Soluble endoglin as a diagnosis glycoprotein in preeclampsia

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**Abstract**

**Background:** Angiogenic factor imbalance, such as that caused by soluble endoglin (sEng), is a feature of preeclampsia. However, the connection between sEng and clinical and laboratory indicators, and the severity of preeclampsia is not entirely understood.

**Methods:** Ninety subjects were incorporated in this study, 30 were healthy pregnant with mean age (35.6) years. (32) mild Preeclampsia case with mean age (32.65) years preeclampsia, and (30) sever PE with mean age (32.65) wherever all women were more than 24 weeks of pregnancy. Mean blood pressure and level of proteinuria were used as indicators of the severity of the disease. ELISA was used to measure the levels of sEng in the serum. Serum lipid profile was measured by enzymatic methods. The qualitative dip-stick technique (CYBOWTM DFI Co Ltd, Republic of Korea) was used to assess the amount of urine protein.

**Results:** A substantial difference between the PE group’s serum sEng concentration and that of the healthy subjects (p 0.001) could be seen. Serum sEng concentrations of patients with moderate PE and those with severe PE differed significantly. Additionally, there were strong positive relationships between the serum sEng concentration and the SBP and proteinuria. serum sEng levels, biochemical indicators, and other factors, however, did not significantly correlate. The diagnostic accuracy (86.2) in distinguishing mild PE from the healthy patient group was good thanks to the excellent area under the curve (AUC = 0.827, p < 0.0001).

**Conclusion:** Levels of sEng in sera of PE patients were elevated. sEng was significantly correlated with PE patients.
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Introduction

Pre-eclampsia (PE) is a pregnancy-related multisystem disorder with no recognized cause. The root cause of PE is currently being investigated. It is believed to take place in two phases, though. The decidua’s fetal trophoblastic invasion impairment and the placenta’s localized hypoxia are included in the first stage [1,2]. The second stage includes the release of molecules associated to placental blood into the mother’s circulation as well as abnormal synthesis of pro-inflammatory, antiangiogenic, and angiogenic factors [3, 4]. Around week 20 of pregnancy, PE frequently shows clinical signs or later in the pregnancy, with the condition regressing after birth. Typical symptoms include proteinuria and elevated blood pressure [5]. Early-onset PE (which manifests before 34 weeks of gestation) and late-onset PE are the two main kinds of PE (which occurs beyond 34 weeks of gestation) [6,7]. Although the precise cause of this pregnancy-related disease is unknown, mounting evidence points to an imbalance between placental pro- and anti-angiogenic hormones that damages maternal vascular endothelium and causes preeclampsia, which then manifests clinically. Serum tests for pro- and anti-angiogenic factors, particularly placental growth factor, soluble vascular endothelial growth factor receptor-1, and soluble fms-like tyrosine kinase-1, have been used to diagnose this disorder, gauge its severity, and assess its therapeutic potential [8-14]. CD105, sometimes referred to as Eng (endoglin), is a transmembrane homodimeric glycoprotein that is extensively produced on the cellular membrane of endothelium. [15]. sEng (soluble Eng), on the other hand, which is produced when Eng is shed from endothelial cell surfaces and enters. The maternal circulation is responsible for the antiangiogenic effects seen in preeclampsia. It does this by adhering to circulating TGF-1 and preventing it from sending signals to endothelial cells (specifically, the endothelium’s usual proangiogenic and vasodilator functions) [16]. These results suggest that sEng may play a role in the preeclampsia’s etiology and the disruption of the angiogenesis pathway may have a significant influence on the emergence of the condition’s clinical and laboratory symptoms as well as its outcomes. The link between blood clinical and test results, as well as sEng levels clinical and test results, as well as sEng levels in preeclampsia patients is poorly understood, despite the wealth of studies examining the roles of sFlt-1 and PlGF in the condition. This study examined whether blood sEng levels in preeclampsia patients might predict severe sickness and poor maternal outcomes.

Methods

PE patients and Healthy pregnant groups

The Baquba Teaching Hospital’s Obstetrics and Gynecology Department conducted this cross-sectional, case-control study from Sep. 2022 to Dec 2023. The Diyala Sciences College’s Ethical Committee granted its permission for this study’s ethical conduct. The research included 22 third-trimester pregnant women with severe PE and 38 with moderate PE at admission (MPE group) (SPE group). 30 healthy and expecting.

- Proteinuria was < 2+ on urine dipstick on at least two random specimens collected more than 4 hours apart after the 24th week of pregnancy, and MPE was SBP 140 mmHg or DBP 90 mmHg validated by 6 or more hours apart.
- SPE was identified by having SBP of at least 160 mmHg, DBP of at least 110 mmHg, proteinuria > 2+ on a urine dipstick, as well as headache, visual disturbances, upper abdominal pain, and oliguria. The SPE group’s whole female population experienced both proteinuria and hypertension.
- Healthy pregnant : Normotensive pregnant women with gestational ages of more than 24 weeks, no chronic medical conditions, and no signs of labor. They had healthy blood pressure and were not hypertensive during pregnancy. Patients having a history of diabetes, kidney illness, hypertension, other cardiovascular issues, or infectious infections with symptoms were not allowed to participate.

