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Preeclampsia and risk of developing bronchopulmonary dysplasia in very preterm neonates

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ABSTRACT

Objective: Bronchopulmonary dysplasia (BPD) is a severe common complication of preterm birth with considerable short and long-term consequences. As more evidence is emerging that dysregulation of angiogenesis is implicated in the pathogenesis of preeclampsia as well as in fetal lung development, we assessed if preeclampsia is associated with development of BPD in very preterm neonates.

Study design: A retrospective cohort study of 308 infants born between 24^{+0} and 31^{+6} weeks of gestation in 2011 and 2012. We performed association analysis with univariable and multivariable logistic regression, adjusting for confounders. Models were additionally adjusted for intermediates, to show how an association can be disguised by over adjusting.

Main outcome measure: BPD was diagnosed at 36^{+0} weeks postmenstrual age and defined as the need for oxygen ($FiO2 > 0.21$) for at least 12 h per day, for more than 28 days before or at 36^{+0} weeks postmenstrual age, and classified as mild, moderate or severe.

Results: After applying our exclusion criteria, we report our primary outcome on 247 mother-neonate pairs. Fifty-nine neonates developed BPD (23.9%) which was moderate to severe in 27 of them (10.9%). Preeclampsia was associated with BPD, adjusted odds ratio, 95% confidence interval: 4.22 (1.63, 10.91). However, after adjusting for additional intermediates no statistical significance remained, adjusted odds ratio, 95% confidence interval: 1.87 (0.49, 7.24).

Conclusion: This study shows that early-onset preeclampsia is associated with development of BPD in the very preterm neonate. Part of this association is mediated by fetal growth restriction and mode of delivery.

1. Introduction

Bronchopulmonary dysplasia (BPD) is a severe complication of preterm birth associated with respiratory morbidity and impaired neurodevelopment in later life [1,2]. Its prevalence is still high, with 25% in neonates born < 32 weeks of gestation, in part because more extreme preterm neonates from 24^{+0} weeks post-menstrual age (pma) onwards survive [3]. The pathogenesis of BPD is multifactorial and still not completely understood. What is known, however, is that preterm birth disturbs early lung development and consequently is a risk factor. Gestational age at birth has indeed been found inversely related with the risk for BPD [4–6]. Furthermore, dysregulation of angiogenesis may be implicated in the development of BPD. In animal studies, inhibiting of vascular endothelial growth factor resulted in reduced alveolarization and persistent abnormalities of pulmonary vascular structures [7,8]. A high concentration of endostatin (an anti-angiogenic growth factor) in human cord plasma predicts the development of BPD in very low birth weight infants [9]. Next to BPD, more evidence is emerging for an important role of an anti-angiogenic status in the pathogenesis of preeclampsia [10,11]. It has been hypothesized, therefore, that neonates of mothers with preeclampsia have a higher risk for developing BPD. Tsao et al. showed that an antiangiogenic status of the mother did

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reflect in the neonate, as neonates of mothers with preeclampsia had higher cord blood soluble fms-like thyrosine kinase 1 (sFlt-1) but lower placental growth factor and vascular endothelial growth factor (VEGF) levels. As a result these infants had lower platelet levels [12]. Tang et al. administered sFlt into the amnion sac of pregnant rats at a stage of lung development parallel to human lung development in preterm infants at 24–26 weeks of gestation. This excess of sFlt-1 decreased VEGF signalling and increased apoptosis; reduced alveolarization and pulmonary vascular growth was then observed during infancy of the offspring [13].

Results of several epidemiologic studies assessing the association between preeclampsia and BPD are inconclusive [4,6,14–20]. This can at least partly be explained by unprecise definitions of BPD, the use of data from national registration systems with risk for false positive or false negative diagnosis, and most importantly by adjusting outcome data for intermediates rather than for confounders alone. It is still very difficult to predict who of these neonates will develop BPD. More insight in associations could lead to earlier detection, improve counselling and support hypotheses for future research, eventually leading to better preventive or therapeutic measures [21]. Therefore we addressed the question whether early onset preeclampsia in the mother is associated with development of BPD in the neonate.

