Oxidative Stress and Dyslipidemia as Indicators of Pathogenesis of Preeclampsia in Pregnant Sudanese Women
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ABSTRACT

Background/purpose: Pre-eclampsia contributes remarkably to maternal, fetal, and neonatal morbidity and mortality. Hyperlipidemia in pre-eclampsia has been studied in relation to several factors. The objective of this study was to determine the role of oxidative stress and dyslipidemia as indicators in the pathogenesis of preeclampsia. Patients and methods: This was a cross-sectional (case-control) study conducted to evaluate the role of oxidative stress and dyslipidemia as indicators of pathogenesis and risks of preeclampsia in pregnant Sudanese women attending Wad-Medani Obstetrics and Gynecology Teaching Hospital. Result and conclusion: Pregnant with an increase in BMI have a higher chance of developing PE. Low level of high-density lipoprotein cholesterol and high level of low-density lipoprotein cholesterol define that dyslipidemia increasing the risk of PE. Decreased levels of NO and TAC might reflect the oxidative stress and likely contribute to the pathophysiological mechanisms of PE.

Keywords: Preeclampsia, Oxidative stress, Total antioxidant capacity, Nitric oxide, Dyslipidemia

INTRODUCTION

Pregnancy is one of the most important periods in the life of a woman, a family, and a society [1]. The success of pregnancy is a result of ongoing interactions between the placenta and the maternal immune and cardiovascular systems [2].

Pregnancy is a transient condition, but when it is complicated by preeclampsia (PE) it has lasting effects on both the mother and the fetus [3].

PE is a pregnancy multisystem disorder characterized by hypertension (≥140/90 mmHg), proteinuria (≥300 mg/24h or ≥1+dipstick) with or without edema that appears after 20 weeks of gestation in a previously normotensive non-proteinuric pregnant women [4].

PE found uniquely in the pregnant patient and one that has puzzled scientists for years and one of the “great obstetrical syndromes”[5], is characterized by systemic inflammation, endothelial cell dysfunction, excessive thrombin generation, an anti-angiogenic state and is often associated with multiple organ involvement [6]. However, PE is fundamentally a placental disease which manifests itself, in most cases, by the involvement of the vascular (i.e. hypertension) and renal systems (i.e. proteinuria) [7].

During a healthy pregnancy, there is an elevation in oxygen demand along with an increase in the production of reactive oxygen species (ROS) to carry out signaling for physiological processes in pregnancy, such as oocyte maturation, ovarian steroidogenesis, ovulation, implantation, blastocyst formation, luteolysis and luteal maintenance [8]. Preeclamptic women can present associated endothelial dysfunction, dyslipidemia, and aggravated systemic production of free radicals [9].

PE is one of the most common complications of human pregnancy with an overall incidence 2-12% [10]and the syndrome results in more than 63,000 maternal deaths worldwide annually, 75% are experienced in a mild form, and 25% in a severe form [11]. Prevalence of preeclampsia has increased by up to 30% over the last decade [12].
The exact cause of PE remains uncertain; therefore, PE is still a disease of theories [13]. But although the cause remains largely unknown, the pathogenesis is thought to occur in two main phases, the first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of placental materials into the maternal circulation. This, in turn, leads to the second, symptomatic stage, where in the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the hemolysis, elevated liver enzymes and low platelet account (HELLP) syndrome, eclampsia, and other end-organ damage [14]. At the cellular level, preeclampsia associated with the release of free radicals by the placenta and therefore generation of oxidative stress. Placenta-borne oxidative and stresses are even sometimes considered as the major molecular determinants of the maternal disease [15].

PATIENTS AND METHODS

This was a cross-sectional (case-control) study conducted to evaluate the role of oxidative stress and dyslipidemia as indicators of pathogenesis and risks of preeclampsia in pregnant Sudanese women attending Wad-Medani Obstetrics and Gynecology Teaching Hospital.

A total of 208 pregnant women were included in this study. They were selected from the wards of the hospital at admission before starting treatment. Informed consent was obtained from each participant before being recruited for the study. The pregnant women were divided into two groups; a patient group of 111 preeclamptic pregnant women, and a control group of 97 normal pregnant women.

Inclusion Criteria

Preeclamptic women with blood pressure ≥ 140/90, and proteinuria ≥300 mg/24hrs or ≥1+dipstick) were included. The controls were healthy pregnant women with no history or family history of PE.

