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# Role of Matrix Metalloproteinase–9 in the Pathogenesis of Preeclampsia

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**Abstract**

**Objectives:** The goal of this research was to investigate whether metalloproteinases could be used as predictors of preeclampsia (PE) during pregnancy.

**Materials and Methods:** This case-control study included 100 pregnant women which they further grouped into PE and control group (each composed of 50 women). Both groups were further subdivided according to their gestational age (GA), using the 37th week of gestation as a divider, as preterm and term infants.

**Results:** In both preterm ($P=0.001$) and term infants ($P=0.001$), mean metalloproteinase-9 (MMP-9) was considerably lower in PE mothers compared to controls, with the difference being greater in preterm infants. In ROC analysis, MMP-9 showed excellent ability to predict PE in preterm infants (AUC = 0.980, cut-off ≤26.2) and good ability to predict PE in term infants (AUC 0.770, cut-off ≤ 34.4).

**Conclusions:** The matrix MMP-9 is a non-specific predictor of PE for term and preterm pregnant women, with higher accuracy for preterm pregnant women.

**Keywords:** Preeclampsia, Term, Preterm, Metalloproteinase-9

## Introduction

Preeclampsia (PE) is a pregnancy-related disease that affects women. It has been described as a pregnancy-related syndrome that affects almost all systems of body organ. This disease is an idiopathic pregnancy disease, which is characterized by proteinuric hypertension, and complicates approximately 5% to 10% of all pregnancies (1). PE syndrome is associated with vasospasm, ischemia change in the placenta and other organs, and increased concentration of hemoglobin (2). These dysfunctions are usually presented in women with severe PE. Although several mechanisms have attempted to explain these events by linking them to the placenta, immune dysfunction, or genetics, the exact mechanism remains to be solved (3). The prevalence of PE varies based on several factors including gestational age (GA), ethnicity, and parity (4-7). In the US its prevalence is approximately 3.4%, which is 1.5–2.0 folds higher in first pregnancy (5), while the global prevalence of it is 4.6% in all pregnancies (8).

Matrix metalloproteinase (MMPs) had been linked to trophoblast invasion (9). MMP has a function as a tissue angiogenic factor, remodel of various tissues (including placental tissue), with variation in its levels in PE women compared to normal women. Extracellular matrix (ECM) appears to be a target of MMP (ECM appears to be important in the normal physiology of the placenta, and abnormalities in ECM associated with pathological conditions) (10).

Active MMP-9 has a high distribution in the embryonic implant site, and it is correlated with the invasion ability of the trophoblasts (11). Several pieces of evidence link MMP-9 with PE, MMP-9 levels in PE cytotrophoblasts, for example, are low, and reduction in the cytotrophoblast activity in vitro after MMP-9 inhibition (12). This study aimed to observe the importance of MMP-9 in predicting PE during pregnancy.

## Material and Methods

### Study Design

This case-control study included 100 pregnant women which further divided into PE and control groups (each composed of 50 women). Both groups were further subdivided according to their GA, using the 37th week of gestation as a divider, as preterm and term infants.

### Study Setting

The study was conducted at Al-Yarmuk Teaching Hospital in Baghdad from March to November 2017. Age, previous obstetrical history: gravidity, parity, and abortion history, GA, body mass index (BMI), primary complaints, past medical history, and past surgical history were all acquired from each participant. In addition, this study included both preterm and full-term pregnant women.

### Participants

The exclusion criteria were having chronic hypertension, diabetes mellitus, heart diseases, renal diseases, twin pregnancy, congenital anomalies, and HELLP syndrome

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**Key Messages**

- Low level of metalloproteinase-9 is associated with preeclampsia.
- Metalloproteinase-9 had excellent ability to predict preeclampsia from normal pregnancy.
- The association of metalloproteinase-9 solidify what we know about the association between preeclampsia and vascular pathogenesis origin of the disease.

(hemolysis, elevated liver enzyme low platelet).

### Preeclampsia

It is defined based on ACOG criteria as a new onset of hypertension in previously normotensive pregnant women, with the presence of proteinuria after the 20$^{th}$ week of gestation (disorder of pregnancy characterized by new-onset hypertension with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mm Hg and proteinuria of > 0.3 g/24 h or ≥ 1+ proteinuria, detected by urine dipstick after 20 weeks of pregnancy, or in the absence of proteinuria, new-onset hypertension with new onset of any one of: thrombocytopenia (platelet count <100 000/μL), renal insufficiency (serum creatinine concentration > 1.1 mg/dL, impaired liver function (raised concentrations of liver transaminases to twice normal), pulmonary edema, or cerebral or visual problems) (2).

