Abstract

Background and objectives

Small for gestational age and preeclampsia have both been described as risk factors for bronchopulmonary dysplasia in preterm neonates, but their respective role in the occurrence of bronchopulmonary dysplasia is debated. We evaluated the relation between small for gestational age and bronchopulmonary dysplasia in neonates born to mothers with preeclampsia. We hypothesized that low birth weight is still associated with bronchopulmonary dysplasia in this homogeneous population.

Methods

Retrospective single-center cohort study including 141 neonates born between 24 and 30 weeks' gestation to mothers with preeclampsia. The main outcome measure was moderate to severe bronchopulmonary dysplasia at 36 weeks' postmenstrual age. Neonates born small for gestational age (birthweight < 10th percentile on the AUDIPOG curves) were compared to those with appropriate birthweight for gestational age by bivariable analyses and logistic regression models, estimating odds ratios (ORs) and 95% confidence intervals (CIs).

Results

Bronchopulmonary dysplasia rates were 61.5% (32/52) and 27.4% (20/73) for small for gestational age and appropriate birthweight for gestational age neonates (p < .001). On adjustment for gestational age and other confounding factors, the risk of moderate to severe bronchopulmonary dysplasia was greater for small for gestational age than appropriate birthweight for gestational age neonates (adjusted OR = 5.9, 95% CI [2.2–15.4]), as was the composite outcome death or moderate to severe bronchopulmonary dysplasia (adjusted OR = 4.7, 95% CI [1.9–11.3]).
Conclusions
Small for gestational age was associated with bronchopulmonary dysplasia in very preterm neonates born to mothers with preeclampsia.

Registration number
CNIL no. 1747084.

Introduction
Bronchopulmonary dysplasia (BPD) is the main respiratory sequelae of preterm birth; it is characterized by arrested alveolar development with reduced number but increased size of alveoli and impaired capillaries [1]. Its incidence is stable despite recent advances in prevention and management and is inversely related to birth weight and gestational age (GA) [2]. Numerous antenatal and postnatal factors that can affect BPD development in an immature lung include infections, patent ductus arteriosus (PDA), mechanical ventilation and hyperoxia [3].

Small for GA (SGA) has been described as a risk factor for BPD. Several studies found the risk of BPD two- to six-fold higher for SGA preterm infants than AGA newborns [2,4,5]. One of the main etiologies of SGA is preeclampsia, which is characterized by gestational hypertension and proteinuria and affects 2% to 8% of pregnancies [6]. Preeclampsia as a risk factor for BPD has several hypotheses. First, this pregnancy disease often leads to SGA and premature birth, because delivery is the only treatment. As well, preeclampsia by itself could induce BPD. Indeed, its pathogenesis involves an imbalance between pro- and anti-angiogenic factors [7,8,9], which are shared by the fetus, and could impair the vascular and alveolar development of the fetal lungs [10,11]. Previous studies of BPD incidence in SGA preterm infants did not account for the causes of growth restriction [12,13]. As a result, they mostly compared SGA infants born to mothers with vascular diseases of pregnancy and AGA infants born to normotensive mothers. However, the BPD–SGA relation may be explained wholly or in part by the presence of preeclampsia.

To help disentangle the respective role of preeclampsia and SGA in the development of BPD, we evaluated the impact of SGA on the occurrence of BPD in neonates born to mothers with preeclampsia. We hypothesized that low birth weight is still associated with BPD in this homogeneous population.

Methods
This retrospective cohort study included preterm infants born between 24 and 30 weeks’ gestation and hospitalized between January 1, 2009 and December 31, 2013 in a level III neonatal intensive care unit at Port Royal Maternity (Cochin hospital, Paris, France). Infants were included if their mothers had preeclampsia (i.e., gestational hypertension [systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg] occurring after gestational week 20) with proteinuria ≥ 0.3 g/24 h, or eclampsia (i.e., preeclampsia with seizures during pregnancy or shortly after delivery). We excluded mothers with preexisting or gestational hypertension and isolated Hemolysis, Elevated Liver enzymes, Low Platelet count syndrome (HELLP syndrome) not associated with preeclampsia and infants with severe birth defects and chromosomal aberrations. Data were retrospectively collected by using the computer database.
Perinat Collection, PremUp. The collection of perinatal data was authorized by the National Data Protection Authority (CNIL no. 1747084) and the study was approved by the ethics committee of the French Neonatal Society. The CNIL authorizations allow us to collect and use data retrospectively from patients hospitalized in the unit. There was no consent specifically requested from families but they receive information about clinical research upon admission to the unit and their non-opposition is collected. All data were fully anonymized.

