Role of dyslipidemia in the development of early-onset preeclampsia

Thabat J. Al-Maiahy, Ali I. Al-Gareeb, Hayden M. Al-Kuraishy

Department of Pharmacology, Toxicology and Medicine College of Medicine, Almustansiriya University, Baghdad, Iraq

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ABSTRACT

Preeclampsia (PE) is a gestational-related disease presented with hypertension, peripheral edema, and proteinuria after 20 weeks of gestation. In PE, there are various metabolic changes like dyslipidemia. In addition, both PE and dyslipidemia are associated with changes of platelet indices. Thus, objective of the current study was to illustrate the potential role of dyslipidemia and platelet changes in pregnant women with PE. This case–control study involved 37 preeclamptic pregnant women as compared to 24 healthy pregnant women as controls. Blood pressure profile, lipid profile, proteinuria, and platelet indices were measured. Blood pressure profile was higher in preeclamptic pregnant women as compared to the controls \( (P < 0.01) \). There was a significant dyslipidemic status in preeclamptic pregnant women compared with the controls \( (P < 0.01) \). Platetetcrit (PCT) and platelet count (PC) were lower in preeclamptic pregnant women compared with the controls \( (P = 0.001) \). On the other hand, platelet distribution width (PDW), mean platelet volume (MPV), and platelet-large cell ratio (P-LCR) were higher in the pregnant women with PE as compared with the controls \( (P = 0.001) \). PCT and PC were insignificantly linked, while P-LCR, MPV and PDW were significantly correlated with total cholesterol, triglyceride, low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio, systolic blood pressure, DBP, and MAP in preeclamptic patients compared with women of normal pregnancy. Both dyslipidemia and alterations in the platelet indices are correlated with blood pressure profile in PE. High MPV and PDW in association with high LDL/HDL ratio in pregnant women herald risk of PE.

Key words: Blood pressure, dyslipidemia, platelet indices, preeclampsia

INTRODUCTION

Preeclampsia (PE) is a gestational-related disease presented with hypertension, peripheral edema, and proteinuria after 20 weeks of gestation.\(^1\) The risk factors of PE are extreme maternal age, nulliparity, obesity, insulin resistance, diabetes mellitus, chronic hypertension, gestational hypertension, twin and multiple gestation, previous preeclamptic pregnancy, and black race.\(^2\)

The pathogenesis of PE is linked to the different etiopathological factors, including vascular, oxidative stress, genetic, and immune. However, the pathogenesis of PE remains obscure, making management and prevention of PE a current of challenge. There is unanimity of opinion concerning the standpoint in the
pathogenesis of PE, Al-Maiahy et al. illustrate that poor placentation and trophoblastic neovascularization are the initial pathological changes with subsequent development of PE due to inflammation and oxidative stress-induced-vasoconstrictions.\[3\]

In PE, there are various metabolic changes like dyslipidemia, which is one of metabolic changes linked with high body mass index (BMI) during pregnancy. Physiologic hyperlipidemia is not atherogenic; however, hyperlipidemia is associated with the severity of hypertension in PE since; dyslipidemia in PE is highly prevalent in women with elevated BMI and obesity, that linked with placental dysfunction in PE.\[4\]

There is opinion unanimity, that both PE and dyslipidemia are associated with changes of platelet indices. Jäger et al.\[5\] found that platelets hyper-reactivity in patients with dyslipidemia, as well, Thalor et al.,\[6\] observed that changes in the platelet indices are linked with the severity of PE. Moreover, there are significant interactions between dyslipidemia and alteration in the platelet indices during PE, which together contribute in the development of PE.\[7\]

Thus, objective of the current study was to illustrate the potential role of dyslipidemia and platelet changes in pregnant women with PE.

