Early predictors of preterm labor and preeclampsia: A prospective study

Ali Babacan (*), Özgür Dündar (*), Murat Muhcu (*), Ercüment Müngen (*), Vedat Atay (*), Cem Kızılaslan (**), Yaşam Kemal Akpak (***)

SUMMARY

Aims: This study aimed to investigate various clinical/biochemical parameters as potential predictors of preeclampsia and preterm labor. MMP-2, MMP-9, pregnancy-associated plasma protein A (PAPP-A), fms-like tyrosine kinase 1, and beta human chorionic gonadotropin (β-HCG) levels were measured and Doppler ultrasonography measurements were made in pregnant women at 11-14 weeks of gestation. Findings were recorded and patients were followed until delivery.

Results: Patients consisted of preeclampsia and/or preterm labor cases (n=40) and selected controls were pregnant women with a normal pregnancy period who delivered between 37 and 40 weeks of gestation (n=55). Multivariate analysis identified high fms-like tyrosine kinase 1 level (OR, 1.004; 95% CI: 1.001-1.007, p= 0.005), high UtA PI (OR, 30.6; 95% CI: 1.1-852, p= 0.044) and presence of any notch (OR, 36.4; 95% CI: 1.6-826, p= 0.024) as independent predictors of preeclampsia; whereas only maternal MMP-9 level emerged as a significant predictor of preterm birth (OR, 1.001; 95% CI: 1.000-1.001, p< 0.001).

Conclusions: These parameters deserve further investigation for their potential use (either alone or in combination) in the prediction of preeclampsia and preterm birth in the clinical setting.

Key Words: preterm labor, preeclampsia, Doppler ultrasonography, matrix metalloproteinase (MMP), pregnancy-associated plasma protein A (PAPP-A), fms-like tyrosine kinase 1, beta human chorionic gonadotropin (β-HCG).

ÖZET

Erken doğum ve preeklampsinin erken belirteçleri: prospektif bir çalışma

Bu çalışmanın amacı, değişik klinik ve biyokimyasal parametreleri, preeklampsi ve erken doğumun oluşum belirteçleri olarak değerlendirilmektedir. Gebelikliğinde 11-14 haftaların sona ermesiyle olan kadınlardan MMP-2, MMP-9, gebelikle iliskili plazma protein A (PAPP-A), fms-benzeri tirozin kinaz 1, insan beta koriyonik gonadotropini (β-HCG) düzeyleri ölçülmüştür ve Doppler ultrason ölçümleri yapılmıştır. Bulgular kaydedilmiş ve hastalar daha sonra verilmiştir. Preeklampsi ve/veya erken doğum oluşan 40 hafta çalışma grubunu, gebelikçinin 37 ile 40. haftalarında normal doğum yapmış seklin-même 55 hasta kontrol grubuna ayrılmıştır. Çok değişkenli analiz, yüksek fms-benzeri tirozin kinaz 1 düzeyi (OR, 1.004; 95% CI: 1.001-1.007, p= 0.005), yüksek UtA PI değerleri (OR, 30.6; 95% CI: 1.1-852, p= 0.044) ve herhangi bir notch olması durumu (OR, 36.4; 95% CI: 1.6-826, p= 0.024) preeklampsinin bağımsız belirteçleri olarak belirlenmiştir. Erken doğumun oluşum belirteçleri olarak is saade onun MMP-9 düzeyi bulunmuştur (OR, 1.001; 95% CI: 1.000-1.001, p< 0.001). Klinik ortamda bu parametrelerin preeklampsi ve erken doğum tahmin etmedeki değerlerinin (tek başına ya da kombinasyon olarak) daha iki çalışmalarında araştırılması gerekmektedir.

Anahtar Kelimeler: erken doğum, preeklampsi, Doppler ultrason, matriks metalloproteinaz (MMP), gebelikle iliskili plazma protein A (PAPP-A), tirozin kinaz, insan beta koriyonik gonadotropini (β-HCG)

Introduction

Preeclampsia is an important cause of mortality and morbidity affecting 1 to 2 % of pregnancies (1). Preterm labor is even more prevalent complicating approximately 12% of all pregnancies (2, 3). Although the exact mechanism of preeclampsia has not been definitely understood, vascular and inflammatory factors have been proposed for its pathogenesis (4); and a multitude of risk factors have been proposed for preterm birth (2).

