

# Hypertensive Disorders during Pregnancy and Risk of Bronchopulmonary Dysplasia in Very Preterm Infants

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Am J Perinatol

## Abstract

**Introduction** It is not yet fully known whether hypertensive disorders (HTD) during pregnancy impose an increased risk of development of bronchopulmonary dysplasia (BPD) in preterm newborn infants.

**Objective** To test the hypothesis that preeclampsia and other HTD are associated with the development of BPD in preterm infants.

**Materials and Methods** Data on mothers and preterm infants with gestational age 24 to 30 weeks were prospectively analyzed in 11 Portuguese level III centers. Statistical analysis was performed using IBM SPSS statistics 23.

**Results** A total of 494 preterm infants from 410 mothers were enrolled, and 119 (28%) of the 425 babies, still alive at 36 weeks, developed BPD. The association between chronic arterial hypertension, chronic arterial hypertension with superimposed preeclampsia, and gestational hypertension in mothers and BPD in preterm infants was not significant ( $p = 0.115$ ;  $p = 0.248$ ;  $p = 0.060$ , respectively). The association between preeclampsia-eclampsia and BPD was significant ( $p = 0.007$ ). The multivariate analysis revealed an association between preeclampsia-eclampsia and BPD (odds ratio [OR] = 4.6; 95% confidence interval [CI] 1.529–13.819;  $p = 0.007$ ) and a protective effect for BPD when preeclampsia occurred superimposed on chronic arterial hypertension in mothers (OR = 0.077; 95%CI 0.009–0.632;  $p = 0.017$ ).

**Conclusion** The results of this study support the association of preeclampsia in mothers with BPD in preterm babies and suggest that chronic hypertension may be protective for preterm babies.

## Keywords

- hypertensive disorders of pregnancy
- preeclampsia
- preterm newborn
- bronchopulmonary dysplasia
- perinatology

Hypertensive disorders (HTD) during pregnancy remain a major health issue for women and their infants worldwide.

Preeclampsia, either alone or superimposed on pre-existing (chronic) hypertension, presents a major risk to mothers.<sup>1</sup>

\* See Appendix for a list of members of the Hypertensive Disorders of Pregnancy Study Group.

An estimated 15 to 20% of all preterm births are attributable to preeclampsia.<sup>2</sup>

The associated complications of prematurity are inversely related to gestational age at delivery.<sup>3,4</sup> Bronchopulmonary dysplasia (BPD), a chronic lung disease that occurs in very preterm infants arises from arrested alveolar and vascular development of the lungs, reduces their capacity for gas exchange and results in the affected newborn infants being chronically dependent on oxygen therapy and respiratory medications, and consequently at increased risk for re-hospitalizations during the first years of life. More severely affected patients will need tracheostomy, ventilatory support, and oxygen therapy at home and face an increased risk of death.<sup>5</sup>

It is not yet fully known whether HTD during pregnancy impose an increased risk of developing BPD in preterm newborn infants of affected mothers. The findings of studies that assessed this association are still inconclusive. Some studies found an increased incidence of BPD in preterm infants exposed to HTD in mothers,<sup>6,7</sup> and some found increased incidence of BPD in infants exposed to preeclampsia alone.<sup>8,9</sup> On the other hand, a study by Yen et al<sup>10</sup> found reduced risk for BPD in relatively mature (31–34 weeks of gestational age), very low birthweight infants of mothers with preeclampsia. O'Shea JE et al<sup>11</sup> and Soliman et al<sup>12</sup> did not find any association between preeclampsia in mothers and BPD in extremely low birthweight preterm infants (<28 weeks/ < 1000 g of birthweight), as well as BPD in those with less than 32 weeks of gestation time. A recent publication from the EPIPAGE-2 Cohort study<sup>13</sup> concluded that placenta-mediated pregnancy complications with fetal consequences are associated with moderate-to-severe BPD in very preterm infants, independent of gestational age and birthweight, but isolated maternal HTD are not.

