Prolactin and risk of preeclampsia: A single institution, cross-sectional study

Thabat J. Al-Maiahy¹, Ali I. Al-Gareeb², Hayder M. Al-kuraishy²

¹Department of Gynecology and Obstetrics, College of Medicine Almustansiriya University, Baghdad, Iraq
²Department of Pharmacology, Toxicology and Medicine, College of Medicine Almustansiriya University, Baghdad, Iraq

Objective: To illustrate the association between prolactin serum level and severity of preeclampsia.

Methods: In this cross-sectional study, 31 pregnant women with preeclampsia were enrolled as Group ¹ and 20 healthy pregnant women as Group ². Routine investigations and prolactin serum levels were assessed together with blood pressure changes. The unpaired t-test was used to determine the differences and correlation coefficient for the evaluation of correlation.

Results: Prolactin serum levels were higher in preeclampsia patients compared with those of the healthy pregnant women (P<0.001). The severity of preeclampsia was linked with prolactin serum levels since 20 patients with preeclampsia showed mild preeclampsia that illustrated relatively lower prolactin serum levels compared with 11 patients with severe preeclampsia (P<0.001). The severity of mean arterial blood pressure was significantly correlated with prolactin serum levels (r=0.78, P<0.001).

Conclusions: Prolactin serum levels are elevated in patients with preeclampsia and correlated with the severity of preeclampsia. High but not normal prolactin might be implicated in the pathogenesis of preeclampsia.
Prolactin (PRL) is a hormone secreted from the anterior pituitary gland which is involved in body metabolism, regulation of immune function, lactation and sex drive. Thyrotropin-releasing factor (hormone) (TRH) stimulates the secretion of PRL while hypothalamic dopamine inhibits it. Moreover, extra-pituitary PRL is secreted from decidua and myometrium which is not affected by dopamine and TRH. Extra-pituitary PRL is responsible for different autocrine and paracrine effects on placental and maternal vascular endothelium[4].

During normal pregnancy, high levels of progesterone and estrogen elevate PRL level by 10-20 folds. Normal PRL level is 12-17 μg/L in non-pregnant women, 16 μg/L in the first trimester of pregnancy, 49 μg/L in the second trimester of pregnancy and 113 μg/L in the third trimester of pregnancy[5]. Moreover, 16-kD PRL and 14-kD PRL levels are elevated over that of 23 kD PRL in PE. Bernard et al[6] illustrated that 16-kD PRL is split from native 23 kD PRL by protease cathepsin when 16-kD PRL level is elevated, leading to endothelial damage via inhibition of nitric oxide synthase and urokinase activity with activation of plasminogen activator inhibitor-1.

Normally, intact PRL has a significant angiogenic effect through activation of vascular endothelial growth factors whereas 16-kD PRL inhibits angiogenic process with vasospastic effects on terminal capillaries due to suppression of vasodilator effect of nitric oxide (NO). In addition, the failure of angiogenesis is a primary event during the pathogenesis of PE[7].

Clapp et al illustrated that vasoinhibins are family of N-terminal of PRL which are formed due to the conversion of PRL by metalloproteases or cathepsin-D. Vasooinhibins lead to vasoconstriction through inhibition of angiogenesis[8].

It has been illustrated that defective placenta in patients with PE is a source of 16-kD PRL as this fragment is increased in urine and amniotic fluid[9]. This association of 16-kD PRL and endothelial dysfunction gives a clue regarding high PRL level as a risk factor in the pathogenesis of PE. Moreover, intravenous infusion of PRL leads to peripheral vasoconstriction due to inhibition of vasodilator β2 receptors and endothelial dysfunction.

However, the animal model study illustrated that the chronic administration of PRL leads to an increase in urinary sodium and potassium without significant changes in BP[10]. Therefore, there is an association between hypertension and high PRL levels.

The present study was to illustrate the association between PRL serum levels and severity of PE.

2. Materials and methods

2.1. Study subject

A total of 31 pregnant women with PE (ranging from 22 to 35 years; ≥20 gestational weeks) and 20 healthy pregnant women (ranging from 21 to 34 years; ≥20 gestational weeks) were recruited in this study. All recruited women were from the Consultant Unit in Department of Obstetrics and Gynecology of Baghdad Medical City in Iraq. Selection of pregnant women was based on the diagnostic criteria of the American College of Obstetrician and Gynecologist recommendation[11]. Written and verbal informed consents were obtained from all recruited pregnant women according to the recommendation of the Ethical Committee (approval No. 32AR in 22/4/2018) in College of Medicine, Al-Mustansiriyia University, Iraq, Baghdad, Iraq.