Risk assessment for the development of these conditions may help to identify the individuals at higher risk and to develop preventive strategies. To date, several markers have been tested as potential predictors of pregnancy related hypertensive conditions and preterm labor, including uterine artery Doppler measurements and several biochemical markers (5-15). Doppler examination is a non-invasive and useful method that gives valuable information on the development of the fetus and the placenta. Several ultrasonography parameters, particularly uterine artery indices and presence of uterine artery notch has been associated with preeclampsia (15-18).

Pregnancy-associated plasma protein A (PAPP-A), is a peptide which can be detected during pregnancy in maternal circulation. It is suggested to be involved in local proliferative processes (19, 20). Decreased plasma levels of PAPP-A have been reported in association with preeclampsia (21, 22).

Placental soluble fms-like tyrosine kinase 1 (sFlt1) is an antagonist of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). High levels have been found in maternal blood during preeclampsia. In addition, increased levels of this molecule is associated with decreased circulating levels of VEGF and PIGF (23).

Human chorionic gonadotropin (HCG) is a hormone that play role in the maintenance of the corpus luteum during early pregnancy. Several recent studies pointed out to a relation between human chorionic gonadotropin levels and adverse pregnancy outcomes (24-26).

Matrix metalloproteinases (MMPs), gelatinase A (MMP-2) and gelatinase B (MMP-9) in particular, are thought to play role in adverse pregnancy outcomes since they seem to have role in uterine and placental artery remodeling (27, 28).

This study aimed to investigate clinical and biochemical parameters as predictors of two different adverse pregnancy outcomes, namely preeclampsia and preterm labor.

Materials and methods

Patients
This prospective study included pregnant women admitting to Obstetrics and Gynecology Outpatient Clinic of GATA Haydarpasa Research and Training Hospital between October 2011 and October 2012 for routine obstetrical follow-up visits at their 11 to 14 weeks of gestation. Exclusion criteria were as follows: multiple pregnancy, early or late abortion, systemic disease and patients who are not planning to deliver in our institution. During the study period, about 6000 outpatient admissions occurred in our clinic, among them 520 were pregnant women admitting for their routine follow-up examination at 11-14 weeks and fulfilling eligibility criteria. All patients provided informed consent prior to study entry and study protocol was approved by local ethics committee. The study was conducted in accordance with Declaration of Helsinki. Patients underwent a thorough obstetrical work-up including history and physical examination, and ultrasonography examination at 11-14 week visit, blood samples were obtained and stored until delivery. Findings were recorded and patients were followed until delivery. Biochemical analyses of stored blood samples were done for patients who developed preeclampsia and/or preterm birth and for 55 randomly selected controls among uncomplicated pregnancies. Figure 1 shows the study diagram.

Figure 1. Study diagram

**Study assessments**

Maternal venous blood samples were obtained for the assessments of MMP-2, MMP-9, PAPP-A, fms-like tyrosine kinase 1, and beta human chorionic gonadotropin (β-HCG) levels during 11-14 week visit and the samples were stored until delivery. Blood samples were obtained in the morning when fasting and stored at -80 C in deep freezer (New Brunswick Scientific Model - U410, UK). All maternal serum biochemical markers analyses were done using BOSTER Human Biomarker ELISA device and kits. In addition, following transabdominal ultrasonography assessments were made using Voluson E8 Expert Scanner (GE Healthcare, Wauwatosa, WI, USA) ultrasonography device and 2-7 MHz convex probe: crown-rump length (CRL), nuchal thickness, presence of uterine artery notch, uterine artery pulsatility index (UtA PI), uterine artery resistance index (UtA RI), uterine artery systolic/diastolic ratio (UtA S/D). Ultrasonography measurements were done as previously described (29).

**Definition of pregnancy outcomes**

Preeclampsia was defined as the onset of hypertension (>140/90 mmHg at two successive measurements at least 6 hours apart) at the second half of the pregnancy which disappears after delivery plus proteinuria (300 mg/d or >1+) (30). Preterm delivery was defined as delivery before 37 weeks of gestational age (2).

