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Fetal Growth Restriction and Pulmonary Hypertension in Premature Infants with Bronchopulmonary Dysplasia

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Abstract

Objective—To identify the association between birth weight (BW)-for-gestational age (GA) and pulmonary hypertension (PHTN) at 36 weeks in infants with moderate-severe bronchopulmonary dysplasia (BPD).

Study Design—In this retrospective cohort study, we followed 138 premature infants (≤28wks) with moderate and severe BPD (NIH consensus definition) born at Prentice Women's Hospital between 2005 and 2009. BW percentiles were calculated using the Fenton growth curve for premature infants. PHTN was determined using a standardized algorithm of echocardiogram review at 36 weeks. Logistic regression was used to evaluate the associations between BW percentile subgroups and PHTN, taking into account antenatal and neonatal factors that were related to PHTN.

Results—PHTN was associated with small BW-for-GA, ranging from thresholds of <10th to <25th percentile (P<0.001). These associations remained significant when comparing BW <25th percentile to the reference group (50–89th percentile); after adjustment for GA, gender, multiple gestation, race/ethnicity (OR=4.2; 95% CI=1.5, 12.1); and after further adjustment for maternal vascular disease, intrauterine infection, oligohydramnios, and relevant postnatal factors (OR=5.7;

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CONFLICT OF INTEREST

There are no conflicts of interest or competing interests to disclose.

95% CI=1.5, 21.2). Longitudinal follow-up of this cohort showed a trend towards higher morbidity and death among PHTN infants with BW <25th percentile.

Conclusion—BW-for-GA is an important predictor of PHTN in premature infants with moderate/severe BPD. Our findings contribute to the growing evidence supporting fetal mechanisms of later onset pulmonary vascular disease.

Keywords

intrauterine growth restriction; small-for-gestational age; pulmonary vascular disease; preterm birth

INTRODUCTION

Approximately one-half of extremely premature infants (born ≤28 weeks of gestation) develop bronchopulmonary dysplasia (BPD), and pulmonary hypertension (PHTN) in the preterm infant with BPD is an increasingly recognized problem. Approximately one-third of infants with BPD will have persistently elevated pulmonary arterial pressures associated with moderate to severe oxygen dependence, cardiopulmonary instability, and right heart dysfunction. PHTN in infants with BPD is also associated with greater morbidity and mortality, including more severe BPD, long-term mechanical ventilation support, poor growth and neurodevelopmental outcome.[1, 2] The development of PHTN in BPD is associated with a four-fold increased likelihood of death.[3] Despite the growing number of infants diagnosed with BPD-associated PHTN, little is known about the risk factors for this devastating disease.[4]

Intrauterine growth restriction (IUGR) is an increasingly recognized problem among premature infants. The mechanisms of IUGR are multifactorial, and in the prematurely born infant this often manifests at birth as a mild to severe decrease in birth weight (BW)-for-gestational age (GA). Extremely premature infants who are born small-for-gestational age (SGA) are at increased risk of developing BPD, and IUGR has been shown to be an independent risk factor.[5, 6] A growing body of evidence in animal models demonstrates that IUGR may have lasting effects on lung structure and function, with alveolar and vascular abnormalities suggestive of BPD-associated PHTN.[7, 8] Several reports on the incidence of PHTN in premature infants have recently been published, including a recent prospective study of extremely low BW (<1000g) infants.[9] An important gap in these studies is the evaluation of growth restriction and related early covariates in the development of PHTN.

SGA has long been recognized as an important risk factor for PHTN in term and late preterm infants. However, the independent association between SGA and PHTN, and the threshold for defining SGA in the extremely preterm population particularly among infants with moderate-severe BPD, remains unclear. Our objective was to identify the associations between BW percentiles and PHTN, and to determine whether common antecedents of extremely preterm birth would modify this association.

METHODS

Study Design and Patients

We conducted a 5-year retrospective cohort study, in which the medical records of all infants and their mothers delivering at ≤28 completed weeks gestation (GA range 23 0/7 to 28 6/7 weeks; January 2005-December 2009) at Northwestern Memorial/Prentice Women's Hospital were reviewed. Infants who survived to 36 weeks with moderate or severe BPD, defined according to the National Institutes of Health (NIH) consensus definition, were identified and included in this study.[10] Excluded were births for which solid GA dating criteria as defined by the American Congress of Obstetricians and Gynecologists (ACOG) could not be extracted from the medical record (see below), and infants with known congenital or chromosomal anomalies. Since all babies at our institution who remain on supplemental oxygen at 36 weeks corrected age (CA) received an echocardiogram evaluation at or around this time, this inclusion criteria allowed us to minimize the confounding effects of variable availability of echocardiograms prior to this time point, such as that which might be seen with mild BPD (oxygen dependence at 28 days but not at 36 weeks). This study was approved by the institutional review boards of Northwestern University/Northwestern Memorial Hospital and Children's Memorial Hospital.