MATERIALS AND METHODS

Study design

The current study involved 37 preeclamptic pregnant women aged 28–36 (31.85 ± 5.94) years compared with matched 24 healthy pregnant women as controls were recruited consecutively from the primary health center during routine visits of the antenatal care unit, during the period of June-October 2019. Selection of pregnant women was in harmony with the diagnostic criteria of Global Obstetrician and Gynecologist recommendation.\[8\] Written and informed verbal consents were attaining from all patients and controls. Subsequent of the comprehensive full history concerning parity, pregnancy-related complications, current and previous pharmacotherapy, the recruited pregnant women and controls were recruited into two groups: Group A: Preeclamptic women (n = 37) and Group B: healthy controls (n = 24).

Any pregnant women with chronic hypertension, gestational hypertension, cardiovascular complications, endocrine disorders, metabolic disorders, gestational diabetes mellitus, chronic sepsis, urinary tract infections (UTIs), multiple pregnancy, hepatic disorders, and chronic kidney disorders were excluded from this study.

**Assessment of anthropometric variables**

In the present study, BMI was estimated by explicit method, also blood pressure of patients and controls were measured at the supine position by digital sphygmomanometer 2 h apart.\[9\]

Gestational age was determined by the calculation the pregnancy period from the 1\textsuperscript{st} day of the last menstrual cycle in addition to the ultrasonographic imaging measurements.

**Assessment of biochemical parameters**

Throughout the routine visiting, 10 mL of blood from all cases and controls, were centrifuged and stored for afterward investigation. Measurement of blood urea and serum creatinine was done by colometric assay. Besides, lipid profile such as triglyceride (TG), total cholesterol (TC), and high-density lipoprotein (HDL) were estimated by colorimetric kits. Both low-density lipoprotein (LDL) and very LDL were estimated in harmony to Al-kuraishy et al. method.\[10\] The second 5 ml of blood was stored in ethylenediaminetetraacetic acid (EDTA) tubes and used for the assessment of complete blood count (CBC) by automated hematology analyzer system (Abbot Diagnostics Santa Clara, USA). Parameters of CBC such as packed cell volume, white blood cell, mean platelet volume (MPV), platelet distribution width (PDW), and pleteletcrit (total platelet mass) were estimated.\[11\]

**Measurement of proteinuria**

Mid-stream urine from each patient and controls were collected in a special container and the amount of proteinuria was assessed by urinary dipstick method.\[12\]

**Data analysis**

Data analysis was performed using SPSS (IBM SPSS Statistics for Windows version 21.00,2017, Amonk, NY, IBM, CORP, USA) and presented as means ± standard deviation. Correlation of coefficient was done to find the correlation of different variables. The level of significance was considered when value of $P < 0.05$.

RESULTS

**Study flow**

Consort flow-diagram [Figure 1], illustrates that 4 (6.15%) of patients were excluded due to gestational diabetes and UTI, and hence, only 61 pregnant women were involved in this study.

**Demographic characteristics**

In this study, age and BMI of pregnant women with PE were comparable and were not differed from that of controls ($P > 0.05$) and ($P > 0.05$) correspondingly. Percentage of primigravidae was superior in PE (40.54%) as compared to the controls (12.50%), ($P < 0.05$). Cesarean section (CS) to normal vaginal delivery ratio was high (27:10) compared...
with healthy controls (4:20), \( P = 0.008 \). Moreover, 81.08% of preeclamptic patients used folic acid 1 mg/day compared with 54.17% of the controls \( P = 0.02 \). Other characteristics are described in Table 1.

**Biochemical variables in preeclamptic patients**

Regarding biochemical parameters, which was higher in the pregnant women with PE as compared with controls TC, TG, and LDL serum levels were higher preeclamptic patients as compared to the controls \( P = 0.001 \), whereas HDL serum level was lower in preeclamptic patients compared with the controls \( P = 0.03 \). As well, athrogenic profile and LDL/HDL were elevated in the preeclamptic women compared with the controls \( P < 0.01 \) [Table 2]. In preeclamptic patients, proteinuria and blood pressure profile were higher in the preeclamptic patients compared with the controls \( P < 0.01 \) [Table 3].

**Platelet indices in preeclamptic patients**

Pletetetcrit (PCT) and platelet count (PC) were reduced in preeclamptic patients compared with the controls \( P = 0.001 \). However, MPV, PDW, and P-LCR were superior in preeclamptic women as in contrast with the controls \( P = 0.001 \) [Table 4].