**Statistical analysis**

SPSS version 21 was used for the analysis of data. Descriptive statistics are presented as means±SD or number (percentage), where appropriate. Normality was tested using Shapfiro-Wilk test and graphical methods. For the comparison of normally distributed continuous variables, student t test for independent samples was used. Mann Whitney U test was used for the comparison of continuous variables without normal distribution. Categorical variables were compared using Pearson chi square test or Fisher’s exact test, where appropriate. Stepwise logistic regression was used for multivariate analysis to identify the independent predictors of preeclampsia or preterm delivery. Diagnostic parameters including sensitivity and specificity of independent predictors in predicting adverse pregnancy outcomes were calculated. Receiver operator characteristic curve (ROC) was generated to examine the accuracy of estimations and potential cutoff values. A p value smaller than 0.05 was considered an indication for statistical significance.

**Results**

**Patient characteristics**

The mean age of the whole study population (n=95) was 30.5 ± 4.3 years. The median gestational age at the time of first trimester visit was 12 weeks 2 days (range, 11 weeks 1 day to 13 weeks 6 days). Patients consisted of preeclampsia and/or preterm labor cases (n=40). Controls were pregnant women randomly selected from uncomplicated pregnancies (n=55). Table I and II shows demographical and clinical characteristics of subjects with regard to preeclampsia and preterm birth, respectively. Six pregnancies had intrauterine growth retardation (IUGR) and one intrauterine exitus occurred. Among 6 IUGR, 3 had preeclampsia and 2 of these preeclampsia cases had HELLP syndrome.

**Preeclampsia**

Preeclampsia developed in a total of 25 pregnancies. In the group of patients that developed preeclampsia, the mean age, maternal MMP-2, MMP-9, and fms-like tyrosine kinase 1 levels, UtA PI, UtA RI, and UtA S/D was significantly higher in the group of patients that developed preeclampsia, the mean age, maternal MMP-2, MMP-9, and fms-like tyrosine kinase 1 levels, UtA PI, UtA RI, and UtA S/D was significantly higher and maternal PAPP-A levels were significantly lower at first trimester visit when compared to patients that did not develop preeclampsia during their pregnancy (Table I). In addition, presence of notch (either unilateral or bilateral) was significantly more frequent in the preeclampsia group (Table I). Multivariate analysis identified a high fms-like tyrosine kinase 1 level (p=0.005), a high UtA PI (p=0.044) and presence of notch (either unilateral or bilateral) (p=0.024) as independent predictors of preeclampsia (Table III). Area under the receiver operator characteristics (ROC) curve for predicting preeclampsia is...
### Table I. Comparison of the patients with or without preeclampsia with regard to demographical and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No preeclampsia (n=70)</th>
<th>Preeclampsia (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29.9 ± 4.1</td>
<td>32.2 ± 4.6</td>
<td>0.021*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4 ± 1.6</td>
<td>25.4 ± 3.0</td>
<td>0.995**</td>
</tr>
<tr>
<td>Primigravida, n (%)</td>
<td>56 (80.0%)</td>
<td>17 (68.0%)</td>
<td>0.222‡</td>
</tr>
<tr>
<td>Biochemical assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-2, ng/ml</td>
<td>2483 ± 1350</td>
<td>3979 ± 3397</td>
<td>0.011†</td>
</tr>
<tr>
<td>MMP-9, ng/ml</td>
<td>17908 ± 2570</td>
<td>21610 ± 1638</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fms-like tyrosine kinase 1, pg/ml</td>
<td>5059 ± 950</td>
<td>6447 ± 492</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PAPP-A, MoM</td>
<td>1.22 ± 0.62</td>
<td>1.02 ± 0.81</td>
<td>0.020†</td>
</tr>
<tr>
<td>B-HCG, IU/ml</td>
<td>1.34 ± 0.88</td>
<td>1.15 ± 0.62</td>
<td>0.532‡</td>
</tr>
<tr>
<td>USG assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRL, mm</td>
<td>59.2 ± 7.8</td>
<td>62.0 ± 7.8</td>
<td>0.114*</td>
</tr>
<tr>
<td>Nuchal thickness, mm</td>
<td>1.46 ± 0.59</td>
<td>1.39 ± 0.29</td>
<td>0.765†</td>
</tr>
<tr>
<td>Presence of any notch n (%)</td>
<td>27 (38.6%)</td>
<td>24 (96.0%)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Presence of bilateral notch n (%)</td>
<td>6 (8.6%)</td>
<td>11 (44.0%)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>UtA PI</td>
<td>1.53 ± 0.45</td>
<td>2.18 ± 0.36</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>UtA RI</td>
<td>0.66 ± 0.12</td>
<td>0.72 ± 0.10</td>
<td>0.020‡</td>
</tr>
<tr>
<td>UtA S/D</td>
<td>3.49 ± 1.05</td>
<td>3.89 ± 0.88</td>
<td>0.023‡</td>
</tr>
</tbody>
</table>

Unless otherwise stated, data are presented as mean ± standard deviation.

