Combined estimation of serum soluble endoglin and placental protein-13 at first trimester as early predictors for development and severity of pre-eclampsia

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Abstract
Objectives: Evaluation of the ability of estimated serum levels of placental protein 13 (PP13) and soluble endoglin (sEng) at the 12th week gestational age (GA) for early prediction for development of pre-eclampsia (PE).

Patients & Methods: the study included 180 primigravida with singleton fetus and free of PE-risk factors. At the 12th week GA, all women underwent complete clinical examination and gave venous blood samples for ELISA estimation of baseline serum PP13 and sEng level. All women were followed-up 4-weekly till delivery for development of PE manifestations.

Results: Ninety women developed PE; 28 early and 62 late PE. Twenty-one had severe and 69 had mild PE. The remaining 90 women completed their pregnancy free of hypertensive manifestations (Control group). PE women were older and had higher body weight (BW) than controls. Baseline serum PP13 levels were significantly lower in PE than control women, in late than in early-onset PE and in severe than in mild PE. On contrary, estimated serum sEng were significantly higher in PE women especially those who developed late-onset and/or severe PE. Statistical analyses find high baseline serum sEng and BW as significant specific and low serum PP13 as significant sensitive predictors for development of PE, while baseline high serum sEng and low serum PP13 and old age as significant specific predictors for late-onset PE and high baseline DBP as significant specific predictor, but low serum PP13 as significant sensitive predictor for severe PE

Conclusion: Combined serum assay for PP13 and sEng early in pregnancy allowed prediction of development of PE and patients' stratification according to timing of development and its predicted severity.

Keywords: Pre-eclampsia, Placental Protein 13, Soluble Endoglin, PE severity prediction

Introduction
Hypertensive disorders represent a major concern of maternal health. Pre-eclampsia (PE) may affect about 5% of pregnant women (Correa et al., 2016), and is one of the most frequent causes of maternal and fetal morbidity and mortality (Ghesquière et al., 2016). PE may develop as early-onset or late-onset PE and according to severity PE may be mild or severe (Poon & Nicolaides, 2014). Early-onset and severe PE are associated with a higher incidence of adverse maternal, fetal and neonatal outcome (Leaños-Miranda et al., 2013).

Etiology of PE is still unknown but it is well documented that impaired or shallow placentation is a major contributor to its development (Huppertz et al., 2013). Shallow placentation induces placental oxidative and endoplasmic reticulum stress (Redman et al., 2014) causing subsequent release of factors which affect endothelial functions into the maternal circulation (Redman & Sargent, 2009). Moreover, altered expression of vasoconstrictor and anti-angiogenic factors was detected in endothelial cells of pregnant PE women and may explain PE associated vascular dysfunction (Lee & Nevo, 2016).

Endoglin is an arginylglycylaspartic acid-containing counter-receptor for β1 integrins and is highly expressed during angiogenesis by endothelial cells. Soluble
endoglin (sEng) inhibited adhesion of vascular endothelial cells to mural cells (Rossi et al., 2016).

Galectins are glycan-binding proteins which are involved in regulation of immune responses may affect maternal-fetal immune tolerance (Than et al., 2014a). Three of the five human cluster galectins on chromosome 19 are solely expressed in the placenta and may enable deep placentation through immunoregulatory mechanisms (Than et al., 2014b). Placental protein 13 (PP13) is one of galectin-13, has a "jelly-roll" fold and carbohydrate-recognition domain (Sammar et al., 2014) and is highly expressed by the syncytiotrophoblast to be released into maternal circulation (Blois et al., 2015). Human PP13 as experimentally in animal model causes significant vasodilatation in isolated arteries so reduces blood pressure and prolonged exposure induced increased elaboration and angiogenesis of uteroplacental arteries (Gizurarson et al., 2013).

Biomarkers estimated early in pregnancy may allow stratification of women as high and low risk pregnancies so as to define surveillance in pregnancy and give chances for early intervention (Wu et al., 2015). Thus, the current study aimed to evaluate the ability of estimation of serum PP13 and soluble endoglin at the 12th week gestational age for early prediction for development of PE.

