The association between urinary placental protein 13 and soluble fms-like tyrosine kinase-1 in preeclamptic women in the third trimester of pregnancy

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ABSTRACT

Background: Preeclampsia (PE) is diagnosed after 20 weeks of gestation. This multisystem disorder affects 2-7% of pregnant women. Preeclampsia (PE) is a serious complication of pregnancy and one of the main causes of maternal and neonatal mortality and morbidity in the world. The inadequate placentation process results in a change in anti-angiogenic factors levels, such as placental protein 13 and soluble fms-like tyrosine kinase 1 (sFlt-1).

Objectives: To investigate the correlation between urinary placental protein (placental protein 13) and soluble fms like tyrosine kinase-1(sFLT-1) in preeclamptic women in their third trimester of pregnancy.

Methods: A case-control study was carried out from August 2018 till January 2019. Urine samples were collected from pregnant women at Al-Elweyia Hospital, Al-Hakeem Hospital, and Al-Imamain alkadhimain Medical City. The patient groups include fifty women with preeclampsia in the third trimester (25 mild and 25 severe). Fifty healthy pregnant women (at their third trimester of pregnancy) were studied as a control group.

Results: The mean urinary placental protein 13 levels were decreased in women with preeclampsia significantly (P ≤ 0.05) (mild and severe) compared with healthy women (43.44 ± 4.914 pg/ml, 33.34 ± 1.863 pg/ml, and 51.84 ± 2.60 pg/ml) respectively. Also, urinary SFLT-1 concentrations were decreased non-significantly (P > 0.05) in women with preeclampsia (mild and severe) compared with healthy women (5.71 ± 0.414 ng/ml, 5.31 ± 0.38 ng/ml and 6.01 ± 0.282 ng/ml) respectively.

Conclusion: Urinary placental protein and soluble fms-like tyrosine kinase-1 levels in the third trimester of pregnancy were significantly correlated with the severity of preeclampsia, and urinary levels of placental protein 13 were found to be decreased significantly in patients with preeclampsia than in healthy pregnant women in the 3rd trimester of pregnancy.
Keywords  Placental protein 13, Soluble fms-like tyrosine kinase-1, Preeclampsia, Galectin 13, PP13

INTRODUCTION

Preeclampsia is a pregnancy-associated multisystem disorder that complicates 2-10 % of pregnancies in the western world. It is accompanied by a neonatal and perinatal mortality rate of 10 % worldwide.

Early-onset PE (i.e., PE requiring delivery before 34 weeks of gestation) is associated with an increased risk of both short- and long-term maternal complications and perinatal mortality and morbidity.

The diagnosis is based mainly on elevated blood pressure [BP], especially new-onset hypertension [systolic blood pressure ≥ 140 mmHg, or diastolic ≥ 90 mmHg], with proteinuria or other manifestations such as renal impairment, thrombocytopenia, hepatic dysfunction, pulmonary edema, or cerebral/visual disturbances.

The clinical features of preeclampsia are proteinuria and hypertension that occur after 20 weeks of gestation in women who were not previously diagnosed to be hypertensive. Other signs and symptoms of preeclampsia are edema and headache (ACOG, 2019).

Placental protein 13 [Galectin-13] is an exclusive protein expressed by the placenta. It plays a significant role in adhesion of the placenta to the uterus and expansion of maternal arteries by remodeling.

Placental protein 13 is one of the 56 known placental proteins identified so far; it is a 32-kDa homodimer protein and was purified from the placenta.

Placental protein 13 binds to β-galactoside residues of several proteins on the cell surface, cytoskeleton, and extracellular matrix, thereby generating various responses such as immune responses and influencing other functions like apoptosis and molecular recognition.

The availability of the purified native and recombinant placental protein 13 have stimulated the generation of various poly- and monoclonal antibodies, followed by the development of an ELISA immune-diagnostic kit, with these tools in hands, a comparative analysis of PLACENTAL PROTEIN 13 levels in maternal blood was conducted in many studies.