Criteria for inclusion

Absence of labor contractions, an early membrane rupture, or clinical chorioamnionitis were the criteria for the PE group. None of the patients included had any of the following conditions, which were ruled out through regular consultations, clinical examinations, and laboratory tests: underlying diabetes, renal illnesses, chronic hypertension, or symptomatic infectious diseases. Before being enrolled in the trial, for a minimum of seven days, the pregnant women did not get corticosteroids.

Sample collection

Blood samples were taken from the patients’ antecubital veins while they were lying supine after a minimum of eight hours of fasting and one hour of rest. The serum was then collected and stored at -20 C until use; whereas the urine that was still in the sterile container was examined with a Dipstick.

Urine sample: First morning urine sample was taken in a clean container free from any detergent. A midstream sample was taken, and it was put in a sterile container. The sample was then moved to an all-
ELISA plate reader (ca Inc., San Diego, CA, USA). The concentrations of sEng were measured using an automated enzymatic technique was used to evaluate the serum lipid profile testing.

**Statistical analysis**
Using SPSS, the statistical analysis was completed (version 25). For numerical variables having normally distributed data, the data were converted into the average and the variation from the mean, respectively, and for categorical variables, into frequency/percentage. While a t-test performed independently, and an ANOVA test were employed to see whether there was a significant difference between the typically numerical variables. P 0.05 was used as the significant level The Pearson correlation and t-test were used to calculate the correlation’s significance for the relationship between the two quantitative variables. Using the receiver operating characteristic (ROC) curve approach, it was possible to evaluate the utility of sEng as a diagnostic marker or disease-screening tool. Additionally, it was possible to determine the value range of the cut-off of the serum sEng concentration that has the maximum specificity and sensitivity for diagnostics.

**Results**

**PE (preeclampsia) patient groups and healthy persons’ anthropometric and biochemical features**

The mean ages of the normal participant group (43.6 ±4.7) and the PE patients (43.5 ±10.7) are shown in Table 1, with p > 0.05, respectively. Between the healthy subject group’s (29.2 ±3.7 kg/m2) and PE patients’ (28.7 ±3.76 kg/m2) mean BMIs, there was no significant difference (p > 0.05). The findings from the subgroups, which included 30 patients with newly diagnosed PE and 30 individuals with continued diabetes, are given in Table 2.

**A healthy pregnant woman’s serum sEng in PE groups**

The level of serum sEng was significantly higher in pregnant patients with PE(58.31) ng/ml compared to the healthy pregnant group (82.53±15.16 ng/ml) (p < 0.05), and it was also significantly higher in severe PE patients (51.26 ± 7.05) ng/ml compared to the moderate PE patients group (67.08±6.59) ng/ml. These findings are depicted in Figure 1 (A, B).

![Figure 1: A: Serum sEng levels were compared between the healthy pregnant group (n = 30) and PE patients (n = 60). B: The sEng levels in serum of patients with moderate PE (n = 38) and severe PE (n = 22). This is the middle value (25th and 75th percentiles).](image-url)
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### Table 1: Anthropometries and biochemical markers of healthy individuals and patient with PE

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Mild PE pregnant (n = 58)</th>
<th>Sever PE pregnant (n = 32)</th>
<th>LSD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.19 NS</td>
<td>0.20 NS</td>
<td>-0.22 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.24 NS</td>
<td>0.18 NS</td>
<td>-0.13 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>PW</td>
<td>0.21 NS</td>
<td>-0.44 *</td>
<td>-0.32 *</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>No Child</td>
<td>-0.15 NS</td>
<td>-0.04 NS</td>
<td>0.30 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Systole P</td>
<td>0.06 NS</td>
<td>0.36*</td>
<td>0.54 **</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Diastole P</td>
<td>0.08 NS</td>
<td>0.04 NS</td>
<td>0.30 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.02 NS</td>
<td>0.15 NS</td>
<td>0.29 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.31 NS</td>
<td>0.008 NS</td>
<td>0.15 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>0.57 *</td>
<td>-0.07 NS</td>
<td>-0.28 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>-0.21 NS</td>
<td>0.16 NS</td>
<td>0.21 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>0.27 NS</td>
<td>-0.02 NS</td>
<td>-0.06 NS</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>proteinuria</td>
<td>0.07 NS</td>
<td>0.47 *</td>
<td>0.74 **</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* (P≤0.05), ** (P≤0.01), NS: Non-Significant.