2. Methods

2.1. Design and procedures

We performed a retrospective cohort study and included all singletons born between 24^{+0} and 31^{+6} weeks of gestation in 2011 and 2012 in a large academic level III perinatal centre in the Netherlands. We excluded infants with a major congenital anomaly. Two investigators (FW, maternal data & JR, neonatal data) systematically extracted medical information from digital records of the department of Obstetrics and Gynaecology, the division of neonatology and the registration system of the Neonatal Intensive Care Unit). At this stage they were blinded to the neonatal outcome and maternal outcome, respectively. Almost all included neonates had been transferred to a non-academic hospital before 36 weeks pma. As registration of the diagnosis BPD in a national database in a referral-based health care system may not be accurate [22], JR visited the hospitals involved to extract the follow-up information until 36 weeks pma, including all days of ventilation and oxygen administration and results of the oxygen reduction test if performed. Any ambiguities were solved in consensus meetings. This concerned six children who had an intercurrent disease or operation for which they briefly needed mechanical ventilation at 36 weeks pma. In these cases, receiving respiratory support just before onset of the intercurrent disease determined the classification of BPD. The study protocol was approved by the local institutional review board, (MEC-2014-013).

2.2. Main determinants

Preeclampsia was defined as new onset hypertension (systolic blood pressure $\geq$140 mmHg or a diastolic blood pressure $\geq$90 mmHg, measured twice), after 20 weeks of gestation with the coexistence of one or more of the following new-onset conditions: 1) proteinuria ($\geq$0.3 g/24 h or a protein-creatinine-ratio $\geq$30 mg/mmol), 2) other maternal organ dysfunction or 3) fetal growth restriction, according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria [23]. Superimposed preeclampsia was defined as preeclampsia in patients with chronic hypertension. All cases concerned early onset preeclampsia (< 32 weeks of gestation) [24]. HELLP syndrome was defined as thrombocytes less than 100×10^9/L, both aspartate aminotransferase and alanine aminotransferase more than 70 U/L, and lactate dehydrogenase more than 600 U/L [25].

2.3. Outcome measures

Our primary outcome measure BPD was defined according to the National Institute of Child Health and Human Development (NICHD) Consensus Statement and the classification of severity as proposed by Jobe et al. [26]. This entailed the need for oxygen (Fraction of inspired Oxygen (FiO_2) > 0.21) for at least 12 h per day, for more than 28 days before or at 36 weeks pma with a classification as follows: mild if $FiO_2 = 0.21$, or $0.21 < FiO_2 \leq 0.30$ without any incidents during phase out of oxygen in an oxygen-reduction test; moderate if $0.21 < FiO_2 < 0.30$ and an oxygen reduction test with incidents during phase out, or an oxygen reduction test was indicated but not performed; severe if FiO2 $\geq$ 0.30, or admission of continuous positive airway pressure or mechanical ventilation was required (Table S1). Secondary we analysed the association of preeclampsia with the combined outcome measure 'deceased or BPD', and with 'uneventful survival', defined as: no BPD, no retinopathy of prematurity (ROP), no sepsis, no necrotizing enterocolitis with Bell's criteria 1–3 and no interventricular haemorrhage (IVH) at 36^{+0} weeks pma.

2.4. Covariates

Gestational age was calculated based on a first trimester ultrasound. Prolonged preterm prelabour rupture of membranes (prolonged pPROM) was defined as delivery > 24 h after pPROM. Chorioamnionitis was clinically diagnosed if there was maternal fever ($\geq$38 °C), maternal or fetal tachycardia, or increased levels of c-reactive protein or white blood cell/leukocyte count without any other cause, justifying adaptation of clinical management. A pathological diagnosis of chorioamnionitis was made if microscopic invasion of neutrophilic granulocytes was major. We choose prolonged pPROM as a substitute for chorioamnionitis as this is a more objective measure and had a good correlation with clinical chorioamnionitis as well as with the diagnosis based on pathology results [27]. A completed course of antenatal corticosteroids was rated as "yes" if delivery of the neonate was at least 24 or 12 h after the last dose of twice betamethasone 12 mg every 24 h, or the last dose of four times dexamethasone every 12 h, respectively.