Outcomes
The primary outcome was moderate to severe BPD defined as oxygen requirement for at least 28 days and persistent need for oxygen or ventilatory support at 36 weeks' postmenstrual age (PMA) [1]. The secondary outcomes were the composite outcome death or moderate to severe BPD at 36 weeks' PMA and the main complications of prematurity: in-hospital deaths, necrotizing enterocolitis, neonatal late-onset infections, severe cerebral lesions, PDA, hemodynamic insufficiency requiring vascular filling or inotropic drugs, hyperglycemia requiring insulin treatment, and retinopathy of prematurity.

Perinatal data
Maternal and neonatal data were collected from medical records. Abnormal Doppler findings during pregnancy mean reduced, absent, or reversed umbilical artery end-diastolic flow; increased middle cerebral artery end-diastolic flow or cerebral redistribution process; reduced, absent, or reversed atrial flow in the ductus venosus; diastolic notch or abnormal pulsatility index on uterine artery. The antenatal corticosteroid course was considered complete if betamethasone was administered twice at 24-h intervals, incomplete if only one injection was administered, or absent. GA was estimated by the first trimester ultrasound if available and otherwise with the last menstrual date. SGA was classified as birth weight below the 10th percentile according to the sex-specific AUDIPOG curves [14] and AGA otherwise. PDA was diagnosed with clinical signs and echocardiographic findings. Necrotizing enterocolitis was diagnosed as Bell’s stage ≥ 2 [15]. Neonatal late-onset infections were defined as any positive culture from blood, cerebrospinal fluid, tracheal aspirate or urine sample occurring more than 72 h after birth. Severe cerebral lesions were considered grade III and IV intraventricular hemorrhage (IVH III-IV) according to the Papile classification and periventricular leukomalacia [16].

Ventilation protocols, fluid intake and PDA management were unchanged throughout the study. High-frequency oscillation ventilation (HFO) was used if hypercarbia or hypoxia persisted despite high pressure with conventional ventilation and in cases of pulmonary hemorrhage. Inhaled corticosteroids were used for extubating infants with continuous assisted-ventilation dependency. Systemic corticosteroids were used in rescue for infants with severe respiratory disease, repeated extubation failure and continuous assisted-ventilation dependency.

Statistical analysis
Categorical variables are described with number (%) and were compared by chi-square or Fisher exact test. Continuous variables are described with median and interquartile range (IQR) and were compared by Wilcoxon test. We compared the main maternal, obstetrical and neonatal characteristics between SGA and AGA newborns. The associations between SGA and neonatal outcomes were analyzed by bivariable analyses, then adjusted on GA. The associations between SGA and moderate or severe BPD and death or moderate to severe BPD were further adjusted on potential confounding factors selected among characteristics associated
with BPD in our sample and relevant factors from the literature. Results from logistic regression models were quantified by odds ratios (ORs) and 95% confidence intervals (95% CIs). Significance was set at $p \leq .05$. Analyses involved use of SAS v9.3 (SAS Inst. Inc., Cary, NC, USA).

**Results**

**Prenatal and neonatal characteristics at birth**

We screened 778 infants born between 24 and 30 weeks’ gestation and hospitalized between January 1, 2009 and December 31, 2013 (Fig 1). We analyzed data for 141 neonates (81 AGA and 60 SGA) born to mothers with preeclampsia between 2009 and 2013 and hospitalized in the Cochin Port Royal neonatal intensive care unit (Fig 1). SGA and AGA neonates did not differ in prenatal or neonatal characteristics (Table 1) or rates of multiple pregnancies, cesarean-section deliveries and antenatal steroid use. Abnormal Doppler findings during pregnancy were more frequent and GA at birth was lower for SGA than AGA neonates. At birth, lactate level and Clinical Risk Index for Babies (CRIB) score were significantly higher and platelet count was lower for SGA than AGA neonates.