**Correlations of platelet indices in preeclamptic patients**

P-LCR, PDW, and MPV were correlated with LDL/HDL, TG, and AI in preeclamptic patients compared with the controls [Table 5]. As well, P-LCR, PDW, and MPV were correlated with blood pressure profile [Table 6]. Besides, all lipid profiles correlated positively with blood pressure profile (systolic blood pressure [SBP], diastolic blood pressure [DBP], and mean arterial pressure [MAP]) significantly, with exception of HDL serum level which was negatively correlated with MAP only and not with SBP or DBP [Table 7].

**DISCUSSION**

Findings of this study illustrated that preeclamptic pregnant women demonstrated an advanced BMI but not significantly differed from that of the controls since; high BMI and obesity are regarded as possible risk factor in the progression of PE.\(^{[13]}\) As well, our findings showed that there was a higher percentage of a primigravida

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**Table 1: Characteristics of the present study**

| Characteristics          | Controls | PE       | 95% CI             | \( P \) |
|--------------------------|----------|----------|--------------------|--------|
| \( n \)                  | 24       | 37       |                    |        |
| Age (years)              | 30.71±5.93 | 31.85±5.94 | −2.013–4.213          | 0.48   |
| BMI (kg/m\(^2\))         | 28.77±2.45 | 29.94±2.81 | −0.273–2.533         | 0.11   |
| GA (weeks)               | 27.69±2.31 | 28.94±3.05 | −0.210–2.710          | 0.09   |
| Primigravida (%)         | 3 (12.50) | 15 (40.54) | 4.719–45.975          | 0.02*  |
| CS:NVD ratio             | 4:20     | 27:10    | 4.411–39.454          | 0.008* |
| History of abortion%     | 2        | 39       | 16.477–53.129         | 0.001* |
| White race               | 23 (95.83) | 33 (89.19) | −10.710–20.954        | 0.35   |
| Black race               | 1 (4.17)  | 4 (10.81) | −10.710–21.856        | 0.31   |
| Smoking                  | 2 (8.33)  | 7 (18.91) | −9.314–27.005         | 0.25   |
| Medications              |          |          |                    |        |
| Anti-hypertensive        | 32 (86.47) |          |                    |        |
| Ferrous sulphate         | 19 (79.17) | 29 (78.38) | −21.353–20.201        | 0.94   |
| Folic acid               | 13 (54.17) | 30 (81.08) | 3.339–48.208          | 0.02*  |

\(^{*}P<0.05, \ ^{*}P<0.01. \text{BMI: Body mass index, GA: Gestational age, CS: Cesarean section, NVD: Normal vaginal delivery, CI: Confidence interval, PE: Preeclampsia}\)
Table 2: Lipid profile in the early-onset preeclampsia

| Parameters       | Controls (n=24) | PE (n=37)     | 95% CI          | P     |
|------------------|----------------|---------------|-----------------|-------|
| TC (mg/dL)       | 154.29±12.81   | 174.29±19.81  | 10.864–29.135   | 0.001*|
| TG (mg/dL)       | 148.73±9.74    | 186.96±13.42  | 31.874–44.585   | 0.001*|
| HDL (mg/dL)      | 45.87±8.51     | 41.61±6.94    | −8.241–0.279    | 0.03* |
| VLDL (mg/dL)     | 9.17±2.52      | 8.32±2.41     | −2.136–0.436    | 0.19  |
| LDL-C (mg/dL)    | 78.70±9.85     | 95.30±10.62   | 11.182–22.015   | 0.004*|
| AI               | 0.151±0.02     | 0.293±0.04    | 0.124–0.159     | 0.001*|
| LDL/HDL ratio    | 1.71±0.75      | 2.29±0.86     | 0.150–1.009     | 0.009*|

*P<0.05, *P<0.01. TC: Total cholesterol; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein-cholesterol; VLDL: Very low density lipoprotein, AI: Atherogenic index, PE: Preeclampsia, CI: Confidence interval