Exclusion Criteria

For both patients and controls, pregnant women with pre-gestational cardiac, hepatic or renal disorders, diabetes mellitus, primary or secondary lipid disorders, severe anemia, those suffering from any other systemic or endocrine disorder were excluded.

A questionnaire was designed to obtain personal data, anthropometric measurements, social and medical information, and clinical investigations.

Blood (5 ml) from the median cubital vein was drawn from each participant and put in plain containers, left at room temperature for 30 minutes to clot and then centrifuged for 20 minutes at 5000 rpm. Then serum was separated and used for the measurement of TC, LDL, HDL, TG, NO, and TAC.

Levels of TC, LDL, HDL, TG were measured using fully automated A15 chemical analyzer manufactured by Biosystems Company S.A Costa Brava30, 08030 Barcelona (Spain).

The serum NO and total TAC were measured by Huma Reader HS Microtiter plate ELISA Reader manufactured by BioAssay Systems Company. Corporate Place, Hayward, CA 94545, USA.

RESULTS

The body mass index of preeclamptic women was significantly higher than that of normal pregnant women (25.33 ± 0.16 versus 24.65 ± 0.18, p=0.005) (Figure 1). The systolic blood pressure/diastolic blood pressure of the preeclamptic women showed significant elevation compared to normal pregnant women (148.83 ± 0.89/96.85 ± 0.44 versus 108.04 ± 0.78/74.90 ± 0.57, p<0.001 and p<0.001 respectively) (Figure 2).
Figure 1 The body mass index of the preeclamptic group and control group

Figure 2 The systolic blood pressure/diastolic blood pressure of cases and controls

Table 1 shows the characteristics of preeclamptic patients and controls regarding residence area and parity. The majority of preeclamptic women have a family history of PE (82.9%), no history of previous PE (71.2%) and late onset of PE (97.3%).

Table 1 Characteristics and description of study groups

| Characteristic | Patients | Controls | Total | p-value |
|---------------|----------|----------|-------|---------|
| Residence Area |          |          |       |         |
| Rural         | 64 (57.7%) | 57 (58.8%) | 121 (58.2%) | 0.889 |
| Urban         | 47 (42.3%) | 40 (41.2%) | 87 (41.8%) |         |
| Total         | 111 (100%) | 97 (100%) | 208 (100%) |         |
Kadhim, et al. Parity

| Parity              | Patients (N = 111) | Controls (N = 97) | p-value |
|---------------------|--------------------|-------------------|---------|
| Primiparous         | 54 (48.6%)         | 37 (38.1%)        | 91 (43.8%) | 0.185
| Multiparous         | 41 (36.9%)         | 48 (49.5%)        | 89 (42.8%) |
| Grand multiparous   | 16 (14.4%)         | 12 (12.4%)        | 28 (13.5%) |
| Total               | 111 (100%)         | 97 (100%)         | 208 (100%) |

The biochemical parameters of cases and controls were presented as mean ± SEM. All the measured parameters differed significantly between the two study groups (Table 2). The TC, LDL, and TG were significantly higher in preeclamptic women than controls (p<0.001, p<0.001 and p<0.007 respectively). The HDL level was significantly decreased in preeclamptic patients when compared with control group (p<0.001). Levels of NO and TAC were significantly lower (p ≤ 0.001) in preeclamptic women than the control group.

Table 2 Comparison of biochemical parameters of the study groups

| Parameter | Patients (N = 111) | Controls (N = 97) | p-value |
|-----------|--------------------|-------------------|---------|
| TC        | 155.34 ± 3.64      | 137.61 ± 3.68     | 0.001   |
| LDL       | 101.76 ± 2.43      | 76.68 ± 2.29      | <0.001  |
| HDL       | 36.91 ± 0.52       | 43.22 ± 0.97      | <0.001  |
| TG        | 142.26 ± 2.68      | 129.96 ± 3.66     | 0.007   |
| NO        | 61.69 ± 1.34       | 79.33 ± 1.06      | <0.001  |
| TAC       | 230.68 ± 10.68     | 291.66 ± 8.30     | <0.001  |

Pregnant women that have a high level of TC, LDL and low level of HDL were more likely to develop PE compared with pregnant women with normal levels.

