OBSTETRICS

Is a history of preeclampsia associated with an increased risk of a small for gestational age infant in a future pregnancy?

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BACKGROUND: A history of preeclampsia is associated with an increased risk of subsequent preeclampsia, but it is unclear whether women with prior preeclampsia are at increased risk of having a small-for-gestational-age infant in their subsequent pregnancy, even if they do not develop preeclampsia.

OBJECTIVE: The objective of this study was to evaluate whether women with preeclampsia in a prior pregnancy are at increased risk of having a pregnancy complicated by a small-for-gestational-age infant, even in the absence of recurrent preeclampsia.

STUDY DESIGN: This was a secondary analysis of data from 2 multicenter, randomized controlled trials evaluating the role of aspirin in preeclampsia prevention in healthy nulliparas and women at high risk of preeclampsia (ie, with chronic hypertension or a history of preeclampsia). Women who developed preeclampsia in a subsequent pregnancy and women with pregestational diabetes or with a multiple gestation were excluded. The association between a history of preeclampsia and the subsequent birth of a small-for-gestational-age infant was determined in both a univariable and multivariable analysis.

RESULTS: A total of 4052 women were included in the analysis: 2972 healthy nulliparas, 499 women with a history of preeclampsia, and 581 women with chronic hypertension. The frequency of delivery of a small-for-gestational-age infant significantly differed by clinical history (5.1% vs 9.2% vs 12.1% in healthy nulliparas, women with a history of preeclampsia, and women with chronic hypertension, respectively, $P < .001$). Compared with healthy nulliparas, a history of preeclampsia was associated with a significantly increased odds for a small-for-gestational-age infant, even if recurrent preeclampsia did not occur (adjusted odds ratio, 1.48, 95% confidence interval, 1.02—2.17).

CONCLUSION: Even in the absence of recurrent preeclampsia, women with a history of preeclampsia are at a higher risk of delivering a small-for-gestational-age infant in a subsequent pregnancy.

Key words: preeclampsia, prior pregnancy, small-for-gestational-age infant, subsequent preeclampsia

It is well established that a pregnancy complicated by preeclampsia increases the risk of delivery of a small-for-gestational-age infant.[1,2] The pathophysiology is attributable to an underlying propensity toward abnormal placentation.[3] Abnormalities in the development of the placental vasculature lead to diminished uteroplacental-fetal blood flow, which ultimately results in fetal growth restriction.[2-5]

Once women have had preeclampsia, they are at increased risk of recurrent preeclampsia[6] and the attendant risks of an small-for-gestational-age birth.[2] However, it remains unclear whether the risk for an small-for-gestational-age birth also is elevated in women with a history of preeclampsia but without recurrent preeclampsia.

Although the data point toward a higher risk of obstetric complications in women with a history of preeclampsia, including preterm birth, placental abruption, small-for-gestational-age infants and stillbirth, most studies examining this association grouped subsequent pregnancies, without a separate evaluation of the outcomes of successive pregnancies in the absence of recurrent preeclampsia.[7-11] Therefore, our objective was to estimate the frequency of small-for-gestational-age births in women with prior preeclampsia in whom preeclampsia did not recur and to determine whether this frequency was elevated compared with nulliparas. We hypothesized that even in the absence of recurrent preeclampsia, women with a history of preeclampsia are at increased risk of a subsequent small-for-gestational-age birth.

Materials and Methods

This was a secondary analysis of data from the following 2 multicenter, randomized controlled trials conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network: 1) prevention of preeclampsia with low-dose aspirin in healthy nulliparous women[12] and 2) low-dose aspirin to prevent preeclampsia in high-risk women.[13]

These trials examined whether low-dose aspirin therapy, initiated between 13 and 26 weeks, could reduce the incidence of preeclampsia compared with placebo. Because neither trial identified a significant reduction in the incidence of small-for-gestational-age infants in women randomized to aspirin, the present analysis included the entire study group without stratification by study arm. Also, in the present analysis, we excluded women who developed recurrent preeclampsia, had pregestational diabetes, or had a multiple gestation.[14-16]

A woman was defined as having a small-for-gestational-age infant based on a birth weight below the 10th percentile of normative birthweights for