**Neonatal clinical course**

SGA newborns more frequently required HFO ventilation and final extubation occurred later than did AGA newborns (Table 2). They also had a longer duration of non-invasive ventilation. SGA infants more frequently received inhaled corticosteroids than AGA infants, although not significantly (13.3% vs 4.9%, $p = .08$). Insulin requirement was twice more frequent for SGA than AGA infants. SGA infants also more frequently needed vascular filling and inotropic drugs as well as red blood cell transfusions, and the platelet count nadir was significantly lower than AGA newborns.

**Primary and secondary outcomes**

Overall, 61.5% (32/52) and 27.4% (20/73) of SGA and AGA newborns showed moderate or severe BPD ($p < .001$; Table 3). This difference remained significant after adjustment for GA (OR = 5.2, 95% CI [2.2–12.4]). In addition, the composite outcome death or moderate to severe BPD at 36 weeks’ PMA was more frequent for SGA than AGA newborns (66.7% vs 34.6%, $p < .001$), which persisted after adjustment for GA (OR = 4.1, 95% CI [1.9–9.1]). Death, severe neurological injury, retinopathy and necrotizing enterocolitis did not differ between SGA and AGA infants. Late-onset infections were more frequent in SGA than AGA infants (76.7% vs 53.1%, $p < .01$, adjusted on GA OR = 2.8, 95% CI [1.3–6.1]).

As compared with infants with no or mild BPD, those with moderate to severe BPD had lower median GA (27.6 vs 28.6 weeks, $p < .001$), lower median birth weight (690 vs 900 g, $p < .001$), higher lactate level at birth (4.8 vs 4.0 mmol/L, $p < .01$), and higher rate of PDA (73.1% vs 43.8%, $p < .01$) and more frequently received more than 2 doses of surfactant (44.2% vs 13.7%, $p < .001$). Male sex and antenatal corticosteroids use were not significantly associated with moderate or severe BPD in our population. However, because these variables are frequently described in the BPD literature, they were selected as potential confounding factors. On multivariate regression, risk of moderate to severe BPD was greater for SGA than AGA infants (OR = 5.9, 95% CI [2.2–15.4]), as was death or moderate to severe BPD (OR = 4.7, 95% CI [1.9–11.3]) (Table 4). Except for the dose number of exogenous surfactant, none of the other confounding factors (male sex, lactate level at birth, antenatal steroids and PDA) was significantly associated with the occurrence of BPD or the composite outcome death or moderate to severe BPD at 36 weeks’ PMA.
Fig 1. Flow chart of preterm infants in the study.

778 infants born at 24+0 – 29+6 weeks between 01/01/2009 and 31/12/2013

17 exclusions
(2 medical terminations of pregnancy, 9 intrauterine fetal deaths, 6 deaths in delivery room)

761 infants admitted in Port-Royal neonatal intensive care unit

614 exclusions
(Absence of maternal preeclampsia)

147 eligible infants

6 exclusions
(Chromosomal aberrations or severe birth)

141 infants analyzed

AGA: BW ≥ 10th percentile: 81 infants
SGA: BW < 10th percentile: 60 infants

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A second analysis using birthweight z-score as a continuous variable and adjusted on the same potential confounding factors than the previous multivariate analysis was performed, and similar results were found: higher adjusted risk of moderate to severe BPD with decreasing birthweight z-score (OR = 0.25 [0.12–0.51], p < .001), and higher risk of death or moderate to severe BPD with decreasing birthweight z-score (OR = 0.32 [0.17–0.59], p < .01).

**Discussion**

Among very preterm infants born between 24 and 30 weeks’ gestation to mothers with pre-eclampsia, SGA was associated with increased frequency of moderate or severe BPD and death or moderate to severe BPD at 36 weeks’ PMA.

The link between SGA and BPD has already been highlighted in several studies [2,4,5,17,18,19,20,21,22]. In the population-based cohort from Zeitlin et al., including 4525 infants born between 24 and 30 weeks’ gestation in nine European countries, BPD rate significantly increased with decreasing birth weight for GA; the adjusted OR for BPD was 6.4 with birth weight below the 10th percentile versus birth weight between the 50th and 74th percentile [2]. A French study in 2014 highlighted that a birth weight below the third percentile on AUDIPOG curves in infants born before 32 week’s gestation, is a stronger risk factor for BPD than extreme prematurity [21]. However, few studies have analyzed vascular diseases of pregnancy that may themselves be associated with BPD. Indeed, there is growing evidences that an appropriate angiogenic state is required for normal pulmonary vascular and alveolar development [10,11], and some studies found lower level of vascular endothelial growth factor (VEGF) in tracheal aspirates and higher level of soluble VEGF receptor (sVEGF-R or sFlt-1) in preterm infants with than without BPD [23]. Tang et al. showed that injection of sFlt-1 in
amniotic fluid impaired the lung growth of rat pups [24]. Preeclampsia, as an anti-angiogenic state, might impair lung angiogenesis and lead to BPD, however, the link between preeclampsia and BPD is still not fully understood.