Respiratory distress syndrome of the neonate (RDS) was defined as respiratory distress early postpartum with the need of surfactant therapy. The number of surfactant doses was registered. Admission of postnatal steroids, dexamethasone or hydrocortisone, were registered. Sepsis was registered as early onset (< 72 h after birth) or late onset (> 72 h after birth) and registered as 'proven' with a positive blood culture and as 'clinical' upon clinical signs and/or a high C-reactive protein level followed by treatment with antibiotics for 5 days or more. Patent ductus arteriosus was registered if confirmed by ultrasound, either treated with medication or surgical ligation. If medication failed and surgical ligation was still necessary, it was registered as 'patent ductus arteriosus needing surgical ligation'. Necrotizing enterocolitis (NEC) was defined as a clinical presentation in combination with an abdominal X-ray, meeting Bell's criteria $\geq$2. Retinopathy of prematurity (ROP) was defined as ROP grade 1 and up in one or two eyes, diagnosed by a trained paediatric ophthalmologist. Intraventricular haemorrhage was defined as all subependymal or choroid plexus bleedings with breakthrough in the lateral ventricle. Both uni- and bilateral bleedings were included. Diagnosis was made by routine cerebral ultrasound performed by trained neonatologists.

2.5. Statistical analysis

Descriptive statistics of continuous variables are presented as mean (SD) when distribution is normal, and as median (IQR) when distribution is skewed. Descriptive statistics of discrete variables are presented as valid percentage (absolute numbers), this means that percentages are calculated without taking missing values into account. Differences in baseline characteristics of continuous variables were tested using

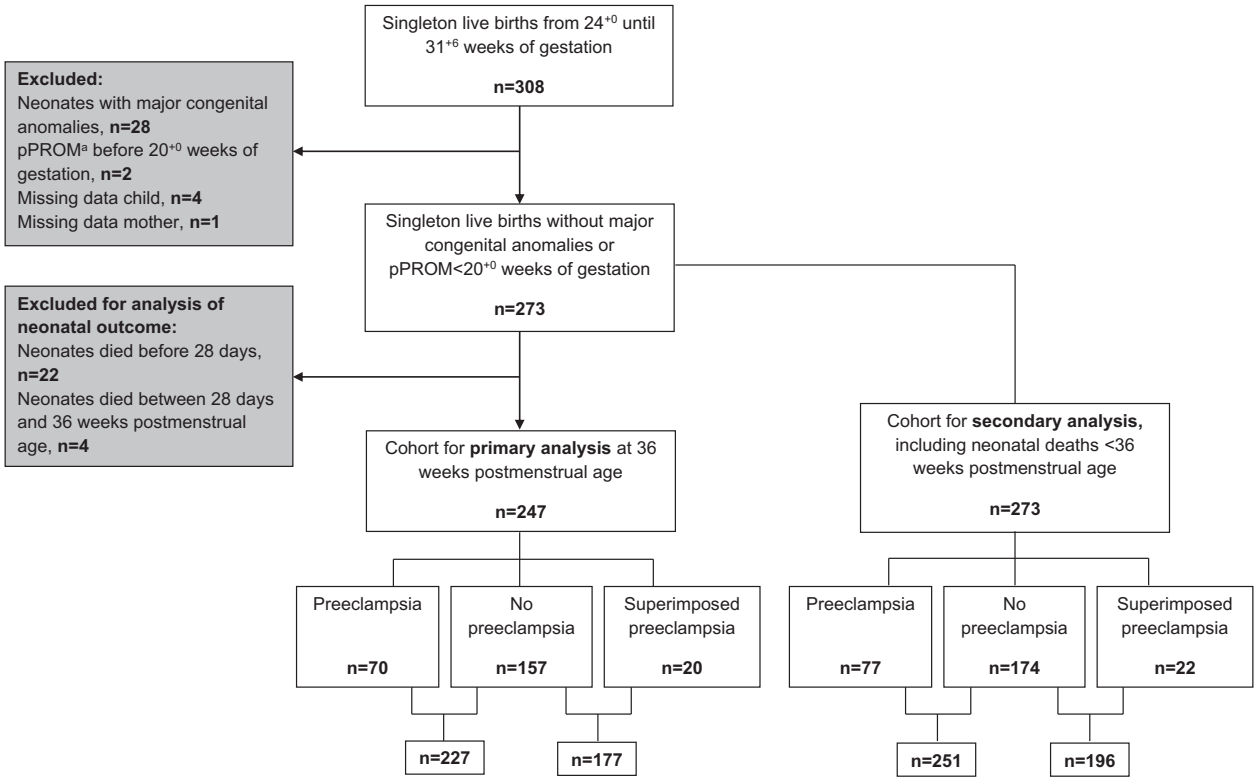
Student's *t* or if non parametric with the Mann-Whitney *U* test. Categorical variables were tested with the Chi-square test. We used univariable and multivariable binary logistic regression models to examine the associations of the primary determinants preeclampsia or superimposed preeclampsia, with the primary outcome BPD of the neonate, and in addition with our secondary outcome measures 'deceased or BPD' and 'uneventful survival'. After crude analysis, models were adjusted for confounders: nulliparity, prolonged pPROM, gestational age at birth and child's gender [6,15,18,28]. Secondly, models were additionally adjusted for the following intermediates: administration of antenatal steroids, birth weight Z-scores, mode of delivery, RDS, invasive ventilation, administration of postnatal steroids, clinical or proven sepsis and treatment of a persistent ductus arteriosus. An intermediate is a cofactor which is in between the pathway from the determinant to the outcome measure. The cause of very preterm labor (e.g. preeclampsia versus spontaneous contractions) influences very much the likelihood of completed antenatal corticosteroids and the chance of delivering by cesarean section, both influence chances of RDS, wet lung and risk for (invasive) ventilation. We therefore treated 'antenatal corticosteroids' and 'mode of delivery' as an intermediate. The intermediate model served to show how an association can be disguised by over adjusting. In addition, we performed a mediation analysis on variables importantly attenuating the association to show which mediators can partly explain the association found. The difference between the original effect estimates and the effect estimates after additional adjustment for potential mediators was expressed as percentage change. The proportion mediation was calculated as (indirect effect)/(indirect effect + direct effect).

