Original Article

# Evaluation of Serum Kallistatin Levels in Women with Preeclampsia and its Role in Assessing Preeclampsia Severity

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## Abstract

**Background:** Preeclampsia (PE) is a hypertension condition that often manifests after 20 weeks of gestation. It is regarded as a leading cause of death among mothers and babies globally. **Aim:** To evaluate how serum kallistatin affects PE severity. **Patients and Methods:** A case–control study that included three groups of 95 third trimester pregnant women with viable fetuses was chosen. Group M (32 mild PE), Group S (31 severe PE), and Group C (32 control pregnant normotensives). Serum kallistatin, complete blood count, liver, and renal functions were compared between groups, at An Al-Yarmouk Teaching Hospital Obstetrics and Gynecology. **Results:** The concentrations of serum kallistatin in severe PE were markedly lower than those in mild and normotensive pregnant women. (1.79, 3.24, and 4.55, $P < 0.001$). Kallistatin accurately predicted mild, severe, and normotensive PE. All healthy women's parameters did not correlate with kallistatin. In PE, age, gestational age, and platelets correlated directly with kallistatin, but systolic and diastolic blood pressure, alanine transaminase, aspartate aminotransferase, and total serum bilirubin correlated inversely. Kallistatin had higher sensitivity than specificity and comparable negative to positive predictive values. **Conclusions:** Mother's serum kallistatin is inversely related to PE severity and significantly lower in PE patients than normotensives. Kallistatin's sensitivity and specificity for predicting PE in normotensive women were 93.7% and 68.8%, respectively, using a threshold value ≤3.92 ng/ml using a threshold value ≤2.136 ng/ml, 90.3%, and 93.8% predicted severe PE from mild PE, respectively.

**Keywords:** Kallistatin, prediction, preeclampsia, severity

## Introduction

Preeclampsia (PE) is a leading cause of maternal and neonatal morbidity and mortality, complicating 2%–8% of pregnancies worldwide.[1,2] Globally, PE has been estimated to cause between 10% and 25% of perinatal loss. Actually, PE is the third leading cause of death among mothers after bleeding and embolism.[3,4] The impaired placental function appears to be critical in the etiology underlying PE.[5]

The prevailing theory is that relative ischemia within the placenta releases vasoactive substances into the bloodstream, leading to endothelial-mediated organ damage and clinical symptoms of the condition.[6,7] The effect of oxidative stress has the potential to play an essential part in the pathogenesis of PE.[8]

Kallistatin is an endogenous protein in numerous human tissues that has pleiotropic effects such as vasodilation and suppression of angiogenesis, inflammation, oxidative stress, apoptosis, fibrosis, and tumor growth.[9] Kallistatin was found to be a powerful vasodilator, showing its importance in circulatory function. Kallistatin has 2 sites, a heparin-binding site, and an active site. The active site is critical for suppressing tissue kallikrein (TK) function and controlling TK/kinin-mediated biological reactions. The TK-kinin system plays an important part in preventing hypertension, cardiac, cerebral, and renal damage,[10] increasing endothelial nitric oxide synthase (NOS) expression and activation. Therefore, kallistatin through these effects relaxes blood vessels and lowers blood pressure, any impairment in the NO pathway has been linked to the development and severity of PE.[11] The NO pathway plays an essential part in ovulation, implantation, changing

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vascular structure of the uterus, peripheral vascular resistance regulation, and vasoactivity. Furthermore, the NO pathway has both paracrine and autocrine actions in the placenta, which regulates fetoplacental circulation.[12]

Despite the pathophysiology of PE is not entirely clarified, the presence of maternal vascularity impairment is necessary for PE. *In vivo* and *ex vivo* studies have demonstrated a link between a failure in the nitric oxide signal pathway and the development of PE as well as its severity. In preeclamptic patients, there was a decrease in nitric oxide bioavailability and a rise in molecules inhibiting NOS and anti-angiogenic factors.[13,14] Because the active component of kallistatin induces NOS; consequently, a decrease in serum kallistatin levels in preeclamptic patients may result in decreasing nitric oxide synthesis.[15]

We illustrated the manuscript's novelty. As research has indicated that changes in kallistatin levels may be linked to impairment of endothelial function, a characteristic feature of PE.

