



## Preterm birth, low birthweight, and small for gestational age among women with preeclampsia: Does maternal age matter?

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### ABSTRACT

**Objectives:** To better understand the effects of maternal age on birth outcomes among preeclampsia (PE) patients, we examined the rates of preterm birth, low birthweight, and small for gestational age (SGA) among different age groups and explored whether maternal age was associated with those adverse outcomes.

**Study design:** This is a multicenter retrospective study. Data from 1128 PE patients, including 580 with early onset PE and 548 with late onset PE, were analyzed.

**Main outcome measures:** Maternal age was categorized into three groups: < 25, 25–34, and ≥ 35 years. The outcome variables were preterm birth (< 37 weeks; subgroups: < 28 weeks, 28–33 weeks, and 34–36 weeks), low birthweight (< 2500 g; subgroups: < 1500 g and < 1000 g), and SGA. Logistic regression was used to analyze the associations between maternal age groups and outcomes.

**Results:** In early onset PE, compared with maternal age 25–34 years, maternal age ≥ 35 years was associated with elevated risk for preterm delivery before 28 weeks, and maternal age < 25 years was associated with elevated risk for low birthweight and SGA. When the analysis was restricted to women who underwent cesarean section, elevated risks for preterm birth and/or low birthweight were observed for women younger than 25 years in both early and late onset PE.

**Conclusions:** Among women with PE, maternal age < 25 years could add risk to preterm birth and/or low birthweight. For women with early onset PE, maternal age ≥ 35 years is a risk factor for preterm delivery before 28 weeks.

### 1. Introduction

Preeclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality [1,2]. As a multifactorial disease with pathophysiology not yet fully understood, the only definitive treatment for PE is to end the pregnancy and deliver the fetus and placenta. Based on the timing of disease onset, PE is classified into 2 subtypes, the early onset PE (< 34 weeks) and the late onset PE (≥ 34 weeks) [1–3]. The early onset PE is a life-threatening maternal complication and often has severe maternal and fetal consequences, while late onset PE often results mainly in maternal consequences [4,5].

For women with PE in the preterm phase of pregnancy, expectant management is generally indicated to prolong gestation and improve fetal maturity [6,7]. Delivery will be indicated if maternal or fetal conditions warranting intervention exists. As a consequence, preterm birth (< 37 weeks) is a common outcome of PE [5,8,9]. Since gestational age directly affects fetal weight, and PE is also associated with significant fetal growth restriction [10,11], preterm birth in PE is commonly accompanied with low birthweight and small for gestational age (SGA) [5,8,9]. Bilano et al. (2014) [9] conducted a secondary analysis of the WHO Global Survey on Maternal and Perinatal Health. Data from 24 low and middle-income countries showed that the rates of

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preterm birth in PE patients were 12.28–76.09%, while the rates of low birthweight were ranged from 13.65 to 39.71%. The study of Lisonkova et al. (2013) [5] reported the birth outcomes in early and late onset PE. For early onset PE, 87.8% patients delivered at 20–33 weeks, 7.3% delivered at 34–36 weeks, and 4.9% delivered after 37 weeks. For late onset PE, 23.4% delivered at 34–36 weeks, and 76.6% delivered after 37 weeks. The rates of low birthweight (< 2500 g) and SGA in early onset PE were 86.1% and 32.1%, respectively. And in late onset PE, those rates were 23.4% and 16.1%. Previous studies had revealed that premature delivery, both delivery before 34 weeks and between 34 and 36 weeks could have long term effects on neonate, like the increased risk of neurodevelopmental impairment, respiratory and gastrointestinal complications [12–14]. Similarly, both low birthweight and SGA are predictors for lifelong health [15–17]. Therefore, the high rates of preterm delivery, low birthweight, and SGA in PE patients demonstrated an urgent need for better management strategies.

Identification of high risk patients could allow the initiation of risk specific management and treatment plans. Both young and advanced maternal ages were found to be associated with elevated risk for preterm birth, low birthweight, and SGA [18–20]. For PE patients, whether younger and advanced maternal age indicate higher risks for preterm delivery and low birthweight is less clear. Lamminpää et al. (2012)[21] reported that among PE patients, advanced maternal age ( $\geq 35$  years) was a risk factor for preterm birth before 37 weeks and before 34 weeks. But this study had not investigated the association between young maternal age and preterm birth rate. Also, this study categorized all PE patients into one analysis group, which would mask the differences between early and late onset PE on birth outcomes. Therefore, we conducted the present study. By using retrospective data from 1128 PE patients, we investigated the rates of preterm birth, low birthweight, and SGA among different maternal age groups, and estimated associations between maternal age and risks for those adverse outcomes among patients with early onset and late onset PE.

