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Risk of abnormal fetal growth in women with early- and late-onset preeclampsia

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ABSTRACT

Objectives: To investigate the risks of delivering small-for-gestational-age (SGA) and large-for-gestational-age (LGA) infants in women with early- (delivered before 34 weeks of gestation) and late-onset (delivered at or after 34 weeks of gestation) preeclampsia.

Study design: We conducted a retrospective cohort study of 29,494 singleton deliveries after 24 weeks' gestation, excluding pregnancies complicated by fetal anomalies, stillbirths, and prepregnancy diabetes mellitus. Univariate and multivariate logistic analyses adjusted for potential confounding factors, including prepregnancy body mass index (BMI), gestational weight gain (GWG), and gestational diabetes mellitus (GDM), were performed.

Results: Among women who delivered before 34 weeks, significantly more women with preeclampsia delivered SGA infants than women without preeclampsia (50.6% vs. 7.0%; adjusted odds ratio [OR] 16.3; 95% confidence interval [CI] 8.1–32.9). Among women who delivered at or after 34 weeks, women with preeclampsia had higher rates of delivering SGA (25.5% vs. 7.0%) and LGA (13.7% vs. 9.9%) infants than women without preeclampsia. After adjustment for confounding factors, preeclampsia remained a significant risk factor for delivering SGA infants (adjusted OR 5.7; 95% CI 4.6–7.1), but the association between preeclampsia and the delivery of LGA infants was diminished (adjusted OR 0.8; 95% CI 0.6–1.1).

Conclusions: Our results confirm that preeclampsia is associated with SGA and that the association is stronger with early-onset disease. Although women with late-onset preeclampsia had a higher rate of delivering LGA infants, the association between late-onset preeclampsia and LGA is due to confounding factors, such as high prepregnancy BMI, excessive GWG, and GDM, related to maternal metabolic abnormalities.

1. Introduction

Preeclampsia, defined as new onset of hypertension and proteinuria after 20 weeks of gestation, is one of the leading causes of maternal and perinatal morbidity and mortality [1]. Although the exact cause remains unclear, the most recognized predisposing condition to preeclampsia is inadequate transformation of maternal spiral arteries by extravillous trophoblasts during the early stage of pregnancy [2]. As a result, perfusion of the intervillous space is reduced or becomes more variable [3,4], stimulating the placenta to produce and release increased amounts of vasoactive factors into maternal circulation and contributing to exaggerated inflammatory responses and endothelial cell dysfunction in the mother [5,6]. At the same time, a profound change in the flow to the intervillous space may have stress-inducing effects on the villous trophoblasts, leading to suboptimal placental performance. For these reasons, it is generally assumed that preeclampsia is associated with reduced fetal growth [7,8]. Indeed, epidemiological studies have confirmed that women with preeclampsia are at an increased risk of delivering small-for-gestational-age (SGA) infants [9–13].

Independent of SGA infants, several studies have demonstrated that women with preeclampsia have a higher rate of delivering large-for-gestational-age (LGA) infants than normotensive women, and this association became more significant when preeclampsia was diagnosed at later stages of gestation [11–15]. Heterogeneous pregnancy outcomes challenge the hypothesis that preeclampsia is a uniform disease caused by defective trophoblast invasion, impaired intervillous perfusion, and subsequent placental dysfunction. However, it remains debatable whether preeclamptic women are at higher risk for delivering LGA infants, as most prior studies did not adjust for confounders for LGA

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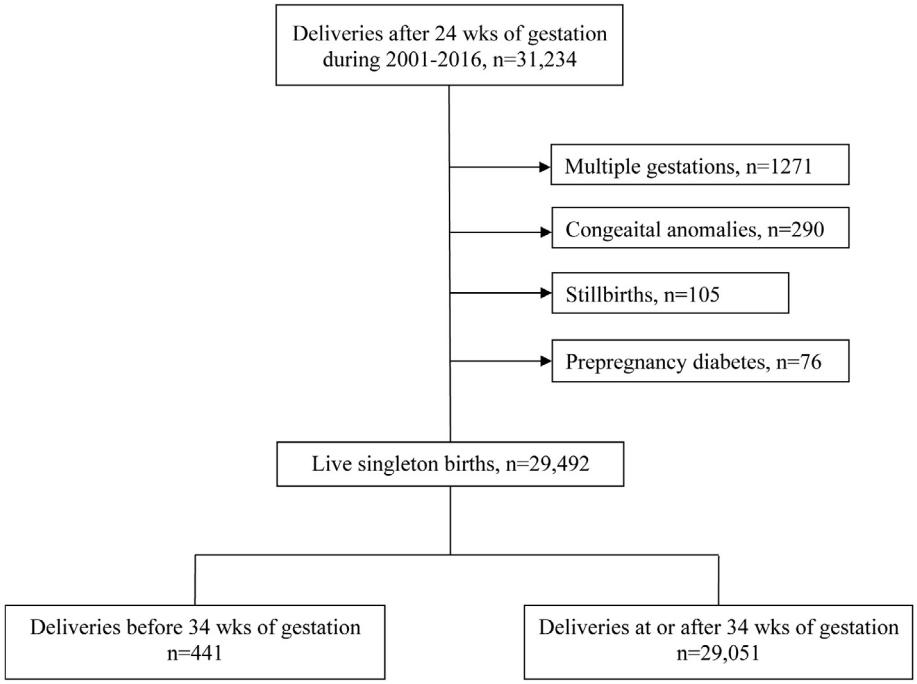
Fig. 1.