Table 3: Blood pressure profile and laboratory findings in the preeclamptic pregnant women

| Parameters       | Controls (n=24) | PE (n=37)     | 95% CI          | P     |
|------------------|----------------|---------------|-----------------|-------|
| SBP (mmHg)       | 117.61±7.84    | 149.94±8.53   | 27.99–36.66     | 0.0001*|
| DBP (mmHg)       | 67.95±9.33     | 97.89±6.52    | 25.88–33.99     | 0.001*|
| MAP (mmHg)       | 85.00±6.41     | 115.00±9.21   | 25.68–34.31     | 0.003*|
| Blood urea (mg/dL) | 22.58±5.93   | 25.86±6.84    | −0.757–7.317    | 0.10  |
| Serum creatinine (mg/dL) | 1.12±0.56 | 1.39±0.74    | −0.084–0.624    | 0.13  |
| Hb (g/L)         | 11.68±2.62     | 11.98±2.57    | −1.058–1.658    | 0.66  |
| Proteinuria (mg/dL) | 12.81±4.85 | 351.08±14.97  | 331.96–344.57   | 0.0001*|

*P<0.01. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PE: Preeclampsia, CI: Confidence interval, Hb: Hemoglobin

Table 4: Platelet indices in preeclampsia patients

| Parameters       | Controls (n=24) | PE (n=37)     | 95% CI          | P     |
|------------------|----------------|---------------|-----------------|-------|
| PCT (%)          | 0.28±0.04      | 0.25±0.03     | −0.048–0.012    | 0.001*|
| PC (×10³/mm³)    | 342.63±75.61   | 211.85±90.72  | −175.48–86.17   | 0.001*|
| MPV (fL)         | 8.21±1.08      | 11.85±1.22    | 3.027–4.252     | 0.001*|
| PDW (fL)         | 15.89±1.42     | 17.39±1.99    | 0.561–4.438     | 0.002*|
| P-LCR (%)        | 22.96±7.93     | 29.96±7.91    | 2.321–11.678    | 0.004*|

*P<0.01. PCT: Platetecrit, PC: Platelet count, MPV: mean platelet volume, PDW: Platelet distribution width, P-LCR: Platelet-large cell ratio

Table 5: Correlation of atherogenic indices with the platelet indices in the preeclamptic pregnant women

| Platelet indices | AI P | LDL/HDL P | TC P | TG P |
|------------------|------|-----------|------|------|
| PCT (%)          | 0.31 | 0.06      | 0.29 | 0.08 |
| PC (×10³/mm³)    | 0.22 | 0.19      | 0.23 | 0.17 |
| MPV (fL)         | 0.48 | 0.002*    | 0.56 | 0.0003* |
| PDW (fL)         | 0.55 | 0.004*    | 0.52 | 0.0009* |
| P-LCR (%)        | 0.49 | 0.002*    | 0.76 | 0.0001* |

*P<0.05, *P<0.01. PCT: Platetecrit, PC: Platelet count, MPV: Mean platelet volume, PDW: Platelet distribution width, P-LCR: Platelet-large cell ratio, TC: Total cholesterol, TG: Triglyceride, AI: Atherogenic index, r: Correlation, P: Significance of difference

with history of previous CS and abortion, which together increase the risk and incidence of subsequent PE. As well, there were 18.91% of our preeclamptic patients were cigarette smoking, this low percentage of smoking might increase the risk of PE since; smoking is observed paradoxically to be a protective cause alongside the progress of PE through carbon monoxide induced-vasodilatation.\cite{14}

Moreover, the present study demonstrated the typical presentation of PE in the pregnant women; as there were significant hypertension and proteinuria in the preeclamptic pregnant women compared with healthy controls. This type of PE is called early-onset PE since the gestational age of all recruited preeclamptic women started after 20 and before 34 weeks of gestation.\cite{15}

