclampsia, or placenta abruption was higher. Endocan has the potential to play a significant part in the diagnosis of this unfavorable maternal outcome.

It's possible that it's due to the following things:

1. African and American women were included among the pregnant ladies, although they did not belong to the same group.

2. The proportion of patients with severe pulmonary embolism versus moderate pulmonary embolism or early versus late onset of PE

3. The number of participants in each study varied, which led to different conclusions.

When compared with pregnant women who did not experience any complications during their pregnancy, those who had severe PE had considerably greater levels of uric acid in their serum.

There is a correlation that is both positive and substantial between blood pressure and serum uric acid levels in patients with severe pulmonary edema.

Toshinwal et al. demonstrate that there is a substantial difference between PE that is moderate and PE that is severe, which suggests that uric acid is an effective marker of the disease's severity.

According to the findings of this research, serum uric acid can be an effective indicator of maternal and foetal problems in cases of severe preeclampsia. This is in agreement with what Shirish

Toshinwal and others have stated. [29]According to the findings of another study conducted by Ionnis Bellus and colleagues, the levels of s. uric acid significantly increased in normotensive pregnant women. [30]

Serum uric acid has a substantial positive link with blood pressure and a relationship in severe PE that is consistent with this study. Jwan M.Z. and Awat I.H. et al. revealed considerable increase in the serum uric acid level over normotensive pregnant women [31]. One of the earliest and most constant signs of preeclampsia is an elevated blood level of uric acid, which is also known as hyperuricemia.

When compared to the group with normal uric acid levels, the hyperuricaemia group had a statistically significant increase in the number of unfavorable foetal and mother outcomes. In preeclampsia patients, the presence of blood uric acid was found to be a significant predictor for both low birth weight and early delivery, as the results of this study demonstrated.

In patients who have preeclampsia, hyperuricaemia is not only a sign that the severity of the condition is present, but it also suggests that the pregnancy will not end well for the foetus. [32]

5. Conclusion and Recommendations

The levels of endocan (EMS-1) and serum uric acid were found to be higher in women who were experiencing severe preeclampsia. When it comes to predicting a negative outcome for the pregnancy, the performance of serum endocan seems to fall short.

There is a need for additional research to be carried out in order to determine the role that endocan plays in the progression of preeclampsia.

This research is restricted in the following ways:

1. There were a relatively low number of people in the sample; bigger prospective investigations are required.

2. The participants in the study were gathered from a single hospital, and additional research is required to examine the effectiveness of Endocan in predicting the occurrence of unfavourable pregnancy outcomes.

Acknowledgement

The authors would like to Al-Kindy College of Medicine, University of Bagdad, Iraq; additionally, the authors wish to express gratitude to thank Al-Elwiya Maternity Teaching Hospital.

References

1. Arun Jeyabalan, MD Epidemiology of preeclampsia: Impact of obesity. National Library of Medicine. 2013 Oct; 71(0 1): 10.1111/nure.12055.
2. Kee-Hak Lim, MD ,Kee-Hak Lim, MD . Preeclampsia. American College of Obstetricians and Gynecologists.2022. Aug.18;71(0 1): 10.
3. R Nirupama, S Divyashree, P Janhavi, S P Muthukumar, Ravindra. Preeclampsia: pathophysiology and management. National Library of Medicine.2021 Feb.;50 (2):101975.
4. Unterscheider, J., O'Donoghue, K., Daly, S., Geary, M. P., Kennelly, M. M., McAuliffe, F. M., ... & Malone, F. D. Fetal growth restriction and the risk of perinatal mortality–case studies from the multicenter PORTO study. *BMC Pregnancy and childbirth*.2014:*14*(1):1-6.
5. Webster k, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ.2019;366 (72):5119.

