Published in final edited form as:

Placenta. 2014 August ; 35(8): 570–574. doi:10.1016/j.placenta.2014.05.003.

Placental Pathologic Changes of Maternal Vascular Underperfusion in Bronchopulmonary Dysplasia and Pulmonary Hypertension

Karen K. Mestan, MD^a, Jennifer Check, MD^a, Lucy Minturn, BA^{a,e}, Sushmita Yallapragada, MD^a, Kathryn N. Farrow, MD, PhD^a, Xin Liu, MD, PhD^b, Emily Su, MD^c, Nicolas Porta, MD^a, Nina Gotteiner, MD^d, and Linda M. Ernst, MD^e

^aDepartment of Pediatrics, Division of Neonatology, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital, Box #45, Chicago, IL, USA 60611

^bDepartment of Pediatrics, Mary Ann and J. Milburn Smith Child Health Research Program, Ann & Robert H. Lurie Children's Hospital Research Center, Chicago, IL, USA 60611

^cDepartment of Obstetrics and Gynecology, Divisions of Maternal Fetal Medicine & Reproductive Biology Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA 60611

^dDepartment of Pediatrics, Division of Cardiology, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA 60611

^eDepartment of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA 60611

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Corresponding author: Karen Mestan, MD, Department of Pediatrics/Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box #45, Chicago, IL 60611, USA, Telephone: 312-227-5283, Fax: 312-227-9758, k-mestan@northwestern.edu.

CONTRIBUTORS

Karen K. Mestan: Dr. Mestan conceptualized and designed the study, prepared the results, drafted the initial manuscript, and approved the final manuscript as submitted.

Jennifer Check: Dr. Check designed and implemented the data collection and data management procedures for clinical, placental and echocardiogram data.

Lucy Minturn: Ms. Minturn designed and implemented the data collection, entry, and management procedures for placental pathology data.

Sushmita Yallapragada: Dr. Yallapragada assisted with the design and implementation of data collection procedures, data analysis, and presentation of results.

Kathryn N. Farrow: Dr. Farrow assisted with design and generating the hypothesis for this study, interpretation and organization of the neonatal data pertaining to chronic lung disease.

Xin Liu: Dr. Liu designed/implemented the data analysis procedures, and prepared the results.

Emily Su: Dr. Su assisted with maternal, antenatal, and intrapartum data collection procedures, interpretation of maternal and placental information.

Nicolas Porta and Nina Gotteiner: Drs. Porta and Gotteiner designed/implemented the data collection, interpretation, and analysis of echo and pulmonary hypertension information.

Linda M. Ernst: Dr. Ernst conceptualized and designed the study, prepared the results, provided oversight and implemented placental pathology data collection and analysis.

All of the above authors reviewed and revised the manuscript, and approved the final manuscript as submitted. Each of the above authors attest that there are no conflicts of interest to disclose.

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Abstract

Introduction—Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy, and BPD-associated pulmonary hypertension (PH) is a serious complication that can negatively impact later childhood health. There is growing evidence that lung injury leading to BPD and PH is due to chronic fetal hypoxia-ischemia. The purpose of this study was to investigate whether placental pathologic changes of maternal vascular underperfusion (MVU) are associated with BPD, and further increased with PH.

Methods—We conducted a 5-year retrospective cohort study of premature infants born ≤ 28 weeks. BPD was defined as persistent oxygen requirement at 36 weeks corrected gestational age. PH was identified using a standardized algorithm of echocardiogram review. Archived placental slides underwent standardized masked histopathologic review. Logistic regression modeling was performed, taking into account important maternal and infant covariates.

Results—Among 283 births, 121 had MVU, of which 67 (55%) developed BPD, and 24 (20%) had PH. Among the common neonatal complications of extreme prematurity, BPD was the only outcome that was increased with MVU ($P < 0.001$). After adjustment for birth weight, fetal growth restriction, preeclampsia and other factors, infants with MVU were more likely to develop BPD (adjusted odds ratio=2.6; 95% confidence interval=1.4, 4.8). Certain MVU sublesions (fibrinoid necrosis/acute atherosclerosis and distal villous hypoplasia/small terminal villi) were increased with PH ($P < 0.001$).