With this study, we expect to contribute to the current literature on the clinical association between pregnancy HTD in mothers and BPD in infants. Our aim was to test the hypothesis that preeclampsia and other HTD in mothers are associated with the development of BPD in preterm newborn infants with a gestational age of less than 30 weeks, employing a sample of prospectively recruited mothers and infants at 11 level III Portuguese neonatal centers.

## Materials and Methods

A prospective study had been performed at 11 level III obstetrical and neonatal Portuguese centers between January 1, 2015 and December 31, 2016. The study protocol was approved by the Ethics Committees of all centers, and informed consent was provided and signed by all adult participants.

In this study, preterm newborn infants with a gestational age between 24 weeks and 30 weeks (24 weeks and 0 days to 29 weeks and 6 days inclusive), born of mothers who had been observed during pregnancy, were enrolled. In Portugal, the surveillance of pregnancy includes a preconceptional consultation, the first postconceptional consultation as soon as possible before 12 weeks, then after 4 to 6 weeks until 30 weeks' gestation, every 2 to 3 weeks until 36 weeks, and

1 to 2 weeks until delivery. The number of consultations may be adapted when a pathology or a risk factor is observed. Pregnant blood pressure is recorded in each consultation. Infants data were collected prospectively during the time between birth and until they were discharged from the neonatal intensive care unit (NICU). We included multifetal pregnancies as several studies demonstrated that multiple gestation pregnancies are not risk factors for BPD.<sup>14–16</sup> Exclusion criteria included the following: absence of informed consent, outborn newborn infants, those affected by a Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes (TORCH; "Other" infections include syphilis, hepatitis B, coxsackievirus, Epstein-Barr virus, varicella-zoster virus, enteroviruses, human immunodeficiency virus, tuberculosis, and parvovirus B-19) infection, a major congenital anomaly, a chromosomal defect, asphyxia (pH  $\leq$  7.0 and/or Apgar score at 5 min  $<$  3), fetal-fetal transfusion syndrome, fetal growth discrepancy in multiple pregnancies (difference  $>$  20%), severe anemia at admission, diagnosis of an inborn metabolic disorder performed at prenatal consultation or during the neonatal period, and diagnostic suspicion of a neuromuscular disease.

A prestructured data form, including data on demographics, pregnancy, delivery, neonatal morbidity and outcome, necropsy study of the deceased patients, and placental histology, was completed for each infant.

Hypertension during pregnancy and preeclampsia were defined according to the definition of the American College of Obstetricians and Gynecologists.<sup>1</sup> In this study, we considered four groups of HTD occurring during pregnancy:<sup>1</sup> chronic hypertension (of any cause, with blood pressure values over 140/90 mm Hg, documented before pregnancy or before 20 weeks of gestation);<sup>2</sup> preeclampsia-eclampsia (blood pressure values over 140/90 mm Hg along with proteinuria higher than 300 mg in 24 hours, detected after 20 weeks of gestation in a previously normotensive woman; eclampsia was considered to be preeclampsia with seizures during pregnancy or shortly after delivery);<sup>3</sup> chronic hypertension with superimposed preeclampsia;<sup>4</sup> gestational hypertension (systolic blood pressure  $\geq$  140 mm Hg or diastolic blood pressure  $\geq$  90 mm Hg occurring after gestational week 20). Hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome was considered as associated or not to preeclampsia.

BPD was defined as per the National Institute of Health's definition.<sup>17</sup> For the analysis of this study, we considered BPD in infants as dependency on oxygen treatment until 36 weeks of corrected age.