By quantifying the levels of kallistatin in the bloodstream, medical professionals might potentially detect women who are at an elevated susceptibility to developing PE at an earlier stage of pregnancy or track the advancement of the condition. This has the potential to result in enhanced prenatal care and prompt therapies to alleviate the hazards linked to PE, including as high blood pressure and organ impairment.

Moreover, examining the levels of kallistatin in the serum concerning PE could offer a significant understanding of the fundamental mechanisms of the illness. This has the potential to result in the creation of new treatment approaches that target the regulation of kallistatin levels to better prevent or treat PE.

The current work aimed to evaluate the relationship between serum kallistatin and the severity of PE.

## Patients and Methods

### Study design and setting

A case–control study was conducted at Al Yarmouk Teaching Hospital's Department of Obstetrics and Gynecology in collaboration with the hospital's laboratories department and Al-Shameem private laboratory from January to December 2022.

All procedures performed in studies involving pregnant women participants were by the ethical criteria of the institutional or national research committee. According to the Iraqi Council of Medical Specializations—Scientific Council of Obstetrics and Gynecology, all the people who took part in this study gave their verbal consent after being fully informed about it.

The study included 95 pregnant women between 28 and 40 weeks of gestation attending the outpatient clinic or in-patient ward, which were further divided into three groups:

1. Group C (control group): Normotensive pregnant women (32 women)
2. Group M: Mild PE (32 women)
3. Group S: Severe PE (31 women).

PE and its severity were defined according to the American College of Gynecology 2020.[16]

### Exclusion criteria

- Patients with multiple gestations
- Morbid obesity (body mass index [BMI] ≥40 kg/m$^2$)
- Active labor
- Premature rupture of membranes
- Chorioamnionitis
- Congenital anomalies
- Chronic hypertension
- Overt or gestational diabetes
- Sepsis
- Any systemic disease such as severe liver disease and chronic kidney disease.

### Clinical assessment

1. Detailed history was obtained from all the patients
2. General examination, vital signs were measured and recorded
3. Systemic and obstetrical examination.

### Investigation

1. All patients sent for obstetrical ultrasound
2. The studied groups were investigated for the following:
   a. Samples of maternal blood were obtained when admitted and forwarded to laboratories for blood group/cross-matching (if necessary), full blood count, random blood sugar, liver function, renal function tests, and a midstream urine sample for albumin
   b. Maternal blood samples were sent for the measurement of serum kallistatin levels using ELISA test as venous blood samples of 5 ml were collected from the pregnant women in the three groups and were stored in a deep freeze at −20°C till the day of analysis. The level of serum kallistatin was determined using an enzyme-linked immunosorbent test kit, Catalog Number: YLA0854HU, Shanghai YL Biont/China. The sensitivity was 0.22 ng/ml and the detection range was 0.5–200 ng/ml.

### Sample size calculation

This study depends on the study done by Güralp *et al.*[17] Epi Info STATCALC was utilized to compute the sample size based on the following assumptions: - 95% two-sided confidence level, with a power of 80% and 5% a margin of error, serum kallistatin in PE was 27.74 ± 8.29 ng/mL, and in healthy women, it was 36.99 ± 19.64 ng/mL, and the ultimate greatest size of a sample obtained from the Epi-Info output was 84. Thus, the size of the sample was raised to 95 participants to compensate for potential dropouts throughout a follow-up.

### Sample size used

$$n_1 = \frac{\left(\sigma_1^2 + \sigma_2^2 / K\right)\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\Delta^2}$$

### Statistical analysis

Anderson Darling test was done to assess if continuous variables follow a normal distribution. The one-way analysis of variance is used for analyzing the differences among more than two groups, while the *post hoc* Tukey test is utilized to determine the specific pair that shows significance. Linear regression analysis was used to determine the association between the variables. The receiver operator curve assesses the effectiveness of various variables in distinguishing active cases from the control. SPSS version 22.0.0 (Chicago, Illinois, USA), Minitab 17.1.0, MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; 2014), a software application, is utilized for conducting the statistical analysis. The *P* value is considered statistically significant if it is <0.05.

