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Proteinuria in preeclampsia: Not essential to diagnosis but related to disease severity and fetal outcomes

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ABSTRACT

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality globally and proteinuria can be one of the cardinal features of this disease. However, studies about the association of the amount of proteinuria and the severity of preeclampsia, and perinatal outcomes are limited. Data on 239 women with preeclampsia were retrospectively collected from a university teaching hospital from September 2011 to June 2013 and analysed. Data included all clinical parameters and proteinuria in a 24 h urine collection. In cases of severe preeclampsia, significantly fewer patients had proteinuria levels <0.3 g/L in comparison to any of the other groups with proteinuria >0.3 g/L, but there was no difference in cases of severe preeclampsia when proteinuria levels were >0.3 g/L. Furthermore, when proteinuria levels were >0.3 g/L, the frequency of severe preeclampsia in each group was significantly higher than the frequency of mild pre-eclampsia cases. Time of onset was significantly earlier in patients with proteinuria >3 g/L in a 24 h urine collection, but time between the onset of preeclampsia and delivery was not correlated with the amount of proteinuria. The birth weight was significantly lower in patients with proteinuria >3 g/L. The incidence of fetal growth restriction or stillbirth was significantly higher in patients with proteinuria >5 g/L. Our data demonstrate that the amount of proteinuria is not associated with the severe of preeclampsia, once proteinuria is detected, but is related to the severity of preeclampsia. The adverse fetal outcomes appear to be the function of prematurity rather than proteinuria itself.

1. Introduction

Preeclampsia is a pregnancy-specific multisystem disorder with unknown etiology and is a leading cause of maternal and perinatal morbidity and mortality globally [1]. Preeclampsia occurs clinically apparent after 20 weeks of gestation or within the first 4–6 weeks postpartum by new onset hypertension and/or proteinuria [2,3]. It is considered severe if blood pressure is increased substantially or clinical symptoms of end-organ damage (including fetal growth restriction) occur. Currently the only effective "treatment" for this disease is to deliver the placenta at optimal time for both maternal and fetal well-being.

In normal pregnancy, urinary protein excretion substantially increases and total protein excretion is considered abnormal in pregnant women when it exceeds 300 mg in a 24 h urine collection [4]. Proteinuria can be one of the cardinal features of preeclampsia. However, up to 10% of women with clinical and/or histological manifestations of preeclampsia and 20% of women with eclampsia have no proteinuria at the time of initial presentation with clinical symptoms, which are also called "non-proteinuric" preeclampsia [5,6]. This may be because the multiple organ dysfunctions affecting the kidneys and livers can occur without signs of protein and that the amount of proteinuria does not predict the severity of disease progression. Therefore since 2014, the International Society for the Study of Hypertension in Pregnancy [3] and American Society of Obstetrics and Gynaecology [7] have not recommended the use of proteinuria as a criterion with which to diagnose preeclampsia. Although proteinuria is not currently recommended as a criterion to diagnose preeclampsia, in reality clinicians commonly use proteinuria levels to inform clinical decisions regarding delivery of preeclamptic cases [8]. This because the increased levels of proteinuria worsen the progress of preeclampsia and are associated with poor perinatal outcomes [9–11]. These results may suggest

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that the amount of proteinuria is correlated with the severity of preeclampsia and this accordingly affects the management of preeclampsia.

Only a handful of studies have investigated the perinatal outcomes and maternal and fetal complications in preeclampsia in cases with high levels of proteinuria [9,10,12]. To date in particular, investigating the association of the amount of proteinuria in preeclampsia and the severity of preeclampsia is limited. Therefore in this study we performed a retrospective analysis to investigate the association of the amount of proteinuria and the severity and clinical outcomes of preeclampsia. All the data were obtained from a university teaching hospital serving diverse urban and rural areas in China.

2. Materials and methods

This investigation conforms to the principles outlined in the Declaration of Helsinki. This study was approved by the Ethics Committee of First Hospital of Xi'an Jiaotong University, China.

2.1. Study population

This retrospective study was performed at a university teaching hospital serving a diverse urban and rural population of approximately 8 million people in China. Data on 239 women with preeclampsia were collected from the Department of Obstetrics and Gynaecology, First Hospital of Xi'an, Jiaotong University of China from September 2011 to June 2013. The First Hospital of Xi'an Jiaotong University is a main maternal care referral hospital in Xi'an city and large numbers of women with preeclampsia, in particular those women with severe preeclampsia are referred to this hospital,

All women with risk factors for developing preeclampsia such as pre-existing hypertension, a previous pregnancy with preeclampsia, or other underlying medical disorders such as gestational/pre-existing diabetes, or autoimmune diseases were excluded from this study. No pregnancies conceived by *in vitro* fertilisation were included.