### Laboratory Assessment

All of the participants' blood samples were taken and their serum MMP-9 levels were measured. The blood samples were kept for 30 minutes at room temperature and centrifuged after that, and the supernatant was taken and kept at a temperature of -20°C, till the day of testing . The measurement was accomplished using ELISA, a two-step sandwich-type immunoassay in which two antibodies directed to MMP-9 were used: a monoclonal antibody as the capture antibody and a signals polyclonal antibody coated with horse-radish peroxidase as the signals polyclonal antibody (MyBioSource, MBS2512591).

In addition, the concentration of albumin in the urine was measured through collecting urine samples by mid-stream urine or catheter specimens for albumin urine dipsticks. Assessment of renal and liver function was done by measuring serum AST, ALT, urea, and creatinine.

### Sample Size Calculation

According to Feng et al (13) the AUC of MMP-9 for predicting PE was 0.587 (95% CI 0.522–0.652). We assumed a null hypothesis with AUC = 0.750, type I error of 5%, type II error of 10%, and the computed sample size was 106 women in both groups (1:1 ratio). Meanwhile, 100 women were chosen as the sample size based on these calculations (50 in each group).

### Statistical Analysis

The chi-square and the independent t-tests were used for categorical and continuous variables, respectively (following a normal distribution). The overall performance of MMP-9 was tested using a receiver operator characteristics (ROC) analysis, in which the area under the curve (AUC) was used to test the overall performance of MMP-9, and the optimal cut-off (using J-index) and its corresponding sensitivity, specificity, and predictive values were calculated. SPSS version 19 (SPSS inc., Chicago, IL) was used for all analyses.

## Results

This study included 100 women, 50 of whom had delivered premature infants and the other 50 had delivered term infants (both groups had 25 PE and 25 normal pregnancy women). Preterm mothers had significantly higher mean BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) than non-preterm ones. Table 1 shows that PE women had reduced gravidity, parity, abortion, GA, and fundal height.

PE mothers had significantly greater mean BMI, SBP, and DBP than women who delivered term infants. Table 2 shows that parity, abortion, GA, fetal weight, and fundal height were all considerably lower in PE mothers.

**Table 1.** Assessment of Demographic, and Gynecology Data in Women Delivered Preterm Infants

| Variables (Mean ± SD) | Control | Preeclampsia | *P* Value |
|---|---|---|---|
| Number | 25 | 25 | - |
| Age (y) | 28.4 ± 4.1 | 27.9 ± 7.7 | 0.776 |
| BMI (kg/m$^2$) | 30.4 ± 2.7 | 32.6 ± 2.7 | 0.006* |
| Gravidity | 3 ± 1.4 | 1.9 ± 1.3 | 0.006* |
| Parity | 1.7 ± 1.4 | 0.8 ± 0.6 | 0.005* |
| Abortion, n (%) | 7 (28.0%) | 4 (16.0%) | 0.306 |
| GA (by LMP or the early US) | 32.1 ± 2.4 | 32.7 ± 1.2 | 0.219 |
| GA (by late US) | 31.9 ± 1.6 | 28.6 ± 2.2 | <0.001* |
| SBP (mm Hg) | 123.0 ± 5.6 | 172.0 ± 16.0 | <0.001* |
| DBP (mm Hg) | 75.0 ± 2.8 | 114.8 ± 8.0 | <0.001* |
| Fundal height (cm) | 31.3 ± 2.9 | 28.0 ± 2.3 | <0.001* |

BMI, body mass index; GA, gestational age; SBP, systolic blood pressure; DBP, diastolic blood pressure; LMP, last menstrual period; US, ultrasound. *Significant.