Definition of Pulmonary Hypertension (PHTN)

A standardized algorithm was developed *a priori* by our institution's pediatric cardiologist, enabling us to identify echocardiographically evident PHTN via medical record review: 1) If tricuspid regurgitation (TR) was present, the Bernoulli equation was used to estimate right ventricular (RV) pressure and determine whether pulmonary arterial pressure was elevated (estimated RV pressures >33% systemic); 2) If TR was not present, demonstration of at least 2 of the following 4 echocardiographic findings must be made: right ventricular enlargement, right ventricular hypertrophy, interventricular septal flattening, and/or abnormal pulmonary artery Doppler (sawtooth pattern or shortened acceleration time). These criteria were based upon previous reports in the literature[11, 12] combined with our group's report of the correlation between degree of interventricular septal flattening and angiographically measured (cardiac catheterization) PHTN in former premature infants.[13] All echo reports were reviewed by a single neonatologist, masked to each patient's history. These reports were also reviewed separately by a pediatric cardiologist. There were no cases in which PHTN status could not be agreed upon by the two reviewers.

Maternal and Neonatal Covariates

GA was determined based on last normal menstrual period (LNMP) and early ultrasound before 20 weeks gestation.[14] Briefly, LNMP estimate was used whenever confirmed by ultrasound within 1 week or when no ultrasound estimate was obtained. In all other cases, ultrasound estimate was used. Only births that could be accurately dated by this algorithm were included in this study. Continuous variable BW percentiles were determined using the most recent Fenton growth curves for premature infants.[15] Values were calculated using the formula provided by this reference, in which BW in grams was entered for the completed weeks of gestation for each infant.

Comprehensive medical record review was performed for the antenatal indication for preterm delivery: 1) Maternal hypertensive disorders of pregnancy (e.g., preeclampsia/eclampsia, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome), as defined by established ACOG criteria[16]; 2) Prolonged rupture of membranes (ROM) (>18 hours); 3) Low amniotic fluid index (oligohydramnios) in the setting of intact membranes; and 4) Placental disorders including placenta previa and abruption. We also assessed clinical factors that often accompany preterm delivery: 1) Exposure to antenatal steroids (one or more doses of betamethasone or dexamethasone); 2) Placental histopathologic evidence of chorioamnionitis, with and without funisitis; and 3) Presence of non-reassuring fetal heart rate tracing preceding Cesarean delivery. BPD infants were followed longitudinally to neonatal intensive care unit (NICU) discharge, with their outcomes defined as follows: 1) Intraventricular hemorrhage (IVH) based upon classification by Papile, et al.[17]; 2) Necrotizing enterocolitis (NEC) defined as stage IIA or worse according to modified Bell's staging[18]; 3) Diagnoses of retinopathy of prematurity (ROP), periventricular leukomalacia (PVL) and other outcomes were similarly obtained from NICU records for each infant.

Statistical Methods

Continuous variables were compared using Mann-Whitney test. Categorical variables were compared using χ^2 or Fisher's exact tests. Logistic regression models were used first to investigate the univariate associations of the antenatal factors on PHTN, using absence of each covariate as the reference group and adjusting for relevant baseline demographics. Multivariate logistic regression models were then constructed to evaluate the independent associations among 4 BW percentile groups (<25th, 25–49th, 50–89th, and ≥90th percentiles) using the 50–89th percentile group as the reference. Models were then adjusted for baseline demographics (Model 2), and then antenatal factors identified in the univariate analyses with P≤0.5 (Models 3–4). In Model 5, we further adjusted for postnatal factors with P≤0.5 from Table 1. To account for multiple comparisons in all models, a Bonferroni-corrected P-value of <0.0125 was used to indicate statistical significance. All analyses were performed using Stata software (College Station, Texas).

