Preeclampsia and Retinopathy of Prematurity in Preterm Births

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**Keywords:** preeclampsia, retinopathy of prematurity, preterm births

**Abbreviations:**  
aOR—adjusted odds ratio  
CI—confidence interval  
IVH—intraventricular hemorrhage  
PIGF—placental growth factor  
ROP—retinopathy of prematurity  
sFlt1—fms-like tyrosine kinase 1  
sEng—soluble endoglin  
SGA—small for gestational age  
VEGF—vascular endothelial growth factor

**Dr Zhang contributed to the conception, design, acquisition of data, analysis, and interpretation of data; Dr Yu conducted data analysis and drafted the manuscript; Dr Branch contributed to data acquisition; Drs Zhang, Karumanchi, and Branch revised the manuscript critically for important intellectual contents; and all authors approved the final version to be published.**

**WHAT'S KNOWN ON THIS SUBJECT:** Preterm infants are at a high risk for retinopathy of prematurity (ROP). Several postnatal factors are well known to be associated with ROP. However, the relationships between antenatal or maternal risk factors and ROP are poorly understood.

**WHAT THIS STUDY ADDS:** This study used a large cohort database to study the influence of maternal gestational hypertension and preeclampsia on ROP in preterm infants. The results showed that preeclampsia, but not gestational hypertension, was associated with a reduced risk of ROP in preterm births.

**Abstract**

**Objective:** The relationship between gestational hypertension, preeclampsia, and the risk of retinopathy of prematurity (ROP) remains unclear. Thus, we used a large cohort database to study the influence of maternal gestational hypertension and preeclampsia on the occurrence of ROP in preterm infants.

**Methods:** We used data from a previous retrospective cohort study that includes 25,473 eligible preterm neonates. We examined the association between gestational hypertension, preeclampsia, and ROP while controlling for potential confounders by multiple logistic regression analysis.

**Results:** Of the 8758 early preterm infants (gestational age <34 weeks), 1024 (11.69%) had ROP, while of the 16,715 late preterm infants, only 29 (0.17%) had ROP. After adjusting for confounders, preeclampsia was associated with a significantly reduced risk of ROP (adjusted odds ratio [aOR], 0.65; 95% confidence interval [CI], 0.49–0.86 for early preterm birth; aOR, 0.10; 95% CI, 0.01–0.93 for late preterm birth; aOR, 0.66; 95% CI, 0.50–0.87 for all preterm births). Gestational hypertension was not significantly associated with ROP at early or late preterm births.

**Conclusions:** Preeclampsia, but not gestational hypertension, was associated with a reduced risk of ROP in preterm births. *Pediatrics* 2012;130:e101–e107
Preterm infants are at a high risk for developing retinopathy of prematurity (ROP), a multifactorial, severe, vaso-proliferative retinal disorder that may lead to blindness. With the increasing survival rate of preterm infants, ROP has become a leading cause of childhood blindness. Several postnatal factors, including low birth weight, low gestational age, male gender, and supplemental oxygen therapy, are well known to be associated with the development of ROP. However, the relationships between antenatal or maternal risk factors and ROP are poorly understood.

Gestational hypertension and preeclampsia are hypertensive disorders in pregnancy occurring after 20 weeks of gestation. These disorders occur in about 2% to 7% of pregnancies worldwide. Recent studies suggest that mothers with preeclampsia have elevated levels of circulating angiogenic factors, such as the soluble fms-like tyrosine kinase 1 (sFlt1) and endoglin (a co-receptor of transforming growth factor-1) and reduced levels of bioactive proangiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF).

Alterations in circulating angiogenic factors are more dramatic in subjects with preterm preeclampsia and in preeclampsia complicated by fetal growth restriction. Gestational hypertension when it occurs remote from term, is thought to be milder variant of preeclampsia, and has also been associated with a modest alterations in circulating angiogenic factors.