Test for intergroup comparison: * Student’s t test for independent samples, † Mann-Whitney U test, ‡ Pearson chi square test, § Fisher’s exact test.

Abbreviations: BMI, body mass index; MMP, matrix metalloproteinase; PAPP-A, pregnancy-associated plasma protein A; MoM, multiple of the median; B-HCG, beta human chorionic gonadotropin; USG, ultrasonography; CRL, crown-rump length; UtA PI, uterine artery pulsatility index; UtA RI, uterine artery resistance index; UtA S/D, uterine artery systolic/diastolic ratio.

### Table II. Comparison of the patients with or without preterm labor with regard to demographical and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Term labor (n=67)</th>
<th>Preterm labor (n=28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30.0 ± 4.3</td>
<td>31.6 ± 4.2</td>
<td>0.107†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5 ± 2.3</td>
<td>25.3 ± 1.9</td>
<td>0.835†</td>
</tr>
<tr>
<td>Primigravida, n (%)</td>
<td>52 (77.6%)</td>
<td>21 (75.0%)</td>
<td>0.783‡</td>
</tr>
<tr>
<td>Preeclampsia, n (%)</td>
<td>12 (17.9%)</td>
<td>13 (46.4%)</td>
<td>0.004§</td>
</tr>
<tr>
<td>Biochemical assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-2, ng/ml</td>
<td>2693 ± 1685</td>
<td>3314 ± 3037</td>
<td>0.294†</td>
</tr>
<tr>
<td>MMP-9, ng/ml</td>
<td>17962 ± 2615</td>
<td>21081 ± 2187</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fms-like tyrosine kinase 1, pg/ml</td>
<td>5299 ± 1004</td>
<td>5723 ± 1115</td>
<td>0.049†</td>
</tr>
<tr>
<td>PAPP-A, MoM</td>
<td>1.23 ± 0.63</td>
<td>1.03 ± 0.77</td>
<td>0.030†</td>
</tr>
<tr>
<td>B-HCG, IU/ml</td>
<td>1.25 ± 0.80</td>
<td>1.38 ± 0.89</td>
<td>0.462‡</td>
</tr>
<tr>
<td>USG assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRL, mm</td>
<td>59.2 ± 8.0</td>
<td>61.7 ± 7.3</td>
<td>0.166§</td>
</tr>
<tr>
<td>Nuchal thickness, mm</td>
<td>1.42 ± 0.52</td>
<td>1.49 ± 0.56</td>
<td>0.714†</td>
</tr>
<tr>
<td>Presence of any notch n (%)</td>
<td>33 (49.3%)</td>
<td>18 (64.3%)</td>
<td>0.180‡</td>
</tr>
<tr>
<td>Presence of bilateral notch n (%)</td>
<td>11 (16.4%)</td>
<td>6 (21.4%)</td>
<td>0.56†</td>
</tr>
<tr>
<td>UtA PI</td>
<td>1.58 ± 0.50</td>
<td>1.99 ± 0.43</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>UtA RI</td>
<td>0.67 ± 0.13</td>
<td>0.69 ± 0.10</td>
<td>0.298§</td>
</tr>
<tr>
<td>UtA S/D</td>
<td>3.56 ± 1.04</td>
<td>3.68 ± 0.97</td>
<td>0.470†</td>
</tr>
</tbody>
</table>

Unless otherwise stated, data are presented as mean ± standard deviation.

Test for intergroup comparison: * Student’s t test for independent samples, † Mann-Whitney U test, § Pearson chi square test.

Abbreviations: BMI, body mass index; MMP, matrix metalloproteinase; PAPP-A, pregnancy-associated plasma protein A; MoM, multiple of the median; B-HCG, beta human chorionic gonadotropin; USG, ultrasonography; CRL, crown-rump length; UtA PI, uterine artery pulsatility index; UtA RI, uterine artery resistance index; UtA S/D, uterine artery systolic/diastolic ratio.
partially related with pregnancy since they have role in
matrix components and they are involved in inflammation and
endopeptidases and play role in the breakdown of extracellular
molecules. Among them, gelatinases, collagenases, and
stromelysins. Among matrix metalloproteinases (MMPs), gelatinase-A
(MMP-2) and gelatinase-B (MMP-9) are particularly related with
pregnancy since they have role in remodeling of uterine and
placental arteries (32).