**Setting**

Benha University Hospital

**Design**

Prospective clinical double-blinded comparative study

**Patients & Methods**

The study protocol was approved by the Local Ethical Committee. The study was started since Jan 2013 till April 2015 to allow follow-up for the last enrolled case till delivery. All primigravida attending antenatal care unit prior to the 12th week gestational age (GA) were eligible for evaluation. Pregnant women who accepted to participate in the study, attend the clinic 4-weekly since 12th week GA till delivery for follow-up and to donate blood sample on request to undergo the assigned investigations and to sign a fully informed written consent were enrolled in the study. Pregnant women with family history of PE, history of essential hypertension, renal diseases, endocrinopathy, vascular diseases or diabetes mellitus were excluded from the study so as to include only primigravida with singleton fetus and free of PE-risk factors.

At the 1st antenatal visit, eligible women were evaluated for demographic data, complete history taken and full clinical and gynecological examination including ultrasonographic examination to confirm GA, and exclude multiple gestation or fetal congenital abnormalities and to fulfill exclusion criteria. Throughout antenatal visits, women who developed the diagnostic criteria for PE were grouped as PE group and categorized according to time of development of PE into Early-onset PE if diagnosed before the 20th week GA and Late PE if diagnosed later to the 20th week GA. Women who completed their pregnancy free of PE manifestations were grouped as Control group.

Diagnosis of PE relied on the development of gestational hypertension beginning after the 12th week of pregnancy with an absolute blood pressure ≥140 mmHg systolic and/or 90 mmHg diastolic on at least two occasions, 4 hours apart, and proteinuria (one dipstick measurement >2+ on a voided random urine sample) (Gifford et al., 2000). Severe PE was diagnosed if SBP was >160 mmHg, DBP was
Venous blood samples (5 ml) were collected under complete aseptic conditions at time of 1st antenatal visit from the antecubital vein from all pregnant women fulfilling the inclusion criteria. Collected blood samples were allowed to clot and then were centrifuged at 1500×g for 15 min and the serum samples were stored at -70°C until ELISA assayed for estimation of baseline levels of serum soluble endoglin (AdipoGen Inc., Seoul, Korea) (Staff et al., 2007) and human placental protein 13 (PP13) (CUSABIO BIOTECH, Toronto, Canada) (Stefanovic et al., 2015).

Study outcomes
1. The predictability of studied parameters for development of PE.
2. The discriminative ability of the estimated parameters between early and late PE and between severity grades; mild or severe PE.

Statistical analysis
Obtained data were presented as mean±SD, ranges, numbers and percentages. Results were analyzed using One-way ANOVA with post-hoc Tukey HSD Test and Chi-square test (X² test). Possible relationships were investigated using Spearman linear regression. Sensitivity & specificity of estimated parameters as predictors were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared versus the null hypothesis that AUC=0.05. Regression analysis (Stepwise method) was used for stratification of studied parameters as significant predictors for the target disease. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value <0.05 was considered statistically significant.

Results
The study included 90 pregnant women developed pre-eclampsia; 28 women had early and 62 had late PE. According to severity, 21 women developed severe and 69 developed mild PE. The study also included 90 women completed their course of pregnancy free of hypertensive manifestations. Women developed early PE were non-significantly (p>0.05) older with non-significantly higher body mass index. However, PE women had significantly (p<0.05) higher body weight (BW) than control women with significantly (p<0.05) higher body weight among women developed severe than mild PE (Table 1).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control women (n=90)</th>
<th>PE women</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (n=28)</td>
<td>Late (n=62)</td>
<td>Mild (n=21)</td>
<td>Severe (n=69)</td>
<td>Total (n=90)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>26.9±5</td>
<td>25.8±5.1</td>
<td>27.7±5.4</td>
<td>26.9±5.5</td>
<td>27±5.6</td>
<td>27.8±5.6</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.4±5.1</td>
<td>76.4±9.2</td>
<td>75.8±8.1</td>
<td>75.3±7.9*†</td>
<td>78.2±10*</td>
<td>76±8.4*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.5±1.9</td>
<td>169.7±2.4</td>
<td>170±2.6</td>
<td>169.8±2.6</td>
<td>170.1±2.2</td>
<td>169.9±2.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±1.9</td>
<td>26.6±3.3</td>
<td>26.2±2.8</td>
<td>26.1±2.8</td>
<td>27±3.5</td>
<td>26.3±3</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, BMI: Body mass index; *: significant difference versus control group; †: significant difference versus women developed severe PE.