**Table 2.** Assessment of Demographic, and Gynecology Data in Women Delivered Term Infants

| Variables (mean ± SD) | Control | Preeclampsia | *P* Value |
|---|---|---|---|
| Number | 25 | 25 | - |
| Age (y) | 25.6 ± 7.3 | 25.3 ± 7.1 | 0.884 |
| BMI (kg/m²) | 29.6 ± 1.5 | 34.6 ± 3.1 | <0.001* |
| Gravidity | 2.8 ± 2.3 | 1.9 ± 1.0 | 0.079 |
| Parity | 1.7 ± 1.2 | 0.8 ± 0.6 | 0.002* |
| Abortion, n (%) | 3 (12.0%) | 2 (8.0%) | 0.637 |
| GA (by LMP or early US) | 38.3 ± 0.9 | 38.6 ± 0.6 | 0.172 |
| GA (by late US) | 37.7 ± 0.6 | 35.6 ± 1.0 | <0.001* |
| SBP (mm Hg) | 118.4 ± 7.7 | 166.4 ± 9.0 | <0.001* |
| DBP (mm Hg) | 77.0 ± 3.2 | 110.4 ± 6.6 | <0.001* |
| Fundal height (cm) | 36.0 ± 1.1 | 34.7 ± 1.6 | <0.001* |
| Fetal weight (gm) | 3016.2 ± 932.7 | 2396 ± 290.4 | 0.003* |

BMI, body mass index; GA, gestational age; SBP, systolic blood pressure; DBP, diastolic blood pressure; LMP, last menstrual period; US, ultrasound. *Significant.

In both preterm and term infants, mean MMP-9 was considerably lower in PE mothers compared to the mothers of the control group, with the difference being greater in preterm infants (9.2) than in term infants (5.9), as seen in Table 3.

The diagnostic performance of MMP-9 was better in women who delivered preterm compared to those delivered term infants (since the AUC is higher), as illustrated in Table 4 and Figure 1 and 2.

## Discussion

PE is a risky obstetrical condition linked to a high prevalence of maternal morbidity and mortality, especially in underdeveloped countries. (14). Many diagnostic techniques and biomarkers were developed for the early detection of PE such as MMP, which had been investigated PE for understanding its mechanisms and pathogenesis (15).

This study showed significantly lower levels of MMP-9 among preterm and term pregnant women with PE in comparison to healthy pregnant women. This conclusion was in line with the findings of the Plaks et al (11) study in the United States and the Laskowska study (16) in Poland, both of which reported a significant decrease in MMP-9 levels in pregnant women with PE. MMP-9 levels were consistently low in pregnant women with PE in the Narumiya et al trial in Canada (17). Palei et al detected the relationship between the role of MMP and PE and attributed it to their effect on the remodeling of vessels, angiogenesis, and vasodilatation in normal pregnancy (18).

Multiple studies revealed MMP-9 levels to be elevated during pregnancy with or without PE (19). Another study reported that higher levels of MMP-9 among healthy pregnant women are essential for the appropriate development of the maternal-fetal interface (20). A decreased level of MMP-9 is highly related to angiogenesis impairment and dysfunctional trophoblast invasion that is associated with increased blood vessel resistance and placental dysfunction (21). A study conducted in the UK showed low MMP-9 levels among pregnant women with gestational hypertension (22). Low levels of MMP-9 were also detected among pregnancies complicated with intrauterine growth restriction (23).

The present study showed significantly lower levels of MMP-9 among preterm pregnant women (for both PE and control) than term pregnant women ($P < 0.001$). This is similar to the results of Espino et al (24) study in Mexico which reported a higher level of MMP for termed normal pregnancies as compared to preterm pregnancies. Serum

**Table 3**. Assessment of Metalloproteinase–9 According to Birth Status

| Variables | Control | Preeclampsia | *P* Value |
|---|---|---|---|
| Number | 25 | 25 | - |
| Preterm | 31.7 ± 3.4 | 22.5 ± 3.0 | <0.001* |
| Term | 37.7 ± 5.6 | 31.8 ± 5.9 | <0.001* |

*Significant.

**Table 4.** Assessment of the Diagnostic Performance of MMP-9 as a Predictor of PE

| Variables | Cutoff point | AUC | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|
| Preterm | ≤26.2 | 0.980 | 100% | 96% | 100% | 95.6% | 97% |
| Term | ≤34.4 | 0.770 | 76% | 68% | 69% | 62% | 70% |

