Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Maternal preeclampsia and respiratory outcomes in extremely premature infants

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BACKGROUND: Preeclampsia (PE) is a pregnancy complication characterized by an anti-angiogenic environment. This can affect fetal pulmonary vascular and alveolar development but data of the impact of PE on respiratory outcome in extremely premature infants are inconclusive. The objective of this study was to determine if PE is associated with an increased risk for severe respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in extremely premature infants.

METHODS: Prospectively collected single center data from a cohort of infants born at 23–28 w gestational age between January 2005 and December 2015 were analyzed. Logistic regression analysis and generalized estimating equations were used to model the association between PE and severe RDS (≥30% supplemental oxygen on d1), BPD and severe BPD [supplemental oxygen and ≥30% oxygen at 36 w postmenstrual age (PMA), respectively].

RESULTS: The cohort included 1218 infants of whom 23% were exposed to PE. PE was associated with increased risk for severe RDS as well as severe BPD among infants alive at 36w PMA.

CONCLUSION: Exposure to preeclampsia is independently associated with an increased risk for severe RDS and adverse respiratory outcome in extreme premature infants. The mechanisms behind these associations need to be investigated.

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INTRODUCTION

Preeclampsia (PE) is one of the most frequent complications of pregnancy and is associated with considerable perinatal morbidity and mortality.[1] PE manifests as a maternal hypertensive condition with or without multisystem abnormalities and cardiovascular effects. In addition, PE has been associated with intrauterine growth restriction, placental abruption, and preterm birth.

The underlying pathogenesis of PE is not well understood but it is increasingly considered to be a consequence of failed physiologic transformation of the spiral arteries resulting in impaired uteroplacental perfusion. In PE the balance between pro and antiangiogenic factors is disrupted resulting in an antiangiogenic state.[2–4]

Normal lung development depends on a closely orchestrated signaling between the developing epithelium and its vasculature, with lung angiogenesis playing a crucial role in normal alveolar development.[5,6] Given that airway and alveolar development parallel vascular growth, it is possible that the anti-angiogenic intrauterine environment of PE affects fetal lung development. This may predispose extreme premature infants to a more severe respiratory failure shortly after birth and later, to abnormal development of the lung vascular and alveolar structures. However, the evidence on the impact of PE on the respiratory outcome in extremely premature infants is inconclusive because of contradictory findings.[7–13] The objective of this study was to evaluate the association between exposure to PE and the development of severe respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in a cohort of extremely premature infants.

METHODS

Prospectively collected maternal, perinatal and postnatal data from a cohort of all inborn infants of 23–28 weeks gestational age (GA) between January 2005 and December 2015 who were admitted to the neonatal intensive care unit at Holtz Children's Hospital of the Jackson Memorial/University of Miami Medical Center were analyzed. These data are part of the prospective de-identified data collected into the generic perinatal/neonatal database system under the approval of Institutional Review Board (IRB) of the Human Subjects Research Office of the University of Miami and the Jackson Health System Clinical Research Office.

PE was diagnosed as new onset hypertension (systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher) after the 20th week of pregnancy, accompanied with new onset proteinuria and/or any other severe feature including thrombocytopenia, impaired liver function, impaired renal function, pulmonary edema and new onset cerebral or visual disturbances.[14] Chronic hypertension was defined as high BP predating conception or detected prior to 20 weeks of gestation.[14] For purposes of the study, severe RDS was defined as need for ≥30% supplemental oxygen for more than 12 h on day 1 after birth. BPD was defined as the need for supplemental oxygen and severe BPD as need for ≥30% oxygen, both at 36 weeks postmenstrual age (PMA).

Chi-square was used for univariate analysis of categorical variables and *t*-test for continuous variables. Mantel–Haenszel (MH) test was used to estimate the common odds ratio (OR) across different strata.

Logistic regression analysis (LRA) was used to model the association between PE and RDS, BPD and severe BPD. Analysis by

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Table 1. Maternal, pregnancy and demographic information