## Results

There were no significant variations (the $P \geq 0.05$) among groups C, M, and S in their age (30.09 ± 6.47, 27.47 ± 6.08, and 28.16 ± 6.20 years, respectively), BMI (36.47 ± 2.16, 37.03 ± 1.96, and 36.16 ± 1.16 kg/m$^2$, respectively), and gestational age (GA) (27.76 ± 3.34, 28.49 ± 3.79, and 28.43 ± 3.87 weeks, respectively) [Table 1].

**Table 1: Assessment of maternal criteria and blood pressure parameters**

| Variable (mean±SD) | Group C | Group M | Group S | *P* |
|---|---|---|---|---|
| *n* | 32 | 32 | 31 | - |
| Age (years) | 30.09±6.47 | 27.47±6.08 | 28.16±6.20 | 0.226 |
| GA (weeks) | 36.47±2.16 | 37.03±1.96 | 36.16±1.16 | 0.160 |
| BMI (kg/m$^2$) | 27.76±3.34 | 28.49±3.79 | 28.43±3.87 | 0.679 |
| SBP | 114.69±9.83 | 136.25±10.40 | 163.87±9.19 | <0.001 |
| DBP | 71.25±5.68 | 85.16±7.01 | 71.25±5.68 | <0.001 |

Group C: Control group, Group M: Mild preeclampsia group, Group S: Severe preeclampsia, BMI: Body mass index, GA: Gestational age, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation

There was a highly increased significant difference in systolic blood pressure (SBP) observed in group S (severe PE) with a mean 163.87 ± 9.19 mmHg than group M with a mean 136.25 ± 10.40 mmHg and group C with a mean 114.69 ± 9.83 mmHg, respectively, the same in diastolic blood pressure (DBP) which showed highly increased significant difference observed in group S (severe PE) with a mean 104.84 ± 9.26 mmHg than group M with a mean 85.16 ± 7.01 mmHg and group C with a mean 71.25 ± 5.68 mmHg, respectively.

There was a highly increased significant difference observed in group S (severe PE) than group M and group C regarding alanine transaminase (ALT), aspartate transaminase (AST), total serum bilirubin (TSB), and urea and A greatly reduced significant difference was observed in group S (severe PE) compared to group M and group C regarding platelet while there was no significant difference in observed between three groups regarding hemoglobin (Hb), white blood cell (WBC), and creatinine.

Regarding serum kallistatin, there was a highly decreased significant difference observed in group S (severe PE) with a mean of 1.79 ± 0.75 than group M with a mean of 3.24 ± 0.93 and group C with a mean 4.55 ± 1.43, respectively, as shown in Table 2 and Figure 1.

In healthy women, there was no significant correlation between serum kallistatin, SBP, DBP, platelet, ALT, and AST while in women with PE, there was a strong positive correlation observed between serum kallistatin and platelet, a strong negative correlation between serum kallistatin, SBP, DBP, ALT, and AST.

All the investigated parameters did not show a significant correlation with kallistatin. While in PE, women's platelets showed a direct significant correlation with kallistatin, on the other hand, SBP, DBP, ALT, and AST showed an inverse significant correlation with kallistatin, as illustrated by Table 3.

Overall, kallistatin showed higher sensitivity compared to its specificity, while in terms of prediction, it showed comparable

**Table 2: Assessment of blood and investigated parameters**

| Variable | Group C | Group M | Group S | *P* |
|---|---|---|---|---|
| *n* | 32 | 32 | 31 | - |
| Hb (g/dL) | 11.44±0.93 | 12.17±1.41 | 12.18±2.05 | 0.091 |
| WBC ($10^9$/L) | 9.93±2.17 | 10.74±1.53 | 10.17±4.45 | 0.537 |
| PLT ($10^9$/L) | 241.06±88.15 | 229.63±63.30 | 156.16±62.32 | <0.001 |
| ALT (IU/L) | 23.77±4.04 | 20.83±4.82 | 53.55±38.65 | <0.001 |
| AST (IU/L) | 22.80±3.91 | 22.05±4.60 | 65.06±41.78 | <0.001 |
| TSB (mL/dL) | 0.58±0.13 | 0.46±0.13 | 0.88±0.36 | <0.001 |
| Urea (mL/dL) | 23.53±5.22 | 22.66±6.11 | 29.09±8.51 | <0.001 |
| Creatinine (mL/dL) | 0.61±0.14 | 0.62±0.12 | 0.67±0.18 | 0.234 |
| Kallistatin (ng/mL), mean±SD | 4.55±1.43 | 3.24±0.93 | 1.79±0.75 | <0.001 |

Group C: Control group, Group M: Mild preeclampsia group, Group S: Severe preeclampsia, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, TSB: Total serum bilirubin, SD: Standard deviation

negative to positive predictive value, as illustrated by Table 4 and Figures 2, 3.