After detailing the recruited pregnant women’s full history about parity, pregnancy-related complications, current and previous pharmacotherapy, they were assigned into two groups: Group I : 31 pregnant women with PE; Group II : 20 healthy pregnant women (as control group).

2.2. Inclusion criteria

Pregnant women with gestational age of 20 weeks or more with BP equal or more than 140/90 were included in the study. All included patients were selected according to the diagnostic criteria[11].

2.3. Exclusion criteria

At first 44 pregnant women were recruited and only 31 pregnant women with PE were chosen and 13 pregnant women were excluded, 6 due to gestational diabetes mellitus, 5 due to acute urinary tract infection and 2 because of gestational hypertension. The screening of the study was presented in the consort flow diagram (Figure 1).

Any pregnant women with chronic hypertension, gestational hypertension, cardiovascular complications, endocrine disorders, metabolic disorders, gestational diabetes mellitus, psychiatric and mental disorders were excluded.

2.4. Assessment of biochemical parameters

During routine visits to the Consultant Unit, 10 mL of venous blood was taken from each pregnant women for assessments of lipid profile, blood urea, serum creatinine, proteinuria, and PRL serum level. Lipid profile: total cholesterol, triglyceride and high-density lipoprotein (HDL) were measured by colorimetric kits (Cell Biolabs, Inc. San Diego, CA 92126, USA). Very low-density lipoprotein, low-density lipoprotein, (LDL) and cardiac risk ratio were measured according to the previous study[12]. Blood urea, serum creatinine, and proteinuria were also assessed by biochemical calculation and dipstick method, respectively. Assessment of PRL serum level was done by specific enzyme-linked immuno sorbent assay kit method according to the instruction of the manufacturing company (Human ELISA Kit, ab108655, Abcam, USA).

2.5. Assessment of BP changes

BP of each recruited pregnant woman was measured at the supine position from left arm by digital automated BP monitor 2 h apart. Mild PE was classified when BP was more than 140/90 but less
than 160/110. Severe PE was classified when BP was more than 160/110. Pulse pressure = systolic BP (SBP) - diastolic BP (DBP) and mean arterial pressure (MAP)\[13\]. The formula of mean arterial pressure was as below:

\[
\text{MAP} = \frac{\text{SBP} + 2 \times \text{DBP}}{3}
\]

2.6. Statistical analysis

The data were presented as mean ± standard deviation (mean ± SD). Unpaired \( t \)-test was used to determine the differences. Correlation coefficient was done to find the correlation between study variables. Data analysis was done by using SPSS (IBM SPSS Statistics for Windows version 20.0, 2014 Armonk, NY, IBM, Corp., USA). The level of significance was regarded when \( P < 0.05 \).

3. Results

Demographic characteristics of the present study showed that there was an insignificant difference between the mean age of PE patients and that of healthy pregnant women (\( P = 0.450 \)). Regarding the status of parity, PE patients were relative with a low parity compared to the healthy pregnant women (\( P = 0.001 \)). Indeed, there were insignificant differences regarding smoking status, gestational age, and race type (\( P > 0.05 \)). As well, there was a significant difference regarding the type of delivery. Compared with healthy pregnant women, there was a high history of cesarean section over normal vaginal delivery in PE patients (\( P = 0.010 \)). Healthy pregnant women only received tonic agents (95%), while in PE patients 96.77% received methyldopa and only 3.22% received labetalol (Table 1).

Table 1. Sociodemographic characteristics of present study.

| Characteristics                  | Healthy pregnant women (\( n = 20 \)) | Preeclampsia pregnant women (\( n = 31 \)) | \( P \) |
|----------------------------------|--------------------------------------|------------------------------------------|------|
| Age (years)                      | 27.14 ± 6.89                         | 28.65 ± 6.99                             | 0.450|
| Parity (\( n \))                 | 4.00 ± 1.00                           | 3.00 ± 1.00                              | 0.001^1|
| Race (White: Black ratio) (\( n \)) | 18 : 2                                | 30 : 1                                   | 0.070|
| Smoking [\( n(\%) \)]            | 4(20.00)                              | 6(19.35)                                 | 0.950|
| Gestational age (weeks)          | 26.65 ± 3.96                          | 27.89 ± 3.75                             | 0.260|
| Type of delivery [\( n(\%) \)]   |                                       |                                          |      |
| Normal vaginal delivery          | 18(90)                                | 5(16.12)                                 | 0.010^2|
| Cesarean section                 | 2(10)                                 | 26(83.87)                                | 0.010^2|
| Current medications [\( n(\%) \)] |                                       |                                          |      |
| Tonic                            | 19(95)                                | 29(93.54)                                | 0.830|
| Methyldopa                       | ---                                   | 30(96.77)                                | ---  |
| Labetalol                        | ---                                   | 1(3.22)                                  | ---  |

