

# Association of hypoproteinemia in preeclampsia with maternal and perinatal outcomes: A retrospective analysis of high-risk women

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**Background:** The aim of this study was to evaluate maternal and perinatal outcomes in preeclampsia (PE), according to the value of albumin. **Materials and Methods:** Preeclamptic women were retrospectively divided into mild hypoproteinemia (MHP,  $n = 220$ ) and severe hypoproteinemia (SHP,  $n = 79$ ) PE according to the value of albumin. The maternal and perinatal outcomes were evaluated in both groups. **Results:** Two hundred and ninety-nine single pregnancies complicated by PE were included in this study. Gestational age at delivery was earlier in SHP than MHP ( $P < 0.01$ ). Severe hypertension, abnormal liver function, abnormal renal function, ascites, and abruption occurred more frequently in SHP than in MHP ( $P < 0.01$ , 0.03,  $< 0.01$ , 0.01, and 0.04, respectively). Women in SHP had a higher rate of cesarean section than those in MHP ( $P = 0.04$ ). Fetal growth restriction infants were more frequent in SHP than in MHP ( $P < 0.01$ ). The occupancy rate of the Neonatal Intensive Care Unit was higher in SHP than in MHP ( $P < 0.01$ ). **Conclusion:** SHP PE is associated with a higher risk of adverse pregnancy outcome than MHP PE, deserving closer surveillance during pregnancy.

**Key words:** Hypoproteinemia, perinatal, preeclampsia, pregnancy outcome

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## INTRODUCTION

Preeclampsia (PE) is a leading cause of maternal and neonatal mortality and morbidity, complicating 2–5% of all the pregnancies.<sup>[1]</sup> Classically, the presence of proteinuria in women with gestational hypertension is clinically diagnosed as PE and is associated with increased maternal or neonatal morbidity and mortality compared with gestational hypertension.<sup>[2,3]</sup> However, several studies have shown that proteinuria is not a significant predictor of adverse maternal and neonatal outcomes.<sup>[4–8]</sup> The incidence of the disease increased in china, as the opening of the two-child policy, but there was not an indicator of the severe PE.

Severe PE is often combined with hypoalbuminemia; we hypothesize that hypoalbuminemia may serve as an

indicator of the severity of PE. Hypoalbuminemia occurs mainly due to systemic small vessel spasm, increased secretion of angiotensin and damaged and increased permeability of vascular endothelial cells, thereby leading to a large number of proteins and liquid leaking in tissue clearance and a loss of a large number of plasma proteins (especially serum albumin), causing intravascular dehydration. This intravascular dehydration may accelerate the appearance of intravascular lesions, which is thought to be a predisposing factor of the hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome and acute fatty liver of pregnancy. In addition, the reduction of hepatic blood flow due to the production of albumin is decreased. In two recent studies, hypoproteinemia during pregnancy was observed in the PE group in the second trimester before the onset of clinical symptoms, and the authors suggest the possibility of preventing PE by maintaining adequate blood protein levels during early pregnancy.<sup>[9,10]</sup>

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In the present study, we asked whether hypoproteinemia was effective at predicting perinatal risk in women with PE. The aim of our study was to evaluate maternal and perinatal outcomes in women with PE, according to the different value of albumin ( $\leq 25$  g/L and  $< 25$  g/L).

## MATERIALS AND METHODS

In this retrospective cohort study, 299 women from the Maternal and Child Health Hospital of Anhui Province were enrolled between January 2014 and June 2015. The Anhui Medical University Ethics Committee provided ethics approval, and written informed consent was obtained from all participants. Women were divided into two groups: PE with an albumin value of  $>25$  g/L (mild hypoproteinemia [MHP],  $n = 220$ ), PE with an albumin value of  $\leq 25$  g/L (severe hypoproteinemia [SHP],  $n = 79$ ). For the study, SHP was defined as a serum albumin concentration of  $\leq 25$  g/L. Serum albumin was measured at the laboratory of the Maternal and Child Health Hospital of Anhui Province, using the UniCel Dx800 of Beckman Coulter (the United States).

