Qualitative Analysis of Diagnostic Value of 24-h Proteinuria for Preeclampsia

Xu Zhuang, Yun-Yan Chen, Qiong Zhou, Jian-Hua Lin

Department of Obstetrics and Gynecology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

Abstract

Background: Preeclampsia (PE) is a serious idiopathic disease posing a threat to both mothers and fetuses' lives during pregnancy, whose main diagnostic criteria include hypertension with proteinuria. However, American College of Obstetricians and Gynecologists (ACOG) updated the diagnostic criteria for PE and reduced the diagnostic value of proteinuria for patients with PE. Qualitative analysis of the diagnostic value of 24-h proteinuria for patients with PE in China was conducted to evaluate the diagnostic criteria value in the latest ACOG guideline.

Methods: Complete clinical data of 65 patients with hypertensive disorder in pregnancy (HDP) were collected. All patients were delivered to and hospitalized in Renji Hospital. Adverse outcome was defined in case of the emergence of any serious complication for a mother or the fetus. A retrospective study was conducted according to ACOG guideline, to analyze the relationship between each diagnostic criteria of ACOG guideline and maternal and perinatal outcomes. Spearman correlation test was used to detect the association between each diagnostic criterion, its corresponding value, and the adverse pregnancy outcome. Logistic regression was performed to verify the result of Spearman correlation test.

Results: Of 65 HDP patients, the percentage of adverse pregnancy outcome was 63.1%. Adverse pregnancy outcomes constitute diversification. There were 55 cases with 24-h proteinuria value ≥ 0.3 g, of which the adverse outcome rate was 74.5%. While adverse pregnancy outcomes did not appear in the rest 10 HDP patients with proteinuria <0.3 g/24 h. The statistic difference was significant ($P = 0.000$). However, no significant difference was found in other criteria groups (impaired liver function: $P = 0.417$; renal insufficiency: $P = 0.194$; thrombocytopenia: $P = 0.079$; and cerebral or visual symptoms: $P = 0.296$). The correlation coefficient between 24-h proteinuria ≥ 0.3 g and adverse pregnancy outcomes was 0.557 ($P < 0.005$). Impaired liver function ($P = 0.180$), renal insufficiency ($P = 0.077$) and cerebral or visual symptoms ($P = 0.118$) were not related to adverse outcomes. The 24-h proteinuria value (HDP: $r = 0.685$; PE: $r = 0.521$), liver enzyme value (HDP: $r = 0.519$; PE: $r = 0.501$), and creatinine value (HDP: $r = 0.511$; PE: $r = 0.398$) were associated with adverse pregnancy outcomes both in PE and HDP, and the corresponding logistic regression equation can be produced.

Conclusions: The 24-h proteinuria value is still an important diagnostic criterion for PE, and deletion of 24-h proteinuria value from diagnostic criteria for severe PE was not recommended. The diagnostic criteria in ACOG guideline need to be verified in Chinese women.

Key words: American College of Obstetricians and Gynecologists Guideline; Hypertensive Disorders in Pregnancy; Preeclampsia; Pregnancy Outcomes; Proteinuria

Introduction

Preeclampsia (PE) is one of the main causes of maternal mortality in the world, with an incidence rate of 3–5%.[1-3] This disease increases the risk of other cardiovascular diseases, leading to a growth of maternal mortality.[4,5] At the same time, approximately 40% of fetuses result in preterm births before 35 weeks gestation.[6] For decades, PE has been defined worldwide in case of the appearance of elevated blood pressure (BP) with increased proteinuria (≥ 0.3 g/24 h) after 20 weeks.[7] But in 2013, American College of Obstetricians and Gynecologists (ACOG) released new hypertensive disorder in pregnancy (HDP) guideline,

where one major change had been made in the diagnostic criteria for PE, which could be diagnosed in the absence of proteinuria.[8] Hypertensive patients with one of these conditions, including thrombocytopenia, renal insufficiency, impaired liver function, pulmonary oedema, and cerebral or visual symptoms can still be diagnosed as PE, or even severe PE (SPE).[8] The original 24-h proteinuria value >5 g was deleted from the individual diagnostic criteria for SPE,[8] thus posing a big challenge to the diagnostic value of 24-h proteinuria value. Here we conducted a retrospective qualitative analysis to evaluate the diagnostic value of 24-h proteinuria for PE and its prognostic value in maternal-fetal outcomes.