To our knowledge, studies about mortality and morbidity after premature birth often include together several contexts of premature birth or include preeclampsia in vascular

Table 2. Main respiratory, hemodynamic, hematologic and metabolic outcomes by birth weight of preterm infants.

|                                    | AGA (N = 81) | SGA (N = 60) | p       |
|------------------------------------|--------------|--------------|---------|
| **Surfactant:** ≥ 2 doses (n, %)   | 21 (25.9)    | 20 (33.3)    | .34     |
| Pneumothorax (n, %)                | 0 (0.0)      | 1 (1.7)      | .43     |
| Pulmonary hemorrhage (n, %)        | 12 (14.8)    | 10 (16.7)    | .77     |
| Respiratory distress syndrome (n, %)| 48 (59.3)    | 37 (61.7)    | .77     |
| HFO (n, %)                         | 22 (27.2)    | 27 (45.0)    | .03     |
| **Duration of endotracheal ventilation** (days) (median, IQR) | 1.0 (0.2;6.0) | 5.0 (0.5;14.4) | .09     |
| **Duration of non-invasive ventilation** (days) (median, IQR) | 30 (14;40)   | 37 (28;48)   | < .01   |
| Age at final extubation (days) (median, IQR) (for intubated newborns) | 13 (1;23)    | 19 (8;29)    | .09     |
| **Treatment for pulmonary hypertension** (n, %) | 5 (6.2)      | 10 (16.7)    | .05     |
| Steroid therapy before 36 weeks' gestation (n, %) | | |  |
| Systemic                          | 3 (3.7)      | 2 (3.3)      | .99     |
| Inhaled                            | 4 (4.9)      | 8 (13.3)     | .08     |
| Inotropics (n, %)                  | 21 (25.9)    | 25 (41.7)    | .05     |
| Vascular filing (n, %)             | 4 (4.9)      | 9 (15.0)     | .04     |
| PDA (n, %)                         | 48 (59.3)    | 35 (58.3)    | .91     |
| Surgical treatment of PDA (n, %)   | 4 (4.9)      | 6 (10.0)     | .33     |
| Insulin treatment (n, %)           | 22 (27.2)    | 35 (58.3)    | < .001  |
| **Number of red blood cell transfusion** (median, IQR) | 1 (0;2)      | 2 (1;4)      | < .001  |
| Nadir platelets in the 1st week of birth (x10³/mm³) (median, IQR) | 102 (58;152) | 70 (46;128)  | < .01   |

*: Among infants alive at 36 weeks' gestation. HFO: high-frequency oscillation. PDA: patent ductus arteriosus. IQR: interquartile range.

Any missing data for each variable

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Table 3. Primary and secondary neonatal outcomes by birth weight of preterm infants and association after adjustment on GA.

|                                    | AGA (N = 81) | SGA (N = 60) | Adjusted on GA |
|------------------------------------|--------------|--------------|---------------|
|                                   | n  | %   | n  | %   | P      | OR* [95% CI] | P     |
| Moderate or severe BPD*           | 20 | 27.4| 32 | 61.5| < .001 | 5.2 [2.2–12.4] | .001  |
| Death or moderate to severe BPD   | 28 | 34.6| 40 | 66.7| < .001 | 4.1 [1.9–9.1]  | .001  |
| Death                             | 8  | 9.9 | 12 | 20.0| .09   | 2.2 [0.8–5.8]  | .13   |
| Severe neurological injury (IVH grade III-IV, PVL) | 10 | 12.3| 2  | 3.3  | .06   | 0.2 [0.1–1.1]  | .06   |
| Retinopathy stage 2 or 3 *        | 2  | 2.8 | 0  | 0.0  | .51   | NA           |       |
| Late-onset infections             | 43 | 53.1| 46 | 76.7| < .01 | 2.8 [1.3–6.1]  | .01   |
| Necrotizing enterocolitis         | 3  | 3.8 | 2  | 3.3  | .99   | 0.9 [0.1–5.4]  | .88   |