Table III. Results of multivariate analysis of the parameters in predicting preeclampsia and preterm labor

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>MMP-9, ng/ml</em></td>
<td>1.001</td>
<td>1.000-1.002</td>
<td>0.055</td>
</tr>
<tr>
<td>Fms-like tyrosine kinase 1, pg/ml</td>
<td>1.004</td>
<td>1.001-1.007</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of any notch</td>
<td>36.4</td>
<td>1.6-826</td>
<td>0.024</td>
</tr>
<tr>
<td>UtA PI</td>
<td>30.6</td>
<td>1.1-852</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Stepwise logistic regression (forward conditional) was used for multivariate analysis. For continuous variables, odds ratios and confidence intervals are for per unit change in the parameter.

Abbreviations: MMP, matrix metalloproteinase; UtA PI, uterine artery pulsatility index.

0.917 (95% CI, 0.859-0.976, p<0.001) for fms-like tyrosine
kinase 1 indicating excellent accuracy and 0.865 (95% CI, 0.788-0.941, p<0.001) for UtA PI indicating good accuracy
(Figures 1a and 1b). An optimal cut-off value of 5830 for fms-
like tyrosine kinase 1 would result in sensitivity and specificity
levels of 92% and 84% respectively. Corresponding figures for
an optimal cut-off value of 1.75 for UtA PI are 92% and 71%,
respectively.

**Preterm birth**

Preterm birth developed in a total of 28 pregnancies. In the
group of patients with preterm birth, maternal MMP-9 and
fms-like tyrosine kinase 1 levels, and UtA PI were significantly
higher and maternal PAPP-A levels were significantly lower at
the first trimester visit when compared to patients that gave
birth at term (Table II). In addition, presence of preeclampsia
was significantly more frequent in the preterm birth group
(Table II). Only maternal MMP-9 level emerged as a significant
predictor of preterm birth on multivariate analysis (p< 0.001)
(Table III). Area under the ROC curve for preterm birth was 0.821 (95% CI, 0.727-0.915, p<0.001) for MMP-9 indicating good accuracy
(Figure 1c). An optimal cut-off value of 19450 would result in
sensitivity and specificity levels of 81% and 64% respectively.

**Discussion**

This study examined a spectrum of clinical and radiological
parameters as potential predictors of preeclampsia or
preterm birth and found significant relations. Multivariate
analysis identified high fms-like tyrosine kinase 1, high
UtA PI and presence of notch as independent predictors of
preeclampsia. Baumann et al. (12) found increased fms-like
tyrosine kinase-1 levels at the first trimester in women who
subsequently developed preeclampsia; however, Akolekar et
al. (11) did not find an association between fms-like tyrosine
kinase and preeclampsia. Both studies obtained samples
between 11 to 13 weeks of gestation. Similarly, this study
identified fms-like tyrosine kinase 1 levels as a significant
predictor of preeclampsia. In addition, our findings related
to ultrasonographic measurements are in line with previous
observations (8, 9, 15, 31).

