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%;

Table II. Pregnancy management and outcome characteristics (n = 107)

Characteristic	Total sample (n = 107), n (%)	BPD (n = 27), n (%)	Non-BPD (n = 80), n (%)	*P* value*
Male sex	67 (62.6)	20 (74.1)	47 (58.8)	.15
Antenatal steroids	93 (86.9)	23 (85.2)	70 (87.5)	.76
Antenatal antibiotics	20 (18.7)	6 (22.2)	14 (17.5)	.58
Antenatal magnesium	27 (25.2)	8 (29.6)	19 (23.8)	.45
Tocolysis (nifedepine/indomethacin)	41 (38.3)	12 (44.4)	29 (36.2)	.46
Gestational diabetes	6 (5.6)	1 (3.8)	5 (6.2)	.84
Maternal tobacco use	8 (7.5)	7 (25.9)	1 (1.2)	.25
Clinical chorioamnionitis	22 (20.6)	8 (29.6)	14 (17.5)	.18
Spontaneous preterm delivery	78 (72.9)	15 (55.6)	63 (78.8)	.01
Preeclampsia	29 (27.1)	12 (44.4)	17 (21.2)	.01

*Rank-sum test.

P = .29), PVL (7% vs 1%,; *P* = .12), all stages of ROP (28% vs 23%; *P* = .63), and death (10% vs 6%; *P* = .49).

Because the risk of BPD is mediated in part by inflammation, gestational age, and several other potential confounders identified in the bivariate comparison,[19] we examined a logistic model (Table III). In this model, clinical chorioamnionitis was significantly associated with increasing odds of BPD, and advancing gestational age was associated with decreasing odds of BPD. Birth weight *z*-score, male sex, and maternal tobacco use were not associated with an increasing odds of BPD. Interestingly, the OR of BPD after a gestation complicated by preeclampsia in this model was notably higher than in the bivariate model. Stepwise removal of the variables from this model revealed that the differences in the odds of preeclampsia in the bivariate and fully specified models of BPD were due mainly to the effect of 2 variables: the presence of clinical chorioamnionitis and gestational age at delivery (data not shown).

Discussion

There are conflicting reports on the association between fetal exposure to preeclampsia and the risk of complications of prematurity, although the data generally do not support a consistent effect. Exposure to preeclampsia has not been associated with any change in the incidence of RDS, IVH, or PVL.[20-25] Except for one report of an increased rate of NEC,[26] the incidence of this condition also has been found to be unchanged by preeclampsia.[20,22,24] The rate of ROP may be increased in babies exposed to preeclampsia.[25] Our data on the incidence of RDS, NEC, IVH, and PVL are consistent with these previous reports.

Table III. Multivariate ORs (with 95% CIs) for the occurrence of BPD

Variable	OR	95% CI	*P* value
Preeclampsia	18.7	2.44-144.76	.005
Clinical chorioamnionitis	6.41	1.09-37.48	.039
Gestational age	0.37	0.24-0.56	.001
Birth weight *z*-score	0.90	0.51-1.59	.718
Male sex	2.84	0.64-12.59	.168
Maternal tobacco use	5.04	0.57-44.49	.145

The relationship between BPD and preeclampsia has been studied less extensively, and the exisiting studies are conflicting, with reports of preeclampsia increasing[27] and decreasing[28] the risk of BPD. Reports of an association between intrauterine growth retardation (IUGR) and increased risk of BPD[29,30] provide an indirect reflection of preeclampsia, which is associated with IUGR.[31] In the present study, we found a strong positive association between fetal exposure to preeclampsia and the later development of BPD. We also found a nonsignificant trend in the association between fetal exposure to chorioamnionitis and eventual BPD.