As adjustment for gestational age and birth weight could lead to multicollinearity, we choose to adjust for birth weight Z-scores. Results are presented as (adjusted) odds ratios (ORs) with 95% confidence interval (95% CI). We performed a sensitivity analysis excluding all mothers with superimposed preeclampsia. Statistical analyses were performed using IBM SPSS Statistics version 21 for Windows software (SPSS Inc.).

3. Results

The study profile is shown in Fig. 1. In total we analysed 247 mother-neonate pairs for the primary analyses and 273 mother-neonate pairs (including neonatal deaths before 36 weeks pma) for the secondary analysis. The cohort included 4 neonates who also participated in the SToP-BPD study [29] in which patients are randomized to either hydrocortisone or placebo for 22 days, to prevent the development of BPD at 36 weeks pma. We included these neonates to prevent selection bias. All four were ventilator-dependent at 7–14 days pma, one died before 36 weeks pma and the other three developed severe BPD for which two were given postnatal steroids outside the study protocol.

Causes for preterm labour were preeclampsia (19.8%), preterm contractions (29.1%), pPROM (15.8%), cervical insufficiency (1.6%), suspicion of fetal distress (30%) and other maternal morbidity (3.6%, i.e. severe maternal blood loss without fetal distress). Ninety mothers (36.4%) had been diagnosed with preeclampsia of whom 20 (22.2%) had superimposed preeclampsia and 12 (14.1%) had HELLP syndrome. They had never prolonged pPROM, had less clinical chorioamnionitis, and delivered more often with a caesarean section. Infants of preeclamptic mothers were more often female and were on average born at a higher gestational age with a lower birth weight than children of mothers without preeclampsia (Table 1). Of 247 neonates, 59 (23.9%) developed BPD, which was classified as mild in 32 (13.0%), as moderate in 3 (1.2%) and severe in 24 (9.7%). Besides a lower risk for intraventricular haemorrhage and proven sepsis for neonates of mothers with (superimposed) preeclampsia, there were no statistically significant differences in comorbidity (Table 2). The incidence of infants with BPD did not differ between women with (superimposed) preeclampsia (25.6%) or without preeclampsia (22.9%).



[a]Preterm prelabour rupture of membranes (pPROM)

Fig. 1. Flow chart showing the study profile.

Table 1
Baseline characteristics of mothers and their children, stratified by the presence of (superimposed) preeclampsia (PE).

