

# Association between proteinuria and maternal and neonatal outcomes in pre-eclampsia pregnancy: a retrospective observational study

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## Abstract

**Objectives:** To evaluate the association between proteinuria and maternal and neonatal outcomes in pregnant women with pre-eclampsia.

**Methods:** This retrospective study included patients beyond 20 weeks of gestation diagnosed with pre-eclampsia, who were admitted to Suzhou Municipal Hospital between December 2013 and December 2015. Demographic and clinical data were extracted from clinical records, including age, body mass index, newborn weight and Apgar score. Pre-eclampsia risk factors and perinatal outcomes were analysed.

**Results:** A total of 407 patients were enrolled, of whom, 402 with pre-eclampsia were included in the final analyses, divided into two groups: patients with proteinuria ( $n = 364$  [90.55%]) and patients without proteinuria ( $n = 38$  [9.45%]). Newborn 5-min Apgar scores were statistically lower in the proteinuria group versus the group without proteinuria (9.77 versus 9.95). Compared with patients without proteinuria, patients with proteinuria had a significantly higher rate of births before 37 weeks of gestation (50.80% versus 31.60%), but the incidence of preterm membrane rupture was significantly lower (3.8% versus 13.2%).

**Conclusion:** Proteinuria may be associated with adverse maternal and neonatal outcomes in cases of pre-eclampsia.

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## Keywords

Pre-eclampsia, proteinuria, outcome

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## Introduction

Pre-eclampsia, a primary cause of mortality and morbidity in mother and infant, is characterized by the new onset of hypertension with either proteinuria or end-organ dysfunction after 20 weeks of gestation.<sup>1,2</sup> Approximately 4.6% of pregnancies worldwide are associated with pre-eclampsia,<sup>3</sup> and conventionally, pre-eclampsia diagnosis has depended on hypertension and subsequent proteinuria. In pregnancy with pre-eclampsia, maternal organs, such as the lungs, liver, kidneys, heart, systemic vasculature, and coagulation are susceptible to inflammation and endothelial damage.<sup>4</sup> The clinical manifestations of pre-eclampsia vary between individuals, for example, some patients have the clinical features of isolated gestational proteinuria with an absence of hypertension, while others who initially exhibit proteinuria subsequently develop hypertension, or they exhibit hypertension and proteinuria simultaneously.<sup>4</sup> Fortunately, most of the complications associated with pre-eclampsia are resolved after delivery of the placenta.<sup>5</sup>

In general, urinary protein excretion does not significantly change during normal pregnancy, and is considered abnormal during pregnancy when urinary protein excretion exceeds 300 mg/day or gives a positive dipstick test result at a 1+ level.<sup>6</sup> Prior to 2013, pre-eclampsia was classified into mild or severe according to the severity of proteinuria and hypertension. Furthermore, a proteinuria value  $>5$  g/24 h was used to indicate severe pre-eclampsia.<sup>7,8</sup> In 2013, the American College of Obstetricians and Gynecologists removed proteinuria as an essential criterion for the

diagnosis of pre-eclampsia.<sup>7,9</sup> According to the most recent national and international guidelines, proteinuria and foetal growth restriction cannot be considered as an indicator of pregnancy outcome, even if its presence remains essential for diagnosis of pre-eclampsia.<sup>10</sup> Current criteria for diagnosis of pre-eclampsia, according to the International Society for the Study of Hypertension in Pregnancy (ISSHP), are systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg with one or more new onset conditions after 20 weeks' gestation, such as proteinuria ( $\geq 0.3$  g/day), other maternal organ dysfunction (renal insufficiency, liver involvement, neurological complications, haematological complications), and/or uteroplacental dysfunction (foetal growth restriction).<sup>10</sup> To the best of the present authors' knowledge, the relationship between proteinuria and outcomes related to pregnancy with pre-eclampsia remain unknown.

The aim of the present study was to evaluate the association between proteinuria and maternal/neonatal outcomes in pregnant women with pre-eclampsia.

## Patients and methods

### Study population

This retrospective study included patients beyond 20 weeks of gestation, with pre-eclampsia diagnosed according to ISSHP criteria,<sup>10</sup> who were admitted to Suzhou Municipal Hospital, Suzhou City, Jiangsu, China between December 2013 and December 2015. Patients were sequentially enrolled and the clinical inclusion criteria

were the following: (1) aged over 18 years; (2) gestation of at least 18 weeks; and (3) met the criteria for diagnosis of pre-eclampsia.<sup>11</sup> Patients were excluded if they had severe pregnancy complications, and/or severe heart, liver and kidney complications. The study protocol was approved by the Ethics Committee of Suzhou City Hospital (No: K-2019-003-H01), and all patients provided written informed consent.