Data are expressed as mean±SD unless otherwise specified. Unpaired \( t \)-test is used. ^1\( P < 0.01, P < 0.05 \). ---: None, as healthy pregnant women only receive tonic agents.
Concerning BP differences, PE patients showed significant high-pressure profile compared with healthy pregnant women \( (P=0.010) \). MAP was higher in PE patients compared with that of the healthy pregnant women \( (P=0.010) \). Lipid profile was not significantly different in PE patients compared with healthy pregnant women \( (P=0.05) \) except HDL and LDL which were significantly higher in PE patients \( (P=0.010) \). On the other hand, blood urea was higher in PE patients compared with that of the healthy pregnant women \( (P=0.020) \) but serum creatinine was not significantly different \( (P>0.05) \). Indeed, proteinuria was significantly higher in PE patients compared with that of healthy pregnant women \( (P=0.001) \) (Table 2).

PRL serum level was higher in PE patients compared with that of the healthy pregnant women \( (P<0.001) \) (Figure 2). The severity of PE was linked with PRL serum levels since 20 patients with PE showed mild PE that illustrated relatively lower PRL serum levels compared with 11 patients with severe PE \( (P<0.001) \) (Figure 3).

As well, the severity of MAP was significantly correlated with PRL serum levels \( (r=0.78, P<0.001) \) (Figure 4).

### Table 2. Cardio-metabolic variables in patients with preeclampsia compared to healthy pregnant women.

| Variables          | Healthy pregnant women \( (n=20) \) | Preeclampsia pregnant women \( (n=31) \) | 95% CI            | \( P \) |
|--------------------|-------------------------------------|----------------------------------------|------------------|------|
| SBP (mmHg)         | 112.64 ± 9.80                       | 155.89 ± 12.82                        | 36.48-50.01      | 0.001*|
| DBP (mmHg)         | 71.93 ± 6.97                        | 94.81 ± 4.98                          | 19.51-26.24      | 0.001*|
| MAP (mmHg)         | 85.50 ± 6.98                        | 115.17 ± 9.76                         | 24.60-34.73      | 0.001*|
| PP (mmHg)          | 41.71 ± 3.24                        | 61.08 ± 4.87                          | 16.88-21.85      | 0.001*|
| TC (mg/dL)         | 187.87 ± 9.34                       | 190.96 ± 9.07                         | -2.19-8.37       | 0.240 |
| TG (mg/dL)         | 417.89 ± 5.85                       | 200.76 ± 4.87                         | -0.16-5.90       | 0.060 |
| HDL (mg/dL)        | 46.98 ± 4.89                        | 40.98 ± 4.81                          | -8.79-3.20       | 0.010*|
| VLDL (mg/dL)       | 39.57 ± 7.96                        | 40.15 ± 6.96                          | -3.66-4.82       | 0.780 |
| LDL (mg/dL)        | 101.30 ± 12.78                      | 109.80 ± 11.75                        | 1.49-15.50       | 0.010*|
| CRR                | 3.99 ± 1.45                         | 4.65 ± 2.94                           | -0.76-2.08       | 0.350 |
| Blood urea (mg/dL) | 19.97 ± 3.89                        | 22.95 ± 4.78                          | 0.411-5.54       | 0.020*|
| Serum creatinine (mg/dL) | 1.10 ± 0.88          | 1.30 ± 0.78                           | -0.27-0.67       | 0.390 |
| Proteinuria (mg/dL) | 14.78 ± 2.98                       | 322.78 ± 19.98                        | 298.92-317.07    | 0.001*|

Data are expressed as mean±SD. \( P<0.01; \) \( P<0.05 \); SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, PP: pulse pressure, TC: total cholesterol, TG: triglyceride, HDL: high density lipoprotein, VLDL: very low density lipoprotein, LDL: low density lipoprotein, CRR: cardiac risk ratio; CI: confidence interval.
4. Discussion

The present study illustrated that patients with PE were characterized by low parity and high incidence of cesarean section compared to healthy pregnant women as showed by Kosir et al exploring a lower risk of PE in multiparity[14]. Also, the previous study pointed out that high incidence of cesarean section mainly in the first pregnancy was associated with a high risk of subsequent development of PE[15].