### Definitions

PE was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy: (1) Hypertension: Blood pressure  $\geq 140/90$  mmHg on at least two occasions and at least 4–6 h apart; (2) the severe features, such as severe hypertension, platelet count below  $100,000/\mu\text{L}$ , serum creatinine concentration of  $1.1$  mg/dL, or doubling of the serum creatinine concentration in the absence of other renal disease, levels of liver transaminases elevated to twice the normal concentration, pulmonary edema, new-onset cerebral or visual disturbance; (3) proteinuria: More than 300 mg protein in a 24-h urine collection, or a urinary protein-to-creatinine ratio of 0.3, or a urine dipstick protein grade of 1+ or greater if other methods are unavailable. PE was defined by (1) + (2) or (1) + (3). Moreover, exclusion criteria were: Kidney diseases, preexisting proteinuria, essential hypertension or other maternal chronic conditions (autoimmune diseases, diabetes, etc.), and twin pregnancies.<sup>[2]</sup>

Maternal outcomes were evaluated: Delivery mode (spontaneous vaginal, instrumental vaginal, cesarean section [CS]), eclampsia, HELLP syndrome, hypertension, abnormal liver function, abnormal renal function, ascites, oligohydramnios, thrombocytopenia, and abruptio placenta. For these complex cases, the trial management team reviewed the case and a diagnosis was made by two senior deputy chief physicians or chief physicians, acting independently.<sup>[11,12]</sup>

Neonatal outcomes included: Perinatal deaths, preterm birth ( $<37$  and 28 weeks gestation, spontaneous or iatrogenic),

neonatal asphyxia, and fetal growth restriction (FGR, defined as actual birth weight below 10% for gestational age). In the meantime, birth weight was also assessed.<sup>[11,12]</sup>

All statistical analyses were performed using the statistical package SPSS Inc., Chicago, USA, version 13.0. The comparisons of the continuous variables between the two groups were estimated using the *t*-test or Mann–Whitney test. The comparisons of the categorical variables between the groups were estimated using the Chi-square test or Fisher's exact test. A univariate logistic regression was used to analyze the associations between SHP PE with poor maternal and neonatal outcomes.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Pregnant characteristics

A total of 309 women with singleton pregnancies were identified; ten women were excluded due to incomplete outcome data. The clinical characteristics of 299 singleton pregnancies are shown in Table 1. There was no significant difference in age and body mass index between the two groups of pregnant women ( $P = 0.17$  and  $0.23$ , respectively), shown in Table 1.

### Maternal outcomes

The analysis shows that women with SHP were delivered almost 1.5 weeks earlier than the MHP group ( $P \leq 0.01$ ). In the SHP group, the percentage of CS was higher, and the rate of spontaneous delivery was lower ( $P = 0.04$  and  $0.04$ , respectively). Severe hypertension was more frequent in the SHP group than in the MHP group ( $P = 0.01$  and  $<0.01$ , respectively). Women with SHP were more likely to present with abnormal liver or renal function, ascites, and abruptio placenta than women in the MHP group ( $P < 0.05$ ). These results are reported in Table 2.

**Table 1: Maternal characteristics in mild hypoproteinemia and severe hypoproteinemia preeclampsia**

Characteristics	MHP	SHP	P
<i>n</i>	220	79	/
Maternal age (years), %			
Means $\pm$ SD	28.0 $\pm$ 4.6	29.0 $\pm$ 5.7	0.17
$\square$ 35	22 (10.0)	14 (17.7)	
$<35$	198 (90.0)	65 (82.3)	0.11
Maternal BMI (kg/m <sup>2</sup> ), %			
Means $\pm$ SD	29.9 $\pm$ 4.0	29.3 $\pm$ 3.6	0.23
$<25$	12 (5.5)	6 (8.7)	
25–30	83 (37.7)	33 (47.8)	
30–35	101 (45.9)	25 (36.2)	
$\square$ 35	24 (10.9)	5 (7.2)	0.26
Smokers	0	0	/

/= Statistical analysis is not implemented. MHP = Mild hypoproteinemia; SHP = Severe hypoproteinemia; PE = Preeclampsia; SD = Standard deviation; BMI = Body mass index

### Neonatal outcomes

Neonatal outcomes are presented in Table 3; the short-term neonatal outcome was worse in the SHP group. The average birth weight was significantly lighter ( $2498.1 \pm 866.5$  g) in the SHP group than in the MHP group ( $2940.1 \pm 768.0$  g). Neonates of the women in the SHP group were more likely to have FGR, Neonatal Intensive Care Unit admission, and preterm deliveries ( $P < 0.01$ ).