Matrix metalloproteinases (MMPs) are zinc-dependent
endopeptidases and play role in the breakdown of extracellular
matrix components and they are involved in inflammation and
hypertension. Main subtypes of this group of enzymes are
gelatinases, collagenases, and stromelysins. Among them,
gelatinase A (MMP-2) and gelatinase B (MMP-9) are
particularly related with pregnancy since they have role in
remodeling of uterine and placental arteries (32). To date,
several studies have tested the association of these enzymes
with pregnancy associated hypertension disease and
preeclampsia. Montagnana et al. (27) compared serum levels of
non-pregnant, normal pregnant and preeclamptic women. MMP-2 levels were significantly higher in preeclamptic women
when compared to both normal pregnant and non-pregnant
women. However, that study did not find a difference between
normal pregnant and preeclamptic women with regard to
serum MMP-9 levels. In that study, blood samples were not
drawn at a standard time point. Similarly, Narumiya et al. (28)
found significantly higher levels of MMP-2 in preeclamptic
women. In contrast, Palei et al (33) found higher levels of MMP-
9, but not MMP-2, in women with gestational hypertension
when compared to normal pregnant women; however, MMP-9
levels were not higher in preeclamptic women. Similar to this
study, two studies tested MMP-9 and MMP-2 as a predictor
of pregnancy outcomes. Myers et al. (34) obtained samples
from preeclamptic and normal women at 22 weeks, 26 weeks
and at delivery/diagnosis. They found significantly increased
MMP-2 activity at 22 weeks and at diagnosis but not at 26
weeks in patients that developed preeclampsia; nevertheless,
MMP-2 to and tissue inhibitor ratio was disturbed throughout
pregnancy in preeclamptic women. In that study, no difference
was found with regard to MMP-9 activity. Similarly, in the study
by Poon et al. (35), where maternal sera were obtained in the
first trimester MMP-9 did not emerge as an important predictor
of preeclampsia. In this study however, MMP-9 levels did not
emerge as an independent predictor of preeclampsia. Although
MMP-2 levels were significantly higher in preeclamptic women
on univariate analysis, multivariate analysis was unable to
identify it as an independent predictor of preeclampsia.

In this study, two ultrasonography parameters -presence
of uterine notch and UtA PI- have emerged as independent
predictors of preeclampsia. Our findings are in line with
previous findings. In a meta-analysis of large number of
studies, pulsatility index combined with notching was the most
predictive Doppler index for pre-eclampsia (18). In addition,
authors concluded that uterine artery Doppler ultrasonography
predicts more accurately when performed in the second
trimester than in the first-trimester. Our findings support that
these two parameters may still be valuable in the first trimester.
Although B-HCG and PAPP-A levels have been associated to
some degree with preeclampsia risk in several previous studies
(22, 25, 26, 36-38), these two parameters may still be valuable in the first trimester. Our findings support that
these two parameters may still be valuable in the first trimester.
and MMP activity are relatively scarce. Koucky et al. (39) found lower MMP-2 levels in maternal serum of preterm deliveries and Poon et al. (35) found higher MMP-9 levels in these patients, although MMP-9 levels was not found to be useful in predicting preterm birth in the latter study. However, this study identified high MMP-9 levels as the only independent predictor among all parameters tested. These findings overall suggest that matrix metalloproteinases, MMP-9 in particular, predicts preterm labor rather than preeclampsia; partly explaining the variable findings of several previous studies in which preeclampsia and premature labor coexist in a large proportion of patients. This issue deserves further investigation in large-scale studies.

In this study, several important markers such as fms-like tyrosine kinase 1, Ut A PI, presence of notch, PAPP-A and B HCG did not emerge as independent predictors of preterm birth. Similar to our findings, a meta-analysis investigating the biochemical predictors of preterm birth did not identify PAPP-A and B-HCG as significant predictors (40). However, Patil et al. identified low PAPP-A levels as a useful indicator for preterm delivery (37). A recent study identified maternal fms-like tyrosine kinase/placental growth factor (PIGF) ratio as a useful predictor of induced preterm birth (<34+0 weeks) (41). Maternal fms-like tyrosine kinase 1 and ultrasonography parameters including Ut A PI and presence of notch were mostly studied in the context of preeclampsia risk. Further studies are warranted for the potential role of these parameters in predicting preterm birth.

Main limitation of this study is the low sample size, particularly considering that multivariate analysis has been carried out. Several parameters might not have been able to reach statistical significance on multivariate analysis due to low power. Thus, the findings deserve testing on larger samples. In addition, some of these patients might have been using treatments including progesterone, which may be a potential reason of disturbing uniformity of the study population. This may be considered another study limitation.

In conclusion, several clinical and radiological parameters of the first trimester seem to be associated with adverse pregnancy outcomes. The role of MMP-9 in predicting preterm birth in particular, is relatively a novel finding and deserves further investigation. One remarkable finding of this study is the difference between the significant predictors of preeclampsia and preterm birth, which may indicate different pathogenesis for these two conditions. Although, sample size may be considered somewhat small for a detailed multivariate analysis, in its present form the findings of this study provides some insight for the early prediction of the two clinically important conditions, which might help management in clinical setting. Further studies may test these variables, either alone or in combination, in larger sample sizes to support additional evidence for their clinical use.

References