Baseline blood pressure measures showed non-significant (p>0.05) difference between studied patients and controls. In comparison to baseline SBP and DBP, measures determined during follow-up were non-significantly (p>0.05) higher in
control women, while were significantly (p<0.05) higher in PE women. At time of
diagnosis of PE, PE women had significantly (p<0.05) higher blood pressure
measures compared to corresponding measures of control women, irrespective of time
of diagnosis or severity of PE. Women who developed early-onset PE had
significantly (p<0.05) higher SBP but non-significantly (p>0.05) higher DBP
compared to women had late-onset PE. On contrary, women who developed severe
PE had significantly (p<0.05) higher SBP and DBP compared to women developed
mild PE (Table 2).

Table (2): Baseline SBP and DBP measures of PE women categorized according to timing
and severity of PE compared to control women

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>Control women (n=90)</th>
<th>Early (n=28)</th>
<th>Late (n=62)</th>
<th>Mild (n=21)</th>
<th>Severe (n=69)</th>
<th>Total (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP (mmHg)</td>
<td></td>
<td>118.5±4.1</td>
<td>119.4±4.2</td>
<td>118.7±5.3</td>
<td>118.4±5.4</td>
<td>120.4±3.2</td>
<td>118.5±3.6</td>
</tr>
<tr>
<td>SBP at PE diagnosis (mmHg)</td>
<td></td>
<td>121.7±7.6</td>
<td>157.5±12†*</td>
<td>151±7.4</td>
<td>148.8±5†*</td>
<td>168±4.7 †*</td>
<td>153±9.5</td>
</tr>
<tr>
<td>Baseline DBP (mmHg)</td>
<td></td>
<td>83.2±2.9</td>
<td>83.9±2.5</td>
<td>83.6±2.6</td>
<td>86±2.6</td>
<td>82.7±2.2</td>
<td>83.8±2.6</td>
</tr>
<tr>
<td>DBP at PE diagnosis (mmHg)</td>
<td></td>
<td>83.5±2.7</td>
<td>101.3±9.6*</td>
<td>97.3±8.2*</td>
<td>93.9±1.6*</td>
<td>113.9±3.5*</td>
<td>98.6±8.8*</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. Baseline: indicates measures taken at 12th week of pregnancy; PE: Pre-eclampsia; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *: significant difference versus control group; †: significant difference versus corresponding baseline measures; ‡: significant difference versus women developed late PE; ††: significant difference versus women developed severe PE.

Serum levels of PP13 estimated at the 12th week GA (Baseline levels) were
significantly (p=0.001) lower, while estimated serum sEng levels were significantly
higher in PE compared to control women. Among PE women baseline serum levels of
PP13 were significantly lower in women who developed late-onset (p=0.002) and
severe (p=0.040) PE compared to women who developed early-onset and mild PE,
respectively. On contrary, baseline serum sEng levels significantly higher in PE
women who developed late (p=0.001) and severe (p=0.027) PE compared to PE
women with early or mild PE (Table 3).