BPD: bronchopulmonary dysplasia. IVH: intraventricular hemorrhage. PMA: postmenstrual age.
PVL: periventricular leukomalacia.
*: odds ratio (OR) adjusted for GA. 95% CI: 95% confidence interval.
* (among 73 survivors in AGA and 52 survivors in SGA at 36 weeks' PMA)

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disorders of pregnancy without studying separately preeclampsia. Only few studies specifically analyzed neonatal outcomes of newborns born to mothers with preeclampsia. None studied the outcome BPD at 36 weeks’ PMA. One study found increased risk of fetal and neonatal mortality with birth weight below the 10\(^{th}\) percentile but no differences for the other neonatal outcomes [12]. A second study found no significant differences between SGA and AGA infants, but infants born before 28 weeks’ gestation were excluded and the outcome was defined only as “death or need for neonatal intensive care” [13]. Some cohort studies have analyzed the incidence of BPD in different contexts of preterm birth. Eriksson et al., in a large retrospective cohort study in Sweden, including preterm infants born before 37 weeks’ gestation, found a strong association between preeclampsia-related disorders and BPD but did not adjust the analyses for GA [25]. An Italian cohort of 2085 infants born between 23 and 31 weeks’ gestation highlighted greater risk of BPD for those born during pregnancies with disorders of placentation than in a context of infection or inflammation [26]. However, none analysis of these studies were adjusted for birth weight. Overall, few studies approached the risk of BPD considering vascular disorders of pregnancy, and specifically preeclampsia. Otherwise, results often differ according to the studies. The risk of BPD was higher for babies born after pregnancies with vascular disorders and birth weight below the 10\(^{th}\) percentile in the MOSAIC cohort study [2] but higher odds were also observed for SGA born to mothers without vascular disorders. In the study by Durrmeyer et al. [27], preterm infants born to mothers with vascular disease with a birthweight below the 3rd percentile were at higher risk of BPD. A prospective study published in 2010 by Hansen et al. found preeclampsia as a risk factor for DBP with an OR at 2.96 in a population of premature newborns with an average GA 29 week’s gestation [28], while Yen et al. in 2013 found a negative association between preeclampsia and the risk of developing DBP [29]. Lastly, Soliman et al. didn’t find any association between preeclampsia and BPD development in a Canadian population of premature less than 32 week’s gestation [30].

In our study, we focused on a homogenous population of neonates born to mothers with preeclampsia. Moreover, our population concerned more immature infants than those in several already published studies. Moderate or severe BPD and death or moderate to severe BPD were more frequent for SGA than AGA preterm infants and this difference persisted after adjustment for GA. As SGA is frequently the consequence of fetal growth restriction, this result is consistent with Torchin’s study which showed that vascular pregnancy disorders, such as preeclampsia, HELLP syndrome or eclampsia, were factors involved in BPD development only if associated with fetal growth restriction [31].

### Table 4. Association between birth weight and moderate to severe bronchopulmonary dysplasia (BPD) and death or moderate to severe BPD at 36 weeks’ post-menstrual age (PMA).

| Birth weight | Moderate or severe BPD at 36 weeks’ PMA | Death or moderate to severe BPD at 36 weeks’ PMA |
|--------------|----------------------------------------|-----------------------------------------------|
|              | aOR\(^{+}\) 95% CI P                   | aOR\(^{+}\) 95% CI p                           |
| ≥ 10\(^{th}\) percentile | 1                                     | 1                                             |
| < 10\(^{th}\) percentile | 5.9 [2.2–15.4] 4.7 [1.9–11.3]          |                                                |
| GA (weeks)   | 0.4 [0.3–0.7] < .01                     | 0.5 [0.3–0.7] < .001                           |

BPD: bronchopulmonary dysplasia. PMA: postmenstrual age. PDA: patent ductus arteriosus.

aOR: adjusted odds ratio. 95% CI: 95% confidence interval.

\(^{+}\): Adjusted on birth weight, gestational age, gender, lactate at birth, antenatal steroids, exogenous surfactant and patent ductus arteriosus.