A full cycle of antenatal steroids was considered in our data analysis when at least 12 hours had elapsed after the last dose of dexamethasone (four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart) or betamethasone (two doses of 12 mg of betamethasone given intramuscularly 24 hours apart) was administered to the mother, as per the National Institutes of Health's (NIH) Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes.<sup>18</sup> An incomplete cycle was considered when at least 12 hours had elapsed after the first dose of dexamethasone or betamethasone administration, and a full cycle was not completed. Antenatal magnesium sulfate for fetal

neuroprotection was considered if the mother received a 4 g intravenous (IV) loading dose over 30 minutes, followed by a 1 g/h maintenance infusion until birth.<sup>19</sup> Clinical chorioamnionitis was defined as maternal fever combined with two or more findings of maternal tachycardia, fetal tachycardia, leukocytosis and/or elevated C-reactive protein, uterine tenderness, and/or malodorous amniotic fluid.<sup>20</sup> Histological chorioamnionitis was defined as infiltration of polymorphonuclear leukocytes in the fetal membranes and chorionic plate; chorionic vasculitis was defined as infiltration of polymorphonuclear leukocytes in the wall of chorionic vessels and funisitis as the presence of these cells in the umbilical cord blood vessels' wall and Wharto's jelly.<sup>21</sup> The definition of cervical insufficiency was established clinically or was considered as a dilation of internal cervical with shortening of the cervix less than 25 mm and "funneling" of 25% and more found upon ultrasound examination of the cervix.<sup>22</sup> Placental abruption was defined as a premature separation of the placenta before delivery.<sup>23</sup> Two groups were considered for the time length of rupture of membranes before birth—less than 24 hours and longer than 24 hours.

Gestational age (considered in complete weeks) was assessed by date of embryo transfer (for in vitro fertilization), menstrual age (women with regular menstrual cycles), ultrasound examination (when a discrepancy of one or more weeks existed between the age derived by menstrual dating and the age derived sonographically, or in the absence of a menstrual date),<sup>24</sup> or the New Ballard Score (in the absence of obstetrical indices).<sup>25</sup> Small birth weight for gestational age was defined as birthweight below the third percentile of Fenton's fetal growth charts.<sup>26</sup>

All participating centers use the same delivery room resuscitation practices and NICU treatment guidelines for preemies treatment, according to the guidelines of the Portuguese Society of Neonatology (available at [www.luso-neonatalogia.com](http://www.luso-neonatalogia.com)). We counted early nasal continuous airway positive pressure (early NCPAP) in our analysis if it started in the first 15 minutes after birth.

Respiratory distress syndrome (RDS) was defined and treated according to the European Consensus on RDS of 2013.<sup>27</sup> Non-invasive ventilation is preferred in preterm newborn infants with respiratory drive. Conventional mechanical ventilation is used in cases of NCPAP failure or preterm infants without respiratory drive. Only one center uses high-frequency oscillatory ventilation (HFOV) as the primary mode; all other centers use HFOV as rescue ventilation. The strategy of permissive hypercapnia is advocated in all centers. Caffeine citrate had been routinely used since day 1 of life, independent of apnea, until 34 weeks of gestational age. Oxygen was used to maintain saturations given by pulse oximetry ( $\text{SpO}_2$ ) in the range of 90 to 95%, and over 95% in patients with established BPD or over 36 weeks post-menstrual age.<sup>28</sup> Parenteral nutrition is used by all centers as soon as there is clinical stability, preferably since day 1 of life, starting with a volume of 70 mL/kg/day, with daily increments until 150 mg/kg/day by day 7 of life. Incubator humidity is usually 70% during the first week. Hemodynamically significant patent ductus arteriosus was screened and diagnosed on the basis of the echocardiographic findings