## Discussion

PE, which affects between 2% and 8% of human pregnancies, is described as a new onset of hypertension and proteinuria emerging in a previously normotensive woman after the 20th week of gestation.[18,19]

PE is associated with high morbidity and mortality among mothers and newborns. Without knowing the specific cause, mounting evidence demonstrates that PE is a multisystem disorder that involves widespread maternal vascular endothelial malfunction.[2,20]

Kallistatin, a serine proteinase inhibitor found in humans, has recently been discovered as an inhibitor of TK. It exhibits a high affinity for TK, but a low affinity for other serine proteinases including chymotrypsin and elastase.[21]

There was no significant difference ($P \geq 0.05$) among groups C, M, and S in their age (30.09 ± 6.47, 27.47 ± 6.08, and 28.16 ± 6.20 years, respectively), BMI (36.47 ± 2.16, 37.03 ± 1.96, and 36.16 ± 1.16 kg/m$^2$, respectively), and GA (27.76 ± 3.34, 28.49 ± 3.79, and 28.43 ± 3.87 weeks, respectively).

In the same line, Güralp *et al*.,[17] who aimed to ascertain the serum concentrations of the serine proteinase inhibitor kallistatin in women with PE. The clinical and biochemical data of 55 consecutive women with an early-onset PE (EOPE) and 55 consecutive women with a late-onset PE (LOPE) were compared with 110 consecutive GA GA-matched (±1 week) pregnant women with an uneventful pregnancy. They revealed that there was no substantial variation in demographic data, mean age, BMI, or GA across the study groups.

Furthermore, our findings have been reinforced by Yuan *et al*.,[10] who are interested in looking at the mother's plasma concentrations of TK in normal and preeclamptic pregnancies. Ninety-six women with singleton pregnancies were categorized as normal, mild PE, or PE with severe symptoms. They found that there was no statistically significant difference between the three studied groups regarding age and GA.

There was a highly increased significant difference in SBP observed in group S (severe PE) with a mean 163.87 ± 9.19 mmHg than group M with a mean 136.25 ± 10.40 mmHg and group C with a mean 114.69 ± 9.83 mmHg, respectively, the same in DBP which showed highly increased significant difference observed in group S (severe PE) with mean 104.84 ± 9.26 mmHg than group M with mean 85.16 ± 7.01 mmHg and group C with mean 71.25 ± 5.68 mmHg, respectively.

Our findings have been reinforced by Yuan *et al*.,[10] who revealed that there were highly significant differences in SBP and DBP between the mild PE, PE with severe features, and control groups. There was a highly increased significant difference in SBP and DBP observed in PE with severe features than in mild PE and the control group.

Furthermore, Güralp *et al*.,[17] who demonstrate that there were highly significant differences in SBP and DBP between PE and non-PE and between EOPE and the control group.

There was a highly increased significant difference observed in group S (severe PE) than group M and group C regarding ALT, AST, TSB, and urea and there was a highly decreased

**Table 3: Correlation between kallistatin with various variables**

| Variables | Kallistatin | | | |
|---|---|---|---|---|
| | Healthy women | | PE | |
| | *r* | *P* | *r* | *P* |
| SBP (mmHg) | 0.189 | 0.300 | −0.409 | 0.001 significant |
| DBP (mmHg) | 0.052 | 0.779 | −0.399 | 0.001 significant |
| Platelet ($10^9$/L) | −0.165 | 0.366 | 0.487 | <0.001 significant |
| ALT (IU/L) | 0.262 | 0.148 | −0.355 | 0.004 significant |
| AST (IU/L) | 0.010 | 0.957 | −0.421 | 0.001 significant |

*r*: Correlation coefficient, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ALT: Alanine transaminase, AST: Aspartate transaminase, PE: Preeclampsia