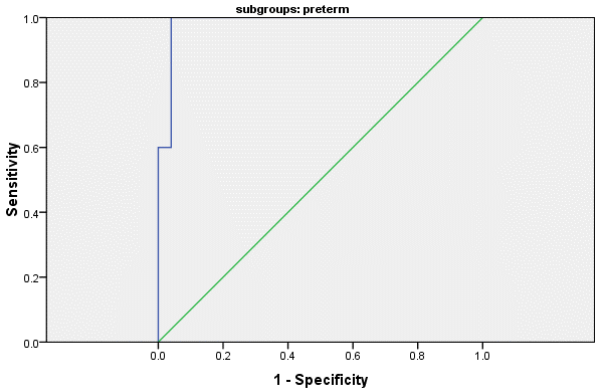


**Figure 1.** ROC curve for MMP-9 Prediction of PE in Preterm Infants.

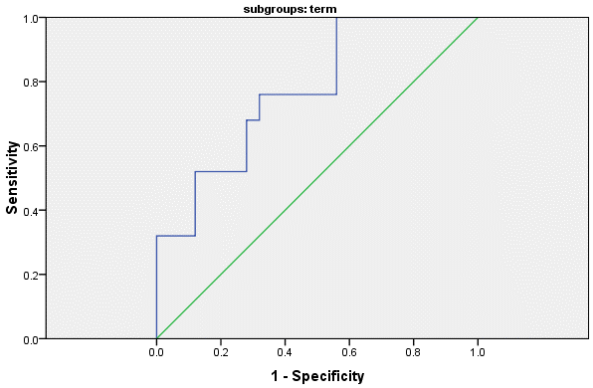


**Figure 2.** MMP-9 ROC Curve for PE Prediction in Term Infants Delivered.

MMP-9 level was increased among pregnant women with PE and reached a peak in the first and third trimesters of pregnancy (25). These imbalances in MMP-9 levels during pregnancy and between MMP-9 and its inhibitors had a bad effect on the structure and function of vasculatures among pregnant women with PE which appeared before the clinical signs of PE (24).

Our study revealed that an MMP-9 level of ≤26.2 is significantly predictive for PE among preterm pregnant women (sensitivity 100%, specificity 96%, and accuracy 97%). This finding coincides with the results of Babacan et al (26) study in Turkey which stated that an MMP-9 level of 23.5 is a significant predictor of PE among preterm pregnant women. Another study carried out by Myers et al in the UK on pregnant women with PE and normal pregnant women in early and late pregnancy found significantly high MMP-2 activity during early pregnancy for the prediction of PE with no MMP-9 predictive activity (27).

Our study found that an MMP-9 level of 34.4 is a significant predictor of PE in term pregnancy with validity findings lower than that for preterm pregnant women (sensitivity 76%, specificity 68%, and accuracy 70%). This finding was close to the results of Poon et al study in the UK which reported that an MMP-9 level of 53.2 is a significant predictor of PE in late pregnancy but with lower accuracy than MMP-9 prediction of PE in early pregnancy (28). A previous study carried out by Laskowska (29) in Poland on 125 pregnant women with 29 preterm PE, 31 term PE and 65 healthy pregnant (control) found significantly lower levels of MMP-9 among pregnant women with preterm and term PE than healthy women which could be used as an early diagnostic marker of PE. This Polish study also found that predictive validity results of MMP-9 among preterm pregnant women are better than that for term pregnant women (29). Researchers in the United States observed a negative relationship between GA and active MMP-9 expression in normal pregnancy, with no significant differences in MMP-9 levels in PE (30). MMP-9 levels were shown to be higher in pregnant women with PE regardless of pregnancy trimester when compared to normal pregnancy, according to Prochazka et al (31).

## Conclusions

The matrix MMP-9 is a non-specific predictor of PE for term and preterm pregnant women, but with higher accuracy for preterm ones. The matrix MMP-9 level is variable according to gestational of PE and healthy pregnant women.

### Authors' Contribution

**Conceptualization:** Ali M. Mourad, Zina Abdulla, Maryam T. Abbas.
**Methodology:** Zina Abdulla, Maryam T. Abbas, Hayder A. Fawzi.
**Formal analysis:** Hayder A. Fawzi.
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**Resources:** Ali M. Mourad, Hayder A. Fawzi.
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**Writing–review and editing:** Ali M. Mourad, Zina Abdulla, Hayder A. Fawzi.
**Writing–original draft preparation:** Zina Abdulla, Maryam T. Abbas.
**Project administration:** Zina Abdulla, Maryam T. Abbas.
**Funding acquisition:** Zina Abdulla, Maryam T. Abbas.

### Conflict of Interests

Authors declare that they have no conflict of interests.

### Ethical Issues

The Ethical Council of Al- Mustansiriyah University College of Medicine approved the study (ethical code: 6/2018/037). All participants gave written informed consent following the Helsinki statement (as revised in Edinburgh 2000).

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