	PE ($n = 279$)	Non-PE ($n = 939$)	p	Mean difference or unadjusted odds ratio (95% CI)
Gestational age (weeks)	26.2 ± 1.5	25.5 ± 1.6	<.001	.62 (.40–.83)
Birth weight (g)	739 ± 221	830 ± 230	<.001	−91 (−121–−60)
Small for gestational age	77 (28)	61 (7)	<.001	5.49 (3.79–7.94)
Race (Black)	167 (60)	442 (47)	.001	1.68 (1.28–2.20)
Gender (male)	133 (48)	512 (55)	.035	.76 (.58–.99)
Maternal age >35 years	57 (20)	133 (14)	.025	1.56 (1.10–2.20)
Maternal diabetes	25 (9)	47 (5)	.035	1.87 (1.13–3.10)
Maternal chronic hypertension	104 (37)	78 (8)	<.001	7.52 (5.44–10.38)
Magnesium sulfate	253 (91)	488 (52)	<.001	8.99 (5.89–13.7)
Antenatal steroids	273 (98)	834 (89)	<.001	5.73 (2.49, 13.19)
Chorioamnionitis	1 (0.4)	131 (14)	<.001	.02 (.003–.16)
Multiple gestation	36 (13)	251 (27)	<.001	.41 (.28–.59)
Prolonged rupture of membranes	9 (3)	273 (29)	<.001	.08 (.04–.16)
Delivery by cesarean section	271 (97)	625 (67)	<.001	17.0 (8.3–34.8)
Patent ductus arteriosus	200 (72)	653 (70)	.493	1.11 (.83–1.49)
Sepsis	93 (33)	294 (31)	.524	1.09 (.83–1.46)

Data are number (%), mean ± SD or odds ratio (95% confidence interval)

Table 2. Respiratory outcomes

	Severe RDS[a]			BPD[b]			Severe BPD[b]		
GA (weeks)	PE ($n = 275$)	Non-PE ($n = 915$)	Unadjusted OR (95% CI)	PE ($n = 241$)	Non-PE ($n = 792$)	Unadjusted OR (95% CI)	PE ($n = 241$)	Non-PE ($n = 792$)	Unadjusted OR (95% CI)
23–24	21 (43)	81 (33)	1.54 (.82–2.87)	23 (68)	100 (60)	1.40 (.64–3.06)	17 (50)	60 (36)	1.78 (.85–3.75)
25–26	37 (40)	76 (21)	2.45 (1.51–3.99)	45 (54)	106 (33)	2.46 (1.51–4.01)	32 (39)	51 (16)	3.38 (1.98–5.77)
27–28	38 (29)	50 (16)	2.08 (1.28–3.37)	38 (31)	42 (14)	2.70 (1.64–4.47)	28 (23)	21 (7)	3.86 (2.10–7.12)
All	96 (35)[c]	207 (23)	1.83 (1.37–2.46)	106 (44)[d]	248 (31)	1.72 (1.28–2.31)	77 (32) [e]	132 (17)	2.35 (1.69–3.26)

Data are number (%) or odds ratio (95% confidence interval)
[a]Severe RDS among infants alive at day 1
[b]BPD and severe BPD among infants alive at 36 weeks postmenstrual age
[c]MH common OR adjusted for GA (95% CI): 2.1 (1.5–2.7), $p < .001$
[d]MH common OR adjusted for GA (95% CI): 2.3 (1.7–3.2), $p < .001$
[e]MH common OR adjusted for GA (95% CI): 3.0 (2.1–4.3), $p < .001$

generalized estimating equations (GEE) was used to test these associations while adjusting for correlation on these outcomes between siblings. To account for the potential censoring effect on severe RDS of death on day 1 and on BPD or severe BPD of death before 36 weeks PMA, the associations between PE and the composite variables severe RDS or death on d1, BPD or death before 36w PMA, and severe BPD or death before 36w PMA were also evaluated by LRA and GEE.

LRA and GEE models adjusted for year of birth, GA, race, gender, small for gestational age (SGA, defined as birth weight <10th percentile), chorioamnionitis, maternal chronic hypertension, multiple birth, maternal diabetes, prolonged rupture of membranes, defined as >18 h, administration of antenatal steroids and $MgSO_4$. Additionally, sepsis, patent ductus arteriosus (PDA) and severe RDS were included in the models for BPD and severe BPD.

MH common odds ratio was used to evaluate the risk for BPD associated with PE across the strata of infants born to mother with or without chronic hypertension. To evaluate the interaction between PE and maternal chronic hypertension was evaluated in the statistical models by introducing the interaction term.

All statistical analyses were performed using SPSS version 24 (IBM Corporation, NY).

RESULTS

The cohort consisted of 1218 consecutive inborn infants of which 280 (23%) were exposed to PE. PE exposed infants were of a higher gestational age but weighed less at birth compared to the non-exposed infants. Maternal and demographic characteristics and prenatal risk factors of the PE exposed and non-exposed infants are shown in Table 1. In this cohort, 286 infants (24%) were twins or multiples. There were no trends in the proportion of infants born to mothers with PE during the 11 year period (22% in years 2005–07, 23% in years 2008–10, 26% in years 2011–13, and 21% in years 2014–15).