Preeclamptic women tended to develop oxidative stress by 7.6 times for NO and 2.6-fold for TAC which in turn leads to the development of PE (Table 3).

Table 3 Comparison of risk estimate considering the parameters of lipid profile, tissue damage and oxidative stress between preeclamptic women and controls

| Parameter | Patients | Controls | Total | p-value | Chi value | OR (CI: 95%) |
|-----------|----------|----------|-------|---------|-----------|--------------|
| TC        |          |          |       | 0.111   | 3.243     | 2.414 (0.904 - 6.449) |
| Normal    | 95 (85.6%) | 87 (94.6%) | 182 (89.7%) | <0.001 | 15.066 | 7.739 (0.906 - 60.103) |
| High      | 16 (14.4%) | 5 (5.4%) | 21 (10.3%) |       |           |              |
| LDL       |          |          |       | 0.039   | 4.705     | 4.070 (1.942 - 8.530) |
| Normal    | 103(92.8%) | 95 (99%) | 198 (95.6%) |       |           |              |
| High      | 8 (7.2%) | 1 (1.0%) | 9 (4.4%) |       |           |              |
| HDL       |          |          |       | <0.001  | 15.066    | 4.070 (1.942 - 8.530) |
| Low risk  | 73 (65.8%) | 85 (89.5%) | 158 (76.5%) |       |           |              |
| High risk | 38 (34.2%) | 10 (10.5%) | 48 (23.5%) |       |           |              |
| Total     | 111 (100%) | 95 (100%) | 206 (100%) |       |           |              |
| TG        |          |          |       | 0.884   | 0.062     | 1.076 (0.607 - 1.906) |
| Normal    | 108(97.3%) | 84 (97.9%) | 202 (97.6%) |       |           |              |
| High      | 3 (2.7%) | 2 (2.1%) | 4 (2.4%) |       |           |              |
| NO        |          |          |       | <0.001  | 44.922    | 7.605 (4.090 - 14.139) |
| Low risk  | 33(29.7%) | 74 (76.3%) | 107 (51.4%) |       |           |              |
| High risk | 78 (70.3%) | 23 (23.7%) | 101 (48.6%) |       |           |              |
| Total     | 111 (100%) | 97 (100%) | 208 (100%) |       |           |              |
| TAC       |          |          |       | 0.011   | 6.855     | 2.618 (1.254 - 5.464) |
| Low risk  | 13 (11.7%) | 25 (25.8%) | 38 (18.3%) |       |           |              |
| High risk | 98 (88.3%) | 72 (74.2%) | 170 (81.7%) |       |           |              |
| Total     | 111 (100%) | 97 (100%) | 208 (100%) |       |           |              |
Correlation of measured parameters with NO

Table 4 shows the correlation of BMI, blood pressure, TC, LDL, HDL, TG and TAC with NO. NO was negatively correlated with SBP (r = -0.493, p ≤ 0.001), DBP (r = -0.538, p ≤ 0.001), TC (r = -0.174, p=0.013), LDL (r = -0.270, p ≤ 0.001), TG (r = -0.133, p=0.055), BMI (r = -0.075, p=0.285), while it was positively correlated with HDL (r = 0.180, p=0.009) and TAC (r=0.181, p=0.009).

| Parameter          | Correlation coefficient (r) | p-value |
|--------------------|-----------------------------|---------|
| BMI                | -0.075                      | 0.285   |
| Systolic blood pressure | -0.493**                  | <0.001  |
| Diastolic blood pressure | -0.538**              | <0.001  |
| TC                 | -0.174*                     | 0.013   |
| LDL                | -0.270**                    | <0.001  |
| HDL                | 0.180**                     | 0.009   |
| Triglyceride       | -0.133                      | 0.055   |
| TAC                | 0.181**                     | 0.009   |

Correlation of measured parameters with TAC

Correlation of BMI, blood pressure, TC, LDL, HDL, LDH and NO with TAC is shown in Tables 4 and 5. TAC was negatively correlated with SBP (r = -0.285, p ≤ 0.001), DBP (r = -0.268, p ≤ 0.001), BMI (r = -0.063, p=0.365), TC (r = - 0.006, p=0.937), LDL (r = -0.086, p=0.219), while it was positively correlated with HDL (r=0.227, p=0.001) and NO (r=0.181, p=0.009) (Table 5).