A role for angiogenesis and, in particular, VEGF signaling in the pathogenesis of ROP has been clearly established. Because ROP is a relatively proangiogenic state, an antiangiogenic state in mothers with gestational hypertension/preeclampsia might protect the infant for ROP. The few studies in which these possible associations have been investigated have reported conflicting conclusions. Zayed et al showed no associations between maternal new-onset gestational hypertension and ROP severity score at the examination when ROP was most severe. In contrast, Filho et al reported that preeclampsia was associated with a reduced risk for severe ROP by 80% in very low birth weight (birth weight ≤1500 g) and very preterm birth (gestational age ≤32 weeks) infants. However, the study by Filho et al included only 324 patients, and 7.4% of them had severe ROP. Thus, a possible association between gestational hypertension, preeclampsia, and ROP has not been adequately investigated across the full spectrum of preterm births. We explored the influence of maternal gestational hypertension and preeclampsia on the occurrence of ROP in preterm births using data from a large multicenter study.

**METHODS**

The Consortium on Safe Labor included 12 clinical centers (with 19 hospitals) across 9 American College of Obstetricians and Gynecologists US districts. A total of 228,688 deliveries with 233,844 newborns between 2002 and 2008 were included in the study; 87% of the births occurred between 2005 and 2007. All the births at 23 weeks’ gestation or later in these institutions were included. Participating institutions extracted detailed information from their electronic medical records on maternal demographic characteristics, medical history, reproductive and prenatal history, labor and delivery summary, and postpartum and newborn information. Information from the neonatal intensive care unit was linked to the newborn records. Data on labor progression were extracted from the electronic labor database, and maternal and newborn discharge summaries (in International Classification of Diseases, Ninth Revision, Clinical Modification codes) were linked to each delivery. This project was approved by the institutional review boards of all participating institutions. Data transferred from the clinical centers were mapped to predefined common codes for each variable at the data coordinating center. Data inquiries, cleaning, recoding, and logic checking were performed. To validate data, eligible charts were selected, and investigators were asked to recollect data with chart abstraction done by hand. We compared the hand-collected information from the medical charts with the downloaded from the electronic medical records and found that the electronic data were very accurate.

In the current analysis, the following maternal variables were used: maternal age, gravidity, parity, race, smoking during pregnancy, use of alcohol and illicit drugs, number of fetuses, diabetes, renal disease, type of onset of labor (spontaneous and induced), and mode of delivery. Postnatal variables included gestational age, birth weight, gender, small for gestational age (SGA) (<10th percentile), Apgar score at 5 minutes, resuscitation in delivery room, intraventricular hemorrhage (IVH), ROP, and neonatal blood transfusion. ROP was defined as a clinical diagnosis in the neonatal intensive care unit without recorded zone and stage. Hypertensive disorders were clinically classified as chronic hypertension, gestational hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, and unspecified hypertension as defined by American College of Obstetricians and Gynecologists. Preterm birth was further divided as early (23–33 weeks, inclusive) or late (34–36 weeks, inclusive).

The original study included 228,688 births. To avoid intraperson correlation, we only used the first birth of a woman in this study (N = 206,969). Among them, 26,990 women had preterm birth defined as gestational age
<37 weeks. We further excluded women with the following conditions: preexisting diabetes, chronic hypertension, preeclampsia superimposed on chronic hypertension, unspecified hypertension, renal disease, and fetal death. There were 22,518 women and 25,473 newborns remaining for analysis.

We first compared maternal and newborn characteristics in terms of exposure (normotensive, gestational hypertension, preeclampsia/eclampsia) and outcomes (ROP or not) separated by early and late preterm birth, respectively. Student t test and χ² test were used for continuous and categorical variables, respectively. We included variables that were statistically significantly associated both the exposure and outcome in multiple logistic regression models. All tests were 2-sided with α = .05, and all statistical analyses were performed by using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

The occurrences of maternal gestational hypertension and preeclampsia in all preterm infants were associated with lower gravidity and parity, higher prepregnancy BMI, white race, non-smoker status, and less use of illicit drugs. In late preterm births, the occurrences of maternal gestational hypertension and preeclampsia were associated with gestational diabetes. In addition, maternal preeclampsia was associated with older maternal ages (Table 1).

Table 2 shows that of the 8758 early preterm infants (<34 weeks), 1024 (11.69%) had ROP, while of the 16,715 late preterm infants (34–36 weeks), only 29 (0.17%) had ROP. In early preterm births, ROP was associated with lower frequencies of gestational hypertension and preeclampsia, older maternal age, more African Americans, triplets, less likely to have had alcohol use, induced labor, shorter gestation, lower birth weight, higher percentages of SGA and Apgar score <7, more female infants, more likely to have used intubation and blood transfusions, and higher incidence of IVH. Among late preterm infants, ROP was associated with being African American, lower percentage of gestational hypertension and preeclampsia, shorter gestational age, lower birth weight, higher percentage of SGA, more likely to have used intubation and blood transfusions, and IVH.