Discussion—Placental MVU may identify BPD infants who were exposed to intrauterine hypoxia-ischemia, which increases their risk for development of PH disease.

Conclusions—Our findings have important implications for providing earlier and more effective therapies for BPD.

Keywords

placenta; bronchopulmonary dysplasia; pulmonary hypertension; premature infant; preeclampsia; fetal growth restriction

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy, affecting one-half of extremely premature infants (born ≤ 28 weeks). BPD-associated pulmonary hypertension (PH) is an increasingly recognized pulmonary vascular problem in over one-third of BPD infants, characterized by persistently elevated pulmonary arterial pressures, chronic hypoxia, cardiopulmonary instability, right heart dysfunction, and early childhood death.(1, 2) The severity of BPD and presence of PH disease are often not apparent until several weeks to months after birth. Early, accessible biological markers that delineate the fetal pathophysiology of an individual infants' lung disease may be helpful in guiding the neonatal management of premature infants, so that BPD may be minimized or prevented. Despite extensive research, such markers have not yet been identified.

Placental pathologic findings related to preeclampsia and fetal growth restriction (FGR) may serve as promising early predictors of BPD and PH. This is because chronic vascular

malperfusion of the placental bed during fetal development may lead to pulmonary vascular remodeling, the hallmark of PH disease and to a lesser extent a proposed mechanism of BPD. Maternal vascular underperfusion (MVU) of the placental bed is perhaps best understood as a marker of preeclampsia, and has been shown to negatively impact the fetus as it is a prominent lesion in FGR.(3) Preeclampsia and FGR are also risk factors for BPD and PH,(4–6) although not reliably present in all cases given the multifactorial nature of these diseases. Moreover, not all cases of MVU are accompanied by clinically apparent preeclampsia or FGR, especially in cases of extremely preterm birth since delivery of the fetus may occur before maternal signs are manifest. Therefore, an important question is whether MVU could serve as an independent earlier predictor of BPD and PH.

The objectives of this study were, firstly, to evaluate the association between placental MVU and BPD among infants born ≥ 28 weeks gestational age (GA), and secondly, to further investigate the association between MVU and BPD-associated PH. We hypothesized that the presence of MVU is predictive of BPD, and most prominent among BPD infants who develop PH at 36 weeks corrected age (CA).

PATIENTS AND METHODS

Study Design and Patients

We conducted a five-year retrospective cohort study at Northwestern Prentice Women's Hospital, in which all infants born ≥ 28 completed weeks (GA range 23^{0/7} to 28^{6/7} weeks) between January 2005 and December 2009 were identified. Standardized chart reviews were performed. Archived placental pathology slides from each delivery were retrieved and reviewed by a single perinatal pathologist using a standardized algorithm (see below). All infants who were inborn at Prentice and for whom placental tissues were retrievable were included. Excluded were births in which reliable GA dating criteria as defined by the American Congress of Obstetricians and Gynecologists (ACOG) could not be determined, and infants with known congenital or chromosomal anomalies. This study was approved by the institutional review boards at Northwestern University and Ann & Robert H. Lurie Children's Hospital.

Maternal and Infant Covariates

Clinical information was collected using standardized abstraction forms that included data on intrapartum management, pregnancy complications and birth outcomes. Variables previously reported in the literature and observed in the clinical setting with preterm birth, placental dysfunction, and BPD were selected for analysis according to MVU status. GA was determined based on last normal menstrual period, confirmed by ultrasounds obtained prior to 20 weeks gestation.(7) Maternal preeclampsia and other hypertensive disorders of pregnancy, such as eclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, were defined according to ACOG criteria.(8) FGR was defined as birth weight (BW) < 10th percentile for GA based upon Fenton growth curves for premature infants.(9) Infant outcomes were classified using Bell's staging criteria for necrotizing enterocolitis (NEC),(10) Papille's criteria for intraventricular hemorrhage (IVH),(11) and stage 2 or higher retinopathy of prematurity (ROP) as indicated in the medical records.