To further explore the relationship between preeclampsia and BPD, we estimated a coefficient of determination that indicates the proportion of variability accounted for by the statistical mode. Strictly speaking, a classic R^2 cannot be determined for a binomial dependent variable; however, Stata software (StataCorp, College Station, Texas) allows approximation of an "R^2" in a comparison of the log-likelihoods of the fully specified model and the minimal model.[32] For our model, this comparison yields a value of 0.54, indicating that approximately 54% of the "variability" in the odds of BPD can be accounted for by the variables listed in Table III. This value suggests that these 6 predictors account for more than 50% of the variation in the odds of BPD. Because we know that multiple postnatal factors contribute to BPD (eg, oxygen toxicity, barotrauma, volume trauma, postnatal infection and inflammation), it is striking that most of the risk factors for the eventual development of BPD are antenatal variables.

This study is limited by the lack of detailed information regarding the postnatal courses of the preterm infants, especially pertaining to factors that influence the incidence of BPD. We also had no information on race, which is an important variable in this partially genetically based disease.[33] Although the sample size is relatively small, we have adequate power to detect a difference in the risk of BPD between infants exposed to preeclampsia and controls, because of the magnitude of the effect. Testing this association in a larger database of maternal characteristics and infant outcomes would be useful.

The association between preeclampsia and increased risk of BPD is biologically plausible. Antiangiogenesis is increasingly understood to play a role in preeclampsia. The cord blood of babies born to preeclamptic mothers contains relatively high levels of sVEGFR-1 and relatively low levels of VEGF.[8] Because airway development parallels vascular growth,[34] the antiangiogenic environment of preeclampsia could result in impaired development of fetal and neonatal airways. This represents an example of a maternal condition exerting a direct effect on fetal development and altering long-term outcome. Specifically, maternal preeclampsia, with its attendant antiangiogenic state, impairs in utero and neonatal pulmonary development, thereby diminishing long-term pulmonary function.

Although PlGF, a member of the VEGF family, is also reduced in preeclampsia,[8] we do not believe that this decrease interferes with lung development. PlGF-null mice develop normally,[35] and those with increased PlGF have compromised lung function.[36] An elevated cord blood PlGF level is correlated with an increased risk of RDS and BPD in preterm infants.[37] The effects of elevated PlGF on reducing alveolar structure and decreasing lung microcirculation due to the loss of VEGF are supported by in vitro and in vivo studies.[38] Thus, the correlations between BPD and preeclampsia and between BPD and cord PlGF both appear to both involve diminished VEGF signaling.

We also found a correlation between BPD and clinical chorioamnionitis. It may be that this second population of infants with BPD had elevated PlGF levels as a result of their inflammatory condition. The exposure of bronchial epithelial cells to proinflammatory cytokines increases PlGF levels in the cells, and when PlGF and cytokine stimuli are maintained, their VEGF expression levels are dramatically reduced, leading to inhibited cell proliferation and increased apoptosis of pulmonary epithelial cells.[38]

The role of antiangiogenesis in BPD risk also might help explain why inhaled nitric oxide (iNO) therapy is more effective in preventing BPD in preterm infants of older gestational age.[39-41] BPD in gestationally younger infants is characterized by uniform arrest of alveolarization and consequent vascularization with minimal fibrotic changes.[42] iNO has been proposed to decrease inflammation[43] and promote alveolar development by inducing angiogenesis.[43] Gestationally younger infants may be at a stage of lung development when they are less able to benefit from the increased angiogenesis and decreased inflammation induced by iNO.

The identification of specific biological markers that predict the risk of BPD offers the hope of developing targeted postnatal interventions to minimize the risk of developing BPD and also allow early identification of BPD in a high-risk group. Animal model research has demonstrated enhanced alveolarization and blood vessel growth with recombinant VEGF therapy.[34,44] Were this replacement therapy to be considered in preterm infants, our data suggest that the subgroup of preterm infants born to preeclamptic mothers, who are expected to have a relative deficiency in VEGF, would benefit the most from such supplementation. Conversely, any plan for the therapeutic use of angiogenic *inhibitors* for maternal or neonatal indications would need to take into consideration the potential impaired fetal and neonatal lung development resulting from the decreased angiogenic environment. Understanding the link between preeclampsia and BPD will help minimize the risk and maximize the benefit of any maternal and neonatal therapeutic interventions. ■

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