according to our national guidelines.<sup>29</sup> The first evaluation was usually performed between 24 and 72 hours of life, with daily evaluation until closure of the ductus. The standard treatment was ibuprofen. Proven neonatal sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture. Clinical sepsis without agent identification was diagnosed in the presence of clinical signs (fever, hypothermia, lethargy, tachypnea, apnea/bradycardia, cyanosis, and hypoglycemia not explained by other diagnosis), associated to at least one laboratory marker (thrombocytopenia, leukopenia, and C-reactive protein elevation) according to our National Program of Infection Control Guidelines.<sup>30</sup> Early onset sepsis and late onset sepsis were considered if diagnosed before and after the first 72 hours of life, respectively. Newborn infants considered affected by pneumonia were those who developed signs of respiratory distress plus some significant indicators from laboratory results of anomalies in white blood cell count, increase in C-reactive protein level or positive blood, urine and/or bronchotracheal sample cultures, and a radiographic pattern compatible with lung infection.<sup>30</sup> Meningitis was considered in light of elevated polymorphonuclear count and biochemical alterations in the cerebrospinal fluid, with or without isolation of microbiological agent.<sup>30</sup> The modified criteria of Bell were used for the diagnosis and staging of necrotizing enterocolitis.<sup>31</sup> Staging of retinopathy of prematurity was done according to the international classification.<sup>32,33</sup> Intraventricular hemorrhage was classified according to Volpe's guidelines.<sup>34</sup> Periventricular leukomalacia was classified according to Vries and Rennie.<sup>35</sup>

## Statistics

Data collection and statistical analysis were performed using IBM SPSS® statistics 23. Categorical variables were described as absolute and relative frequencies, continuous variables with symmetric distribution by mean ( $\pm$ standard deviation), and continuous variables with asymmetric distribution by median (minimum–maximum). Chi-square or Fisher's exact test was applied to compare categorical variables, and independent *t*-tests and Mann–Whitney *U*-tests were used for symmetric and asymmetric continuous variables, respectively. A multivariate analysis by logistic regression was performed to evaluate predictors. A *p*-value  $<0.05$  was considered statistically significant.

## Results

A total of 614 preterm newborn infants with a gestational age of 24 weeks and 0 days to 29 weeks and 6 days inclusive, of observed pregnancies, were delivered in the 11 participative centers during the 2-year period of enrollment. One hundred and twenty (19.5%) preterm newborn infants presented with exclusion criteria (outborn infants = 31; TORCH infection = 1; major congenital anomalies at birth = 9; chromosomopathy = 1; asphyxia with  $\text{pH} \leq 7.0$  and / or Apgar score at 5 minutes  $<3$  = 11; fetal–fetal transfusion syndrome = 14; fetal growth discrepancy = 1; severe anemia at admission = 6; neuromuscular disease = 1; and not consented = 45). A total of 494 preterm neonates delivered from 410 women were enrolled in the study.

**Table 1** Data on mother, gestation, delivery, and demographics for the total sample and the subgroups BPD and no-BPD patients