RESULTS

Over a 5-year period, a total of 407 infants were confirmed as being born ≤28w at Prentice Women's Hospital. Of these, 269 infants had either no or mild BPD, or died prior to 36 weeks. One hundred thirty-eight (34%) survived to 36 weeks and had moderate or severe BPD and were included for further analysis. Table 1 shows the baseline demographics and clinical characteristics of this cohort. The incidence of retinopathy of prematurity and duration of mechanical ventilation were higher in the PHTN group. Rates of sepsis, PDA ligation, and other complications such as IVH and NEC were not different, but several variables appeared to approach significance (P≤0.5). Table 2 shows the univariate analyses of infant BW percentiles and maternal covariates on PHTN. Among the antenatal factors, only preeclampsia/eclampsia/HELLP, funisitis, and oligohydramnios met the threshold for inclusion in subsequent analyses.

Table 3 shows the multivariate logistic regression models of the four BW percentile groups. Infants with birth weights below the 25th percentile cut-off were at higher risk of developing PHTN as compared with the referent group. This association persisted after adjustment for maternal vascular disease (preeclampsia, eclampsia and HELLP), funisitis, and oligohydramnios. Further adjustment for postnatal factors listed in Table 1 with P≤0.5 did not substantially modify the associations.

The echocardiographic findings for infants with PHTN are summarized in Figure 1. There was no single parameter that differed significantly according to SGA status, although almost twice as many infants <25th percentile had right ventricular enlargement. The clinical courses of these infants were followed to NICU discharge. While PHTN infants overall had a higher rate of late pulmonary vasodilator and anti-inflammatory treatments, neonatal morbidities or death, there were no significant differences when comparing PHTN patients with vs. without SGA (Figure 1). The trend towards higher morbidity and mortality in the BW <25th percentile group suggested that in a larger sample, the interaction effects of PHTN and SGA would be significant. Of note, there were 5 reported deaths before NICU discharge among the group of infants with SGA and PHTN (BW ranging from 3rd–8th percentile), while all infants with PHTN at 36 weeks who were not SGA survived to discharge.

DISCUSSION

Our main finding is that extremely premature infants with small BW-for-GA are at increased risk of BPD-associated PHTN, as detected by echocardiogram at 36 weeks. While this association is commonly observed in the clinical setting, there are no reports to date describing the degree of growth restriction and related antenatal covariates in a well-characterized sample of BPD infants, and using a standardized algorithm to define PHTN. We found that the risk of PHTN is substantial, even with mild growth restriction defined as BW<25th percentile. While other antenatal and postnatal factors may contribute to the development of PHTN at 36 weeks, our findings suggest that low BW-for-GA is an important, perhaps independent, predictor of serious and persistent pulmonary vascular disease.

Despite the growing number of infants diagnosed with BPD-associated PHTN in recent years, the risk factors remain poorly understood. In particular, fetal mechanisms that contribute to PHTN are largely understudied. Our findings support the growing body of evidence that certain neonatal disease processes may arise from exposure of the fetus to an abnormal antenatal environment and/or fetal mechanisms which are only now being elucidated.[7, 19, 20]

Placental insufficiency is a common antecedent of fetal growth restriction, although its impact on growth in the prematurely born fetus appears highly variable. This is because there is significant redundancy within the placenta, and studies suggest that at least 40–50% of the placenta must be compromised before there is any antenatal evidence of fetal effect. Therefore, it is not surprising that we found a lack of direct association between maternal vascular disease and other common covariates with PHTN in the univariate analysis (Table

2). An important finding, however, is the persistence of the association between low BW percentile and PHTN, even after adjusting for these antenatal factors (Table 3). This suggests an independent association between SGA and PHTN, and that low BW percentile may serve as an important predictor of later PHTN even when maternal risk factors are not clinically apparent.

The association between PHTN and BPD has been described only recently in multiple centers with different approaches.[1–3, 21] Bhat and colleagues recently reported their findings from a prospective study of extremely low BW infants with PHTN.[9] Despite differences in study design, the profiles of echocardiographic parameters for late PHTN were very similar to ours (Figure 1). Neonatal morbidities were higher in our cohort, reflecting a much sicker population as we restricted observations to moderate-severe BPD infants. Our report provides a profile of risk factors and outcomes of a unique population of NICU patients, and suggests that when evidence of placental insufficiency is present as manifested by SGA growth, these patients are at even higher risk of death or adverse outcome. Furthermore, our cohort includes a wider range of BW (380–1335g) allowing us to more comprehensively investigate the variation due to BW-for-GA. What has been missing in previous reports, including Bhat et al, has been a more definitive threshold for SGA as a risk factor for PHTN and consideration of closely related antenatal events. Our findings suggest that even mild growth restriction, in the presence or absence of other maternal risk factors, is an indication for early screening and intervention.