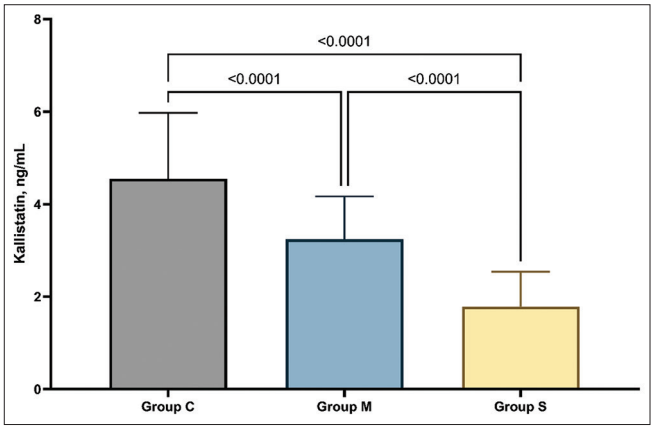


**Figure 1:** Histogram of kallistatin ng/ml

**Table 4: Assessment of cutoff for kallistatin to predict the outcome**

| | Cut off | SN | SP | AUC | 95% CI | *P* | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| PE versus normotensive women | ≤3.92 | 93.7 | 68.8 | 0.878 | 0.795–0.937 | <0.001 | 85.5 | 84.6 |
| Severe versus mild PE | ≤2.136 | 90.3 | 93.8 | 0.946 | 0.858–0.987 | <0.001 | 93.3 | 90.9 |
| Severe PE versus normotensive women | ≤2.22 | 93.6 | 96.9 | 0.970 | 0.892–0.997 | <0.001 | 96.7 | 93.9 |

SN: Sensitivity, SP: Specificity, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, PE: Preeclampsia

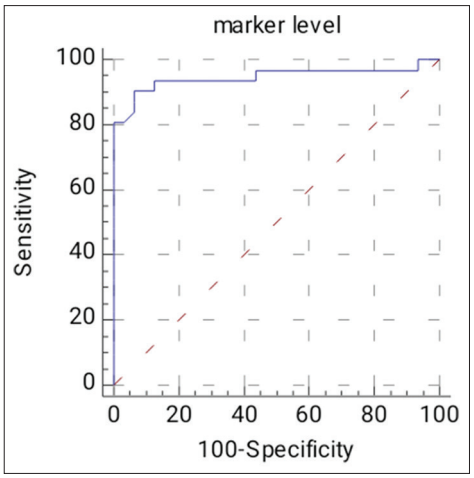


**Figure 2:** Receiver operating characteristic curve for kallistatin for the prediction of severe preeclampsia (PE) from moderate PE

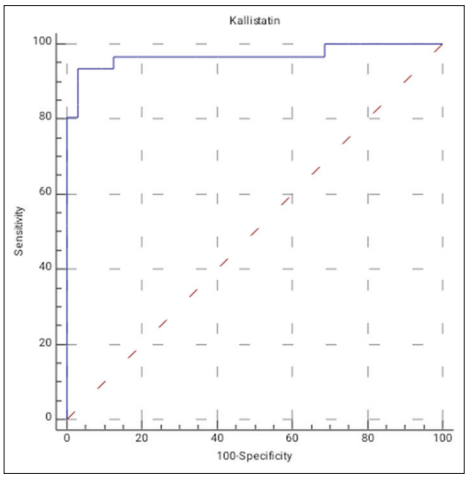


**Figure 3:** Receiver operating characteristic curve for kallistatin for the prediction of severe preeclampsia from normotensive pregnant

significant difference in observed in group S (severe PE) than group M and group C regarding platelet while there was no significant difference in observed between three groups regarding Hb, WBC, and creatinine.

Our findings have been reinforced by Yuan *et al*.,[10] who reported that the AST, ALT, and BUN levels are substantially greater in the PE with severe characteristics group than in the control and mild PE groups.

Regarding serum kallistatin, there was a highly decreased significant difference observed in group S (severe PE) with a mean 1.79 ± 0.75 than group M with a mean 3.24 ± 0.93 and group C with a mean 4.55 ± 1.43, respectively.

In the same line, Güralp *et al*.,[17] who noticed that in women with PE, the mean serum kallistatin levels were considerably lower compared to the GA-matched controls (27.74 ± 8.29 ng/mL vs. 37.86 ± 20.64 ng/mL, $P < 0.001$). In addition, the mean serum kallistatin levels were significantly lower in women with EOPE compared to LOPE (24.85 ± 6.65 ng/mL against 30.87 ± 8.81 ng/mL, $P < 0.001$).