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Besides the main result, we detailed the respiratory management in our population, which indicated more prevalent respiratory morbidity in SGA than AGA infants: the need for endotracheal ventilation including HFO and for non-invasive ventilation was more frequent, and final extubation occurred later. Also, use of inhaled corticosteroids was more frequent for SGA than AGA newborns, although the association was not significant. They were used only to allow weaning of invasive ventilatory support.

We conducted this study to help us distinguish the respective role of preeclampsia and small for gestational age in bronchopulmonary dysplasia. In this study, we confirm that low birth weight for GA is a major factor in BPD development. On the other hand, several studies focused on the role of anti-angiogenic factors in this disease, referring to the “vascular hypothesis of BPD”, which implies a modified balance between pro and anti-angiogenic factors leading to an impaired vascular and alveolar development [32,33]. However, being small for gestational age seems to have an important effect on pulmonary development, even in the specific population of neonates born to mothers with preeclampsia and thus exposed to the same anti-angiogenic state than their AGA peers. Indeed, most studies about angiogenic and anti-angiogenic factors found similar profiles between SGA and AGA infants [34,35]. Only one study, to our knowledge, found discordant angiogenic profiles between preeclampsia alone and preeclampsia with SGA [36]. But these three studies focused on less premature infants than our study. Nevertheless, it is possible that even among mothers with preeclampsia, the impact of maternal disease is variable on the foetus, with increasing severity of preeclampsia/vascular impairment contributing to the SGA state. Thus, SGA infants of preeclamptic mothers could represent a spectrum of disease rather than a separate entity independent of preeclampsia.

Our study presents several limitations: it was a retrospective, single-center cohort. The small sample size reduced the statistical power. We used birth weight as a proxy to identify growth-restricted preterm newborns. BPD status and severity were defined at 36 weeks PMA according to the National Institute of Child Health and Human Development definition [1], which has been shown to be associated with increased mortality and respiratory morbidity during infancy [37]. Therefore, administered respiratory support at 36 weeks PMA was used to classify children. The use of an oxygen reduction test would probably have been better to assess BPD status, but we don’t perform this test routinely in our unit, so we were not able to use that definition retrospectively [38]. In a recent systematic review of all papers published from 2010 and 2015 reporting BPD as an outcome, together with studies that compared BPD definitions between 1978 and 2015, 30% used the NICHD consensus definition and 6% used a physiological definition such as an oxygen challenge test [39]. However, we studied a very homogeneous population of premature infants, and management practices were the same for all newborns. Data collection was almost exhaustive. We analyzed two main outcomes, BPD and death or moderate to severe BPD, to consider a potential competitive effect of these two events and found greater risk of both outcomes for SGA than AGA newborns. Finally, our results agree with previous studies, showing more prevalent respiratory morbidities for SGA than AGA preterm infants.

In conclusion, in a homogeneous population of babies born to mothers with preeclampsia, we highlight the importance of birth weight for GA in the development of BPD. SGA in a context of preeclampsia multiplied by 5.9 in extremely preterm babies the risk of BPD development. These results encourage us to target this population for futures therapeutics studies. Indeed, SGA preterm infants are often excluded in therapeutics studies because of increased risk of complications or deaths in this population of premature children [40]. At present, these results can’t help clinicians in the absence of new therapies tested on this particular population.
Author Contributions

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References

1. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001 Jun; 163 (7):1723–9. https://doi.org/10.1164/ajccm.163.7.2011060 PMID: 11401896

2. Zeitlin J, El Ayoubi M, Jarreau P-H, Draper ES, Blondel B, Künnzel W, et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. J Pediatr. 2010 Nov; 157(5):733–739.e1. https://doi.org/10.1016/j.jpeds.2010.05.002 PMID: 20955846

3. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007 Nov 8; 357 (19):1946–55. https://doi.org/10.1056/NEJMra072779 PMID: 17989387

4. Reiss I, Landmann E, Heckmann M, Mieselwitz B, Gortner L. Increased risk of bronchopulmonary dysplasia and increased mortality in very preterm infants being small for gestational age. Arch Gynecol Obstet. 2003 Nov; 269(1):40–4. https://doi.org/10.1007/s00404-003-0468-9 PMID: 12682849

5. Lal MK, Manktelow BN, Draper ES, Field DJ. Population-based study. Chronic lung disease of prematurity and intrauterine growth retardation: a population-based study. Pediatrics. 2003 Mar; 111(3):483–7. PMID: 12612225

6. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet Lond Engl. 2010 Aug 21; 376(9741):631–44.

7. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. Physiol Bethesda Md. 2009 Jun; 24:147–58.

8. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005 Jun 10; 308 (5728):1592–4. https://doi.org/10.1126/science.1111726 PMID: 15947178

9. Tsatsaris V, Fournier T, Winer N. [Pathophysiology of preeclampsia]. Ann Fr Anesth Reanim. 2010 Mar; 29(3):13–18. https://doi.org/10.1016/j.annafr.2010.02.011 PMID: 20338717

10. Thébault B, Ladha F, Michelakis ED, Sawicka M, Thurston G, Eaton F, et al. Vascular endothelial growth factor gene therapy increases survival, promotes lung angiogenesis, and prevents alveolar damage in hyperoxia-induced lung injury: evidence that angiogenesis participates in alveolarization. Circulation. 2005 Oct 18; 112(16):2477–86. https://doi.org/10.1161/CIRCULATIONAHA.105.541524 PMID: 16230500

11. Thébault B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. Am J Respir Crit Care Med. 2007 May 15; 175 (10):978–85. https://doi.org/10.1164/rcrm.200611-1660PP PMID: 17272782
12. Weiler J, Tong S, Palmer KR. Is fetal growth restriction associated with a more severe maternal phenotype in the setting of early onset pre-eclampsia? A retrospective study. PLoS One. 2011; 6(10):e26937. https://doi.org/10.1371/journal.pone.0026937 PMID: 22046419

13. Hall D. Birthweight and gestational age as predictors of outcome in preterm deliveries for severe pre-eclampsia. J Trop Pediatr. 2003 Jun; 49(3):178–80. https://doi.org/10.1093/tropej/49.3.178 PMID: 12848210

14. Mamelle N, Munoz F, Grandjean H. [Fetal growth from the AUDIPOG study. I. Establishment of reference curves] . J Gynecol Obstet Biol Reprod (Paris). 1996; 25(1):61–70.

15. Bell MJ. Neonatal necrotizing enterocolitis. N Engl J Med. 1978 Feb 2; 298(5):281–2.

16. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978 Apr; 92(4):529–34. PMID: 305471

17. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol. 2004 Aug; 191(2):481–7. https://doi.org/10.1016/j.ajog.2004.01.036 PMID: 15343225

18. Aucott SW, Donohue PK, Northington FJ. Increased morbidity in severe early intrauterine growth restriction. J Perinatol Off J Calif Perinat Assoc. 2004 Jul; 24(7):435–40.

19. Yamakawa T, Itabashi K, Kusuda S, Neonatal Research Network of Japan. Mortality and morbidity risks vary with birth weight standard deviation score in growth restricted extremely preterm infants. Early Hum Dev. 2016 Jan; 92:7–11. https://doi.org/10.1016/j.earlhumdev.2015.10.019 PMID: 26615548

20. Qiu X, Lodha A, Shah PS, Sankaran K, Seshia MMK, Yee W, et al. Neonatal outcomes of small for gestational age preterm infants in Canada. Am J Perinatol. 2012 Feb; 29(2):87–94. https://doi.org/10.1055/s-0031-1295647 PMID: 22131047

21. Soude´ e S, Vuillemin L, Alberti C, Mohamed D, Becquet O, Farnoux C, et al. Fetal growth restriction is worse than extreme prematurity for the developing lung. Neonatology. 2014; 106(4):304–10. https://doi.org/10.1159/000360842 PMID: 25170598

22. Nobile S, Marchionni P, Carnielli VP. Neonatal outcome of small for gestational age preterm infants. Eur J Pediatr. 2017 Aug; 176(8):1083–8. https://doi.org/10.1007/s00431-017-2957-1 PMID: 28660312

23. Hasan J, Beharry KD, Valencia AM, Strauss A, Modanlou HD. Soluble vascular endothelial growth factor receptor-1 in tracheal aspirate fluid of preterm neonates at birth may be predictive of bronchopulmonary dysplasia/chronic lung disease. Pediatrics. 2009 Jun; 123(6):1541–7. https://doi.org/10.1542/peds.2008-1670 PMID: 19482766

24. Tang J-R, Karumanchi SA, Seedorf G, Markham N, Abman SH. Excess soluble vascular endothelial growth factor receptor-1 in amniotic fluid impairs lung growth in rats: linking preeclampsia with bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2012 Jan 1; 302(1):L36–46. https://doi.org/10.1152/ajplung.00294.2011 PMID: 22003089

