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# Isolated proteinuria in Chinese pregnant women with pre-eclampsia: Results of retrospective observational study

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## Abstract

**Objective: To evaluate obstetrical, maternal and neonatal outcomes of isolated proteinuria among Chinese pregnant women.**

**Materials and methods: In this retrospective observational study, we have reviewed the medical records of Chinese pregnant women hospitalized in Department of Gynecology and Obstetrics, Renmin Hospital of Wuhan University, China between March 2013 to March 2016 who had new onset isolated proteinuria, and had urine albumin level of more than 300 mg in 24 h. Each Chinese pregnant woman was followed up from the time of admission to the time of discharge after delivery. Obstetrical, maternal and neonatal outcomes were assessed.**

**Result: A total of 758 hospitalized women were screened for suspected hypertensive disorders at our hospital from March 2013 to March 2016 by collecting their 24 h urine protein. Out of 758 women, a total of 92 women were diagnosed with new onset isolated proteinuria, and were followed from the time of admission until delivery and discharge postpartum, and subjected in retrospective analysis. Of these, a total of 18 women developed Pre-Eclampsia (PE) during their pregnancy, and 11 women developed PE during postpartum period. Pregnant women who had progression to PE were due to greater values of proteinuria. We also noted that earlier PE onset was associated with early-onset proteinuria and multiple gestations. Irrespective of PE progression, maternal outcome was found favorable although high levels of proteinuria was associated with increased risk for intrauterine growth restriction and lower Apgar scores. Isolated proteinuria progressing to PE was associated with late PE onset, and did not affect maternal and neonatal outcomes among Chinese mothers.**

**Conclusion: We suggest significant proportion of Chinese women with new onset isolated proteinuria will develop PE after delivery.**

**Keywords:** Pre-eclampsia, Pregnancy, Proteinuria, Chinese women.

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## Introduction

Pre-Eclampsia (PE) is one of most common causes of complications in pregnant women leading to maternal morbidity and mortality [1], and it is the second most common cause of abnormal pregnancy outcome [2]. PE is commonly observed during second trimester of pregnancy, with blood pressure greater than 140/90 mmHg and presence of albumin in urine (usually more than 300 mg in 24 h) [3]. The prevalence of PE ranges from 4% to 7% among pregnant women [4]. In women with mild to moderate PE, generally no symptoms reported. Pregnant women with severe PE often experienced increased blood pressure, headache, and proteinuria [5].

The majority of women presenting with PE also exhibit proteinuria. Although proteinuria may precede PE, it may also appear in pregnancies uncomplicated by hypertensive diseases. The prognosis of pregnancies with isolated proteinuria is favorable and similar to that of healthy controls [6,7]. Nonetheless, other studies found it to be a heralding sign of PE, with the development of more severe PE, compared with that uncomplicated by proteinuria [6-9]. On a molecular level, it has been shown that the concentrations of placental growth factor and soluble FMS-like tyrosine kinase 1 in women with gestational proteinuria are intermediate between those in normal healthy controls and those in preeclamptic women [6,10]. This finding may imply that gestational proteinuria is a

part of the PE continuum-either subclinical or a mild variant of PE.

In China, it remains disputed whether the isolated proteinuria is due to PE or whether it is merely a physiological sign of alternation in kidney function during pregnancy. There are several attempts made to identify predictive biomarkers associated with renal pathology and onset of PE, but have been unsuccessful thus far [6,10-13]. The objective of the present study was to shed light on the maternal and neonatal consequences of isolated proteinuria and assist in recognition of risk factors for isolated proteinuria progressing to PE among Chinese women. The purpose of this study was to examine maternal and neonatal outcomes of isolated proteinuria and define maternal characteristics for progression to PE among Chinese women.

## Materials and Methods

In this retrospective observational study, Chinese pregnant women hospitalized in Department of Gynaecology and Obstetrics, Renmin Hospital of Wuhan University, China between March 2013 to March 2016 were screened for suspected hypertensive disorders by collecting their 24 h urine protein. We reviewed the medical records of all the hospitalized Chinese pregnant women who were diagnosed with new onset proteinuria (defined as a 24 h urine protein of over 300 mg). Institutional ethics committee approval was obtained from Renmin Hospital of Wuhan University, China. All women had routine dipstick measurements during their antenatal visits. All were negative for proteinuria during the first half of pregnancy. The pregnant women with abnormal kidney function at the time of admission and a diagnosis of PE, as determined by the American task forces on hypertension in pregnancy were excluded. We retrospectively followed all pregnant women from time of admission to the hospital to time of delivery and until discharge from hospital postpartum. The data obtained included demographics, obstetrical history, pre-existing maternal conditions, data regarding the index gestation, repeated 24 h protein collections performed during hospitalization, maternal outcomes during pregnancy and the immediate postpartum period, neonatal outcomes immediately after delivery and placental pathology findings. The primary objective was the incidence of maternal and neonatal outcomes in women presenting with isolated proteinuria. Maternal outcomes examined included progression to PE, eclampsia, HELLP (Hemolysis, Elevated Liver Enzymes and Low Platelets), placental abruption, pulmonary edema, disseminated intravascular coagulation and intensive care unit hospitalizations. Neonatal outcomes examined Included Intrauterine Growth Restriction (IUGR), Apgar scores, NICU admission and length of stay at NICU, intrauterine fetal death and prematurity complications. Our secondary objective was to examine the associations between proteinuria severity and maternal and neonatal outcomes.