## 2. Methods

### 2.1. Study population and diagnostic criteria

The study population was women who diagnosed with PE and delivered at least one live-born infant in five Chinese hospitals (Renji Hospital of Shanghai Jiaotong University School of Medicine, Xiangya Hospital of Central South University, Jiangxi Maternal and Child Health Hospital, Xin Hua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Sixth People's Hospital) between January 2014 and December 2016. Anonymous subject data were retrospectively collected from medical records. The study protocol was reviewed and approved by the Medical Ethics Committee of the Xiangya Hospital of Centre South University (reference number: 20170527). The data collection process has been conducted according to the principles expressed in the Declaration of Helsinki and the authors had no access to information that could identify individual participants during and after data collection.

PE was diagnosed by de novo hypertension (systolic blood pressure  $\geq 140$  mmHg and/or diastolic  $\geq 90$  mmHg) after 20 weeks of gestation and the coexistence of one or more of the following new-onset conditions: proteinuria (urinary protein dip sticks  $\geq 2+$  or 300 mg or more in a 24-hour urine sample); other maternal organ dysfunction, including renal insufficiency, liver involvement, neurological complications, and haematological complications; and uteroplacental dysfunction (foetal growth restriction)[3]. PE was classified into early onset (< 34 weeks) and late onset ( $\geq 34$  weeks) [1–3].

### 2.2. Variables

Maternal age was defined as the age of mother in completed years at the time of delivery, and was categorized into three groups: < 25,

25–34, and  $\geq 35$  years. Since it has been suggested that the optimal age for women to have their children is 25–34 years [22], this age group was used as the reference group for logistic regression analysis. The outcome variables were preterm birth (gestational age less than 37 completed weeks), low birthweight (live infant weighting less than 2500 g at birth, regardless of gestational age), and SGA (infant weighting less than the 10th percentile of the sex- and gestational age-specific birthweight reference for China [23]). Preterm births were subdivided according to gestational age: extremely preterm (less than 28 weeks), moderate to severe preterm (28–33 weeks), and late preterm (34–36 weeks) [24]. Subcategories of low birthweight included very low birthweight (less than 1500 g) and extremely low birthweight (less than 1000 g) [25].

The association analyses were adjusted for potential confounding factors [26], including study site, region of residence (urban/rural), gravidity, history of previous pregnancy induced hypertension (PIH, including PE and gestational hypertension), multiple pregnancy, as well as pregnancy complications and coexisting diseases, including gestational diabetes mellitus (GDM), HELLP Syndrome, intrahepatic cholestasis of pregnancy (ICP), systemic lupus erythematosus (SLE), type 2 diabetes, renal disease, cardiovascular disease, thyroid disease, liver disease, and polycystic ovary syndrome (PCOS).

### 2.3. Statistical analysis

Chi-square test or Fisher exact test was used to compare maternal characteristics and birth outcomes between age groups. Binary logistic regressions were used to analyze the associations between maternal age groups and outcomes, using 25–34 years of age as the reference group. Odds ratios (ORs) and their 95%CI were calculated with adjustment for study sites, residence, gravidity, PIH history, multiple pregnancy, GDM, HELLP Syndrome, ICP, SLE, type 2 diabetes, renal disease, cardiovascular disease, thyroid disease, liver disease, and PCOS. To see whether the association between maternal age and low birthweight was mediated by gestational age, ORs with or without adjustment for gestational age were both estimated. Given that cesarean section is a common practice for PE to ensure the safety of the mother and the fetus, resulting a high rate of medically induced preterm birth in PE patients, to see the association between birth outcomes and maternal age among patients who underwent cesarean delivery, additional analysis restricted to this population were also conducted.

Variables with missing data  $\geq 10\%$  were excluded from the analysis. For included variables, all available data were used for analysis and no imputation method has been used. All tests of hypothesis were two tailed with a type 1 error rate fixed at 5%. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

## 3. Results

Data from 1128 PE women (with 1289 live births) were available for analysis. Among them, 580 were diagnosed with early onset PE, and 548 were diagnosed with late onset PE.

Table 1 showed the general characteristics and the rates of pregnancy complications and coexisting diseases in three maternal age groups. For both early onset and late onset PE, gravidity was significantly different among three age groups, elder maternal age had higher rates of multigravida. For late onset PE, the rates of PIH history and GDM were found to be significantly different among age groups, while the  $\geq 35$  years age group had the highest rates of PIH history (9.5%) and GDM (20.2%).

The distributions of gestational age at delivery and birthweight in three age groups were presented in Fig. 1. For early onset PE, most preterm births were occurred during 28–33 weeks, and the < 25 years age group had the highest rate (54.4%) for 28–33 weeks preterm birth. Meanwhile, the  $\geq 35$  years age group had the highest rate for < 28 weeks preterm birth (8.2%). For late onset PE, around 70% patients

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