### Study protocol

Basic demographic and clinical data were collected from clinical records for all study participants, including age, gravidity, parity (defined as pregnancy carried to a viable gestational age [ $\geq 24$  weeks]), body mass index (BMI), newborn weight, and Apgar score. Patients with pre-eclampsia were divided into two groups: patients with proteinuria and patients without proteinuria. Pre-eclampsia risk factors and perinatal outcomes, such as nulliparity, age, intra-uterine growth restriction, preterm membrane rupture, delivery before the 37th gestational week, foetal distress, and transfer to neonatal intensive care unit, were analysed for all patients.

### Statistical analyses

Data are presented as  $n$  (%) prevalence, mean  $\pm$  SD or median (range), and all statistical analyses were performed using SPSS software, version 20.00 (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to assess the normality of continuous variable distribution. Normally distributed continuous variables were analysed using Student's  $t$ -test, and data without normal distribution were analysed using Mann–Whitney  $U$ -test. Categorical variables were assessed using  $\chi^2$ -test or Fisher's exact test. A  $P$  value  $< 0.05$  was considered to indicate statistical significance.

## Results

A total of 407 patients with pre-eclampsia were initially enrolled. Among these patients, five were excluded (one case had no albuminuria and four cases had no hypertension). Thus, 402 patients with pre-eclampsia met the study inclusion criteria and were included in the final analyses. Of those included, 364 patients (90.55%) were diagnosed with proteinuria (proteinuria group) and the remaining 38 patients (9.45%) did not have proteinuria (group without proteinuria).

Demographic and clinical characteristics of both groups are shown in Table 1. There were no statistically significant between-group differences in terms of BMI, gravidity, parity, time interval between diagnosis and delivery, newborn weight, and first minute Apgar scores. However, there were statistically significant between-group differences in maternal age and fifth minute Apgar scores. Patients with proteinuria were younger than those without proteinuria ( $P = 0.009$ ), and neonatal fifth minute Apgar scores were statistically lower in the proteinuria group ( $P = 0.007$ ), although all fifth minute scores were in the clinically normal range (Table 1).

Pre-eclampsia risk factors and perinatal outcomes in the two patient groups are presented in Table 2. There were no statistically significant between-group differences in rates of nulliparity, age  $\geq 40$  years, intra-uterine growth restriction (in terms of amniotic fluid index  $< 50$ , and mean values for biparietal diameter and abdominal circumference), and rates of foetal distress and use of neonatal intensive care unit. Thus, in the present study population, pre-eclampsia with or without proteinuria was identical in terms of the above risk factors and outcomes. In patients with preeclampsia who had proteinuria, the rate of patients who delivered at  $\leq 37$  weeks of gestation was significantly higher than in those without

**Table 1.** Demographic and clinical characteristics in pregnant females with pre-eclampsia, grouped according to presence or absence of proteinuria.

Variable	Study group		Statistical significance
	Pre-eclampsia with proteinuria (n = 364)	Pre-eclampsia without proteinuria (n = 38)	
Age, years	29.52 ± 5.09	31.79 ± 5.23	P = 0.009
Body mass index, kg/m <sup>2</sup>	29.28 ± 4.11	29.54 ± 4.77	NS
Gravidity, times	36 (34–39)	38 (35–39)	NS
Parity, times	0.38 ± 0.57	0.55 ± 0.60	NS
Interval between diagnosis and delivery, days	3.70 ± 4.72	3.53 ± 4.81	NS
Newborn weight, g	2543.74 ± 827.29	2807.03 ± 773.75	NS
Apgar score 1st min	9.46 ± 1.39	9.68 ± 1.03	NS
Apgar score 5st min	9.77 ± 0.93	9.95 ± 0.23	P = 0.007

Data presented as mean ± SD or median (range).

Normally distributed data were analysed by student's *t*-test; data without normal distribution were analysed using Mann–Whitney *U*-test.

NS, no statistically significant between-group differences (*P* > 0.05).

**Table 2.** Pre-eclampsia risk factors and perinatal outcomes in pregnant females with pre-eclampsia, grouped according to presence or absence of proteinuria.