	Total (n = 494)	BPD (n = 119)	no-BPD (n = 375)	p-Value
Mother's age, mean (SD)	31.7 (5.9)	32.5 (6.4)	31.5 (5.7)	0.101 <sup>a</sup>
First pregnancy, n (%)	245 (49.8)	57 (23.3)	188 (76.7)	0.634 <sup>b</sup>
Spontaneous pregnancy, n (%)	346 (81.8)	89 (25.7)	257 (74.3)	0.101 <sup>b</sup>
Multiple gestation, n (%)	174 (35.2)	29 (16.7)	145 (83.3)	
Twins, n (%)	153 (31.0)	26 (17.0)	127 (83.0)	<b>0.004<sup>b</sup></b>
Triplets, n (%)	21 (4.3)	3 (14.3)	18 (85.7)	<b>0.039<sup>b</sup></b>
Antenatal steroids, n (%)	479 (97.0)	117 (24.4)	362 (75.6)	0.539 <sup>c</sup>
Full cycle, n (%)	365 (73.9)	92 (25.2)	273 (74.8)	0.173 <sup>b</sup>
Cervical incompetence, n (%)	54 (11.0)	20 (37.0)	34 (63.0)	<b>0.019<sup>b</sup></b>
Chronic arterial hypertension, n (%)	48 (9.7)	16 (33.3)	32 (66.7)	0.115 <sup>b</sup>
Preeclampsia, n (%)	74 (15.0)	27 (36.5)	47 (63.5)	<b>0.007<sup>b</sup></b>
Eclampsia, n (%)	1 (0.2)	0 (0)	1 (100.0)	0.999 <sup>b</sup>
Chronic hypertension with superimposed preeclampsia, n (%)	27 (5.5)	9 (33.3)	18 (67.0)	0.248 <sup>b</sup>
HELLP syndrome, n (%)	25 (5.1)	10 (40.0)	15 (60.0)	0.057 <sup>c</sup>
Gestational hypertension, n (%)	45 (9.1)	16 (35.6)	29 (64.4)	0.060 <sup>b</sup>
Gestational diabetes, n (%)	38 (7.7)	15 (39.5)	23 (60.5)	<b>0.021<sup>b</sup></b>
Chronic diseases, n (%) <sup>d</sup>	102 (20.6)	28 (27.5)	74 (72.5)	0.373 <sup>c</sup>
Other pregnancy pathologies <sup>e</sup> n (%)	50 (10.1)	21 (42.0)	29 (58.0)	<b>0.002<sup>b</sup></b>
Placentae study				
Chorioamnionitis, n (%)	153 (31.0)	33 (21.6)	120 (78.4)	0.710 <sup>b</sup>
Funisitis, n (%)	57 (11.5)	18 (31.5)	39 (68.4)	0.085 <sup>b</sup>
Chorionic vasculitis, n (%)	47 (9.5)	12 (25.5)	35 (74.5)	0.159 <sup>b</sup>
Changes compatible with preeclampsia, n (%)	57 (11.5)	15 (26.3)	42 (73.6)	0.641 <sup>b</sup>
Gestational age, mean (SD)	27.6 (10.3)	26.4 (1.7)	28.0 (11.8)	0.140 <sup>a</sup>
Birthweight, mean (SD)	963 (256)	802 (193)	1014 (252)	<b>&lt;0.0001<sup>a</sup></b>
Small for gestational age, n (%)	19 (3.8)	10 (52.6)	9 (47.4)	<b>0.003<sup>b</sup></b>
Gender, n (%)				0.381 <sup>b</sup>
Male	291 (58.9)	66 (22.7)	225 (77.3)	
Female	203 (41.1)	53 (26.1)	150 (73.9)	

Abbreviations: BPD, bronchopulmonary dysplasia; HELLP, hemolysis, elevated liver enzyme levels, and low platelet levels; SD, standard deviation.

<sup>a</sup>Independent *t*-test.

<sup>b</sup>Chi-square test.

<sup>c</sup>Fisher's exact test.

<sup>d</sup>Asthma, inflammatory bowel disease, celiac disease, fibromyalgia, depression, dyslipidemia, hemophilia B, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism, chronic renal failure, obesity, systemic lupus erythematosus, Leiden factor V heterozygosity, thrombophilia, antiphospholipid syndrome, polycystic ovary, uterine myomas, endometriosis,  $\beta$ -thalassemia, breast cancer, ankylosing spondylitis, peripheral venous insufficiency.

<sup>e</sup>Fluorometric abnormalities, fetal growth restriction, depression, appendectomy, urinary tract infection, retroplacental hematoma.

Note: Bold *p*-values are statistically significant.

There were 69 deaths of infants before 36 weeks of gestational age, and 425 newborns were alive at 36 weeks of gestational age, of whom 119 (28%) developed BPD. Data on mother, gestation, delivery, and demographics are reported in ►Table 1. There were no significant differences found in neuroprotection use with magnesium sulfate, rupture of membranes over 18 hours, C-section rates, clinical chorioam-

nionitis, abruptio placentae smoking, alcohol, and drugs use between BPD and non-BPD patients. All four considered groups of pregnancy HTD occurred more frequently in the BPD group, with statistical significance for the preeclampsia-eclampsia group. As expected, BPD patients presented with a lower birthweight compared with no-BPD patients. Overall, neonatal morbidity and mortality are described in ►Table 2.