| Parameter  | Correlation coefficient (r) | p-value |
|------------|-----------------------------|---------|
| BMI        | -0.063                      | 0.365   |
| Systolic blood pressure | -0.285**                  | <0.001  |
| Diastolic blood pressure | -0.268**              | <0.001  |
| TC         | -0.006                      | 0.937   |
| LDL        | -0.086                      | 0.219   |
| HDL        | 0.227**                     | 0.001   |
| NO         | 0.181**                     | 0.009   |

Multiple linear regression analysis of the PE-associated risk and complication factors

Multiple linear regression analysis with forward elimination was conducted to determine among the significant PE-associated risk factors what were the most significant factors that actually contribute to the development of PE as indicated by SBP and DBP.

Because the hypertension is the main clinical manifestation of PE, SBP and DBP were taken as the dependent variable with PE-associated risk factors (BMI, lipid profile, TAC and NO) as independent variables of risk estimate. SBP and DBP were taken in two different models (Table 6).

| Dependent variable | Parameter | Unstandardized coefficient B | SE  | Standardized coefficient β | t     | p-value |
|--------------------|-----------|------------------------------|-----|----------------------------|-------|---------|
| SBP                | BMI       | 1.405                        | 0.666| 0.112                      | 2.111 | 0.036   |
|                    | LDL       | 0.233                        | 0.046| 0.277                      | 5.038 | < 0.001 |
|                    | HDL       | -0.9                         | 0.154| -0.328                     | -5.845| < 0.001 |
|                    | TAC       | -0.026                       | 0.012| -0.121                     | -2.213| 0.028   |
|                    | NO        | -0.454                       | 0.081| -0.318                     | -5.619| < 0.001 |
Systolic Blood Pressure Model

From the output of the multiple linear regression for PE-associated risk factors, the most significant factors that predict the development of PE were BMI (p=0.036, β=0.112), LDL (p ≤ 0.001, β=0.277), HDL (p ≤ 0.001, β=-0.328), TAC (p=0.028, β=-0.121) and NO (p ≤ 0.001, β=-0.318) as shown in Table 4. These results indicate that for an increase of one unit in standard deviations of BMI and LDL the expected increase in standard deviation of SBP was 0.112 and 0.277 respectively. A decrease of one unit in standard deviations of HDL, TAC and NO the expected increase in standard deviation of SBP was 0.328, 0.121 and 0.318 respectively.

Despite TC and TG were significant PE-associated risk factors, they were eliminated from the multiple linear regression analysis models.

Diastolic Blood Pressure Model

From the output of the multiple linear regression for PE-associated risk factors, the most significant predictors for development of PE were BMI (p=0.010, β=0.136), LDL (p ≤ 0.001, β=0.313), HDL (p ≤ 0.001, β =-0.226), TAC (p=0.028, β =-0.110) and NO (p ≤ 0.001, β =-0.377) as presented in Table 4. These results indicate that for an increase of one unit in standard deviations of BMI and LDL the expected increase in standard deviation of SBP was 0.136 and 0.313 respectively. For a decrease of one unit in standard deviations of HDL, TAC and NO, the expected increase in standard deviation of SBP was 0.226, 0.110 and 0.377 respectively.

DISCUSSION

Preeclampsia is a multisystem disorder that remains a major cause of maternal and fetal morbidity and mortality. Yet, no preventive measures are known to preclude the occurrence of the disease. Free radical damage and several metabolic derangements have been implicated in the pathophysiology of this condition [16]. This study aimed to evaluate the role of oxidative stress, dyslipidemia, and markers of tissue damage as indicators of pathogenesis and risk of preeclampsia in pregnant Sudanese women.

In the present study, the ages of the two study groups were not statistically different, while the body mass index was significantly higher in preeclamptic women than the control group.

Pregnancy is associated with physiologic hyperlipidemia, and in normal pregnancy, this feature is not atherogenic and attributed to hormonal changes [17]. Pregnancy-related disorders such as PE are associated with a dysregulation of lipid metabolism manifesting in adverse maternal blood lipid levels [18,19]; inconsistency, the present study showed marked increased levels of TC, TG, and LDL in preeclamptic women than controls, while preeclamptic women revealed a significant decrease in HDL level as compared to controls.