All cases that were coded as preeclampsia in the hospital electronic databases were individually assessed by the senior author to ensure that the criteria for preeclampsia, as described below, were satisfied. Data recorded included maternal age, gestational week at diagnosis, gravidity, parity, blood pressure, proteinuria in a 24 h urine collection, gestational weeks at delivery, birth weight, fetal growth restriction (FGR) and stillbirth. Proteinuria in 24 h urine collection was measured within 24 h after patients admitted to the hospital, before any treatment.

Preeclampsia was defined as a maternal systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg measured on two occasions separated by at least 6 h, and proteinuria >300 mg in a 24 h period, or impaired liver function and lower platelet count, after 20 weeks of gestation in accordance with the guidelines of the American College of Obstetricians and Gynaecologists [13]. Maternal systolic blood pressure $\geq$160 mmHg and/or diastolic blood pressure $\geq$110 mmHg was defined as severe preeclampsia. Preeclampsia occurring earlier than 34 weeks of gestation was defined as early-onset.

2.2. Subgroups

There is no clear consensus on the amount of proteinuria to be considered "heavy/severe" [14]. The majority rely on values $\geq$3 g/L or $\geq$5 g/L in a 24 h urine collection [14], and the definition of "heavy/severe" proteinuria ranging from 2 to 5 g/L in a 24 h urine collection [8]. Therefore based on these studies and the guideline from ACOG (2013), based on the amount of proteinuria in a 24 h urine collection, we divided the preeclampsia into four groups as described below. Group 1: proteinuria in a 24 h urine collection was <0.3 g/L; group 2: proteinuria in a 24 h urine collection was between 0.3 g/L and 3 g/L; group 3: proteinuria in a 24 h urine collection was between 3 g/L and 5 g/L; group 4: proteinuria in a 24 h urine collection was $\geq$5 g/L.

2.3. Statistical analysis

Data were presented as median and range or percentage as appropriate. The statistical differences in maternal age, gestational week at diagnosis, blood pressure, gestational week at delivery, and proteinuria in a 24 h urine collection between subgroups of preeclampsia were assessed by the Mann–Whitney *U* test using the Prism software package. The statistical differences in birth weight were assessed by multiple liner regression using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical differences in the number of cases of severe preeclampsia, FGR or stillbirth between subgroups of preeclampsia were assessed by a Chi-square test using Prism software. P-values of <0.05 were considered significant.

3. Results

3.1. Clinical characteristics of study population

During the study period, 239 women with preeclampsia were included. All clinical details of women with preeclampsia are summarised in Table 1. Of 239 women with preeclampsia, 97 (40.5%) women were diagnosed with mild preeclampsia. There were 41 (16%) patients with FGR and 23 (9.6%) patients with stillbirths.

3.2. The amount of proteinuria in a 24 urine collection was associated with the frequency of severe preeclampsia

To compare the severity of preeclampsia with the amount of proteinuria in a 24 h urine collection, we analysed the correlation of blood pressure (both systolic and diastolic blood pressure) and the amount of proteinuria in a 24 h urine collection. There was no correlation between the blood pressure and the amount of pro-

Table 1
Clinical characteristics of the study population.

	Preeclampsia (n = 239)		
	Early Onset (n = 135)	Mild PE (n = 97)	Severe PE (n = 142)
Maternal age (years, median/range)	30 (18–44)	30 (18–44)	29 (19–44)
Gestational week at diagnosis (weeks, median/range)	31^{+1} (20^{+6}–34)	34^{+5} (21–40^{+4})	32^{+4} (20^{+5}–38^{+6})
Gestational week at delivery (weeks, median/range)	33^{+2} (22^{+6}–37^{+4})	37^{+2} (25–42^{+4})	34^{+4} (22^{+5}–40^{+1})
Systolic blood pressure (mmHg, median/range)	160 (130–240)	145 (130–159)	165 (140–240)
Diastolic blood pressure (mmHg, median/range)	109 (90–150)	100 (80–128)	110 (78–150)
Birth weight (g, median/range)	1780 (920–3330)	2870 (1080–4100)	1870 (920–4195)
24 h proteinuria (g/L, median/range)	2.53 (2.02–18.8)	0.61 (0.07–11.9)	2.41 (0.04–18.8)
AST (IU/L)	24.5 (8.7–384)	21.5 (8.7–253)	25.6 (10.2–384)
ALT (IU/L)	15 (8.7–346)	14.5 (6–346)	16 (3.7–240)
Creatinine (μM)	62 (33.3–177)	57.2 (33.3–120)	62.9 (33–177)