The soluble fms-like tyrosine kinase 1 (sFlt-1) is a splice variant of the receptor 1 for vascular endothelial growth factor A (VEGF-A) that lacks the cytoplasmic and transmembrane domains. By binding to its circulating ligand with high affinity, sFlt-1 inhibits the VEGF-A pathway and impairs endothelial cell homeostasis.

Serum soluble fms-like tyrosine kinase-1 (sFlt-1), also known as a soluble receptor for vascular endothelial factors (VEGF), is a protein that binds and decreases the concentrations of circulating VEGF and PlGF.

This study aimed to evaluate the potential use of placental protein 13 and soluble fms-like tyrosine kinase-1 as biomarkers to predict the risk of developing preeclampsia and assess the severity.
METHODS

A case-control study was conducted on 102 pregnant women in the period between August 2018 and January 2019.

They collected urine samples of pregnant women from the Al-Elweyia Hospital, Al-Hakeem Hospital, and Al- Imamain Al-kadhimain Medical City. The practical part was conducted at the Department of Chemistry and Biochemistry and the Department of anatomy /Histology and Embryology, College of Medicine, Al- Nahrain University, Baghdad, Iraq.

This research was approved by the Institutional Review Board (IRB), and before participation, all women were given an idea about the study, and their written informed consent was taken. All pregnant women included in this study were in the third trimester of pregnancy.

Patients with chronic hypertension, gestational hypertension, renal and liver diseases, diabetes mellitus, smokers, fetal structural anomalies, multiple pregnancies, intrauterine fetal growth restriction from other causes, heart failure, inflammatory disorders, elderly pregnancies, infectious disease, endocrine disease, HELLP syndrome, and collagen vascular disease were excluded from the study.

A random urine sample was collected in a sterile urine collection cup. Pregnant women were instructed to discard the first 20-25ml of urine, and about sixty mL from the mid urine stream were collected. The collected specimen was stored in Eppendorf tubes at -80°C until analysis of placental protein 13(placental protein 13), soluble fms like tyrosine kinase -1 (sFlt-1) concentrations. According to the manufacturer instructions, levels of sFlt-1 and placental protein 13 were measured with a commercially available enzyme-linked immunosorbent assay (ELISA) (Bioassay technology laboratory ).

Statistical analysis

Data were analyzed by statistical packages of SPSS 18.5 (Statistical Packages for Social Sciences-version 18.5). All data were presented as a mean ± SEM. Statistical differences between data of patients and control groups were determined according to the student's t-test. Correlation between the variables was performed by Spearman correlation coefficient. P values were significant if the P-value is ≤ 0.05.

RESULTS:

Table (1) illustrates the age of the patients’ groups (mild and severe preeclampsia) and controls analyzed using a one-way analysis of variance (ANOVA) test, the mean ± SEM of maternal age for the pregnant control group and patients groups (mild and severe preeclampsia) were 29.28±1.08 years, 29.84±1.70 years, and 29.85±1.27 years, respectively. No significant difference (P<0.05) was found among all study groups.

Placental protein 13 levels of control pregnant and patient groups (mild and severe preeclampsia) at the third trimester of pregnancy were 51.84±2.60 pg/ml, 43.44±4.91 pg/ml, and 33.34 ± 1.86 pg/ml, respectively.
There was a significant difference increase \( (P=0.001) \) in the mean of urine placental protein 13 between the patient’s group (mild and severe) and control group; there were significant differences increase \( (p=0.022) \) between the control pregnant group versus mild preeclamptic group in the third trimester of pregnancy; also there were a highly significant difference increase \( (P=0.002) \) between the control pregnant versus severe preeclampsia group (Table 1-2). At the same time, there was no significant difference \( (P=0.062) \) between the mild preeclamptic group versus severe preeclampsia group in the third trimester of pregnancy.