These findings agree with other studies. It was reported that there was a significant increase in TC, LDL and TG with a significant decrease in HDL in the preeclamptic group compared to normotensive group and stated that dyslipidemia plays an important role in the pathogenesis of PE [20-25].

The mechanisms underlying dyslipidemia in PE are implicit. One possibility; inconsequential gestational insulin resistance in PE probably increases the mobilization of fatty acid from visceral adipocytes, leading to overproduction of VLDL by the liver, and suppresses the activity of lipoprotein lipase, culminating in elevated serum TG concentration and reduced serum HDL level which is major risk factor for vascular dysfunction in PE [26]. Alternatively, PE is a state of hypoestrogenemia, which leads to decreased expression of VLDL/apo E receptors resulting in reduced transport of VLDL to the fetal compartment and therefore occurrence of maternal hypertriglyceridemia [3,27]. Further LDL taken up by the fetus is decreased due to reduced fetoplacental perfusion leading to increased LDL [28]. The elevated TG
result in increased atherogenic small dense LDL and reduced HDL levels [29]. For dyslipidemia and PE association, two mechanisms are suggested: firstly, dyslipidemia may induce endothelial dysfunction secondary to oxidative stress and hence the occurrence of PE [30]. Secondly, dyslipidemia may impair trophoblast invasion by the deposition in predisposed vessels, such as the uterine spiral arteries and contributes to the endothelial dysfunction, therefore to a cascade of pathophysiologic events of the development of PE [31]. Lipid excess and oxidative stress can provoke endothelial dysfunction. Alterations of the endothelial dysfunction may underlie the hypertension of PE [32].

In an examination of the placental transcriptome, recognized pathways affected by inflammation, lipotoxicity, and oxidative stress were amplified significantly in placenta from obese women. Besides, RNA-seq analysis recognized pronounced decrease in genes related to angiogenesis and hormone activity, indicating that maternal dyslipidemia can negatively influence mitochondria leading to increased ROS production, oxidative stress and cellular dysfunction [33]. Oxidatively stressed placenta releases a number of trophoblast-derived antiangiogenics (e.g., soluble fms-like tyrosine kinase-1, soluble vascular endothelial growth factor, and soluble endoglin), and proangiogenic (e.g., placenta growth factor) factors that contribute to an exaggerated maternal inflammatory response with generalized endothelial dysfunction [34]. The total cholesterol/high-density lipoprotein ratio (TC/HDL) and the LDL/HDL ratio are two important components and indicators of vascular risk. Interestingly, in this study, 32.43% of preeclamptic patients at atherogenic risk T/HDL > 4.5; and 35.13% of patients are defined with high-risk when LDL/HDL > 3.0 threshold was applied.

PE is characterized by disturbed extravillous trophoblast migration toward uterine spiral arteries leading to increased uteroplacental vascular resistance and by vascular dysfunction resulting in reduced systemic vasodilatory properties. Its pathogenesis is mediated by an altered bioavailability of NO and tissue damage caused by increased levels of ROS [35]. Vascular function modulated by the interference of ROS and NO. Increased ROS production seems to suppress the expression and function of endothelial NO synthase [36].

NO exhibits multiple and complex biological functions and many of its effects can be mostly attributed to its strong oxidant capacity. Thus, NO is an important mediator of immune homeostasis and host defense, and changes in its generation or action can contribute to pathologic states [37].

In this study, maternal serum NO levels were significantly low in the preeclamptic women compared to controls. NO was negatively and significantly correlated with SBP, DBP, TC, LDL, TG, LDH, AST, and CK. While, HDL and TAC showed positive and significant correlation. Several reports ascertain the decreased levels of NO in PE, and its negative correlation with body weight, systolic blood pressure and diastolic blood pressure [38-41]. In contrast, Norris, et al., reported that the production of NO was significantly higher in the uteroplacental, fetoplacental, and peripheral circulation in PE compared to normotensive pregnancies. They attributed the marked increase in NO levels to a compensatory mechanism to the pathological effect of PE [42].

