Maternal Preeclampsia Predicts the Development of Bronchopulmonary Dysplasia

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Objective To test the hypothesis that exposure to preeclampsia is associated with an increased risk of bronchopulmonary dysplasia (BPD).

Study design A prospective cohort study of 107 babies born between 23 and 32 weeks gestation, collecting maternal, neonatal, and placental data.

Results Of the 107 infants studied, 27 (25%) developed BPD. The bivariate odds ratio (OR) for the relationship between pre-eclampsia and BPD was 2.96 (95% confidence interval [CI] = 1.17 to 7.51; $P = .01$). When controlling for gestational age, birth weight *z*-score, chorioamnionitis, and other clinical confounders, the OR of developing BPD was 18.7 (95% CI = 2.44 to 144.76). Including the occurrence of preeclampsia, clinical chorioamnionitis, male sex, and maternal tobacco use in addition to gestational age and birth weight *z*-score accounted for 54% of the variability of the odds of developing BPD.

Conclusions BPD is increased for infants exposed to preeclampsia. This has possible implications for the prevention of BPD with proangiogenic agents, such as vascular endothelial growth factor. *(J Pediatr 2010;156:532-6)*.

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Preeclampsia is increasingly understood to be a disease mediated by an altered angiogenic state.[1] High levels of antiangiogenic factors, such as soluble vascular endothelial growth factor (VEGF) receptor 1 (sVEGFR-1, also known as sFLT-1)[2-4] and soluble endoglin,[4,5] and low functional levels of circulating angiogenic factors, including free maternal VEGF and placental growth factor (PlGF),[3,4,6,7] are associated with preeclampsia. This antiangiogenic environment is shared by the fetus.[8] Cord blood VEGF and PlGF levels are decreased, and sVEGFR-1 level is increased, in babies born to mothers with preeclampsia.[8] There also is evidence of a postnatal association between preeclampsia and VEGF, which is decreased in the tracheal aspirates of preterm babies born to mothers with preeclampsia.[9] How exposure to an antiangiogenic environment may influence fetal development or postnatal health is unclear, however.

An appropriate angiogenic state is required for normal pulmonary vascular development and airway branching, both of which are critical to normal lung development.[10] Adequate VEGF signaling is needed to maintain the alveolar structure of the lungs.[11,12] Preterm infants who develop bronchopulmonary dysplasia (BPD) have lower concentrations of VEGF in tracheal aspirates[9] and higher concentrations of the antiangiogenic growth factor endostatin in cord blood[13] compared with those who do not develop BPD. sVEGFR-1, a soluble VEGF receptor produced during pregnancy,[14,15] negatively regulates angiogenesis by capturing VEGF and PlGF, another member of the VEGF family. sVEGFR1 is greatly increased during preeclampsia, leading to the decreased maternal and fetal VEGF and PlGF levels. Because preeclampsia represents an antiangiogenic state, we hypothesized that babies born to mothers with preeclampsia would be at increased risk of developing BPD due to impaired lung development.

Methods

We conducted a prospective cohort study of 107 consecutively delivered inborn preterm infants born between 23 and 32 completed weeks gestation between September 11, 2006 and March 27, 2008. Maternal data were abstracted from the obstetric medical record. Information on infant outcome was extracted prospectively from the medical record and supplemented by questions to the medical team caring for the infant. This research was approved by the Investigational Review Board of Brigham and Women's Hospital.

BPD	Bronchopulmonary dysplasia	pPROM	Preterm premature rupture of membranes
CI	Confidence interval		
iNO	Inhaled nitric oxide	PVL	Periventricular leukomalacia
IUGR	Intrauterine growth retardation	RDS	Respiratory distress syndrome
IVH	Intraventricular hemorrhage	ROP	Retinopathy of prematurity
NEC	Necrotizing enterocolitis	sVEGF-1	Soluble vascular endothelial growth factor receptor 1
OR	Odds ratio		
PIGF	Placental growth factor	VEGF	Vascular endothelial growth factor

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Table I. Clinical characteristics

Characteristic	Total sample (n = 107), median (25th, 75th quartiles)	BPD (n = 27), median (25th, 75th quartiles)	Non-BPD (n = 80), median (25th, 75th quartiles)	*P* value*
Maternal age, years	33 (27, 36)	33 (29, 36)	33 (27, 36)	.91
Gravidity	2 (1, 3)	2 (1, 3)	1.5 (1, 3)	.59
Parity	0 (0, 1)	0 (0, 1)	0 (0, 1)	.99
Gestational age, weeks	29 (27, 31)	26 (25, 27)	30 (28, 32)	.001
Birth weight, g	1370 (920, 1650)	800 (600, 1020)	1485 (1170, 1740)	.001
Birth weight *z*-score	-0.07	-0.47	0.06	.10

*Rank-sum test.