### Table 3: A correlation between the Anthropometries and biochemical markers and the serum sEng level.

<table>
<thead>
<tr>
<th>Area</th>
<th>Std. Error*</th>
<th>Asymptotic Sig.</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.103</td>
<td>0.058</td>
<td>0.001</td>
<td>0.73</td>
<td>0.73</td>
<td>0.585</td>
</tr>
</tbody>
</table>

Between the groups representing the positive and negative real states, there is at most one tie in the test result variable(s) sEng. Statistics might be skewed:

a. In line with the nonparametric assumption
b. True area is equal to 0.5.

### Table 4: AUC and sEng validity to distinguish between pregnant women in good health and individuals with mild PE.

<table>
<thead>
<tr>
<th>Area</th>
<th>Std. Error*</th>
<th>Asymptotic Sig.</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.83</td>
<td>0.047</td>
<td>0.0001</td>
<td>0.85</td>
<td>0.85</td>
<td>0.758</td>
</tr>
</tbody>
</table>

The test result variable(s) sEng has a tie between the positive and negative actual state groups: Statistics might be skewed:

a. In line with the nonparametric assumption
b. True area is equal to 0.5.

### Table 5: To distinguish between very ill PE patients and the healthy pregnant group, use the AUC and validity of sEng.

A correlation between the severity of the illness and the serum sEng level

As shown in Table 3, there was a significant positive association between the serum sEng concentration and proteinuria in the moderate PE group (R = 0.47, p< 0.05) as well as SBP (R = 0.36, p< 0.05). Additionally, In the group with severe PE, Serum sEng concentration correlated substantially with proteinuria (R = 0.74, p
and vasodilation [20]. Downstream signaling, which includes eNOS activation from attaching to its receptors and suppresses angiogenic protein called soluble Eng prevents TGF-β1 from activating its receptors and promotes angiogenesis [18,19]. An antiangiogenic factor, soluble Eng, inhibits hypoxia endothelial cell death and regulates vascular tone via nitric oxide [18,19]. An antiangiogenic protein called soluble Eng prevents TGF-β1 from attaching to its receptors and suppresses downstream signaling, which includes eNOS activation and vasodilation [20].

Preeclampsia patients have greater serum sEng levels than typical pregnant women. We also found that sEng levels rose with preeclampsia severity, suggesting that they accurately signify the deterioration of the systemic vascular endothelium. Worse preeclampsia symptoms were associated with higher blood sEng levels, including proteinuria exceeding 2g/day. Our findings support the idea that this particular antiangiogenic factor is altered in women with preeclampsia and that these biochemical abnormalities become more prominent as the condition progresses, especially when preterm [21,22].

Additionally, we found that the serum sEng levels and the number of weeks pregnant had a substantial negative correlation. A significant inverse relationship between the blood sEng levels and gestational age at sampling has been shown by prior studies [23,24].

Troisi et al. (2008) linked sEng to pregnancy-related elevated blood pressure [23]. In one PE animal model, sEng-encoding adenovirus induced hypertension, proteinuria, and endothelial dysfunction, which were exacerbated by sEng and sFlt1 coadministration and brought about the help syndrome and prenatal growth restriction [26]. Our experimental results are supported by the positive correlation between systolic blood pressure and PE sEng levels.

Since glomeruli separate the blood and urine compartments, angiogenesis is crucial to renal homeostasis. Genetic studies in mice show that VEGF and PIGF are crucial to renal development and vascular health [27]. sFlt-1 and sEng, anti-angiogenic factors, are linked to glomerular injury and proteinuria. Venkatesha et al. [26] discovered nephrotic-range proteinuria in sEng-treated rats and severe proteinuria in sFlt-1-treated rats. Masuyama et al. [28] found higher proteinuria in high-sEng patients.

Serum sEng has a high AUC of 0.95 and more than 90% sensitivity and specificity for PE diagnosis in normal pregnant women. Based on our findings, sEng is a serum marker with excellent accuracy in identifying PE. Its higher sensitivity and specificity in severe and early-onset PE patients makes it more accurate. De Vivo et al. [29] found that sEng may predict PE early with over 80% sensitivity and specificity in blood samples from 24–28 weeks of gestation. Lim et al. [30] found sEng’s PE prediction AUC to be 0.83. Baumann et al. [31] found an AUC of 0.62 for sEng in predicting late-onset PE in first trimester serum. Our ROC curve study shows that sEng is better at diagnosing PE in normal pregnant women than severe and early-onset cases.

Our study’s strengths include a well-defined, standardized medical regimen for preeclampsia patients and the fact that all samples were taken early in PE, avoiding selection bias. Our study only included...
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PE patients as the case group, and we lost individuals from early pregnancy before PE onset. Thus, longitudinal studies should evaluate sEng, a potential marker, in a larger sample size and follow patients from early pregnancy.

Author Contributions
Ekhlas Abdallah Hassan: conceptualization, analysis, visualization, curation of data, study, writing, original draft.
Shaima Sh. Al-Kilan: Resources, Visualization, editing writing
The final paper was read and authorized by all writers.

Conflict of Interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

References


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