In a normal pregnancy, NO derived from endothelial nitric oxide synthase (eNOS) contributes to the maintenance of vascular tone to increase uterine blood flow [43]. An up-regulation of eNOS, resulting in increased NO production has been shown to contribute to increases in uteroplacental blood flow via changes in vascular tone [44]. In addition, there is evidence that genetic eNOS polymorphisms may affect the susceptibility to hypertensive disorders of pregnancy [45]. A study on 3 polymorphisms of the eNOS gene and the plasma nitric oxide concentrations was conducted in a population of Chinese origin from mainland China. Two variants 298Asp allele and eNOS 4a were strongly associated with higher plasma NO concentrations in pregnant women and suggested to modulate PE susceptibility [46]. Vascular tone is altered by the interference of ROS and NO, increased ROS production seems to suppress the expression of eNOS and hence reduced production of NO [47]. In fact, several studies have shown that impaired vascular relaxation in PE has been attributed to reduced bioavailability of NO produced via endothelial NOS [48]. A reduction in the bioavailability of NO and the imbalance between ROS and antioxidant activity seem to play a critical role in endothelial dysfunction contributing to raising blood pressure and hence pathogenesis of PE [49,50]. NO is also a potent inhibitor of platelet aggregation and activation by both cGMP-dependent and -independent mechanisms [51]. Drugs that target various components of the nitric oxide-soluble guanylyl cyclase pathway can help to increase NO bioavailability, and the delivery of exogenous NO is an attractive therapeutic option [52].

Total antioxidant capacity (TAC) parameter summarizes the overall activity of antioxidants and antioxidant enzymes [53]. Evaluating oxidative stress by measuring TAC can lead to a better understanding of free radical damage
in oxidative stress-related diseases like PE which would be useful to identify the patients with increased risk of progression of the disease and also for monitoring and optimization of antioxidant therapy [54]. In our study, the serum level of TAC was statistically low in the preeclamptic patients compared to controls. TAC was negatively correlated with SBP, DBP, BMI, TC, LDL, and LDH, while it was positively correlated with HDL and NO. Risk estimate considering antioxidants revealed that pregnant women that have a low level of NO and TAC had 7.6 and 2.6 times higher risk to develop oxidative stress which in turn leads to the development of PE. Study findings are in agreement with the study of Hasan and Dina who reported that the serum level of TAC was significantly low in preeclamptic cases signifying that the decrease in TAC leads to an imbalance between prooxidants and antioxidants in those women that go on to develop PE [55]. Oxidative stress reflects an imbalance between the formation of oxidative substances and the innate antioxidants that make up the endogenous defense system [56]. During normal pregnancy, there is a slight increase in oxidative stress, even in the presence of antioxidant systems [57]. In PE, the Abnormal vascular development of the blood vessels in the placenta leads to reduced placental perfusion and induce hypoxia which is by itself a potent stimulus for ROS formation [16].

A genome-wide transcriptomic view identified genes involved in lipid metabolism, angiogenesis, hormone activity, and inflammation to be significantly altered in placenta from obese women. These studies provide evidence for increased lipids and decreased TAC in placenta from obese women, and pinpointed key signaling pathways (increased JNK/FoxO4 signaling) and downstream mediators (HIF-1α and VEGF-A) that provide a link between maternal-obesity, placental inflammation/oxidative stress, and altered angiogenic factors. Obesity provokes cellular stress, which may in turn adversely affect placental development and function[33]. Antioxidants may be utilized to a greater extent to counteract and scavenging free radicals, resulting in the reduction of their levels [58].

The limitations of this study include the relatively small sample size. There were no follow up criteria set. Even with this limitation, the findings of this study serve as a ground for further studies to better understanding the associations of total antioxidant capacity and nitric oxide levels with preeclampsia.

CONCLUSIONS

Women with excessive BMI change have a higher chance of developing PE. Low level of high-density lipoprotein cholesterol and high level of low-density lipoprotein cholesterol define that dyslipidemia increasing the risk of PE. Decreased levels of NO and TAC might reflect the oxidative stress and likely contribute to the pathophysiological mechanisms of PE.

Recommendations

Longitudinal studies with serial measurements of biochemical markers needed to elucidate the pattern of changes and the pathophysiological consequences of such changes during pregnancy that leads to the development of PE. Further studies should be conducted to consider the role of NO and TAC as important factors in the pathogenesis of PE. More studies can clarify the etiological background of PE to provide guidance for the prevention and follow-up of women who experience PE.

DECLARATIONS

Conflict of Interest

The authors declare no potential conflict of interest.

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