Determination of BPD and PH status

The primary outcome was BPD, defined according to the National Institutes of Health consensus definition of supplemental oxygen requirement at 36 weeks CA.(12) The secondary outcome of PH was determined using a standardized algorithm developed by a pediatric cardiologist, which enabled us to identify echocardiographically evident PH via medical record review and has been previously published for this cohort.(5) All babies at our institution with BPD received an echocardiogram evaluation at or around 36 weeks CA. All reports were reviewed by a single neonatologist masked to patient's history, and confirmed by a pediatric cardiologist.

Placental histologic examination

We included only mother-infant pairs for whom the placenta was submitted and adequate histologic samples were available in the Department of Pathology archives. Since the hospital routinely archives placental slides for all births <34 weeks, most all slides were retrievable for the study. Information on trimmed placental weight was obtained from the pathology reports, and placental weight-for age was determined using reference values for singleton and multiple gestation placentas.(13, 14) Archived samples included sections of membranes, umbilical cord, and at least two sections of the placental parenchyma. A comprehensive, standardized histopathology review was performed on the slides by a single perinatal pathologist, who was masked to clinical outcomes. The histologic data were recorded and divided into the following four major pathologic categories:

1. *Maternal vascular underperfusion* (MVU) was the primary predictor. Criteria as defined by Redline et al(3) were used to record pathologic findings in the maternal vasculature of the parietal and basal decidua (vessel changes), which included mural fibrinoid necrosis/acute atherosclerosis (FN/AA), muscularized basal plate arteries (MBPA), and mural hypertrophy of membrane arteries (MHMA). In addition, villous hypoxic lesions (villous changes) including infarcts, increased syncytial knots, villous agglutination, increased perivillous fibrin, distal villous hypoplasia/ small terminal villi were recorded. The degree of MVU was graded as severe if one or more vascular lesions were present, one or more villous lesions were seen, and the placental weight was <10th percentile for GA.(14) If findings of MVU were present, but did not meet all these criteria, a grade of mild MVU was assigned.
2. *Acute inflammation* (AI) was defined by evidence of amniotic fluid infection/acute inflammatory pathology.(15) Maternal AI was identified by neutrophil infiltration of chorion (stage 1), amnion (stage 2), and necrotizing chorioamnionitis (stage 3). Fetal AI was identified by neutrophil diapedesis through the wall of the chorionic vessels or umbilical vein (stage 1), umbilical artery (stage 2), and necrotizing funisitis (stage 3) defined by neutrophil karyorrhexis in a band-like configuration within Wharton's jelly.
3. *Chronic inflammation* (ChI) was defined as presence of significant chronic (lymphocytic or histiocytic) infiltrates in the membranes (chorion and/or amnion), chorionic villi, intervillous space or basal plate. Chronic villitis was defined as lymphocytes or histiocytes infiltrating the chorionic villi and was graded as low

(few, small foci) or high (multiple, large foci). Chronic intervillitis was identified when a lymphohistiocytic infiltrate was present in the intervillous space without a villous infiltrate. Basal ChI was considered diagnostic for chronic deciduitis when plasma cells were identified within the chronic inflammatory infiltrate.

4. *Fetal vascular pathology* (FVP) was defined according to the criteria published by Redline et al.(16) These lesions included the presence of thrombi within chorionic, stem villous, or umbilical vessels. Avascular villi were identified as two or more terminal villi showing total loss of villous capillaries and uniform fibrosis of the villous stroma. A diagnosis of fetal thrombotic vasculopathy was made when multifocal avascular villi were present (>15 villi involved/slide).

Statistical Analysis

Continuous variables were compared using student's t-test or F-test. Categorical variables were compared using Chi-square or Fisher's exact tests. Multivariate logistic regression models were used to determine the odds ratio (OR) and 95% confidence intervals (CI) using the group without any MVU lesions as the reference. Regression models were adjusted for relevant maternal and infant characteristics that were significantly different according to MVU status ($P<0.05$). Stratified analyses were performed to investigate potential interaction effects. All analyses were performed using Stata software version 13.0 (College Station, Texas).