METHODS

Material

This retrospective analysis has been approved by the Ethics Committee of Shanghai Renji Hospital by the principle of informed consent. Sixty-five HDP patients' complete clinical records were collected, and all patients were delivered to and hospitalized in Renji Hospital after prenatal care. Gestational hypertension criteria were defined in case of the appearance of systolic BP (SBP) ≥140 mmHg and (or) diastolic BP (DBP) ≥90 mmHg after 20 weeks.

The exclusion criteria were as follows: (1) Diagnostic insufficiency; (2) no 24-h proteinuria value record before birth; (3) no birth records (or lost); (4) laboratory examinations insufficiency; (5) presence of any diseases, such as systemic lupus erythematosus, kidney diseases, anti-neutrophil cytoplasmic antibodies, and so on, whose main clinical manifestation was associated with proteinuria.

Adverse pregnancy outcome criteria

Adverse pregnancy outcome was defined as the appearance of any serious complication or maternal or perinatal death.

Maternal adverse pregnancy outcomes that may occur included single organ dysfunction (kidney failure, heart failure, and liver failure), oligohydramnios, Hemolysis-elevated liver enzyme-low platelets (HELLP) syndrome, hypoproteinemia concurrent pleural effusion, pericardial effusion or ascites, abruption, or eclampsia.

Perinatal adverse pregnancy outcomes that may occur included fetal distress, asphyxia, intrauterine fetal death, stillbirth, iatrogenic preterm birth, iatrogenic induction, and fetal growth restriction (FGR).

Statistical analysis

Data analysis was conducted by SPSS 13.0 Software (SPSS Inc., Chicago, IL, USA) according to ACOG guideline.[8] Frequency data were analyzed by Chi-square test, and count data were analyzed by t-test or variance (F)-test; Spearman correlation test was used to detect the association between each diagnostic criteria, its corresponding value, and adverse pregnancy outcomes. Logistic regression was performed to verify the result of Spearman correlation test. A $P < 0.05$ was considered statistically significant.

RESULTS

Patients' baseline information

The study enrolled 65 patients with a mean age of 30.54 ± 5.52 years, ranging from 19 years to 45 years.

In 65 patients, the mean gravidity was 2.050 ± 1.165 and the mean parity was 0.290 ± 0.491. There were 48 primipara, 8 multipara, and 9 cases with a uterine scar. Forty-five patients had no family history of hypertension, while others had a family history of hypertension.

In 65 patients, 48 had regular antenatal examinations, while 11 had irregular antenatal examinations, and 6 did not have an antenatal examination.

Early clinical manifestation included 34 patients with hypertension, 7 patients with proteinuria, 12 patients with hypertension and proteinuria, 4 patients with a headache, visual symptoms, 6 patients with edema, and 2 patients with eclampsia.

The maximum mean SBP was 164.26 ± 18.03 mmHg, while the mean maximum DBP was 107.52 ± 12.71 mmHg. The mean value of 24-h proteinuria was 4.233 ± 4.989 g. Ten patients' 24-h proteinuria value was <0.3 g, and 55 patients' 24-h proteinuria value was ≥0.3 g.

Pregnancy outcome of patients with hypertensive disorder in pregnancy

Adverse pregnancy outcome

Of the 65 HDP patients, 41 patients (63.1%) occurred adverse pregnancy outcomes. And iatrogenic preterm birth was the most common adverse pregnancy outcomes occurred in 30 patients (46.2%); other adverse pregnancy outcomes included pleural effusion or ascites in 20 patients (30.8%), oligohydramnios in 7 patients (10.8%), FGR in 6 patients (9.2%), iatrogenic induction and renal failure in 5 patients (7.7%), and heart failure, liver failure or eclampsia in 3 patients (4.6%).