IUGR is a common complication of preterm birth, with an incidence ranging from 5–12% among preterm births in the U.S.[22–24] In a multi-center investigation by Bose and colleagues,[5] fetal growth restriction was found to be an independent prenatal risk factor for BPD. In fact, IUGR was the only prenatal characteristic that was highly predictive of BPD after adjustment for prenatal and neonatal variables. Our findings further suggest that subgroups of BPD, such as those with PHTN, may be more significantly affected by the intrauterine milieu. Accordingly, these infants may require more individualized screening, such as routine echocardiographic assessment, regardless of the severity of their chronic lung disease. Moreover, as newer therapies are being developed to reduce the incidence and severity of PHTN diseases, it is important to recognize that premature infants born SGA are a group at considerable risk.

The use of echocardiogram to identify and measure PHTN in BPD infants has historically been questioned, with the parameters largely based upon correlations with cardiac catheterization in the adult literature. Mourani and colleagues reported that in a group of 25 children with chronic lung disease who underwent cardiac catheterization, echocardiogram evaluation had relatively poor predictive value, with assessment of PHTN severity being very unreliable in children <2 years of age (GA range 23 to 41 weeks; Age at assessment 0.4 to 22 months).[25] Therefore, our method for identifying infants with PHTN is a potential limitation of this study. However, by restricting our observations to a specific time-point (36 weeks CA) we sought to minimize the variation in clinical factors associated with infant's age and size. In addition, our study included only moderate-severe infants with BPD of a narrow GA range, thus minimizing the variability of gestational maturity and the nature of lung disease that may lead to discrepancies between echocardiogram and cardiac

catheterization. The scope of this study is limited, and we acknowledge that we can at most describe the association of BW-for-GA with the presence versus absence of PHTN, for which echocardiogram appears to be adequate for identifying.[25] Describing the relationship with severity of disease will require more invasive studies such as cardiac catheterization. Since these studies impose considerable risk for former premature infants, we anticipate that our findings may help target certain patients for which the benefits of further testing would outweigh these risks.

Other limitations of our study include that retrospective analysis restricts our report to an underlying association, and a more complete understanding of the causes and effects of growth restriction requires further study. This was a single-center study, which allowed us to collect standardized information on all BPD infants, but further investigation on the generalizability of our findings is warranted. Due to sample size, we were not able to fully evaluate the interaction effects of common covariates, but the overall trend suggests that in a larger sample, the association between SGA and PHTN is likely to be independent.

In conclusion, BPD infants exposed to IUGR are at increased risk for PHTN at 36 weeks. Our findings support the growing evidence that fetal exposures may have lasting effects on long-term cardiopulmonary health. The associations reported here have important implications for earlier detection of PHTN in extremely low gestational age infants. Since screening for PHTN in premature infants is not universally performed in NICUs, the disease and its complications may go undetected until long after BPD has been established. Systematic echocardiographic screening in growth-restricted premature infants may be an important tool to potentially reduce the incidence and severity of BPD-associated PHTN.