infants, such as maternal age, parity, prepregnancy diabetes mellitus (DM) or gestational diabetes mellitus (GDM), or adjusted for only a few. Maternal characteristics such as pregestational overweight or obesity and excessive gestational weight gain (GWG) are strong and common risk factors for preeclampsia and LGA infants [1,16,17]; nevertheless, only a few studies have adjusted for the confounding effects of these factors when the association between preeclampsia and the delivery of LGA infants was evaluated.

In clinical practice, a distinction is made between early and late preeclampsia, with the former defined as the onset of the disease before 34 weeks of gestation and the latter as disease onset at or after 34 weeks of gestation [18,19]. This distinction, though arbitrary, is mainly based on the differences in the impact on neonatal morbidity: early-onset preeclampsia is often associated with fetal growth restriction and higher morbidity, necessitates prompt delivery, and has more histological evidence of inadequate transformation of the spiral arteries [2,19]. As a result, it has been postulated that early- and late-onset preeclampsia are different disease entities with different pathophysiologies [20]. We surmised that the rates of abnormal fetal growth, namely SGA and LGA, differ between women with early- and late-onset preeclampsia and conducted a retrospective cohort study to evaluate the risk for SGA and LGA in women with early- and late-onset preeclampsia, respectively, after adjusting for possible confounding factors.

2. Materials and methods

The data for this study were obtained from Taipei Chang Gung Memorial Hospital's computerized obstetrics database. Demographic characteristics, medical and obstetric histories, and information regarding the course of the index pregnancy and perinatal outcomes were collected. This information was collected by trained personnel through daily abstraction from medical and delivery records and via postpartum interviews, if necessary, to collect supplemental information. Audits of these data were routinely performed every two weeks at departmental meetings. Details of the database have been described previously [16,17,21]. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201700888B0).

As elective termination of pregnancy before 24 weeks of gestation is allowed in Taiwan, we included all deliveries after 24 weeks of completed gestation between January 1, 2001, and December 31, 2016, for analysis (n = 31,234), excluding pregnancies complicated by multiple gestations (n = 1271), fetal chromosomal or structural anomalies (n = 290), and stillbirths (n = 105). Women with prepregnancy DM (n = 76) were also excluded. Overall, 29,492 deliveries were analyzed: 441 deliveries occurring before 34 weeks of gestation and 29,051 occurring at or after 34 weeks of gestation. Gestational age was estimated based on the first day of the mother's last normal menstrual period or, if this date was unknown or uncertain, assigned by ultrasound dating. Fig. 1 depicts the sample selection process.

Preeclampsia was defined as gestational hypertension with proteinuria in previously normotensive women [22]. Gestational hypertension was defined as two recordings of systolic blood pressure (BP) of 140 mmHg or higher or diastolic BP of 90 mmHg or higher at least 4 h apart after 20 weeks of gestation. Proteinuria was defined as excretion of greater than or equal to 300 mg of urinary protein in 24 h or a dipstick reading of at least 1+ for midstream urine specimens if 24-h collection was not available. Women taking antihypertensive medicine or with high BP (a systolic BP of 140 mmHg or greater, a diastolic BP of 90 mmHg or greater, or both) known to precede conception or detected before 20 weeks of gestation were considered to have chronic hypertension. Women with chronic hypertension were diagnosed with superimposed preeclampsia with the following findings: (1) a new-onset of proteinuria after 20 weeks of gestation in women who previously had no proteinuria; and (2) a sudden exacerbation of hypertension, a substantial increase in protein excretion, or a platelet count < 100,000/μL in women with proteinuria before 20 weeks of gestation.

Preeclamptic women with the following conditions were regarded as having severe preeclampsia: BP of 160 mmHg systolic or higher or 110 mmHg diastolic or higher, proteinuria of 5 g or higher in a 24-h urine specimen, oligouria (defined as less than 500 mL in 24 h), cerebral or visual disturbance, pulmonary edema, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia (defined as a platelet count < 100,000/μL), and fetal growth restriction. In this hospital, women with preeclampsia were managed according to the guidelines of the American College of Obstetricians and Gynecologists (ACOG) [22]. Delivery is usually recommended for women with mild