To evaluate the association between PE and severe RDS, only infants who were alive at the end of day 1 were included in the analysis ($n = 1190$). PE exposed infants had a higher incidence of severe RDS compared to non-exposed infants across GA strata (Table 2). This association was confirmed by LRA [OR 2.4 (CI: 1.8–3.3)] (Table 3). Analysis by GEE showed the association between PE and severe RDS after adjusting for the correlation between siblings [OR 2.31 (CI: 1.59–3.34)].

LRA showed PE exposure was associated with increased risk for the composite of severe RDS or death on d1 [OR 2.24 (CI: 1.65–3.05)]. Analysis by GEE confirmed this association after

Table 3. Severe RDS

Factor	Adjusted OR (95% CI) by LRA for severe RDS[a]	Adjusted OR (95% Wald CI) by GEE for severe RDS[a,b]
Lower GA (per week)	1.25 (1.15–1.36)	1.21 (1.11–1.33)
Antenatal steroids	0.59 (0.38–0.93)	0.59 (0.37–0.95)
Multiple pregnancy	1.45 (1.06–1.98)	n/a
Preeclampsia	2.40 (1.76–3.29)	2.31 (1.59–3.34)

Only risk factors that were found significantly associated with severe RDS are shown
LRA logistic regression analysis, *GEE* generalized estimating equations, *n/a* not applicable
[a]Severe RDS (defined as need for ≥ 30% supplemental oxygen on day 1) among infants alive at day 1
[b]Adjusted for siblings

Table 4. Risk factors for BPD and severe BPD

Factor	Adjusted OR (95% CI) by LRA for BPD[a]	Adjusted OR (95% Wald CI) by GEE for BPD[a,b]	Adjusted OR (95% CI) by LRA for severe BPD[a]	Adjusted OR (95% Wald CI) by GEE for severe BPD[a,b]
Lower GA (per week)	1.53 (1.36–1.72)	1.14 (1.03–1.25)	1.36 (1.19–1.55)	1.13 (1.01–1.26)
BW < 10th percentile	5.57 (3.15–9.86)	2.21 (1.46–3.34)	3.25 (1.91–5.54)	2.03 (1.32–3.12)
Non-black	1.37 (1.004–1.87)	1.24 (0.94–1.65)	1.34 (0.94–1.92)	1.27 (0.90–1.79)
Male	1.33 (0.98–1.82)	1.19 (0.90–1.58)	1.75 (1.22–2.49)	1.60 (1.15–2.23)
Sepsis	1.67 (1.21–2.32)	2.27 (1.70–3.04)	1.75 (1.22–2.52)	2.30 (1.62–3.27)
PDA	1.45 (1.06–1.98)	3.19 (2.14–4.75)	2.53 (1.41–4.53)	3.47 (2.00–6.02)
On MV at day 1	2.36 (1.51–3.66)	2.09 (1.34–3.27)	2.84 (1.54–5.24)	2.55 (1.36–4.78)
Severe RDS	2.56 (1.79–3.66)	1.62 (1.20–2.19)	2.44 (1.68–3.54)	1.83 (1.30–2.59)
Preeclampsia	1.64 (1.12–2.40)	1.42 (0.96–2.08)	2.18 (1.45–3.28)	2.17 (1.41–3.33)

LRA logistic regression analysis, *GEE* generalized estimating equations
[a]BPD and severe BPD [supplemental oxygen and ≥30% oxygen at 36w postmenstrual age (PMA), respectively] among infants alive at 36 weeks PMA
[b]Adjusted for siblings

adjusting for the correlation between siblings [OR 2.19 (Wald CI: 1.52–3.15)].

The association between PE and BPD was assessed among infants who were alive at 36 weeks PMA ($n = 1033$). PE exposed infants had a significantly higher incidence of BPD and severe BPD compared to non-exposed infants across GA strata (Table 2).

LRA showed PE exposure was associated with increased risk for BPD. However, GEE analysis adjusting for siblings did not show a significant association between PE and increased risk for BPD (Table 4).

LRA showed PE was significantly associated with an increased risk for severe BPD. This association was also shown to be significant after adjustment for siblings by GEE (Table 4).