SFLT-1 levels for control pregnant and patient groups (mild and severe preeclampsia) at the third trimester were 6.01 \( \pm 0.282 \) ng/ml, 5.71 \( \pm 0.414 \) ng/ml, and 5.31 \( \pm 0.38 \) ng/ml, respectively.

There was no significant difference in mean of urine SFLT-1 for patients groups (mild and severe preeclampsia) against the control group, mild preeclamptic group against control pregnant group, severe preeclamptic against control pregnant, severe preeclamptic group against the mild group in the third trimester (Table 2).

### Table 1 The Age of study groups

<table>
<thead>
<tr>
<th>Type</th>
<th>Control</th>
<th>Mild</th>
<th>Severe</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.28 ± 1.08</td>
<td>29.84 ± 1.70</td>
<td>29.85 ± 1.27</td>
<td>0.931 NS</td>
</tr>
</tbody>
</table>

### Table 2 Urinary placental protein 13, and soluble fms like tyrosine kinase-1(SFLT-1) for both control pregnant group and patients groups (mild and severe preeclampsia) at the third trimester of pregnancy

<table>
<thead>
<tr>
<th>Urinary placental protein 13 (pg/ml)</th>
<th>Control 51.84 ± 2.60</th>
<th>P value</th>
<th>Control vs. Mild 0.001*</th>
<th>Control vs. Severe 0.002*</th>
<th>Mild vs. severe 0.062 NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>38.39 ± 2.717</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mild</td>
<td>43.44 ± 4.914</td>
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</tr>
<tr>
<td>Severe</td>
<td>33.34 ± 1.863</td>
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<tr>
<td>Urinary SFLT-1 (ng/ml)</td>
<td>Control 6.01 ± 0.282</td>
<td>0.498 NS</td>
<td>0.396 NS</td>
<td>0.717 NS</td>
<td>0.299 NS</td>
</tr>
<tr>
<td>PE</td>
<td>5.50 ± 0.658</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5.71 ± 0.414</td>
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</tr>
<tr>
<td>Severe</td>
<td>5.31 ± 0.38</td>
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</table>
DISCUSSION:

Placental protein 13 (Galactin 13) is a small protein (32 kD) produced by the placenta, specifically the syncytiotrophoblast. It binds to a protein on the extracellular matrix between the placenta and the endometrium, is thought to be involved in placental implantation and maternal vascular remodeling. Recently this protein has been attracted as a potential marker for early PE diagnosis.

In this study, the maternal urine levels of the placental protein 13 were highly significant decreases in preeclamptic patients groups (mild and severe preeclampsia) compared to controls pregnant.

Decreased levels of PP-13 have been found in patients who developed PE. In a study by Nicolaides et al. (Nicolaides et al., 2006) in patients with severe PE who gave birth before 34 weeks, the placental protein 13 serum levels were lower than in the normotensive individuals. They suggested that effective screening for PE requiring delivery before 34 weeks can potentially be provided by assessment of a combination of maternal serum PP-13 and uterine artery Doppler in the first trimester of pregnancy.

Regarding urinary placental protein 13 and to our knowledge, the present study is the first one concerning the level of urinary placental protein 13 in preeclamptic women at their 3rd trimester.

The present study showed a decrease in urinary soluble fms like tyrosine kinase -1 in preeclampsia (mild and severe) compared with the pregnant control group in the third trimester. A similar result was reported by many studies.

In a study conducted by Tang et al., Serum and urinary sFlt-1 in severe PE patients were higher than those in the mild PE group, and measurements from mild PE patients were significantly higher than controls (P <0.01), in that the elevated levels of sFlt-1 can modify the endothelial integrity of blood vessels, causing hepatic edema and hypertension and proteinuria encountered in preeclamptic patients. Also, blood-brain–barrier damage may occur, leading to brain edema. This aberrant angiogenesis and hypertension are the hallmarks of preeclampsia.

Placental overexpression of sFLT1, specifically in the fetal derived trophoblast cells, was implicated as the underlying cause of preeclampsia.

REFERENCES