Table 3 shows the associations between gestational hypertension, preeclampsia, and risk of ROP after adjusting for gestational age at delivery, mode of delivery, number of fetuses, race, BMI at delivery, birth weight, gender, blood transfusion, congenital anomalies, and IVH. Preeclampsia had a significantly and consistently reduced risk of ROP. The overall relative risk was 0.66 (95% confidence interval [CI], 0.50–0.87) for preeclampsia and 0.85 (95% CI, 0.54–1.34) for gestational hypertension. It appears that the earlier the delivery, the greater the protective effect of preeclampsia. In later preterm births, due to the very low incidence of ROP, the results were unstable.

DISCUSSION

Our study results show that preeclampsia is associated with a significantly lower risk of ROP. While our finding is consistent with a study by Filho et al in which preeclampsia was protective from severe ROP in early preterm infants, the current study, based on a large population, further examined gestational hypertension and included all preterm infants. In addition, our study confirms that low gestational age and birth weight are the most important risk factors for ROP. Clinic risk factors, such as Apgar score <7, use of intubation, blood transfusions, and IVH, were independent risk factors for ROP, as reported by others.

Preeclampsia is a major obstetric problem and significant source of maternal and neonatal morbidity and mortality. Some studies suggested that the incidence of preeclampsia has increased 40% in recent years. Still, few studies have been published to determine the associations of these conditions with ROP, and the report results are conflicting. Zayed et al showed that no associations were found between gestational hypertension and ROP severity score. Holmstrom et al, in a population-based study, reported that preeclampsia was predictive of ROP in very low birth weight infants, whereas Seiberth et al showed that preeclampsia was significantly associated with a reduced risk of ROP. Shah et al reported that preeclampsia reduced the risk for any stage of ROP by 60% in early preterm infants (<32 weeks). The findings from Seiberth and Filho were similar to ours (aOR, 0.66 for all preterm births and 0.58 in births <32 weeks).

A major pathogenic mechanism of retinal neovascularization in ROP appears to be the deregulated overproduction of VEGF, an endothelial cell mitogen that also enhances vascular permeability. sFlt1, a VEGF inhibitor, can bind VEGF and prevent it from signaling through its receptors. Furthermore, in a murine model of proliferative retinopathy, it has been shown that sFlt1 reduces retinal neovascularization by ~50%. Recently, the monotherapy with intravitreal bevacizumab, an anti-VEGF agent, has shown a significant benefit for zone I of ROP in infants. Interestingly, in preeclampsia, maternal antiangiogenic factors such as sFlt1 and soluble endoglin (sEng) have been reported to be markedly elevated. We found that preeclampsia was a protective factor...
<table>
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<th>Characteristic</th>
<th>Normotensive (n = 6399)</th>
<th>Gestational Hypertension (n = 255)</th>
<th><em>P</em></th>
<th>Preeclampsia (n = 805)</th>
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<tr>
<td>Age, mean y (SD)</td>
<td>27.3 (6.7)</td>
<td>26.6 (6.5)</td>
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<td>2.8 (2.0)</td>
<td>2.2 (1.5)</td>
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<td>2.4 (1.8)</td>
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<td>Parity, mean No. (SD)</td>
<td>1.1 (1.4)</td>
<td>0.7 (1.2)</td>
<td>&lt;.0001</td>
<td>0.7 (1.2)</td>
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<td>Pre-BMI, mean kg/m² (SD)</td>
<td>25.4 (6.3)</td>
<td>27.6 (7.7)</td>
<td>.0006</td>
<td>27.1 (6.9)</td>
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<td>Race, No. (%)</td>
<td>2429 (38.0)</td>
<td>98 (37.6)</td>
<td>397 (49.3)</td>
<td>6275 (47.2)</td>
<td>722 (59.2)</td>
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<td>Smoker, No. (%)</td>
<td>767 (12.0)</td>
<td>26 (10.2)</td>
<td>.39</td>
<td>41 (5.1)</td>
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<td>Alcohol use, No. (%)</td>
<td>195 (5.0)</td>
<td>4 (1.6)</td>
<td>.18</td>
<td>22 (2.7)</td>
<td>.66</td>
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<td>Illicit drugs, No. (%)</td>
<td>353 (6.1)</td>
<td>3 (1.3)</td>
<td>.003</td>
<td>16 (2.0)</td>
<td>&lt;.0001</td>
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<td>Mode of delivery, No. (%)</td>
<td>5331 (83.3)</td>
<td>217 (85.1)</td>
<td>687 (85.3)</td>
<td>11 909 (89.5)</td>
<td>1040 (85.3)</td>
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<td>Onset of labor, No. (%)</td>
<td>5729 (89.5)</td>
<td>172 (67.5)</td>
<td>608 (75.7)</td>
<td>10 202 (78.7)</td>
<td>654 (53.7)</td>
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<td>Medical disorders, No. (%)</td>
<td>2152 (33.6)</td>
<td>132 (51.8)</td>
<td>444 (55.2)</td>
<td>2362 (21.5)</td>
<td>331 (27.2)</td>
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* Missing subjects for categorical variables are not included in the analysis.  
* Comparison between preeclampsia and normotensive groups.