To further clarify the associations between SHP PE with CS, poor maternal and neonatal outcomes, a univariate logistic regression was performed to analysis. The results show that SHP was a significant risk factor for CS (odds ratio [OR] 2.99, 95% confidence interval [CI] 1.13–7.91), poor maternal outcomes (OR 5.83, 95% CI 3.32–10.24), and poor neonatal outcomes (OR 4.43, 95% CI 2.57–7.62) in PE women [Table 4].

### DISCUSSION

The pathophysiologic mechanisms of PE are unclear; the leading theory is that defects in placental implantation and function ultimately display as the development of PE. Scholars believe that gestational hypertension and preeclampsia are isolate disease processes with different mechanisms, research evidence includes the differential risk factors between hypertension and PE, specific histologic changes in the placenta and kidneys in PE only, the levels of antiangiogenic peptides of placental origin are elevated in PE but not in gestational hypertension, and a far lower circulating volume in PE compared with gestational hypertension.<sup>[7,8,13-15]</sup> PE patients often complicated with multiple organ hypoperfusion, the reduction of hepatic blood flow due to the production of albumin is decreased, thus lead to the gradual development of hypoproteinemia.

In the prognosis, women with chronic and gestational hypertension usually have good outcomes. However, PE represents one-third of cases of severe obstetric morbidity; the mortality associated with PE and eclampsia was about 0.83 per 100,000 maternities.<sup>[16]</sup> Simultaneously, PE is also strongly related with intrauterine growth restriction, neonatal asphyxia, low birth weight, preterm delivery, and neonatal respiratory distress syndrome.<sup>[4,17]</sup> However, a common robust biomarker has not been detected. In this study, we evaluate maternal and perinatal outcomes in women with PE according to the different value of albumin ( $\leq 25$  g/L and  $< 25$  g/L).

Hypoalbuminemia is considered a factor of poor maternal and neonatal outcomes.<sup>[9,18,19]</sup> In this study, SHP was a significant risk factor for CS (OR 2.99, 95% CI 1.13–7.91), poor maternal outcomes (OR 5.83, 95% CI 3.32–10.24), and poor neonatal outcomes (OR 4.43, 95% CI 2.57–7.62) in PE women. The systemic small artery of women with PE was in spasm; protein absorption and utilization in

**Table 2: Pregnancy outcome in mild hypoproteinemia and severe hypoproteinemia preeclampsia**

Variables (%)	MHP	SHP	P
n	220	79	/
Gestational age at delivery (weeks)	38.0±2.5	36.5±2.8	<0.01
CS	183 (83.2)	74 (93.7)	0.04
Urgent CS	83 (45.4)	35 (47.3)	
Elective CS	100 (54.6)	39 (52.7)	0.89
Spontaneous	37 (16.8)	5 (6.3)	0.04
Eclampsia	1 (0.5)	1 (1.3)	0.46
The highest systolic blood pressure during the course of disease (mmHg)	155.8±13.5	161.0±15.8	0.01
The highest diastolic blood pressure during the course of disease (mmHg)	99.8±10.3	105.2±11.7	<0.01
Abnormal liver function	12 (5.5)	11 (13.9)	0.03
Abnormal renal function	4 (1.8)	11 (13.9)	<0.01
Creatinine (μmol/ml)	58.1±21.0	72.3±22.6	<0.01
HELLP syndrome	2 (0.9)	2 (1.3)	0.61
Ascites	5 (2.3)	10 (12.7)	0.01
Platelets $< 100 \times 10^9$ /L	10 (4.5)	6 (7.6)	0.46
Oligohydramnios	18 (8.2)	5 (6.3)	0.78
Abruptio placenta	4 (1.8)	6 (7.6)	0.04

/= Statistical analysis is not implemented. HELLP = Hemolysis, elevated liver enzymes, and low platelets; MHP = Mild hypoproteinemia; SHP = Severe hypoproteinemia; PE = Preeclampsia; CS = Cesarean section