Table (3): Baseline serum PP13 and sEng estimated in PE women categorized according to
timing and severity of PE compared to control women

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>PP13</th>
<th>sEng</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Total (n=90)</td>
<td>110.2±14.2</td>
<td>1.45±0.76</td>
</tr>
<tr>
<td>PE women</td>
<td>P1 value</td>
<td>68.7±17.6</td>
<td>3.8±0.74</td>
</tr>
<tr>
<td>Time of development</td>
<td></td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Early (n=28)</td>
<td>72.8±16.2</td>
<td>3.26±0.5</td>
<td></td>
</tr>
<tr>
<td>Late (n=62)</td>
<td>59.6±17.4</td>
<td>4.14±0.71</td>
<td></td>
</tr>
<tr>
<td>P2 value</td>
<td>0.002</td>
<td>=0.001</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Mild (n=21)</td>
<td>73.4±15.9</td>
<td>3.75±0.73</td>
</tr>
<tr>
<td>Severe (n=69)</td>
<td>53.5±14.3</td>
<td>4.03±0.77</td>
<td></td>
</tr>
<tr>
<td>P1 value</td>
<td>0.040</td>
<td>0.027</td>
<td></td>
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</tbody>
</table>

Data are presented as mean±SD; PE: Pre-eclampsia; PP13: Placental protein 13; sEng: Soluble endoglin; p<0.05 indicates significant difference.

Spearman's correlation analysis showed a positive significant correlation
between development of PE and both BW and baseline serum sEng levels, while
showed negative significant correlation with baseline serum PP13 levels. However,
development of late-onset PE showed positive significant correlation with age and
baseline serum sEng levels, while showed negative significant correlation with baseline serum PP13 levels. On the other hand, development of severe PE showed positive significant correlation with baseline DBP and serum sEng levels, while showed negative significant correlation with baseline serum PP13 levels (Table 4).

Table (4): Spearman's correlation between baseline data of studied women and development of PE, and being of late-onset or severe type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Development of PE</th>
<th>Late-onset PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.038</td>
<td>&gt;0.05</td>
<td>0.331</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>0.191</td>
<td>0.010</td>
<td>0.034</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.089</td>
<td>&gt;0.05</td>
<td>0.067</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.109</td>
<td>&gt;0.05</td>
<td>0.060</td>
</tr>
<tr>
<td>Serum PP13 (ng/ml)</td>
<td>-0.804</td>
<td>&lt;0.001</td>
<td>-0.340</td>
</tr>
<tr>
<td>Serum sEng (ng/ml)</td>
<td>0.866</td>
<td>&lt;0.001</td>
<td>0.458</td>
</tr>
</tbody>
</table>

PE: Pre-eclampsia; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP13: Placental protein 13; sEng: Soluble endoglin

Regression analysis of baseline data of studied women defined high serum sEng, low serum PP13 and high BW as the significant predictors for development of PE, while defined high serum sEng, low serum PP13 and older women as the significant predictors for development of late-onset PE. Regression analysis defined high serum sEng as the persistently significant predictor for both development of PE in general and especially for late-onset PE. As regards prediction of severe PE, Regression analysis defined high SBP, BW, DBP and low PP13 as the significant predictors in decreasing order of significance with low PP13 as the persistently significant predictor (Table 5).

Table (5): Regression analysis of baseline data as predictors for development of PE and for being of late-onset or severe type

<table>
<thead>
<tr>
<th>Development of PE</th>
<th>Late-onset PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Variable</td>
<td>β</td>
</tr>
<tr>
<td>1</td>
<td>sEng</td>
<td>0.658</td>
</tr>
<tr>
<td>2</td>
<td>PP13</td>
<td>-0.341</td>
</tr>
<tr>
<td>3</td>
<td>BW</td>
<td>0.062</td>
</tr>
<tr>
<td>4</td>
<td>sEng</td>
<td>0.658</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

PE: Pre-eclampsia; sEng: Soluble endoglin; PP13: Placental protein 13; BW: Body weight; DBP: Diastolic blood pressure

ROC curve analysis defined high baseline BW and serum sEng as significant specific and low serum PP13 as significant sensitive predictors for development of PE (Fig. 1), while defined older age, high serum sEng and low serum PP13 as significant specific predictors for development of late-onset PE (Fig. 2) and high baseline DBP as significant specific predictor, but low serum PP13 as significant sensitive predictor for severe PE (Fig. 3).