Deliveries information of patients with hypertensive disorder in pregnancy

The average gestational age at delivery was 35.254 ± 4.109 weeks. According to newborns classification, there were 28 term neonates, 29 preterm neonates, and 8 miscarriage fetuses.

Fifty-four patients received cesarean section, 8 patients were induction birth, and 3 patients were natural vaginal birth.

Diagnostic value of 24-h proteinuria value for preeclampsia according to American College of Obstetricians and Gynecologists guideline

Pregnancy outcome circumstances according to each American College of Obstetricians and Gynecologists guideline's diagnostic criteria (Chi-square test)

In these five diagnostic criteria, according to four separate diagnostic criteria (impaired liver function, elevated serum creatinine [Scr], thrombocytopenia, and cerebral or visual symptoms) for PE, the incidences of adverse pregnancy outcomes were different. All patients with impaired

liver function or renal insufficiency or cerebral or visual symptoms had adverse pregnancy outcomes, and 10 of 11 patients with thrombocytopenia had adverse pregnancy outcomes. Moreover, 38 patients with normal liver function, 36 patients with normal renal function, 31 patients with normal platelet (PLT), and 37 patients without cerebral or visual symptom also had adverse pregnancy outcomes. However, there were no significant differences in the incidence of adverse pregnancy outcomes between patients with normal value and those with abnormal value (impaired liver function: χ^2=0.554, $P = 0.457$; renal insufficiency: χ^2=1.686, $P = 0.194$; thrombocytopenia: χ^2=3.083, $P = 0.079$; and cerebral or visual symptoms: χ^2=1.092, $P = 0.296$). The adverse pregnancy outcomes in HDP patients, separately differed by that 24-h proteinuria value was ≥0.3 g, had a significant difference [χ^2=17.115, $P = 0.000$, Table 1].

Correlation test between diagnostic criteria and adverse pregnancy outcomes
Whether 24-h proteinuria >0.3 g was moderately correlated with adverse pregnancy outcomes (correlation coefficient = 0.557, P = 0.000). Although thrombocytopenia was also associated with adverse pregnancy outcomes, the correlation coefficient was low (r = 0.260, P = 0.036). Impaired liver function (r = 0.168, P = 0.180), renal insufficiency (r = 0.221, P = 0.077), and cerebral or visual symptoms (r = 0.196, P = 0.118) were not related to adverse pregnancy outcomes.

Diagnostic value of each organ function value for preeclampsia
Association between each diagnostic criteria value and adverse pregnancy outcomes in hypertensive disorder in pregnancy
Spearman correlation test was conducted to explore the association between adverse pregnancy outcomes and 24-h proteinuria value, PLT count, liver function (alanine transaminase [ALT] and aspartate transaminase [AST]), renal function (Scr) in HDP patients. The results suggested that 24-h proteinuria value (r = 0.685, P = 0.000), Scr (r = 0.511, P = 0.000), ALT value (r = 0.379, P = 0.002), and AST value (r = 0.579, P = 0.000) were associated with adverse pregnancy outcomes. PLT count (r = −0.203, P = 0.105) and cerebral or visual symptoms (r = 0.196, P = 0.118) were not related to adverse pregnancy outcomes.

Logistic regression correlation analysis was conducted to further validate each confirmed related value, and to draw the regression equation
The results of Logistic regression between adverse outcome and 24-h proteinuria was 0.484 (P = 0.004), with no corresponding constant (β = −0.708, P = 0.074). The corresponding logistic regression equation was as follows:

$$\text{In}\left(\frac{P}{1-P}\right)=0.484X \text{ or } P=\frac{e^{(0.484X)}}{1+e^{(0.484X)}}.$$

Logistic regression results between adverse outcome and other values (Scr, ALT, and AST) were 0.086, 0.053, and 0.167, respectively [Table 2].