Furthermore, in the present study, preeclamptic patients showed dyslipidemic status with high atherogenic index and LDL/HDL ratio. Wojcik-Baszko \textit{et al.}\cite{16} found a positive association and interrelated relationship between dyslipidemia and PE. Recent emerging evidence regarding the development of PE suggests that deregulations of fetomaternal lipid metabolism is linked with the pathogenesis
Table 6: Correlation of platelet indices with blood pressure profile in preeclamptic pregnant women

| Platelet indices | SBP | DBP | MAP |
|------------------|-----|-----|-----|
|                  | r   | P   | r   | P   | r   | P   |
| PCT (%)          | 0.22| 0.19| 0.30| 0.07| 0.31| 0.06|
| PC (×10^12/mm^3) | 0.31| 0.06| 0.31| 0.06| 0.31| 0.06|
| MPV (fL)         | 0.48| 0.002* | 0.46| 0.0003* | 0.43| 0.007* |
| PDW (fL)         | 0.55| 0.004* | 0.72| 0.0009* | 0.49| 0.002* |
| P-LCR (%)        | 0.43| 0.007* | 0.86| 0.00001* | 0.69| 0.0001* |

*P<0.01. PCT: Plateletcrit, PC: Platelet count, MPV: Mean platelet volume, PDW: Platelet distribution width, P-LCR: Platelet-large cell ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, r: Correlation, P: Significance of difference

Table 7: Correlation of blood lipid with blood pressure profile in preeclamptic pregnant women

| Platelet indices | SBP | DBP | MAP |
|------------------|-----|-----|-----|
|                  | r   | P   | r   | P   | r   | P   |
| TC (mg/dl)       | 0.43| 0.007* | 0.39| 0.017* | 0.31| 0.06|
| TG (mg/dl)       | 0.60| 0.0001* | 0.66| 0.0001* | 0.72| 0.00001* |
| HDL (mg/dl)      | −0.21| 0.21 | −0.29| 0.081 | −0.3| 0.04* |
| VLDL (mg/dl)     | 0.55| 0.0004* | 0.39| 0.017* | 0.49| 0.002* |
| LDL (mg/dl)      | 0.43| 0.0007* | 0.86| 0.00001* | 0.69| 0.0001* |
| AI               | 0.65| 0.0001* | 0.76| 0.0001* | 0.64| 0.0001* |
| LDL/HDL ratio    | 0.58| 0.00001* | 0.62| 0.00001* | 0.55| 0.0001* |

*P<0.05, **P<0.01. TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, AI: Atherogenic index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, r: Correlation, P: Significance of difference

Concerning the association between platelet indices and dyslipidemia, the present study illustrated that PCT and PC were not significantly correlated, while MPV, PDW, and P-LCR were significantly correlated with AI, LDL/TC ratio, TC and TG in the pregnant women with PE as compared with controls. Susilowati et al. showed that oxidized LDL (oxLDL) promotes platelet aggregations through reduction of platelet NO; in turn, the activated platelets activate the uptake of oxLDL by macrophages.[24] This interaction leads to significant changes in the platelet indices as shown in the current study. Different studies have been shown that dyslipidemia may affect the metabolic activity of platelets, as oxLDL activates while HDL inhibits the atherogenic activity of platelets.[25] Indeed, LDL/HDL ratio is more important than LDL or HDL alone, as it reflects the metabolic equilibrium since; LDL/HDL ratio is more correlated with platelet indices as shown in the current study. Therefore, dyslipidemic status in the preeclamptic pregnant women contributes to the significant platelet changes, which in turn increase the risk of cardio-metabolic complications in PE. Furthermore, the present found a strong relationship between platelet indices and lipid profile in pregnant women with PE.

This study had some limitations, which were the small sample size, variability of platelet size, serial measurements of MPV were not done, and plasma erythropoietin concentration was not evaluated. Nevertheless, this study is considered as a pilot study for extended forthcoming study to assess the potential link between platelet alterations and their association with the dyslipidemic status in the preeclamptic pregnant women.

CONCLUSION

Initial or early-onset PE is linked with remarkable changes in the platelet indices and lipid profile. Both dyslipidemia and alterations of platelet indices are correlated with blood pressure profile in PE.
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Conflicts of interest
There are no conflicts of interest.

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