Table (6): ROC curve analysis of significant variables determined by Regression analysis as early predictors for development, and for being of late-onset or severe type

<table>
<thead>
<tr>
<th>Development of PE</th>
<th>Late-onset PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>AUC</td>
<td>p</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>BW</td>
<td>0.610</td>
<td>0.011</td>
</tr>
<tr>
<td>PP13</td>
<td>0.036</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sEng</td>
<td>0.962</td>
<td>&lt;0.001</td>
</tr>
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</tbody>
</table>

PE: Pre-eclampsia; BW: Body weight; PP13: Placental protein 13; sEng: Soluble endoglin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Fig. (1): ROC curve analysis of significant variables determined by Regression analysis as early predictors for development of PE

Fig. (2): ROC curve analysis of significant variables determined by Regression analysis as early predictors for late-onset PE
Fig. (3): ROC curve analysis of significant variables determined by Regression analysis as early predictors for severe PE

Discussion

Development and severity of PE is a multifactorial dilemma, PE women were old especially women got late and/or severe PE and had higher body weight (BW) than control women. Statistical analyses showed a positive significant correlation between development of PE and BW and age and both could predict its future development and severity.

In line with these findings, Sohlberg et al., (2012) found short women had increased risks of all types of PE, especially early disease, increased BMI increased these risks and obesity class II-III was associated with a four-fold higher risk PE. Also, Dantas et al., (2013) documented that women who are overweight or old have a higher risk of PE and Thompson et al., (2014) found higher adult weight gain prior to pregnancy may predispose to PE. Moreover, Marchi et al., (2015) out of evaluation of 22 reviews documented that gestational diabetes, PE, gestational hypertension, instrumental and caesarean birth and surgical wound complications are more liable to occur in obese pregnant women than in healthy weight women.

Estimated serum PP13 levels at the 12th week GA were significantly lower in PE than control women, in late than in early-onset PE and in severe than in mild PE. On contrary, estimated serum sEng were significantly higher in PE women especially those who developed late-onset and/or severe PE. Statistical analyses find high baseline serum sEng and BW as significant specific and low serum PP13 as significant sensitive predictors for development of PE, while baseline high serum sEng and low serum PP13 and older age as significant specific predictors for late-onset PE and high baseline DBP as significant specific predictor, but low serum PP13 as significant sensitive predictor for severe PE.

In line with the findings concerning the predictability of baseline serum sEng, Gluchowska et al., (2013) detected significantly higher serum concentrations of sEng in pregnant PE women than in hypertensive and control women and concluded elevated serum concentration of sEng in pregnant women constitutes a risk factor for PE. Also, Tobinaga et al., (2014) detected high serum levels of sEng in PE women.
directly correlated with uterine artery resistance. Moreover, Allen et al., (2014) documented that abnormal maternal blood biomarkers in early pregnancy are significantly associated with PE, particularly early-onset disease, but sEng and inhibin-A were significantly associated with late-onset PE. Thereafter, Rios et al., (2015), detected high plasma levels of sEng and soluble forms of vascular cell adhesion molecule-1, but decreased free vascular endothelial growth factor in women with PE especially of severe-type.

Recently, in 2016, Wang et al. found serum endoglin levels were significantly higher in PE patients than controls, in severe PE than moderate PE and high serum endoglin levels showed sensitivity, specificity and positive and negative predictive values for development of PE of 66%, 80%, 89.2% and 48.5%, respectively. Moreover, Sachan et al., (2016) reported that elevated serum sEng levels could diagnose PE with 100% sensitivity and specificity and were strongly correlated with SBP and DBP and concluded that sEng is a novel marker for diagnosis of PE, and it can be used as a prognostic marker to predict its time of occurrence and severity.