Table 1: Pregnancy outcomes situation of 65 patients with hypertensive disorder according to ACOG guideline (n)

Items	Good outcome	Adverse outcome	P
Impaired liver function			0.457
Abnormal	0	3	
Normal	24	38	
Renal insufficiency			0.194
>1.1 mg/dl	0	5	
≤1.1 mg/dl	24	36	
Thrombocytopenia			0.079
<100,000/ml	1	10	
≥100,000/ml	23	31	
Cerebral or visual symptoms			0.296
Abnormal	0	4	
Normal	24	37	
24-h proteinuria value			0.000
≥0.3 g	14	41	
<0.3 g	10*	0	

*Ten patients without impaired organ function. ACOG: American College of Obstetricians and Gynecologists.

Table 2: Logistic regression results between adverse outcome and other values in HDP

Diagnostic criteria values	β	P
Scr value	0.086	0.000
Constant corresponding to Scr value	−4.671	0.001
ALT value	0.053	0.018
Constant corresponding to ALT value	−0.753	0.166
AST value	0.167	0.001
Constant corresponding to AST value	−3.629	0.002

HDP: Hypertensive disorder in pregnancy; Scr: Serum creatinine; ALT: Alanine aminotransferase; AST: Aspartate transaminase.

Diagnostic value of each organ function value for preeclampsia
Association between each diagnostic criteria values and adverse pregnancy outcomes in preeclampsia
Spearman correlation test was conducted to explore the association between adverse pregnancy outcomes and 24-h proteinuria value, PLT count, liver function (ALT, AST), and renal function (Scr value) in PE patients. The results suggested that 24-h proteinuria value (r = 0.521, P = 0.000), Scr value (r = 0.398, P = 0.003), ALT value (r = 0.299, P = 0.027), and AST value (r = 0.501, P = 0.000) were associated with adverse pregnancy outcomes. PLT count (r = −0.096, P = 0.486) and cerebral or visual symptoms (r = 0.164, P = 0.223) were not related to adverse pregnancy outcomes.

Logistic regression correlation analysis was conducted to further validate each confirmed related value, and to draw the regression equation
Logistic regression result between adverse outcome and 24-h proteinuria was 0.325 (P = 0.021), also with no

corresponding constant ($\beta = -0.010$, $P = 0.982$). The corresponding logistic regression equation was as follows:

$$\ln\left(\frac{P}{1-P}\right) = 0.325X \text{ or } P = \frac{e^{(0.325X)}}{1 + e^{(0.325X)}}.$$

Logistic regression results for adverse outcome and other values (Scr and AST) were 0.069, 0.162, respectively [Table 3].

Association between blood pressure values and adverse pregnancy outcomes in preeclampsia and hypertensive disorder in pregnancy

Association between blood pressure values and adverse pregnancy outcomes in hypertensive disorder in pregnancy
The degrees of SBP and DBP were associated with adverse pregnancy outcomes (SBP: $r = 0.413$, $P = 0.001$; DBP: $r = 0.317$, $P = 0.010$). Logistic regression results between adverse pregnancy outcomes and SBP and DBP were 0.096 ($P = 0.009$) and -0.043 ($P = 0.350$) respectively, with corresponding constant of -10.394 ($P = 0.007$).

Association between blood pressure values and adverse pregnancy outcomes in preeclampsia
The degrees of SBP and DSB were associated with adverse pregnancy outcomes (SBP: $r = 0.381$, $P = 0.004$; DBP: $r = 0.270$, $P = 0.046$). Logistic regression results between adverse pregnancy outcomes and SBP and DBP were 0.118 ($P = 0.010$) and -0.073 ($P = 0.165$) respectively, with corresponding constant of -10.105 ($P = 0.028$).