When evaluated in the entire cohort of 1218 infants, LRA showed PE was associated with increased risk for the composite BPD or death before 36 w PMA [OR 1.50 (CI: 1.05–2.14)]. In contrast, GEE analyses showed this association was not significant after adjusting for correlation between siblings [OR 1.45 (Wald CI: 0.96–2.18)]. LRA showed PE was associated with increased risk for the composite severe BPD or death before 36 w PMA [OR 1.77 (CI: 1.24–2.55)]. This association was also shown to be significant by GEE analysis adjusting for the correlation between siblings [OR 1.86 (Wald CI: 1.23–2.82)].

There was no significant difference in mortality between PE exposed and non-exposed infants [17% in the PE and 18% in the non-PE infants].

To explore the independence of the association between PE and BPD from chronic maternal hypertension, the cohort was stratified according to the exposure to chronic maternal hypertension. Among survivors at 36 weeks PMA, 182 (18%) infants were born to mothers with chronic hypertension. Of these, 104 infants (57%) were also exposed to PE. Within the strata of infants born to mothers with chronic hypertension the incidence of BPD was 46% and 33% in the PE and non-PE infants, respectively. Similarly, within the strata of infants born to mothers without chronic hypertension the incidence of BPD was 42% and 31% in the PE and non-PE infants, respectively. MH test showed a significant increase in risk for BPD associated with PE controlling for chronic maternal hypertension [MH common OR adjusted for GA 2.23 (CI: 1.6–3.2)]. LRA showed the interaction term of PE and maternal chronic hypertension was not associated with increased risk for BPD [OR 1.07 (CI:.45–2.53)] or severe BPD [OR 1.43 (CI: .75–2.73)].

DISCUSSION

In this cohort of extremely preterm infants, PE exposure was associated with an increased risk for severe RDS and severe BPD. These associations were shown to be independent of confounding factors.

The association between PE and increased risk for severe RDS is in agreement with previous reports that showed higher rates of RDS in infants exposed to PE.[15,16] This association is biologically plausible given the experimental evidence suggesting that the anti-angiogenic environment of PE could result in an abnormal fetal and neonatal pulmonary vascular development. Cord blood of babies born to mothers with PE has relatively low levels of VEGF and high levels of anti-angiogenic factors like soluble vascular endothelial growth factor (VEGF) receptor-1, also known as sFlt-1,)

and soluble endoglin (s-ENG) that can affect lung alveolarization and vasculature development.[7,17,18]

Animal experiments indicate a correlation between in utero exposure to a VEGF rich environment and increased surfactant production.[19] Although there is no human data available, it is possible that the in-utero exposure to the anti-VEGF environment with PE could have detrimental effects on surfactant function.

The increased risk for poor respiratory outcome in extremely premature infants from exposure to preeclampsia has not been clearly established. The association between PE and development of severe BPD observed in the present study is in agreement with some reports of increased risk of BPD in infants exposed to PE.[8–10] In contrast, recent studies have not shown an association between PE and BPD.[11–13] The reasons for the different findings are not clear but they may be related to demographic differences due to the greater proportion of infants born to black or Hispanic mothers in the present cohort. The potential interaction between different demographic factors and preeclampsia require examination. In this cohort, analysis by LRA did show an association with BPD but this association was not shown to be significant when evaluated by GEE to adjust for the correlation between siblings on this outcome.

The association between PE and an increased risk for severe BPD shown in the present study, which was adjusted for RDS, suggests the anti-angiogenic uterine environment that results in impaired fetal alveolar and vascular development may predispose these infants to impaired postnatal lung growth.

Chronic maternal hypertension is a major determinant of PE. Therefore, it is difficult to separate the impact of chronic hypertension from that of PE on the respiratory evolution in premature infants. A secondary analysis of the present cohort within the strata of infants exposed to chronic maternal hypertension still showed a significant association between PE and development of severe BPD. The association between PE with RDS and severe BPD was particularly striking among infants born at more advanced gestational age. This suggests the duration of the in-utero exposure to the fetal environment of PE may play an important role in the negative respiratory outcomes. It is also possible that the less striking association between PE and severe RDS or severe BPD in the lower gestational age group is due to the dominant effect of immaturity on these two outcomes over other predisposing factors.

The association between PE and poor respiratory evolution does not establish causality. The results however, show a very strong correlation after adjusting for potential confounding factors such as of chronic maternal hypertension, SGA, and other conditions that could also affect respiratory outcome in premature infants.

In conclusion, analysis of this cohort of extremely premature infant showed exposure to preeclampsia is independently associated with an increased risk for severe RDS and severe BPD. These findings underscore the need to further explore the processes triggered by preeclampsia and develop strategies for early detection and treatment that could prevent some of the detrimental effects on fetal development and neonatal respiratory outcomes.

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ADDITIONAL INFORMATION

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