Variable	Study group		Statistical significance
	Pre-eclampsia with proteinuria (n = 364)	Pre-eclampsia without proteinuria (n = 38)	
Nulliparity	239 (65.7)	19 (50.0)	NS
Age, ≥40 years	13 (3.6)	3 (7.9)	NS
Intrauterine growth restriction			
Biparietal diameter, mm	86.39 ± 9.30	88.56 ± 7.03	NS
Abdominal circumference, mm	297.87 ± 44.94	310.73 ± 38.91	NS
Amniotic fluid index, <50	24 (6.6)	2 (5.3)	NS
Preterm rupture of membrane	14 (3.8)	5 (13.2)	P = 0.010
Gestational age at delivery, ≤37 weeks	185 (50.8)	12 (31.6)	P = 0.024
Foetal distress	54 (14.8)	5 (13.2)	NS
Neonatal intensive care unit	128 (35.2)	9 (23.7)	NS

Data presented as *n* (%) prevalence or mean ± SD.

Normally distributed continuous data were analysed by student's *t*-test; categorical variables were assessed using  $\chi^2$ -test or Fisher's exact test.

NS, no statistically significant between-group differences (*P* > 0.05).

proteinuria (50.8% versus 31.6%, *P* = 0.024). However, the rate of preterm membrane rupture was significantly lower in those with proteinuria versus those without (3.8% versus 13.2%, *P* = 0.01).

## Discussion

Placental delivery remains the treatment for pre-eclampsia, so it is crucial to properly evaluate the severity of pre-eclampsia, study the factors that will influence

prognosis, and select the optimum delivery time.<sup>12,13</sup> The pathological change in pregnant women with pre-eclampsia is systemic arteriolar spasm that can involve all organs, with the kidney being the most commonly affected organ. As a result of renal arteriolar spasm, renal perfusion volume and glomerular filtration rate is decreased, endothelial cells are damaged, glomerular basement membrane permeability is increased, and selective proteinuria occurs.<sup>12,13</sup> In general, an increase in urinary protein means an increase in the degree of kidney function impairment, therefore, the severity of pre-eclampsia may be considered as directly associated with the severity of proteinuria.

Although many studies have shown that high levels of proteinuria are associated with poor perinatal outcomes, the effect of proteinuria on perinatal outcomes has not yet been precisely proven.<sup>8,14</sup> In the present study, patients with pre-eclampsia were divided into two groups according to the presence or absence of proteinuria. Patients with pre-eclampsia accompanied by proteinuria were found to be significantly younger than patients without proteinuria, suggesting that age may be an important factor affecting the presence or absence of proteinuria in pre-eclampsia. In addition, the incidence of preterm membrane rupture was significantly higher in patients with pre-eclampsia who had proteinuria compared with those without proteinuria. Therefore, adequate assessment of the severity of pre-eclampsia, including the presence or absence of proteinuria, may help obstetricians to achieve better management protocols.

The present study found that rates of the perinatal adverse effect of delivery before the 37<sup>th</sup> gestational week were significantly higher in patients with proteinuria. Previously published studies have shown that higher mean levels of proteinuria were associated with maternal adverse

effects,<sup>15</sup> maternal proteinuria may be a good predictor for pre-eclampsia,<sup>16</sup> and adverse perinatal outcomes are higher still in women with proteinuria.<sup>17</sup> Fifth minute newborn Apgar scores in the present study were found to be statistically different between patients with pre-eclampsia who had proteinuria versus those without proteinuria, however, scores were clinically normal in both groups. The presence of proteinuria during gestation has been shown to increase the risk of maternal complications, and was observed to be associated with a significant incidence of newborn Apgar scores <7.<sup>18</sup> Furthermore, severe and massive proteinuria was found to be associated with a significantly higher incidence of Apgar scores <7 compared with mild proteinuria.<sup>19</sup> Conversely, other studies have shown that there are no significant associations between proteinuria and outcome in pregnant women and fetuses.<sup>20-23</sup>

The results of the present study may be limited by several factors. First, the study was a retrospective design, and the single-centre setting with relatively small sample size may limit with wider generalizability of the results; secondly, some relevant variables were not taken into account due to the retrospective data collection; and thirdly, the data were not adjusted for two baseline variables (maternal age and Apgar score). Future research should involve a prospective multi-centre study with larger sample size, a relatively large number of parameters and the presence of long-term patient outcomes to explore the adverse prenatal outcomes of proteinuria in pre-eclampsia progression.

In summary, as one of the major characteristics of pre-eclampsia, proteinuria does not necessarily appear together with hypertension, as some cases present with hypertension alone. The present study showed that patients with pre-eclampsia and proteinuria may have the adverse perinatal outcome of delivery before 37 weeks of

gestation, and the incidence of preterm membrane rupture was significantly higher in patients with pre-eclampsia and proteinuria than in those without proteinuria. The results suggest that proteinuria may have an adverse effect on maternal and neonatal outcomes in pregnant women with pre-eclampsia.


### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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