RESULTS

A total of 330 infants 28 weeks GA were inborn and admitted at Prentice between January 1, 2005 and December 31, 2009. Of this group, 37 had incomplete reports for the following reasons: 27 had missing slides or incomplete maternal record information necessary to locate the appropriate slides, and 10 births had placental tissues available but could not be designated due to multiple gestation status or mislabeling. Therefore, a total of 293 mother-infant pairs with complete placental data were available. For 10 infants in this cohort, the BPD status could not be confirmed due to death prior to 36 weeks CA ($N=7$) and incomplete documentation in the medical record ($N=3$).

The demographic, clinical, and histologic characteristics of the 283 births are shown in Table 1. Birth weight, multiple gestation, spontaneous preterm labor, chorioamnionitis and placental weight-for-age were decreased with MVU, while rates of preeclampsia, HELLP, other maternal hypertensive diagnoses, C-section and FGR were increased. AI was inversely associated with MVU. Among the common complications of extremely preterm birth, BPD was the only diagnosis that was increased with MVU ($P<0.001$).

In the logistic regression models of MVU on BPD, the crude OR was 2.6 (95% CI=1.6, 4.1). After adjustment for the significantly different covariates identified in Table 1, the association remained significant (OR=2.6; 95% CI=1.4, 4.8). Stratification by the presence versus absence of preeclampsia and FGR yielded non-significant associations. When stratified by the presence versus absence of AI, the associations were modified but remained

significant within each strata (OR=2.2; 95% CI=1.1, 4.3 vs. OR=3.3; 95% CI=1.4, 7.6 respectively).

MVU characteristics of BPD and PH

The incidence of PH among BPD infants was 29%. Table 2 shows the frequency of MVU and MVU sublesions according to BPD only and BPD with PH groups. Among the most common MVU sublesions, increased syncytial knots and DVH/STV were present in more than 40% of BPD and greater than 50% of PH cases. When comparing the infants with BPD accompanied by PH to infants with No BPD or PH, both types of sublesions (vessel and villous changes) were increased with PH disease ($P<0.01$), with the most prominent lesions being FN/AA and DVH/STV ($P<0.001$).

DISCUSSION

We found that placental MVU is associated with the development of BPD among extremely premature infants. When taking into account maternal, infant, and other placental histologic covariates, the MVU on BPD association was robust. MVU also appeared to be more strongly associated with BPD as compared to other major neonatal outcomes. Lastly, certain MVU sublesions were particularly prominent among BPD infants who developed PH disease. Our findings support the role for placental vascular markers as early predictors of BPD and PH.

MVU is one of the most common placental vascular lesions reported in high-risk pregnancies. It is associated with preeclampsia and other gestational hypertensive disorders (eclampsia and HELLP). The infant outcomes that often accompany these complications are also associated with MVU, and include fetal growth restriction and stillbirth.(3) The pulmonary outcomes associated with MVU in extremely preterm infants are under-reported. In one previous study of infants <32 weeks born between 1995 and 1997, Redline and colleagues reported an inverse association between BPD and FN/AA.(17) However, the associations with MVU in particular and with other MVU sublesions were not studied as directly as we demonstrate here. The distinction between BPD with and without PH disease, and interaction effects of AI were also not considered previously. Differences in neonatal deaths, which constituted 12% of FN/AA cases in our cohort, or perhaps changes in the pathophysiology of BPD over the past decade (18) might have accounted for the inverse association reported by Redline.

Although BPD has long been recognized as an inflammatory condition, there is recent evidence that fetal stressors that adversely affect pulmonary vascular growth, such as in utero hypoxia-ischemia, may have important contributions in later onset neonatal chronic lung disease. An important example of this is the sheep model of chronic fetal hypoxia, in which Rozance and colleagues have shown that uteroplacental insufficiency leads to the classic histologic lung findings of BPD (e.g., disrupted alveolar development and pulmonary vascular remodeling).(19) Interestingly, the pulmonary vascular components of their model closely resemble the placental histologic description of MVU.