Original data, n = 247 Baseline characteristics	(superimposed) PE[a] % (n)[c] 36.4 (90)	No PE % (n)[c] 63.6 (157)	*P*-value[b]
Mothers			
Age at delivery (years)[d]	30.3 (5.6)	30.3 (5.4)	0.91
Body mass index (kg/m^2)[e]	24 (22–29)	23.0 (20–27)	0.10
Missing, n	*23*	*43*	
Nulliparity	73.3 (66)	60.5 (95)	0.04
First trimester ultrasound	95.2 (80)	97.3 (1 4 2)	0.43
Missing, n	*6*	*11*	
Prolonged pPROM[f]	0 (0)	28.0 (44)	n/a
Chorioamnionitis	1 (1,2)	39.0 (55)	< 0.001
Missing, n	*9*	*16*	
Caesarean section	95.6 (86)	38.2 (60)	< 0.001
Diabetes mellitus	3.3 (3)	1.3 (2)	0.29
Gestational diabetes	3.3 (3)	4.5 (7)	0.67
(Gestational) hypertensive disorder			
Chronic hypertension	22.2 (20)	1.3 (2)	< 0.001
GH[g]	n/a	0.4 (1)	n/a
Neonates			
Gender, male	42.2 (38)	63.1 (99)	0.002
Gestational age at birth (weeks)[e]	29.9 (28.6–31.0)	28.9 (26.8–30.8)	< 0.001
Birth weight (grams)[e]	1100 (945–1331)	1280 (983–1547)	0.001
Birth weight z-score[e]	−0.89 (−1.47; −0.60)	0.08 (−0.26; 0.60)	< 0.001
Antenatal corticosteroids completed	78.9 (71)	52.2 (82)	< 0.001
5 min Apgar < 7	12.2 (11)	17.2 (27)	0.29
pH umbilical cord[e]	7.27 (7.22–7.32)	7.33 (7.27–7.37)	< 0.001
Missing, n	*10*	*13*	

[a] Mothers with preeclampsia and superimposed preeclampsia
[b] Differences in baseline characteristics of continuous variables were tested using Student's *t*, or if non-parametric with the Mann-Whitney *U* test. Categorical variables were tested with the Chi-square test.
[c] Values are valid percentages (without taking missing values into account) with (absolute numbers).
[d] means (SD).
[e] medians (IQR).
[f] Preterm prelabour rupture of membranes > 24 h (prolonged pPROM).
[g] Gestational hypertension (GH).

Multivariable logistic regression analysis of mothers with preeclampsia compared to mothers without preeclampsia showed significant associations between preeclampsia and BPD, preeclampsia and 'moderate to severe BPD'and thirdly for preeclampsia and 'deceased or BPD', after adjusting for confounders; the ORs (95%CI) were respectively 4.22 (1.63, 10.91), 3.94 (1.24, 12.49) and 3.76 (1.61, 8.82) (Tables 3a and b). After additional adjustment for intermediates, these associations showed no statistical significance anymoreTherefore, neonates of mothers with and without preeclampsia had similar chances of developing BPD, to survive uneventfully or to decease in the first 36 weeks of life. If we added the intermediates one by one, birth weight z-score and mode of delivery were most important in attenuating the association. Antenatal corticosteroids did not change the association found. Mediation analysis showed the mediation proportion of birth weight z-score to be 44% and of mode of delivery 53% (Table S2). The results of the multivariable analysis of mothers with superimposed PE were similar to the results of woman with preeclampsia (supplementary Table S3a and b).

Preeclamptic mothers with an infant who developed BPD did not differ clinically from preeclamptic mothers with an infant who did not develop BPD with regard to blood pressure, severity of proteinuria, deviating laboratory results or intravenous treatment with magnesiumsulphate or antihypertensive medication. There was no significant difference between neonates with or without BPD in the time elapsed between diagnosis of preeclampsia and date of birth, median (interquartile range) 5.0 (2.5–7.5) and 3.5 (2.0–8.8) days respectively (p = 0.50). Gestational age at birth did differ significantly, p < 0.001 (supplementary Table S4).

4. Discussion

In this cohort of 247 mother-neonate pairs we found a strong association of preeclampsia in the mother with BPD in the neonate (OR, 95%CI: 4.22 (1.63, 10.91)). This association attenuated into non-significant, when adjusting for intermediates on the pathway from preeclampsia to BPD, particularly after adjusting for mode of delivery and birth weight Z-scores.