Spearman's ρ coefficients analysis was performed for ordinal or continuous variables that are not normally distributed. Comparison between women with proteinuria who developed PE and those who did not was performed by two-sided T-tests for continuous variables and by Fisher's exact tests for discrete variables. Data from each patient was coded and analysed using Graph Pad Prism statistical analysis software (version 6.0).

## Results

During the 3 year time period of the study, 758 hospitalized women underwent a 24 h urine protein collection test as part of the workup for suspected hypertensive disorders. Out of 758 hospitalized women, 169 were diagnosed with proteinuria as the results of their 24 h urine protein collection test exceeded 300 mg/24 h. Out of 169 women diagnosed with proteinuria, 94 women diagnosed with new onset isolated proteinuria with normal creatinine values at the time of diagnosis. Of total 94 women with new onset isolated proteinuria, 2 women were lost to follow-up. Thus, a total of 92 women of new onset isolated proteinuria were followed from the time of admission until delivery and discharge postpartum, and were subjected to retrospective analysis. Mean level of proteinuria at the time of diagnosis was 935.6 mg/24 h. Table 1 represents summary of obstetrical characteristics of pregnant women with new onset isolated proteinuria.

Associations between patient characteristics and proteinuria severity are presented in Table 2. We have observed that the established risk factors for pre-eclampsia (primiparity, diabetes, hypertension, history of PE in a previous gestation and obesity) were not found to be risk factors for isolated gestational proteinuria. We observed that the obstetrical characteristics such as earlier gestational age at delivery, Apgar score, gestational age at diagnosis of PE, lower new-born weight were found to be associated with proteinuria severity (Table 2). A comparison between the 29 women who developed PE and those who did not is presented in Table 3. In univariate analyses smoking, previous cesarean surgery, primiparity, type 2 diabetes, body mass index, chronic hypertension, history of PE, maternal age, gestational age and proteinuria at diagnosis were not found to be risk factors for progression to PE. Analysis results showed that the women with higher maximal levels of proteinuria were at greater risk for the development of PE ($P<0.05$), whereas the value of proteinuria at diagnosis was unrelated to PE progression. In our study, PE complications such as eclampsia, placental abruption, pulmonary edema, intrauterine fetal death, disseminated intravascular coagulation were observed. Only one woman was diagnosed with HELLP during gestation. A sub-analysis of the group of 29 women who developed PE during gestation is presented in Table 4. The results suggested that earlier PE onset during pregnancy was associated with an earlier diagnosis of proteinuria ($P<0.005$).

***Table 1.*** *Maternal and obstetrical characteristic of pregnant women with new onset isolated proteinuria.*

| Variables | N=92 (n (%)) | Mean (SD) |
|---|---|---|
| **Maternal characteristics** | | |
| Age (years) | 92 | 32.9 (3.8) |
| Smoking, n (%) | 16 (17.4) | - |
| Primiparity, n (%) | 55 (59.8) | - |
| Type 2 diabetes, n (%) | 15 (16) | - |
| Chronic hypertension, n (%) | 7 (7.6) | - |
| History of PE, n (%) | 9 (9.8) | - |
| Previous cesarean section, n (%) | 16 (17.3) | - |
| **Obstetrical characteristics** | | |
| Proteinuria at diagnosis (mg/24 h) | 92 | 935.6 (133) |
| Maximal proteinuria reached during pregnancy (mg/24 h) | 92 | 1571.6 (921) |
| Gestational age at delivery (Weeks) | 92 | 34 (3.24) |
| Apgar score at 5′ | 92 | 9.3 (1.4) |
| Abbreviation: BMI: Body Mass Index. P<0.05 refers to statistically significant values; P>0.05 refers to no statistically significant values. | | |

***Table 2.*** *Associations between patient characteristics and proteinuria severity.*

| Variables | Proteinuria at diagnosis | | Maximal proteinuria | |
|---|---|---|---|---|
| | Correlation coefficient | P value | Correlation coefficient | P value |
| Maternal characteristics | | | | |
| Maternal Age (years) | -0.01 | >0.05 | 0.03 | >0.05 |
| Weight gain during pregnancy (kg) | 0.01 | >0.05 | -0.05 | >0.05 |
| Smoking | -0.06 | >0.05 | -0.05 | >0.05 |
| Diabetes | 0.06 | >0.05 | 0.03 | >0.05 |
| Chronic hypertension | 0.03 | >0.05 | 0.03 | >0.05 |
| History of PE | 0.05 | >0.05 | 0.02 | >0.05 |
| Previous cesarean section | -0.04 | >0.05 | -0.09 | >0.05 |
| Obstetrical characteristics | | | | |
| Earlier gestational age at delivery (weeks) | 0.38 | <0.05 | 0.49 | <0.05 |
| Apgar score | 0.29 | <0.05 | 0.23 | <0.05 |
| Gestational age at diagnosis of PE (weeks) | 0.24 | <0.05 | 0.27 | <0.05 |
| Lower new-born weight (g) | 0.37 | <0.05 | 0.23 | <0.05 |
| Intrauterine growth restriction | 0.01 | >0.05 | 0.18 | <0.05 |
| Abbreviation: BMI: Body Mass Index. P<0.05 refers to statistically significant values; P>0.05 refers to no statistically significant values. | | | | |