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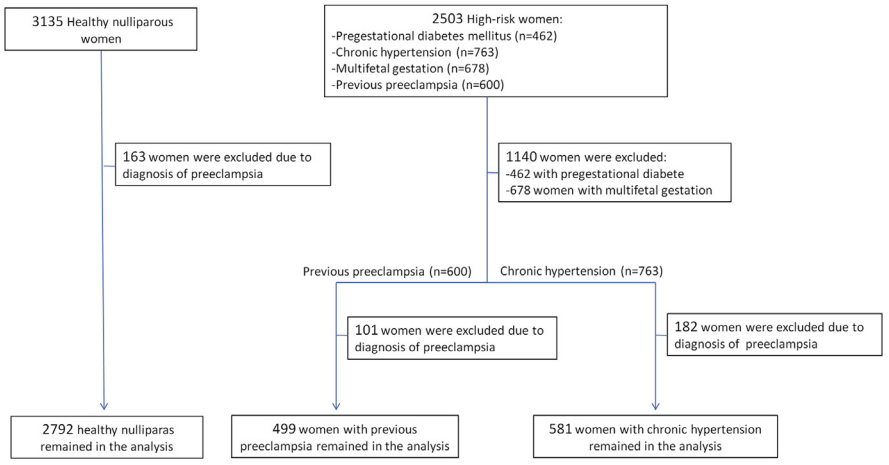
FIGURE
Flow chart detailing exclusion criteria applied to the present analysis



Palatnik. A history of preeclampsia and risk for SGA infant. Am J Obstet Gynecol 2016.

singletons at the time of the original trials.[17] Preeclampsia was defined as hypertension (defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg on 2 occasions 4 hours apart) plus proteinuria (either ≥300 mg per 24 hours or 2+ or more by dipstick on 2 or more occasions 4 hours apart).

Obstetric history was categorized as follows: 1) nulliparous women without chronic comorbidities (healthy nulliparas); 2) women with a history of preeclampsia but no other chronic comorbidities; and 3) women with chronic hypertension. The last group was included to estimate whether women with a history of preeclampsia have a comparable risk for having a small-for-gestational-age infant as women with chronic hypertension.

Secondary maternal outcomes examined included frequency of placental abruption (diagnosed in the presence of vaginal bleeding with uterine tenderness and confirmed by placental pathology) and postpartum hemorrhage requiring blood transfusion. Secondary neonatal outcomes examined included gestational age at delivery and the frequencies of Apgar score <7 at 5 minutes, intensive care unit admission, and perinatal death (defined as any fetal or neonatal death after 23 weeks of gestation).

All analyses were performed with Stata version 12.0 (StataCorp, College Station, TX). All tests were two tailed and $P < .05$ was used to define statistical significance. Univariable comparisons were conducted with χ^2, Fisher exact, or one-way analysis of variance, as appropriate. Multivariable logistic regression was used to estimate the independent association between a history of preeclampsia (without recurrent preeclampsia) and delivery of a small-for-gestational-age infant in a subsequent pregnancy. Potential confounding variables were entered into the regression equation if they differed between groups in univariable analysis at a level of $P < .05$.

This study used publicly available deidentified data and was considered exempt by the Institutional Review Board at Northwestern University.

Results

A total of 5638 women were enrolled in the original trials. After exclusion of women with pregestational diabetes (n = 462), women with multifetal gestation (n = 678), and women who developed preeclampsia in a current pregnancy (n = 446), 4052 women remained eligible for analysis. Of these, 2972 (73.3%) were healthy nulliparous women, 499 (12.3%) had a prior pregnancy complicated by preeclampsia, and 581 (14.3%) women had chronic hypertension (Figure).

Maternal and neonatal characteristics of the study population, stratified by obstetric history, are depicted in Table 1. Women in all 3 risk groups differed in age, body mass index, race/ethnicity, education, marital status, tobacco use, and the presence of gestational diabetes.

Pregnancy outcomes are shown in Table 2. Compared with healthy nulliparas, the frequency of a small-for-gestational-age infant was significantly higher among women with a history of preeclampsia and was similar to the frequency of a small-for-gestational-age infant in pregnancies complicated by chronic hypertension.

Mean birthweight also was significantly lower among women with a history of preeclampsia compared with healthy nulliparas. Other neonatal secondary outcomes such as preterm delivery, perinatal death, Apgar score <7 at 5 minutes, and neonatal intensive care unit admission were more frequent among women with a history of preeclampsia compared with healthy nulliparas. The frequency of placental abruption was higher among women with history of preeclampsia compared with the healthy nulliparous women.

These observed adverse neonatal and maternal adverse outcomes were similar between the healthy nulliparous women and those with chronic hypertension. There were no differences in postpartum hemorrhage requiring transfusion or maternal deaths between the groups.

Compared with healthy nulliparas, after adjusting for potential confounding variables in a multivariable regression, a history of preeclampsia was significantly more likely to be associated with a delivery of a small-for-gestational-age infant (Table 3). Similarly, the risks of preterm delivery (odds ratio, 2.25, 95% confidence interval, 1.69−3.00) and neonatal intensive care unit admission (odds ratio, 1.71, 95% confidence interval, 1.23−2.39) also were significantly increased among women with a history of preeclampsia. After a multivariable analysis, the other maternal and neonatal outcomes were not significantly

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