**Table 3: Short-term neonatal outcome in mild hypoproteinemia and severe hypoproteinemia preeclampsia**

Variables	MHP	SHP	P
n	218	79	/
Birth weight (g)			
Mean±SD	2940.1±768.0	2498.1±866.5	<0.01
FGR (%)	13 (6.0)	15 (19.0)	<0.01
Neonatal asphyxia (%)	5 (2.3)	5 (6.3)	0.18
NICU admission (%)	41 (18.8)	33 (41.8)	<0.01
Preterm birth (%)	54 (24.8)	41 (51.9)	<0.01
Intrauterine demise (%)	2 (0.9)	0	/

/= Statistical analysis is not implemented. MHP = Mild hypoproteinemia; SHP = Severe hypoproteinemia; PE = Preeclampsia; SD = Standard deviation; FGR = Fetal growth restriction; NICU = Neonatal Intensive Care Unit

**Table 4: The associations between severe hypoproteinemia preeclampsia with cesarean section, poor maternal and neonatal outcomes**

Variables	MHP	SHP	OR	95% CI
n	220	79	/	/
CS (n)	183	74	2.99	1.13-7.91
Poor maternal outcomes* (n)	39	44	5.83	3.32-10.24
Poor neonatal outcomes* (n)	57	48	4.43	2.57-7.62

\*Abnormal liver or renal function, HELLP syndrome, ascites, oligohydramnios, abruptio placenta; \*FGR, neonatal asphyxia, preterm birth, intrauterine demise,

/= Statistical analysis is not implemented. MHP = Mild hypoproteinemia; SHP = Severe hypoproteinemia; CS = Cesarean section; FGR = Fetal growth restriction; HELLP = Hemolysis, elevated liver enzymes, and low platelets; OR = Odds ratio; CI = Confidence interval

the gastrointestinal tract were affected, often causing the emergence of hypoproteinemia. Hypoalbuminemia indicates that the conditions are further exacerbated in

PE and further affects the function of various organs, such as retinal damage, white matter lesions, pericardial effusion, ascites, and liver and kidney dysfunction.<sup>[10,20]</sup> In our study, the presence of SHP has been associated with increased risk of CS, severe hypertension, abnormal liver or renal function, ascites, and abruptio placenta. The percentage of CS in SHP was 93.7%, higher than in the MHP group. The incidence of abnormal liver or renal function in SHP (13.9%) was significantly higher than in MHP (5.5% and 1.8%, respectively), and the difference was statistically significant ( $P = 0.03$  and  $<0.01$ , respectively).

Placental vascular spasm in PE increases blood flow resistance from mother to the fetus, resulting in chronic fetal hypoxia. With a high number of the mother's protein lost and protein and other nutrient deficiencies, these factors can lead to intrauterine growth restriction and low birth weight.<sup>[9,20,21]</sup> Our results support the pathophysiology described above. Women with SHP PE were more likely to deliver preterm infants (41, 51.9%,  $P < 0.01$ ), lower average birth weight ( $2498.1 \pm 866.5$  vs.  $2940.1 \pm 768.0$  g,  $P < 0.01$ ), FGR (15, 19.0%,  $P < 0.01$ ) than those with MHP PE.

It seems likely that many unknown risk factors may be present in women with PE, and it is unclear whether this finding occurred as a pathophysiology of latent PE or was responsible for it. However, we show here that SHP is a risk factor for women with PE. The main limitation of our study is the limited sample size. Further studies with enlarged samples should be performed to prove our data.

## CONCLUSION

SHP PE is associated with a higher risk of adverse maternal and neonatal outcomes than MHP PE, deserving closer surveillance during pregnancy.

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Nil.

### Conflicts of interest

The authors have no conflicts of interest.

## AUTHORS' CONTRIBUTION

HBC and XTW performed the design and coordinated the study, data collecting, agreed for all aspects of the work, and prepared the manuscript. FT provided assistance in the design, data collecting, analysis, and interpretation of data of the study and participated in manuscript preparation. XDF participated in data collecting and manuscript preparation. All the authors read and approved the content of the manuscript.

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