Despite previous reports in the literature on chorioamnionitis and BPD, we did not find significant associations with placental inflammatory lesions. In our cohort, there was a tendency for AI lesions to be less prominent with BPD and PH, a finding reported in other large studies.(17, 20, 21) When stratified by AI, the MVU on BPD association was modified but remained significant within each strata. This would suggest that there are independent and potentially interactive effects among vascular and inflammatory processes that warrant further investigation in a larger sample. We speculate that the relative lack of consideration of vascular lesions such as MVU in previous studies may account for the highly variable results on AI reported in the literature.(20)

Among the sublesions of MVU, FN/AA and DVH/STV were most prominent with PH disease. These lesions are indicators of abnormal trophoblast invasion and inadequate vascular remodeling of the endometrial spiral arterioles. These pathologic vessels have small lumens (low capacitance) and thick walls (high resistance) with a tendency to undergo fibrinoid necrosis secondary to high pressure flow within the vessels. Overall, the net effect of the abnormal vascular remodeling is inadequate and abnormal perfusion of the intervillous space and developing chorionic villi. As pregnancy progresses, ongoing decreased maternal perfusion of the intervillous space leads to chronic fetal hypoxia, an important underlying mechanism of fetal growth restriction, and BPD. Interestingly, these lesions have distinct features that are similar to the lung histopathology of BPD in Rozance's sheep model(19) and in human lung tissue showing thickened pulmonary arterioles at autopsy in infants with severe BPD and PH.(22)

Important limitations include the retrospective nature of this study, and potential for bias due to unavailable placental records. Masked review of placental slides and review by a single perinatal pathologist were strategies to minimize bias. Furthermore, the rates of BPD and PH among infants who were outborn or who had missing placental pathology data were similar to the infants included in this analysis. As a single-center study, our results will need to be confirmed in multi-center investigations for generalizability. A larger sample of PH infants will be needed to further investigate the interactions among MVU sublesions, and with other clinical and histologic factors. However, a strength of being a single-center study was that we were able to achieve comprehensive and standardized collection of placental and clinical data, including a standardized algorithm for PH. This is the first relatively large study reporting the association between placental histopathology and BPD-associated PH.

In conclusion, the prominence of placental MVU among BPD infants provides further evidence that fetal mechanisms can lead to cardiopulmonary disease in early childhood. In the clinical setting, MVU may be helpful in identifying subsets of infants for whom BPD has been mediated by intrauterine hypoxia-ischemia, thus increasing their risk of developing PH. Since early management and prevention strategies for BPD now include a wide range of anti-inflammatory, pulmonary vasodilatory and vascular growth agents, our findings have important implications for providing more targeted and effective therapies for individual patients.

Acknowledgments

FUNDING SOURCES

This project was supported by NHLBI Grant K23 HL093302 (PI: Mestan), and the Northwestern Memorial Foundation Friends of Prentice Grants Initiative (PI: Mestan).

We thank neonatology fellows Dr. Stephannie Baehl-Voller for her assistance with the medical record review and clinical data collection for this study.

Abbreviations

AI	acute inflammation
BPD	bronchopulmonary dysplasia
BW	birth weight
CA	corrected age
ChI	chronic inflammation
CI	confidence interval
FGR	fetal growth restriction
DVH/STV	distal villous hypoplasia/small terminal villi
FN/AA	fibrinoid necrosis/acute atherosclerosis
FVP	fetal vascular pathology
GA	gestational age
HELLP	hypertension, elevated liver enzymes, low platelets
MBPA	muscularized basal plate arteries
MHMA	mural hypertrophy of membrane arteries
MVU	maternal vascular underperfusion
NEC	necrotizing enterocolitis
OR	odds ratio
PH	pulmonary hypertension
ROP	retinopathy of prematurity

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- We conducted a 5-year retrospective cohort study of extremely premature infants
- Placental MVU was increased among infants who develop BPD
- Fibrinoid necrosis and distal villous hypoplasia were further increased with PH
- In clinical settings, MVU may help predict development of BPD and BPD-associated PH