DISCUSSION

Whether proteinuria is essential to the diagnosis of PE? This study found that there was no significant difference in adverse pregnancy outcomes between HDP patients with thrombocytopenia, renal insufficiency, impaired liver function, cerebral or visual symptoms, and patients without those abnormal situations. Therefore, whether the latest diagnostic criteria in ACOG guideline regarding hypertension as the only essential diagnostic criteria for PE remains questionable. There was a statistically significant difference of adverse pregnancy outcomes between patients with proteinuria and those without proteinuria, and adverse pregnancy outcomes had a positive correlation with proteinuria. So proteinuria is a valuable index in the

Table 3: Logistic regression results between adverse outcome and other values in PE

Diagnostic criteria values	β	P
Scr value	0.069	0.009
Constant corresponding to Scr value	−3.261	0.040
ALT value	0.053	0.060
Constant corresponding to ALT value	−0.242	0.718
AST value	0.162	0.008
Constant corresponding to AST value	−3.068	0.033

PE: Preeclampsia; Scr: Serum creatinine; ALT: Alanine aminotransferase; AST: Aspartate transaminase.

management of PE and should still be used as an essential diagnostic criterion for PE. Our data did not support the new diagnostic criteria in ACOG guideline for PE.

Severe proteinuria production coupled with liver cell damage and albumin deficiency cause hypoalbuminemia, increasing the plasma colloid osmotic pressure, blood concentration, inadequate tissue perfusion, and finally leading to a vicious circulation.[9,10] Therefore, patients with impaired liver function or renal insufficiency may also be with the appearance of proteinuria, or even be with increased progression of proteinuria. It was suggested that other organ damage can also accompany with proteinuria. Our study also found that even four cases of patients appeared nervous system or visual symptoms, which should be diagnosed as SPE according to ACOG guideline, but these are not an indication for immediate termination of pregnancy. Moreover, 3 patients had an abdominal cavity or pericardial effusion, with 24-h proteinuria values over 2 g. Also, this study showed that hypertensive patients without proteinuria were also without other organ damage. In summary, it was not recommended diagnostic criteria for PE can be without the appearance of proteinuria.

Spearman correlation test showed that 24-h proteinuria value had an independently positive correlated with PE or HDP, and logistic regression validated the relationship. The logistic equation reflected that the percentage of adverse pregnancy outcomes of HDP or PE patients was nearly 100%, accompanied with increased 24-h proteinuria. As a result, it is also suggested that 24-h proteinuria levels can be used as an independent positive predictor for prognosis and diagnostic indicators of disease exacerbation.

However, the logistic equation also revealed that adverse pregnancy outcomes also occurred even with a low 24-h proteinuria value, which suggested 24-h proteinuria value had a low negative predictive value. A report also pointed out that 17% of patients occurred with eclampsia without proteinuria in 2008.[11] The 23rd edition Williams Obstetrics noted proteinuria may occur later, and even in the onset of eclampsia or the postpartum.[11] Therefore, when simple gestational hypertension (GH) patients (exclude other obstetrics, medical, and surgical diseases affected pregnancy outcome) occurred adverse pregnancy outcomes, there was still a question whether it was accompanied with proteinuria or the onset time of proteinuria. It was speculated that GH or PE was a systemic disease.

In this study, there were some limitations. This study was a retrospective single-center research with limited samples, and a multicenter study with larger samples should be conducted to confirm our results in future.

In conclusion, it is not recommended that the diagnostic criteria for PE can be without the appearance of proteinuria, even in patients with other organ dysfunction. And whether the diagnostic criterion in ACOG guideline was suitable for Chinese patients need to be further verified in a prospective cohort. The degree of proteinuria in PE or GH had a high

positive predictive value for adverse pregnancy outcomes. And it is not recommended that 24-h proteinuria value >5 g was deleted from original diagnostic criteria for PE. The 24-h proteinuria value in PE had a low value of negative predicting, even patients with lower proteinuria also need to be considered with other circumstances, such as high BP.

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Conflicts of interest

There are no conflicts of interest.

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