**Table 2** Neonatal morbidity and mortality

	Total (n = 494)	BPD (n = 119)	no-BPD (n = 375)	p-Value
RDS, n (%)	444 (89.9)	116 (26.1)	328 (73.9)	<b>0.001<sup>a</sup></b>
Surfactant, n (%)	370 (74.8)	108 (29.2)	262 (70.8)	<b>&lt;0.0001<sup>b</sup></b>
MV, n (%)	461 (93.3)	119 (25.8)	342 (74.2)	<b>&lt;0.0001<sup>a</sup></b>
Days of oxygen therapy, median (min–max)	34 (1–182)	79 (43–122)	20 (1–152)	<b>&lt;0.0001<sup>c</sup></b>
HS-PDA, n (%)	190 (38.5)	71 (37.4)	119 (62.6)	<b>&lt;0.0001<sup>b</sup></b>
Medical treatment, n (%)	149 (30.2)	54 (36.2)	95 (63.8)	<b>&lt;0.0001<sup>b</sup></b>
Surgical closure, n (%)	44 (8.9)	31 (70.4)	13 (29.6)	<b>&lt;0.0001<sup>b</sup></b>
NEC $\geq$ 2, n (%)	32 (6.5)	11 (34.3)	21 (65.7)	0.164 <sup>b</sup>
IVH = 3, n (%)	82 (16.6)	22 (26.8)	60 (73.2)	0.525 <sup>b</sup>
PVI, n (%)	49 (9.9)	11 (22.4)	38 (77.6)	0.777 <sup>b</sup>
cLPV, n (%)	78 (15.8)	30 (38.5)	48 (61.5)	<b>0.001<sup>b</sup></b>
ROP $\geq$ 2, n (%)	109 (22.1)	52 (47.7)	57 (52.3)	<b>&lt;0.0001<sup>b</sup></b>
Early sepsis, n (%)	100 (20.2)	28 (28.0)	72 (72.0)	0.275 <sup>b</sup>
Nosocomial sepsis, n (%)	273 (55.2)	106 (38.8)	167 (61.2)	<b>&lt;0.0001<sup>b</sup></b>
Pneumonia, n (%)	66 (13.4)	33 (50.0)	33 (50.0)	<b>&lt;0.0001<sup>b</sup></b>
Meningitis, n (%)	6 (1.3)	3 (50.0)	3 (50.0)	0.151 <sup>a</sup>
Deceased, n (%)				
Deceased < 36 weeks GA	74 (15.0)	3 (4.0)	71 (96.0)	<b>&lt;0.0001<sup>a</sup></b>
n (%) deceased $\geq$ 36	69 (14.0)	0 (0)	69 (100.0)	<b>&lt;0.0001<sup>a</sup></b>
Weeks GA, n (%)	5 (1.0)	3 (60.0)	2 (40.0)	0.061 <sup>a</sup>
Day of death, median (min–max)	8 (1–147)	105 (95–147)	7 (1–87)	<b>0.0001<sup>c</sup></b>
Length of stay of survivors, median (min–max)	67 (10–195)	92 (50–182)	60 (10–195)	<b>&lt;0.0001<sup>c</sup></b>

Abbreviations: BPD, bronchopulmonary dysplasia; cLPV, cystic leukomalacia periventricular; GA, gestational age; HFNC, high-flow nasal cannula; HS-PDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular hemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; PVI, periventricular venous infarction; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

<sup>a</sup>Fisher's exact test.

<sup>b</sup>Chi-square test.

<sup>c</sup>Mann–Whitney U-test.

Note: Bold p-values are statistically significant.