25. Eriksson L, Haglund B, Odlinl V, Altman M, Kieler H. Prenatal inflammatory risk factors for development of bronchopulmonary dysplasia. Pediatr Pulmonol. 2014 Jul; 49(7):665–70. https://doi.org/10.1002/ppul.22881 PMID: 24039136

26. Gagliardi L, Rusconi F, Da Fré M, Mello G, Carnielli V, Di Lallo D, et al. Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based ACTION cohort study. Pediatr Res. 2013 Jun; 73(6):794–801. https://doi.org/10.1038/pr.2013.52 PMID: 23493168

27. Durrmeyer X, Kayem G, Sinico M, Dassieu G, Danan C, Decobert F. Perinatal risk factors for bronchopulmonary dysplasia in extremely low gestational age infants: a pregnancy disorder-based approach. J Pediatr. 2012 Apr; 160(4):578–583.e2. https://doi.org/10.1016/j.jpeds.2011.09.025 PMID: 22048041

28. Hansen AR, Barnès CM, Folkman J, McElrath TF. Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. J Pediatr. 2010 Apr; 156(4):532–6. https://doi.org/10.1016/j.jpeds.2009.10.018 PMID: 20004912

29. Yen T-A, Yang H-I, Hsieh W-S, Chou H-C, Chen C-Y, Tsou K-I, et al. Preeclampsia and the risk of bronchopulmonary dysplasia in VLBW infants: a population based study. PloS One. 2013; 8(9):e75168. https://doi.org/10.1371/journal.pone.0075168 PMID: 24073247

30. Soliman N, Chaput K, Alshaikh B, Yusuf K. Preeclampsia and the Risk of Bronchopulmonary Dysplasia in Preterm Infants Less Than 32 Weeks’ Gestation. Am J Perinatol. 2017; 34(6):585–92. https://doi.org/10.1055/s-0036-1594017 PMID: 27919118

31. Torchin H, Ancel P-Y, Goffinet F, Hascoët J-M, Truffert P, Tran D, et al. Placental Complications and Bronchopulmonary Dysplasia: EPIPAGE-2 Cohort Study. Pediatrics. 2016 Mar; 137(3):e20152163. https://doi.org/10.1542/peds.2015-2163 PMID: 26908662
32. Abman SH. Bronchopulmonary dysplasia: “a vascular hypothesis.” Am J Respir Crit Care Med. 2001 Nov 15; 164(10 Pt 1):1755–6. https://doi.org/10.1164/ajrccm.164.10.2109111c PMID: 11734417

33. Ozkan H, Cetinkaya M, Koksal N. Increased incidence of bronchopulmonary dysplasia in preterm infants exposed to preeclampsia. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2012 Dec; 25(12):2681–5.

34. Alahakoon TI, Zhang W, Trudinger BJ, Lee VW. Discordant clinical presentations of preeclampsia and intrauterine fetal growth restriction with similar pro- and anti-angiogenic profiles. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2014 Dec; 27 (18):1854–9.

35. Vatten LJ, Åsvold BO, Eskild A. Angiogenic factors in maternal circulation and preeclampsia with or without fetal growth restriction. Acta Obstet Gynecol Scand. 2012 Dec; 91(12):1388–94. https://doi.org/10.1111/j.1600-0412.2012.01516.x PMID: 22882089

36. Nanjo S, Minami S, Mizoguchi M, Yamamoto M, Yahata T, Toujima S, et al. Levels of serum-circulating angiogenic factors within 1 week prior to delivery are closely related to conditions of pregnant women with pre-eclampsia, gestational hypertension, and/or fetal growth restriction. J Obstet Gynaecol Res. 2017 Dec; 43(12):1805–14. https://doi.org/10.1111/1345-1600.13452 PMID: 28929598

37. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005 Dec; 116 (6):1353–60. https://doi.org/10.1542/peds.2005-0249 PMID: 16322158

38. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol Off J Calif Perinat Assoc. 2003 Sep; 23(6):451–6.

39. Hines D, Modi N, Lee SK, Isayama T, Sjörs G, Gagliardi L, et al. Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. Acta Paediatr Oslo Nor 1992. 2017 Mar; 106(3):366–74.

40. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet Lond Engl. 2016 Apr 30; 387 (10030):1827–36.