Table 1

Maternal and Infant Characteristics According to MVU Status

	No MVU N=162	Any MVU N=121	P
Gestational age (weeks $\pm$ s.d.)	26.7 $\pm$ 1.5	26.8 $\pm$ 1.5	0.41
Birth weight (grams $\pm$ s.d.)	959.1 $\pm$ 234.8	880.2 $\pm$ 238.4	0.01
Gender:			
Male, n (%)	95 (59)	67 (55)	0.58
Female	67 (41)	54 (45)	
Race/ethnicity:			
Black	59 (36)	39 (32)	0.44
White	55 (34)	38 (31)	
Hispanic	12 (7)	8 (7)	
Other	36 (22)	36 (30)	
Multiple gestation	60 (37)	23 (19)	0.001
Spontaneous preterm labor	139 (86)	68 (56)	<0.001
C-section delivery	89 (55)	81 (67)	0.04
Antenatal steroids	125 (77)	101 (83)	0.22
Preeclampsia ^a	5 (3)	43 (36)	<0.001
Eclampsia	0 (0)	1 (0)	0.43
HELLP	1 (0)	8 (7)	0.01
Pregnancy-induced hypertension	1 (0)	7 (6)	0.02
Chronic hypertension	3 (2)	10 (8)	0.02
Oligohydramnios	11 (7)	9 (7)	0.82
Clinical chorioamnionitis	35 (22)	10 (8)	0.003
Fetal growth restriction (FGR) ^b	9 (6)	23 (19)	0.001
Placental weight small-for-gestational age (SGA)	7 (4)	38 (31)	<0.001
Other placental lesions:			
Acute inflammation (AI)	124 (77)	51 (42)	<0.001
Chronic inflammation (ChI)	41 (25)	32 (26)	0.83
Fetal vascular pathology (FVP)	21 (13)	18 (15)	0.64
Infant outcomes:			
BPD ^c	53 (33)	67 (55)	<0.001

	No MVU N=162	Any MVU N=121	P
Necrotizing enterocolitis (Bell's stage 2+)	23 (14)	28 (23)	0.06
Severe intraventricular hemorrhage	28 (17)	14 (12)	0.24
Retinopathy of prematurity (stage 2+)	51 (31)	44 (36)	0.30
NICU death > 36 weeks	2 (1)	3 (2)	0.65

^aMaternal preeclampsia, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), other hypertensive disorders of pregnancy, and oligohydramnios were defined according to ACOG criteria. Clinical chorioamnionitis was defined using Gibbs criteria, which included presence of intrapartum fever >38°C with two or more of the following signs: elevated maternal WBC >15,000 leukocytes/mm³; maternal or fetal tachycardia; uterine tenderness and/or foul-smelling amniotic fluid or vaginal discharge.

^bFGR was defined as birth weight <10th percentile for gestational age based upon Fenton growth curves for premature infants. SGA placental weight was determined using references values for singleton and multiple placentas, as published by Pinar, et al.

^cBPD was defined as persistent supplemental oxygen requirement at 36 weeks corrected gestational age.

Table 2

Placental MVU characteristics according to BPD and PH status.

	No BPD or PH N=165	BPD only N=84	BPD-associated PH ^a N=34	p ^b
Maternal vascular underperfusion (any)	56 (34)	43 (51) *	22 (65) *	0.001
Severe MVU	6 (4)	9 (11)	6 (18)	0.01
Vessel changes:				
FN/AA	6 (4)	8 (10)	8 (24) **	0.001
MBPA	16 (10)	12 (14)	10 (29) *	0.01
MHMA	10 (6)	9 (11)	6 (18)	0.07
Villous changes:				
Infarcts	10 (6)	14 (17)	4 (12)	0.02
Increased syncytial knots	53 (32)	39 (46)	20 (59) *	0.01
Villous agglutination	4 (2)	4 (5)	2 (6)	0.36
Increased perivillous fibrin	7 (4)	2 (2)	2 (6)	0.67
DVH/STV	36 (22)	36 (43) *	18 (53) **	<0.001

^aPH status was determined based upon an algorithm using the following echocardiogram findings at 36 weeks corrected age: 1) Estimated right ventricular (RV) pressures >33% systemic based upon tricuspid regurgitation (TR); 2) If TR not present, demonstration of at least 2 of the following 4 echocardiographic findings: RV enlargement, RV hypertrophy, intraventricular septal flattening and/or abnormal pulmonary artery Doppler.

^bP-value calculated using Chi-square or Fisher's exact tests for differences in proportions among the 3 groups.

* P<0.01, versus No BPD or PH;

** P<0.001, versus No BPD or PH.