Maternal Data

Gestational age was defined according to the following hierarchy. Dating according to embryo transfer for in vitro fertilization was preferred over a firm last menstrual period with confirming first or second trimester ultrasound, and either of these 2 methods were preferred over a pregnancy dated solely by second trimester ultrasound.

We compared preterm deliveries due to preeclampsia to those due to spontaneous indications. Preeclampsia was defined as new-onset hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg in 2 measurements made more than 6 hours apart) in a formerly normotensive patient, accompanied by proteinuria of at least 300 mg in 24 hours.[16]

Indications for spontaneous preterm delivery were preterm labor, preterm premature rupture of membranes (pPROM), cervical insufficiency, and abruption.[17] Preterm labor was defined as progressive cervical change in the setting of regular uterine contractions. pPROM was defined as clinically confirmed amniorrhexis occurring before the onset of regular uterine contractions. Cervical insufficiency was defined as the presence of an advanced cervical exam absent uterine activity. Placental abruption was defined as the presence of clinically significant vaginal bleeding with or without uterine activity on presentation. Chorioamnionitis was defined as the presence of one or more of the following conditions: maternal fever > 100.6°F, maternal or fetal tachycardia, and fundal tenderness.[18]

In our institution, betamethasone is the only antenatal steroid used. It is administered in the standard fashion as two 12-mg intramuscular injections given 24 hours apart. A course of betamethasone is defined as the period from the first dose to 24 hours after the second dose.

Neonatal Information

BPD, the primary infant outcome of interest, was defined as the use of supplemental oxygen at 36 weeks postmenstrual age. Birth weight was estimated as a gestational age–specific *z*-score. Other infant outcome variables included respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP). Data on infections and mortality also were collected. Race is not routinely documented in the medical record.

Statistical Analysis

Because we could not be assured of the underlying distribution of the respective variables, we choose a conservative nonparametric analysis. Continuous variables are reported, with median and interquartile range. Continuous variables were compared using the rank-sum test, and categorical variables were compared using the χ^2 test. Multivariate logistic regression was used to estimate the odds ratio (OR) of BPD after controlling for relevant clinical characteristics. Potential confounding variables for the relationship between BPD and preeclampsia were selected when a bivariate *P* value was < .25.[19]

Results

We enrolled 107 mother–infant pairs (Table I). Indications for delivery included preeclampsia (n = 29; 27.1%), preterm labor (n = 35; 32.7%), pPROM (n = 29; 27.1%), cervical insufficiency (n = 10; 9.4%), and placental abruption (n = 4; 3.7%). A total of 27 (25.2%) babies met the criteria for the diagnosis of BPD. Maternal age, gravity, and parity were equivalent in the group with BPD and the group without BPD. As expected, infants who eventually developed BPD tended to be both born at significantly earlier gestational ages and lower birth weights than those who did not develop BPD. The birth weight *z*-scores were similar for the 2 groups (-0.47 and 0.06, respectively; *P* = .10).

The infants who developed BPD and those who did not did not differ in terms of sex, antenatal medication exposure, gestational diabetes status, maternal smoking, or the presence of clinical chorioamnionitis (Table II). The likelihood of developing BPD was significantly greater in infants born of pregnancies complicated by preeclampsia compared with those born of pregnancies complicated by other causes of preterm delivery. The bivariate OR for the relationship between preeclampsia and BPD was 2.96 (95% CI = 1.17 to 7.51; *P* = .01), indicating that, before accounting for the potential effect of confounding variables, preeclampsia is associated with an almost 3-fold increase in the likelihood of developing BPD. Those babies not delivered for preeclampsia were delivered in the setting of a spontaneous preterm delivery, explaining the apparent protective effect of spontaneous preterm delivery with regard to BPD. The 2 groups had similar rates of RDS (62% vs 58%; *P* = .68), all stages of NEC (14% vs 5%; *P* = .13), all grades of IVH (24% vs 15%;