Several strengths of this study are worth mentioning. First, it comprises of detailed data of all extreme preterm deliveries (i.e. < 32 weeks of gestation) in 2011 and 2012 for a large region of the Netherlands. (The Erasmus MC-Sophia Children's Hospital has one of the largest level III NICU of Western Europe.) In countries with a referral-based health care system, registration of perinatal data and the diagnosis BPD in a national database may not be accurate [22]. Therefore, two dedicated researchers collected all maternal and neonatal data with very little loss to follow up, including site visits to the hospitals to which the neonates were discharged. Secondly, a correct due date is of great importance when analysing data in preterm births. In our cohort 96.5% has had a first trimester ultrasound. In addition, selection bias was prevented by selecting a cohort based on gestational age in two randomly chosen years. Cohorts based on 'very low birth weight infants' will automatically include many growth restricted neonates, particularly of mothers with preeclampsia and placental insufficiency. Given that the risk for BPD is declining significantly with an increase of gestational age, growth restricted neonates with a higher gestational age are relatively protected compared to infants with a birth weight on the 50th percentile, but with a much lower gestational age. As birth weight is an

Table 2
Incidence of neonatal morbidity and ventilation, stratified by presence of (superimposed) preeclampsia (PE).

Original data, n = 247 Neonatal morbidity	Total % (n)[c] 100 (247)	(superimposed) PE[a] % (n)[c] 36.4 (90)	No PE % (n)[c] 63.6 (157)	*P*-value[b]
BPD[d]	23.9 (59)	25.6 (23)	22.9 (36)	0.65
Mild	13.0 (32)	12.2 (11)	13.4 (21)	0.38
Moderate or severe	10.9 (27)	13.3 (12)	9.6 (15)	0.43
RDS[e]	44.9 (111)	52.2 (47)	40.8 (64)	0.04
Postnatal steroids	2.0 (5)	2.2 (2)	1.9 (3)	0.86
Missing, n	*1*	*1*	*0*	
Ventilation				
Invasive (days)	1 (0–5)	1 (0–5)	1 (0–6)	0.21
Non-invasive (days)	24 (6–39)	23 (6–37)	25 (6–42)	0.26
Nasal cannula (days)	8 (4–14)	7 (3–11)	10 (4–15)	0.01
Persistent ductus arteriosus	19.4 (48)	14.4 (13)	22.2 (36)	0.18
Sepsis				
Clinical diagnosis	26.3 (65)	31.1 (28)	23.6 (37)	0.64
Proven by culture	25.5 (63)	16.7 (15)	30.6 (48)	0.04
IVH[f] ≥ grade II	10.1 (25)	3.3 (3)	14.0 (22)	0.01
ROP[g]				
ROP stage I, n(%)	15.0 (36)	15.9 (14)	14.5 (22)	0.78
ROP > stage II, n(%)	5.0 (12)	4.5 (4)	5.3 (8)	0.83
Missing, n	*7*	*2*	*5*	
NEC[h], Bells stage 2 or 3	4.0 (10)	1.1 (1)	5.7 (9)	0.11

[a] Mothers with preeclampsia and superimposed preeclampsia.
[b] Differences in baseline characteristics of continuous variables were tested using Student's *t* or if non parametric with the Mann-Whitney *U* test. Categorical variables were tested with the Chi-square test.
[c] Values are valid percentages (without taking missing values into account) with (absolute numbers) or medians (IQR).
[d] Bronchopulmonary dysplasia.
[e] Respiratory distress syndrome (RDS) defined as the need for surfactant therapy early postpartum.
[f] Interventricular haemorrhage (IVH).
[g] Retinopathy of prematurity (ROP).
[h] Necrotising enterocolitis (NEC).

Table 3a
Multivariable logistic regression analysis of bronchopulmonary dysplasia (BPD), in relation to maternal preeclampsia.

Original data n = 227	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
No BPD	*Reference*	*Reference*	*Reference*
BPD	1.00 (0.51, 1.95)	**4.22 (1.63, 10.91)**	1.87 (0.49, 7.24)
None or mild BPD	*Reference*	*Reference*	*Reference*
Moderate or severe BPD	1.40 (0.58, 3.67)	**3.94 (1.24, 12.49)**	1.65 (0.30, 9.24)

[a] Adjusted for potential confounders: nulliparity, prolonged pPROM, gestational age at birth and gender.
[b] Adjusted for above-mentioned confounders and additionally for the following intermediates: antenatal corticosteroids, birth weight Z-score, mode of delivery, respiratory distress syndrome, invasive ventilation, admission of postnatal corticosteroids, clinical or proven sepsis, treatment of a persistent ductus arteriosus.