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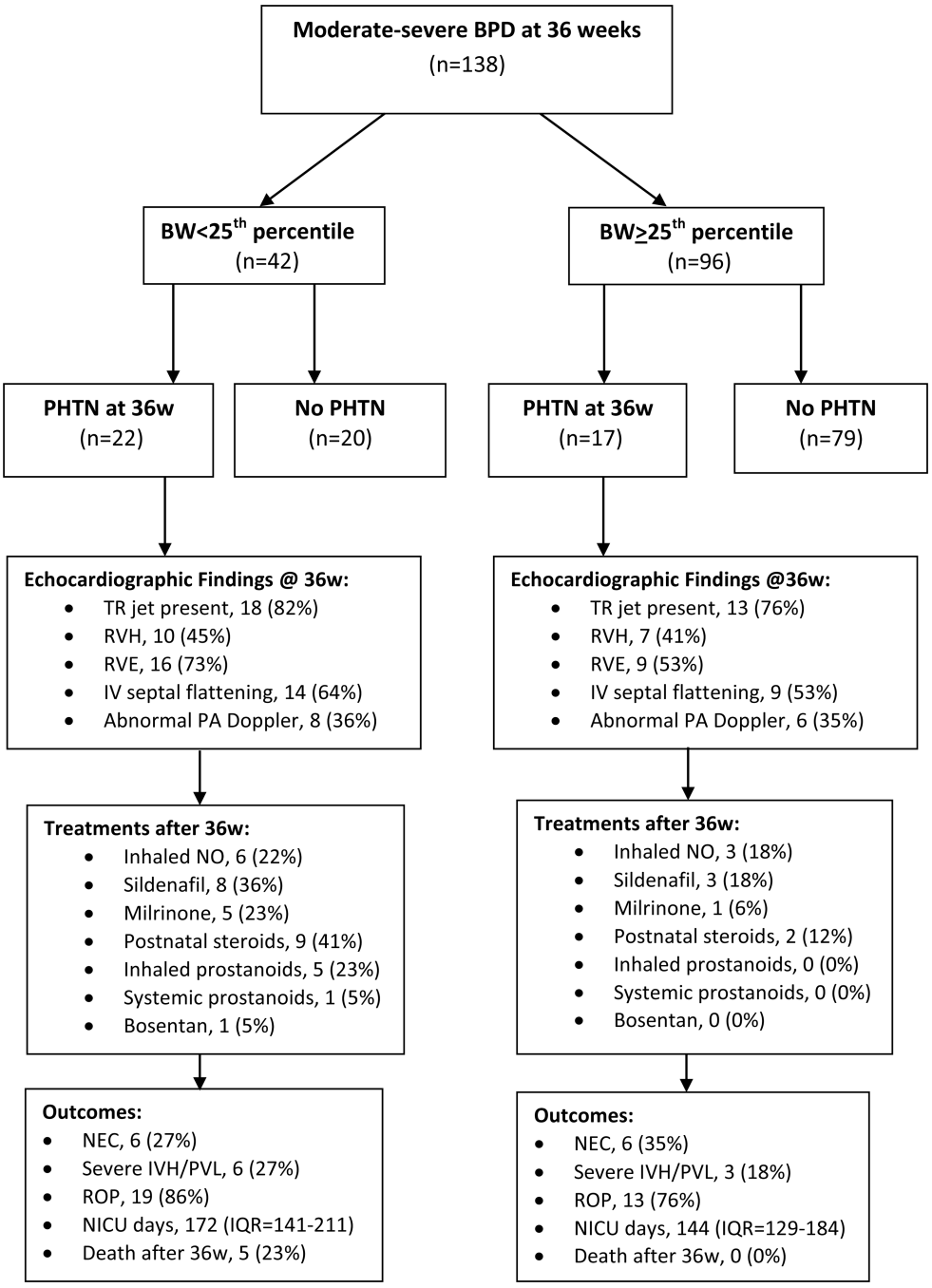

Figure 1.

Clinical course and outcomes of moderate-severe BPD infants with PHTN at 36 weeks. BW <25th percentile cut-off is used here, based upon associations described in Tables 2 and 3. P=N.S. for all of these parameters when comparing <25th versus ≥25th percentile infants with PHTN.

Table 1

Maternal and infant characteristics of the BPD cohort (N=138)

	BPD, no PHTN (n=99)	BPD, with PHTN (n=39)	P*
Gestational age weeks, mean±SD	26.3±1.5	25.5±1.2	0.003
Male gender, n(%)	66(67)	20(51)	0.10
Birth weight grams, mean±SD	862.9±190.9	695.9±190.9	<0.001
Maternal age years, mean±SD	29.4±6.4	28.1±6.7	0.27
Race/ethnicity, n(%) Black White Other	29(29) 41(41) 29(29)	22(56) 7(18) 10(26)	0.02
Multiple Gestation, n(%)	31(31)	5(13)	0.03
Neonatal and Postnatal Factors**			
1-minute Apgar score, median (IQR)	4(2–5)	3(1–5)	0.20
5-minute Apgar score	7(5–8)	7(6–8)	0.85
Surfactant (≥2 doses), n(%)	57(58)	26(67)	0.33
Severe IVH (grade 3–4)	15(15)	8(21)	0.46
Periventricular leukomalacia (PVL)	6(6)	1(3)	0.67
ROP, stage 2 or worse	47(47)	25(64)	0.04
ROP requiring laser surgery	20(20)	18(46)	0.001
Necrotizing enterocolitis (NEC, stage IIA)	27(27)	12(31)	0.92
Culture+ treated sepsis	33(33)	18(46)	0.16
Patent ductus arteriosus (PDA, any)	53(54)	22(56)	0.85
PDA requiring ligation	23(23)	13(33)	0.28
Aortopulmonary collaterals (APC)	7(7)	3(8)	1.00
Intubated @ 36 weeks CA	12(12)	16(41)	<0.001
Day of life to final extubation, median (IQR)	33(11–46)	58(45–84)	<0.001