The multivariate analysis by logistic regression including all risk factors for BPD (gender, gestational age, birth weight, maternal age, multiple pregnancy, intrauterine growth restriction, other pregnancy pathologies, RSD, mechanical

ventilation, hemodynamically significant patent ductus arteriosus, pneumonia, and nosocomial sepsis) revealed that preeclampsia–eclampsia was an independent risk factor for BPD in this sample (**Table 3**). Chronic arterial

**Table 3** Multivariate analysis of BPD risk factors by logistic regression

	ORad	95% CI	p-Value
Mother's age, years	1.1	1.001–1.134	<b>0.046</b>
Preeclampsia–eclampsia	4.6	1.529–13.819	<b>0.007</b>
Gestational diabetes	3.6	1.091–11.611	<b>0.035</b>
Chronic arterial hypertension with superimposed preeclampsia	0.077	0.009–0.632	<b>0.017</b>
Days of mechanical ventilation	1.09	1.066–1.113	<b>&lt;0.0001</b>

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; ORad, adjusted odds ratio for each variable listed in the table; no confounders were identified.

Note: Bold p-values are statistically significant.

Mother's age is a continuous variable; the OR increases for each advancing year.



hypertension with superimposed preeclampsia in mothers had a protective effect in BPD development among infants, compared with those with preeclampsia–eclampsia only. Mother's age, gestational diabetes, and days of mechanical ventilation were associated with BPD in neonates in this sample. Mother's age is a continuous variable; the odds ratio (OR) increases for each advancing year.

## Discussion

The objective of this study was to assess if preeclampsia and other HTD of pregnancy are associated with the development of BPD in preterm newborn infants with a gestational age of less than 30 weeks. According to our results, only preeclampsia showed a significant association to the development of BPD. Chronic hypertension, chronic hypertension with superimposed preeclampsia and gestational hypertension did not show a significant association to BPD.

Some studies reporting an increased incidence of BPD in infants exposed to preeclampsia have already been published.<sup>8,9</sup>

Another interesting finding of our study was that pre-existing chronic arterial hypertension in mothers developing preeclampsia presented “protective” odds of developing BPD. As far as we know, this is a novel finding and deserves further research. Although chronic arterial hypertension has been associated to placental underperfusion and increased risk for BPD,<sup>6,7,36</sup> we speculate that a mechanism of accelerated lung maturation may be present, which decreases the deleterious effect of the preeclampsia on fetal lung development. This finding needs further confirmation by other studies regarding the effect of HTD during pregnancy on BPD.

Another finding in the multivariate analysis of our study was that increasing age of the mother was a risk factor for BPD. It is known that preeclampsia is more common in primigravida women and age greater than 40 years of age increases risk as does a previous history of preeclampsia.<sup>1</sup> Preeclampsia was the only antenatal pathology that was more prevalent in the women included in this study, and BPD group were older than no-BPD mothers, suggesting that an increase in mothers age will increase the risk for preeclampsia and consequently for BPD in offspring.

BPD is the most common form of chronic lung disease in infancy.<sup>37</sup> At present, BPD primarily occurs in extremely premature infants (23–29 weeks of gestation) born during the late canalicular/early sacular stage of lung development and is characterized by arrested alveolarization, abnormal microvascular angiogenesis, and inter-alveolar fibrosis.<sup>38</sup> With progress at the medical treatment level, an increasing number of premature BPD infants are born, and they are at increased risk for numerous complications and re-hospitalization since BPD affects many vital organ systems.<sup>17</sup>

The pathogenesis of BPD is multifactorial, and a complex view of this issue (“multiple hits” hypothesis) has emerged, which includes along with low gestational age and birth-weight, antenatal exposure to a proinflammatory environment, and various postnatal inflammation-triggering events, such as mechanical ventilation, oxidative stress, sepsis,

patent ductus arteriosus, and excessive fluid volume administration.<sup>17,39–43</sup> Our results found similar risk factors for BPD as those described in literature.