Table 3b
Multivariable logistic regression analysis of 'deceased or BPD' and 'uneventful survival', in relation to maternal preeclampsia.

Original data n = 251	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
Not deceased and no BPD	*Reference*	*Reference*	*Reference*
Deceased[c] or BPD	0.97 (0.54, 1.75)	**3.76 (1.61, 8.82)**	2.05 (0.55, 7.70)
No uneventful survival[d]	*Reference*	*Reference*	*Reference*
Uneventful survival[d]	1.17 (0.66, 2.09)	0.75 (0.38, 1.48)	0.45 (0.10, 2.09)

[a] Adjusted for potential confounders: nulliparity, prolonged pPROM, gestational age at birth and gender.
[b] Adjusted for above-mentioned confounders and additionally for the following intermediates: antenatal corticosteroids, birth weight Z-score, mode of delivery, respiratory distress syndrome, invasive ventilation, admission of postnatal corticosteroids, clinical or proven sepsis, treatment of a persistent ductus arteriosus.
[c] Deceased within 24 h: 1.6% (n = 4), between day 1 and 7: 1.6% (n = 4), between day 7 and 28: 4.8% (n = 12), between 28 days and 36 weeks postmenstrual age: 1.6% (n = 4).
[d] Uneventful survival is defined as survival without BPD, retinopathy of prematurity, sepsis, necrotizing enterocolitis Bell's stage 1–3 or intraventricular haemorrhage ≥ grade 2.

influential intermediate, adjusting for birth weight Z-scores cannot correct selection bias [30].

Some limitations need to be addressed as well. Although we thoroughly collected data, the retrospective nature of the data had some drawbacks. For example, reliable information on smoking habits and ethnicity was not available. As smoking decreases the risk for preeclampsia and increases the risk for IUGR and BPD, and BPD is probably partly a genetic/epigenetic disease, our results are potentially influenced by this missing information.

Although some studies assessing the association between preeclampsia and BPD find no statistical significant or negative associations [15,17,18], most recent studies show a positive association [4,6,14,16,19,20]. This discrepancy can be explained by the use of different definitions for the outcome measure [17], by considerable loss to follow up (probably mostly healthy neonates of healthy mothers) and by selecting cohorts based on very low birth weight [15,18] as described above. Additionally, in most previous studies, analyses were adjusted for intermediates rather than for confounders alone, which could have influenced results [31,32]. Overall, statistical association analysis in preterm births is difficult, as there is no healthy group to compare with. In addition it can be arguable which variables are confounders and which are intermediates (i.e. on the pathway from primary determinant to neonatal outcome measure). In association analyses one does not want to over-adjust, as this can disguise relevant associations [31,32]. However, part of the association found can be explained by some of the intermediates, therefore mediation analysis is increasingly being applied in epidemiological research and can help interpret the results.

Some studies show a strong significant association between very low birth weight and chronic lung disease (e.g. BPD) [33,34]. It is not clear, however, if the low birth weight causes the higher risk or that causality lies in factors preceding an IUGR. One could hypothesize that the association is rather based on placental insufficiency causing an altered angiogenic status and eventually fetal growth restriction. A recent study showed that pathologic changes of maternal vascular under perfusion of the placenta are significantly associated with BPD and subsequently with pulmonary hypertension [35]. In several cases of extremely preterm birth without signs of preeclampsia or fetal growth restriction, the pathologic changes in the placenta and the association with BPD were already present. This hampers epidemiologic association analyses [35]. Besides the hypothesis that the anti-angiogenic status disturbs lung development and is associated with BPD (as described in the introduction), also length of exposure to such an environment could hypothetically be of influence. Active management (iatrogenic preterm delivery) could therefore hypothetically also be beneficial to the neonate and not only to the mother.

5. Conclusion

This study shows that early-onset preeclampsia is associated with development of bronchopulmonary dysplasia in the very preterm neonate, part of this association is mediated by fetal growth restriction and mode of delivery. Future research should focus on elucidating not only the pathogenesis of BPD in the offspring of mothers with preeclampsia, but also on the pathogenesis of placental dysfunction and a disturbed angiogenetic status, as the latter may lead to disturbed fetal lung development in the offspring of woman with hypertensive diseases.

6. Disclosure

The authors report no conflict of interest.

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Appendix A. Supplementary data

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