The possible explanation of our findings may be due to decreased NO bioavailability in PE patients, as kallistatin's active element is responsible for stimulating NOS, and decreased levels of kallistatin in PE patients can lead to a significant reduction in NO synthesis. On the other hand, the heparin-binding domain of kallistatin has been shown to inhibit several molecules involved in the pathophysiology of PE.[22]

In the study that has been done to examine the amount of kallistatin in pregnancy, Chao *et al*.[23] found that the level of kallistatin in the plasma of 21 healthy pregnant women was significantly lower than the level of kallistatin in 30 healthy women and men. The cause of this decline was thought to be either decreased production during pregnancy or might be due to increased plasma dilution.

In a study by Madeddu *et al*.,[24] the authors found that urinary excretion of kallistatin was significantly more in women with pregnancy-induced hypertension compared to normal pregnancy, especially in 24–26 weeks of gestation. Thus, it may suggest an enhanced urinary excretion of kallistatin predisposes to a further decrease in its levels leading to lower levels of PE compared to normotensive pregnant women.

Chao *et al*.[23] reported that kallistatin levels in bodily fluids, blood cells, and tissues in health and illness; a novel human TK inhibitor. Journal of Laboratory and Clinical Medicine, 127,[6] 612–620. A considerably decreased kallistatin level (7.2 μg/ml, with a standard deviation of 2.5 μg/ml, $P < 0.001$) was seen in plasma samples obtained from nine patients suffering from liver disease and ten patients suffering from sepsis (7.7 μg/ml, with a standard deviation of 3.5 μg/ml, $P < 0.001$). In addition, 21 pregnant women's kallistatin levels (14.9 ± 3.3 μg/ml) were substantially lower than those of healthy individuals.

In healthy women, there was no significant correlation between serum kallistatin, SBP, DBP, platelet, ALT, and AST while in women with PE, there was a strong positive correlation observed between serum kallistatin and platelet, a strong negative correlation between serum kallistatin, SBP, DBP, ALT, and AST.

Güralp *et al*.,[17] who found that serum kallistatin showed a positive correlation with GA at sampling and GA at birth and negative correlations with creatinine and SBP and DBP.

A similar correlation was demonstrated in animal studies, in one of these studies, both normotensive and hypertensive rats had a quick and immediate drop in blood pressure after receiving an intravenous bolus injection of isolated kallistatin.[25]

Another animal investigation discovered that kallistatin enhances vascular relaxation of isolated aortic rings and lowers renal perfusion pressure in isolated rat kidneys. They observed that kallistatin prevents angiogenesis in a rat model of hindlimb ischemia by inhibiting the proliferation, migration, and adhesion of endothelial cells *in vitro*. These findings were consistent with kallistatin's emerging functions in blood pressure regulation and blood vessel remodeling.[26]

## Conclusions

Mother's serum kallistatin is inversely related to PE severity and significantly lower in PE patients than normotensives. Kallistatin's sensitivity and specificity for predicting PE in normotensive women were 93.7% and 68.8%, respectively, with a cutoff point of ≤3.92 ng/ml with a cutoff of ≤2.136 ng/ml, 90.3%, and 93.8% predicted severe PE from mild PE, respectively.

### Points of strengths

An important advantage of assessing blood kallistatin levels in women with PE is its capacity to serve as a biomarker for predicting or diagnosing the disorder. Kallistatin, a serine proteinase inhibitor, is essential for the regulation of blood pressure and vascular function. Research indicates that alterations in kallistatin levels may be connected to the dysfunction of endothelial cells which is a defining hallmark of PE.

By measuring kallistatin levels in the bloodstream, medical professionals might potentially identify women who have an elevated possibility of getting PE early in their pregnancy or track the advancement of the condition. This has the potential to result in enhanced prenatal care and prompt therapies to alleviate the hazards linked to PE, including as high blood pressure and organ impairment.

Moreover, examining the levels of kallistatin in the serum in relation to PE could offer a significant understanding of the fundamental mechanisms of the illness. This has the potential to result in the creation of new treatment approaches that target the regulation of kallistatin levels to better prevent or treat PE.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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