6. Burwick, R. M., & Feinberg, B. B. Complement activation and regulation in preeclampsia and hemolysis, elevated liver enzymes, and low platelet count syndrome. *American Journal of Obstetrics and Gynecology*. 2020; 2:10:59-S1070.
7. Jennifer A Hutcheon, Sarka Lisonkova, K S Joseph. Epidemiology of preeclampsia and the other hypertensive disorders of pregnancy. National Library of Medicine. 2011 Aug;25(4):391-403.
8. Uzma Shamsi. Epidemiology and risk factors of preeclampsia; an overview of observational studies. Al Am een J Med Sci. 2013; 6(4):292-300.
9. Peres, G. M., Mariana, M., & Cairrão, E. Preeclampsia and eclampsia: An update on the pharmacological treatment applied in Portugal. *Journal of cardiovascular development and disease*.2018; *5*(1):32-35.
10. Auger, N., Luo, Z. C., Nuyt, A. M., Kaufman, J. S., Naimi, A. I., Platt, R. W., & Fraser, W. D. Secular trends in preeclampsia incidence and outcomes in a large Canada database. *Canadian Journal of Cardiology* 2016;*32*(8): 987-e15.
11. Porreco, R. P., & Barkey, R. Peripartum intensive care. *The Journal of Maternal-Fetal & Neonatal Medicine*. (\2010;*23*(10):1136-1138.
12. Jason J. District Health Board, Auckland, New Zealand. Hypertensive Disorders. Dewhurst's textbook of Obstetrics & Gynecology. 2018:73.
13. Furuya, M., Kurasawa, K., Nagahama, K., Kawachi, K., Nozawa, A., Takahashi, T., & Aoki, I. Disrupted balance of angiogenic and antiangiogenic signallings in preeclampsia. *Journal of pregnancy*.2010;1(3):56-64.
14. Brosens, I., Puttemans, P., & Benagiano, G. Placental bed research: I. The placental bed from spiral arteries is remodelling to the great obstetrical syndromes. *American Journal of Obstetrics and Gynecology*. 2019;*221*(5):437-456.
15. Wu, F., Tian, F. J., Lin, Y., & Xu, W. M. Oxidative stress: placenta function and dysfunction. *American Journal of reproductive immunology*. 2016;*76*(4): 258-271.
16. Tenório, M. B., Ferreira, R. C., Moura, F. A., Bueno, N. B., de Oliveira, A. C. M., & Goulart, M. O. F. Cross-talk between oxidative stress and inflammation in preeclampsia. *Oxidative Medicine and cellular longevity*.*2019*;12(2);55-61.
17. Szpera-Gozdziewicz, A., & Breborowicz, G. H. Endothelial dysfunction in the pathogenesis of preeclampsia. *Front Biosci (Landmark Ed)* 2014; *19*(1):734.
18. Christopher W. Ives. Preeclampsia—Pathophysiology and Clinical Presentations. JACC Journals › JACC › Archives › Vol. 76 No. 14. 2020 Oct, 76 (14) 1690–1702
19. H Z Wang, Y Jin, P Wang, C Han, Z P Wang, M Y Dong. Alteration of serum endocan in normal pregnancy and preeclampsia. 2017;44(3):419-422.
20. Kornacki J. ,Wirstlein P. , Wender . Ozeowska. Markers of Endothelial injury and dysfunction in early and late onset of preeclampsia. Life. 2020; 10:239.
21. Adekola H, Romero R, Chaemsaithong P. Endocan, a putative endothelial cell marker, is elevated in preeclampsia, decreased in acute pyelonephritis, and unchanged in other obstetrical syndromes. J Matern Neonatal Med. 2015;28(14):1621–32.
22. Joost SJW, Gerarda W, Siccos, Marielle VP, Marijke F. New prognostic marker to develop early_onset preeclampsia. Preg.Hypertens 2013;3:94-5.

23. Muzaffer Camak,Hakki ,Yilmaz, Baglar ,Tahir Darcin,Osama Inan,Aynaur Aktas.Serum levels of endocan correlate with the presence and severity of preeclampsia. Clin Exp Hypertens.2016;38(2):137-42.
24. Xia Lan, Zhaoming Liu. Circulating endocan and preeclampsia. Portland Press.2020;40(1):BSR20193219.
25. Yuksel MA, Tuten A, Oncul M, Serdar A, Yuksel Iikbak, Toprak M et al. Serum endian concentration in women with preeclampsia. Arch Gynecol Obstet. 2015;292(1):69–73.
26. Ana Cristina›dos Santos Lopes, Suellen Rodrigues Martins, Luci Maria SantAna Dusse,Melina de Barros Pinheiro, Patrícia Nessralla Alpoim. Are Endocan Plasma Levels Altered in Preeclampsia? Rev Bras Ginecol Obstet 2021;43(3):232–234.
27. H.Z.way, Y.Jin, Wang , C.Han, Z. P. Wang, M.Y. Dong. Alteration of serum endocan in normal pregnancy and preeclampsia. Clin. Exp. Obstet. Gynecol. 2017; 44(3);419-422.
28. Gokce Naz Kucukbas, Cem Yasar Sanhal, Dilek Uyger. Plasma Endocan levels in Early and late-onset preeclampsia. foetal and paediatric pathology 2021;40(3):214-221.
29. Shirish Toshniwal, Arkriti R.Lamba.Serum uric acid as a marker of severity of preeclampsia. International J Reprod, Contracep, Obstet Gynecol.2017; Nov;6(11);4915-4917.
30. Ioannis Bellos, Vesillios Pergiliotis, Dimitrios Loutradis,Georgios Daskalakis.The prognostic role of serum uric acid levels in preeclampsia. National Library Of Medicine.2020 May;22(5):826-834.
31. JM Zangana, Awat IH. Serum uric acid as a predictor of perinatal outcomes in women with preeclampsia. International Journal of Medical Research & Health Sciences.2018;7(3):168-174.
32. Nahar, Anwer Khan, Khatun, S. F., & Khan, N. A. Estimation of Serum Uric Acid Level in Preeclamptic Women Determine the Severity of Preeclampsia. Modern Medical College Journal. 2020;11(1):35–40.