Moreover, 19.35% patients with PE of the present study were smokers; this low percentage of smoking might increase the risk of PE since smoking reduces the risk of PE due to paradoxical protective effect as illustrated by Tanaka et al[16].

In our study, there was a significant high SBP and DBP in PE patients compared to healthy pregnant women as showed by Nissaisorakarn et al illustrating high BP is an integral part in the diagnosis of PE[17].

High BP in PE patients is due to abnormal trophoblastic invasion during placental development which leads to placental ischemia and subsequent dysfunction. These changes participate in releasing different anti-angiogenic factors which cause peripheral vasoconstriction and development of hypertension in the second half of pregnancy[18].

Blood lipids including total cholesterol, triglyceride, and very low-density lipoprotein were not significantly differed but LDL and HDL were significantly differed compared to the healthy pregnant women. These findings are in part corresponded with different studies that illustrated alteration in lipid profile may contribute to the development of PE[19,20].

Ghossein-Doha et al reported a significant association between PE and risk of future heart failure due to augmentation of cardiac risk ratio in patients with PE[21], but in the present study insignificant increased in cardiac risk ratio might be due to small sample size and/ or single center study.

Indeed, the present study showed that blood urea and proteinuria were significantly increased in patients with PE compared to the healthy pregnant women due to subclinical kidney damage that induced by PE; it was associated with the severity of PE as disclosed by Eswarappta et al[22]. On the contrary, the severity of PE cannot be estimated by the level of proteinuria since proteinuria is linked with fetal and maternal complications[23].

Moreover, the present study definitely demonstrated that PRL serum level was high in patients with PE as revealed by Chang et al, whose study confirmed three-fold increases in PRL serum level are adequate to increase SBP and DBP due to impairment of endothelial NO productions[24].

Previously, there was a strong controversy about PRL levels in patients with PE as Ranta et al accounted that PRL levels had no clinical significance in pathogenesis and severity of PE[25]. Meanwhile, Miyakawa et al explained that high PRL levels in PE was not linked with the pathogenesis of PE but it increased due to PE induced-renal dysfunction[26].

But recent studies disclosed a complex mechanism linked between high PRL levels and risk of PE. PRL is also produced by different tissues and modified by various enzymatic types, so different molecular forms are produced. One of these is 16kDa PRL which acts as an anti-angiogenic factor in the pathogenesis of PE[27]. Indeed, increased cathepsin D activity in cardiomyocyte of patients with PE increases the risk of cardiomyopathy due to the formation of 16kDa PRL[28].

Therefore, high PRL serum level is regarded as a potential risk factor of PE-related complications since Leanos-Miranda et al proved that auto-antibodies against circulating PRL in PE pregnant women with systemic lupus erythematosus protect against PE linked complications. Thus, PRL antibody could be a therapeutic potential for the management of PE[29]. Furthermore, the severity of PE is associated with high PRL serum levels as well as urinary PRL[30], as matched with findings of the present study.

Additionally, the findings of the present study illustrated the significant correlation between MAP and high PRL serum levels as divulged by Masumoto et al who demonstrated a significant correlation between PRL serum levels with PE and pregnancy induced-hypertension[31].

Normally, the elevation of PRL serum level during pregnancy leads to vasodilatation due to activation of carboxypeptidase-D, which provokes the release of endothelial NO. But the very high elevation of PRL leads to induction of cathepsin-D which converts native PRL into 16kDa PRL which causes vasoconstriction due to suppression of endothelial NO[32,33].

Regarding the second important pathway following the elevation of PRL serum levels in patients with PE, PRL level is cleaved by placental cathepsin-D into vasooinhibins which act as antiangiogenic factor via inhibition of NO synthesis leading to vasoconstriction and hypertension[34]. Besides, Kim et al confirmed that cathepsin-D levels are increased in patients with PE, but this elevation is not correlated with the severity of PE and feto-maternal complications[35].

Limitations of the present study were small sample size and single center study. As well, 16kDa PRL, vasooinhibin and cathepsin-D were not assessed differentially, but in spite of these limitations, this study is regarded as a new study confirming the relation between PRL serum levels and severity of PE. However, large scale studies are recommended to elucidate the differential effects of different pharmacotherapy on PRL serum levels in patients with PE.

In conclusion, PRL serum levels are elevated in patients with PE and correlated with the severity of PE. High but not normal PRL might be implicated in the pathogenesis of PE.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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