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TABLE 1 Characteristics of Mothers With Early (<34 wk) and Late Preterm Births (34–36 wk)
for ROP in preterm infants. We speculate that elevated antiangiogenic factors produced by the placenta into the systemic circulation may also have effects in the fetus.

There could be several pathways that may lead to a higher fetal exposure to antiangiogenic factors. First, we know that hypoxic response is central to both preeclampsia and ROP pathogenesis. If there is genetic tendency by the fetus to make more antiangiogenic factors (sFlt1, sEng) in response to hypoxia, both the placenta (fetal tissue) and the retina make more antiangiogenic factors. In turn, this may lead to more preeclampsia and likely less ROP. Second, elevated maternal levels of antiangiogenic factors (sFlt1, sEng) may cross through the placenta to enter the fetal circulation. However, clinical studies do not support this hypothesis. Third, the fetus may be exposed to antiangiogenic factors via the amniotic fluid that surrounds the fetus. Indeed, amniotic fluid of preeclamptics serves as a rich source of both sFlt1 and sEng. We hypothesize that these antiangiogenic factors in the amniotic fluid may be absorbed via the exposed cornea epithelium to the retina, which in turn may protect from retinopathy. While we do not know the precise mechanisms, we hypothesize that the antiangiogenic factors (sFlt1, sEng) may attain an effective concentration in the eyes to interfere with retinal vascular development. In addition, Yelumalai et al suggested that plasma levels of sFlt1 were elevated in preeclampsia, although it was not significantly increased in the patients with gestational hypertension. Hirashima et al found that sFlt1/PlGF ratio was modestly elevated in gestational hypertension, but significantly lower than in patients with preeclampsia. These data suggest that gestational hypertension may be a milder subclinical variant of...
preeclampsia and may explain why the reduced risk of ROP was very significant in preeclampsia but not in gestational hypertension.

Ours is a unique, large, cohort study of preterm infants with ROP born to mothers with gestational hypertension or preeclampsia. However, the limitations are worth noting. The diagnosis of ROP in our study was based on clinical record before discharge. This may explain why the incidence of ROP in our study was somewhat lower than that in a previous report. The incidence of any stage of ROP was 29.9% among births ≤32 weeks and <1500 g in a previous study but the corresponding rate was 22.9% in our study. However, the potential under-reporting of ROP in our study may not have substantially biased our results. For example, the aOR for the association between preeclampsia and ROP was 0.58 (95% CI, 0.43–0.79) in our study versus 0.41 (95% CI, 0.20–0.82) in the study by Filho et al. In addition, our study does not have information on ROP stages and zones, precluding additional analysis. Despite these limitations, our large multicenter study confirms that maternal preeclampsia is associated with a significantly reduced risk of ROP in preterm births. Future studies elucidating the mechanisms of these findings may foster better understanding of retinal angiogenesis in health and in disease.

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**Preeclampsia and Retinopathy of Prematurity in Preterm Births**
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