*Calculated using student's t-test or Mann-Whitney test for continuous variables and X^2 and Fisher's exact tests for categorical variables.

**Intraventricular hemorrhage (IVH) was based upon classification by Papile, et al.[17] Necrotizing enterocolitis (NEC) was defined as stage IIA or worse according to modified Bell's staging.

Table 2

Univariate Analyses of Fetal Growth and Antenatal Factors on PHTN status at 36 weeks

	BPD, no PHTN (N=99)	**BPD, PHTN (N=39)**	**Odds Ratio (95% CI) ***	**P**
BW for gestational age percentile: ** <10th percentile, n(%) <25th percentile 25–49th percentile 50–89th percentile ≥90th percentile	8(8) 20(20) 31(31) 43(43) 5(5)	15(38) 22(56) 2(5) 12(31) 3(8)	9.7 (3.1, 30.3) 6.2 (2.4, 16.1) 0.1 (0.02, 0.5) 0.6 (0.2, 1.4) 1.4 (0.3, 7.0)	**<0.001** **<0.001** **0.004** 0.24 0.66
Preeclampsia/eclampsia/HELLP, n(%)	21(21)	11(28)	0.6 (0.2, 1.8)	0.34
Prolonged ROM (>18h)	18 (18)	9 (23)	0.8 (0.4, 1.9)	0.66
Oligohydramnios	9 (9)	6 (15)	1.6 (0.5, 5.3)	0.45
Placental previa or abruption	8 (8)	3 (8)	1.4 (0.3, 6.4)	0.64
Antenatal steroids	77 (77)	29 (74)	0.9 (0.3, 2.3)	0.80
Histologic chorioamnionitis	45 (45)	19 (49)	1.3 (0.4, 4.1)	0.67
Funisitis	33(33)	13(33)	0.7(0.3, 1.7)	0.44
Non-reassuring fetal heart tracing	19(19)	8 (21)	0.9 (0.3, 2.9)	0.96

* All models adjusted for gestational age, infant gender, multiple gestation and maternal race/ethnicity. Odds ratios and 95% CI calculated via univariate logistic regression, using the absence of each covariate as the reference group.

** Birth weight percentiles determined by fetal-infant (Fenton) growth curves for premature infants, with birth weight in grams plotted against completed weeks gestation at birth for each infant.[15]

Table 3

Multivariate Logistic Regression Models of Birth Weight-for-Gestational Age on PHTN Status at 36 weeks.

BW Percentile	Model 1	Model 2	Model 3	Model 4	Model 5
<25th	**3.9(1.6, 9.5)***	**4.2(1.5, 12.1)***	**6.0(1.6, 21.9)***	**5.9(1.6, 21.7)***	**5.7(1.5, 21.2)***
25–49th	0.2(0.05, 1.1)	0.2(0.04, 1.1)	0.3(0.04, 1.4)	0.2(0.04, 1.4)	0.2(0.03, 1.0)
50–89th	REF	REF	REF	REF	REF
≥90th	2.2(0.4, 10.3)	1.8(0.3, 9.7)	1.9(0.3, 10.0)	1.8(0.3, 9.8)	1.9(0.3, 11.6)

Model 1: Crude, Odds Ratio (95% CI)
Model 2: Adjusted for gestational age (weeks), gender, multiple gestation and maternal race/ethnicity
Model 3 Model 2 + further adjusted for preeclampsia/eclampsia and HELLP
Model 4 Model 3 + further adjusted for funisitis and oligohydramnios
Model 5: Model 4 + further adjusted for surfactant doses, severe IVH, ROP, sepsis, PDA ligation, and duration of mechanical ventilation.

* P<0.0125, based upon Bonferroni-correction for multiple comparison; Log-likelihood values ranged from −62.0 to −61.3 in models 2 through 5.