As regards the predictive value of estimation of baseline PP13 for PE, El-Sherbiny et al., (2012) detected significantly lower maternal serum PP13 levels and lower PP13 mRNA expression level in PE women compared to controls and concluded that it could be reliable markers for early detection of PE. Huppertz et al., (2013), out of meta-analysis, showed that 1st trimester low serum PP13 levels can predict PE development later in pregnancy. Also, Svirsky et al., (2013) reported that among severe PE women with singletons PP13 levels were significantly reduced, but were higher in twins and concluded that serum PP13 levels corresponds to placental mass. Thereafter, Meiri et al., (2014) detected significantly lower serum PP13 levels in PE women compared with unaffected ones and concluded that low PP13 was a better predictor for PE versus major risk factors especially in young nulliparous. Recently, De Muro et al., (2016) documented that reduced plasma PP13 levels could be a promising tool for prediction of PE in an early stage of pregnancy.

**Conclusion**

The obtained results allowed concluding that combined serum assay for PP13 and sEng early in pregnancy allowed prediction of development of PE and patients' stratification according to timing of development and its predicted severity.

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الملخص العربي

القياس المجتمعي للإندوجلين القابل للذوبان وبروتين المشيمة-13 في الأشهر الثلاثة الأولى للحمل كمؤشرات مبكرة للتنبؤ بحدوث وشدة متلازمة ما قبل تسمم الحمل

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هدف العمل: تقييم قدرة قياس مستويات بروتين المشيمة-13 والإندوجلين القابل للذوبان بالمصل عند الأسبوع 12 من الحمل على التوقع المبكر لحدوث متلازمة ما قبل الحمل.

المريض وطرق الدراسة: شملت الدراسة 180 سيدة حامل للمرة الأولى وحاملين واحد وليست لديها أي مسبب لحدوث متلازمة ما قبل الحمل. تم القحص الاكلينيكي وسحب عينات الدم لتقدير مستويات بروتين المشيمة-13 والإندوجلين القابل للذوبان بالمصل، ثم متابعة المرضى شهريا لحدوث متلازمة ما قبل الحمل.

النتائج: أصيبت 90 سيدة بمتلازمة ما قبل تسمم الحمل، 28 مبكرة و62 متأخرة، 69 طفيفة و21 شديدة، واتممت 90 سيدة حملها بدون ارتفاع لضغط الدم. وجد أن كتلة الجسم عند المصابات أعلى عن غير المصابات. وجد أن مستوي بروتين المشيمة-13 كان مرتفع بفقار ذو دلالة إحصائية عند المصابات مقارنة بغير المصابات، والمصابات بالمتلازمة المتأخرة عن المبكرة، والمصابات بالمتلازمة الشديدة عن البسيطة. بينما كان مستوي مرتفع بفقار ذو دلالة إحصائية عند المصابات مقارنة بغير المصابات، والمصابات بالمتلازمة المتأخرة عن المبكرة، والمصابات بالمتلازمة الشديدة عن البسيطة. ووجد أن ارتفاع مستوي الإندوجلين القابل للذوبان ووزن الجسم، انخفاض مستوي بروتين المشيمة-13 لها توقعية عالية ذات دلالة إحصائية لتحدي حدوث متلازمة ما قبل تسمم الحمل، ووجد أن ارتفاع مستوي الإندوجلين القابل للذوبان وعمر السيدة، انخفاض مستوي بروتين المشيمة-13 لها توقعية عالية ذات دلالة إحصائية لتحدي حدوث متلازمة ما قبل تسمم الحمل المتأخرة، ووجد أن ارتفاع ضغط الدم وانخفاض مستوي بروتين المشيمة-13 لها توقعية عالية ذات دلالة إحصائية لتحدي حدوث متلازمة ما قبل تسمم الحمل الشديدة.

الاستنتاج: القياس المجتمعي للإندوجلين القابل للذوبان وبروتين المشيمة-13 بفضل الدم يمكن من التنبؤ المبكر بحدوث وشدة متلازمة ما قبل تسمم الحمل.