Although the pathophysiology of preeclampsia is poorly defined, evidence suggests that abnormal placentation, characterized by shallow invasion of maternal arteries, compromises uterine blood flow at the expense of the growing placenta and fetus.<sup>44</sup> The resulting hypoxia and ischemia may restrict fetal angiogenesis.<sup>45</sup> Considering the growing evidence suggesting that preservation of in-utero vascular growth is critical for maintenance of alveolarization (“vascular hypothesis of BPD”), it is possible that preeclampsia may alter critical lung vessel interactions necessary for normal lung development.<sup>14,46</sup> Pregnancy hypertensive diseases, such as preeclampsia, are associated with an altered angiogenic state, with elevation of some anti-angiogenic factors (soluble vascular endothelial growth factor receptor [sVEGFR-1] and soluble endoglin) and functional decrease of circulating pro-angiogenic factors (VEGF and placental growth factor). An adequate angiogenic state is required for normal pulmonary vascular development and multiplication of the fetal airways.<sup>8</sup>

Further research is needed to better understand the biological mechanisms linking *in utero* disruption of angiogenesis, including preeclampsia, and resultant impairments in fetal growth on important neonatal outcomes.<sup>47</sup> Increasing circulating soluble Flt-1, a soluble form of VEGF receptor-1 that can bind both VEGF and placenta growth factor (PGF), was thought to be responsible for the pathogenesis of preeclampsia through impairing the angiogenic state. In developing lungs, disruption of VEGF signaling impairs angiogenesis and decreases alveolarization.<sup>10</sup>

A recent study by Hansen et al with 107 preterm infants (23–32 weeks of gestational age) showed that maternal preeclampsia was associated with an increased risk for development of BPD in infants.<sup>8</sup>

In a study by Soliman,<sup>12</sup> maternal preeclampsia was not a significant risk factor for BPD in a cohort of 319 infants with a gestational age below 32 weeks. The study by Soliman et al differs from our study mainly in the fact that we included infants with gestational age below 30 weeks, a group in which the association between maternal preeclampsia and infants' BPD is much stronger. By excluding older infants (30–32 weeks) in which the risk of developing BPD is significantly lower, we have increased the predictive power of this study.

In the study by Ozkan et al,<sup>9</sup> which included 332 preterm infants born under 32 weeks of gestational age, there was a significant association between maternal preeclampsia and BPD. However, in this study, pregnancies affected by chorioamnionitis, cigarette smoking, prolonged rupture of membranes, diabetes, and use of any medication due to maternal diseases during pregnancy were excluded. These exclusion criteria selected a different sample of patients and could have been responsible for the more powerful association observed between maternal preeclampsia and BPD.

Additional studies have shown that BPD occurs in cases of mothers with preeclampsia that is severe enough to cause

intrauterine growth restriction.<sup>14</sup> One systematic review of 15 studies (20,779 patients) found an association between maternal arterial HTD and BPD, although because of substantial heterogeneity and possible publication bias, this result should be interpreted cautiously.<sup>6</sup>

Another finding of our study was that maternal gestational diabetes was an independent risk factor for infants' BPD development. This finding is not new, although recent literature on this issue suggests that well-controlled maternal gestational diabetes does not impose an increased risk for infants' BPD.<sup>48–50</sup>

A limitation of this study is the fact that maintaining peripheral saturations 90 to 95% early and over 95% once 36 weeks may affect generalizability of our results. A significant proportion of the US and other countries centers target 87 to 93% (or thereabouts) prior to 33 to 34 weeks then over 90% afterward, and BPD rates are different among centers that use different criteria.

In conclusion, the results of this study contribute to the scientific evidence that maternal preeclampsia–eclampsia is a significant independent risk factor for BPD. Furthermore, our results suggest that maternal chronic arterial hypertension may serve as a protective barrier for BPD when mothers develop superimposed preeclampsia–eclampsia during pregnancy. Our results may be used in future meta-analyses to further clarify the role of HTD during pregnancy on BPD of preterm newborn babies.

#### Funding

None.

#### Conflict of Interest

None.

#### Acknowledgments

The authors acknowledge all the collaborating elements in this study and appreciate all the staff members of the departments where it was performed.

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