***Table 3.*** *Comparison between women with isolated proteinuria who developed PE to those who did not develop PE.*

| Variables | No PE (N=63) | PE (N=29) | P value |
|---|---|---|---|
| Smoking during pregnancy, n (%) | 7 (11) | 9 (31) | >0.05 |
| Previous cesarean surgery, n (%) | 9 (14) | 7 (24) | >0.05 |

| | | | |
|---|---|---|---|
| Chronic hypertension, n (%) | 3 (5) | 4 (14) | >0.05 |
| History of PE, n (%) | 4 (6) | 5 (17) | >0.05 |
| Type 2 Diabetes, n (%) | 6 (10) | 9 (31) | >0.05 |
| BMI >30 kg/m2, n (%) | 9 (14) | 7 (24) | >0.05 |
| BMI (kg/m2) at diagnosis, mean (SD) | 28.2 (2.1) | 29.7 (2.6) | >0.05 |
| Primiparity, n (%) | 49 (78) | 6 (21) | >0.05 |
| Maternal age (years), mean (SD) | 32.15 (3.1) | 33.82 (4.2) | >0.05 |
| Gestational age at diagnosis (Weeks), mean (SD) | 33.82 (3.8) | 34.02 (4.1) | >0.05 |
| Maximal proteinuria reached during pregnancy (mg/24 h), mean (SD) | 1321.12 (769.2) | 1742.12 (324.1) | <0.05 |
| Proteinuria at diagnosis in mg/24 h, mean (SD) | 931.3 (135) | 939.3 (165) | >0.05 |

Abbreviation: BMI: Body Mass Index. P <0.05 refers to statistically significant values; P >0.05 refers to no statistically significant values.

***Table 4.*** *Risk factors for earlier PE onset in 29 women with isolated proteinuria.*

| Variable | Sample correlation | P value |
|---|---|---|
| Gestational age at diagnosis | 0.81 | <0.05 |
| Type 2 diabetes | 0.07 | >0.05 |

P<0.05 refers to statistically significant values; P>0.05 refers to no statistically significant values.

## Discussion

This was the first retrospective case control study designed to evaluate maternal and neonatal outcomes of isolated proteinuria and define maternal characteristics for progression to PE among Chinese pregnant women. Our finding showed that risk factors associated with PE were not associated with isolated proteinuria or with maximal levels of urinary protein. In contrast to a previous finding, that published study suggested similar risk factors for proteinuria and PE [6]. In this published study, the diagnosis of proteinuria was made according to the insensitive dipstick measurement [6,14], which is now no longer used as a criterion for proteinuria according to the latest guidelines of the American task force on hypertension [6,15].

In our study, we observed that greater values of maximal proteinuria were reached in women who were diagnosed with proteinuria at an earlier gestational age; this is consistent with the finding supported by previous trials that demonstrated increasing proteinuria during the early 3rd trimester [6,16,17]. Although the majority of these women did not go on to develop PE, greater maximal values and greater increments in proteinuria values were associated with greater chances for progression to PE [6]. The presence of isolated proteinuria in itself did not subject the pregnancy to maternal risks and maternal outcome was favorable in all cases. Risk factor for PE progression in multivariate logistic regression analysis was greater values of proteinuria. Although these results inarguably prove that proteinuria is a risk factor for PE, most women with isolated proteinuria do not progress to PE [6]. Our findings are in accordance with a previous study confirming greater PE chances with greater thresholds of proteinuria and reinforce the latest task force recommendations of 2013 that exclude the severity of proteinuria from the criterions describing PE with severe features [6]. In the women with PE onset during pregnancy, earlier diagnoses of isolated proteinuria were associated with an earlier PE onset.

In our study, maternal outcome in women who did not progress to PE was found favorable. A total of 17% (16/92) of women delivered by cesarean section. There were no cases of placental abruption or blood product requirements during and after delivery. Since it is well established that perinatal outcome is more favorable in late-onset PE, as compared to opposed to early-onset PE (<34 weeks), this can explain why neonatal outcome was mostly favorable.

Our study results suggested that the isolated gestational proteinuria is a progressive condition, we therefore recommend to closely follow-up for all pregnant women who experienced signs and symptoms of PE during pregnancy and after delivery. We also recommend to perform routine assessment of fetal. Our recommendation is more significant in women with risk factors for PE progression (i.e. greater values of urinary protein). Future research is still needed to set threshold values of proteinuria that increase the chances for PE progression.

## Conclusion

We conclude that new onset gestational isolated proteinuria is associated with PE in Chinese pregnant women. Our results suggested that to closely monitor all the pregnant women who experienced signs and symptoms of PE during pregnancy.

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