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Association of Maternal Hypertensive Disorders During Pregnancy With Severe Bronchopulmonary Dysplasia: A Systematic Review and Meta-Analysis

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Disclosure
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: This meta-analysis was performed to examine the association between maternal hypertension during pregnancy (HDP) and neonatal bronchopulmonary dysplasia (BPD).
Methods: We systematically searched PubMed, EMBASE, the Cochrane Library, and the KoreaMed database for relevant studies. We used the Newcastle-Ottawa Scale for quality assessment of all included studies. The meta-analysis was performed using Comprehensive Meta-Analysis software (version 3.3).
Results: We included 35 studies that fulfilled the inclusion criteria; the total number of infants evaluated came to 97,399 through review process. Maternal HDP was not significantly associated with any definition of BPD, i.e., oxygen dependency at 36 weeks of gestation (odds ratio [OR], 1.162; 95% confidence interval [CI], 0.991–1.362; $P = 0.064$) in pooled analysis of 29 studies or oxygen dependency at 28 days of age (OR, 1.084; 95% CI, 0.660–1.780; $P = 0.751$) in pooled analysis of 8 studies. Maternal HDP was significantly associated only with severe BPD (OR, 2.341; 95% CI, 1.726–3.174; $P < 0.001$). BPD was not associated with HDP in the overall analysis (OR, 1.131; 95% CI, 0.977–1.309; $P = 0.100$) or subgroup analysis according to the definition of HDP.
Conclusion: Maternal HDP was not associated with neonatal BPD defined by the duration of oxygen dependency (at either 36 weeks of gestation or 28 days of life) but was associated with severe BPD.

Keywords: Bronchopulmonary Dysplasia; Hypertension, Pregnancy Induced; Infant, Newborn

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is characterized by prolonged oxygen dependency or ventilator support of preterm infants.[1,2] Various perinatal factors may affect BPD development, including lung damage and impaired alveolar and vascular development.[1-3] Efforts have been made to predict the occurrence of BPD soon after birth[4] and to prevent BPD in preterm infants using various ventilator strategies[5] and the early caffeine use.[6] However, the incidence of BPD has not decreased over the past 10 years in infants born at

Author Contributions

Conceptualization: Park HW. Data curation: Lim G, Kim YJ, Park HW. Formal analysis: Lim G, Kim YJ, Park HW. Investigation: Lim G, Kim YJ. Methodology: Lim G, Kim YJ, Park HW. Supervision: Chung S, Park YM, Kim KS, Park HW. Writing - original draft: Lim G. Writing - review & editing: Kim YJ, Chung S, Park YM, Kim KS, Park HW.

less than 30 weeks of gestation in Korea.[7] Apart from postnatal care, prenatal management is important to prevent BPD. Hypertension during pregnancy (HDP) has been reported as a risk factor for BPD.[8-12] HDP (including pre-eclampsia) causes various prenatal morbidities, including preterm birth, intra-uterine growth restriction, and maternal complications.[13,14] The placental pathology of HDP is characterized by placental insufficiency, decreased fetal perfusion, and intrauterine growth restriction; these are also risk factors for BPD.[15,16] We performed this meta-analysis to examine the association between maternal HDP and neonatal BPD in the preterm infants.

METHODS

Search strategy and study selection

We searched PubMed, EMBASE, the Cochrane Library, and the KoreaMed database for relevant studies. We used the following search terms: infant, premature, neonate, pregnancy-induced hypertension, pre-eclampsia, eclampsia, hypertension, BPD, and/or chronic lung disease. The last search was performed on June 18, 2019. The titles and abstracts of all articles were initially screened, and the full-text articles were then reviewed by two authors (Park HW and Lim G) using predefined selection criteria. We excluded case reports, case series, review articles, editorials, and comments. The reference lists of included studies were manually searched, as were other electronic databases. No language restriction was imposed; studies were translated if necessary.

Inclusion and exclusion criteria

We included randomized controlled trials, observational studies (cohort studies or case-control studies), and cross-sectional studies in the analysis. Single-arm cohort studies without comparison groups, case reports, case series and animal studies were excluded. Types of HDP included gestational hypertension, pre-eclampsia-eclampsia and pre-eclampsia superimposed on chronic hypertension (based on a report from the National High Blood Pressure Education Program Working Group[14]). The definition of elevated blood pressure (BP) varied among the studies, including systolic BP (sBP) ≥ 140 mmHg and/or diastolic BP (dBP) ≥ 90 mmHg,[8,16-37] an increase in sBP ≥ 25 mmHg and/or dBP ≥ 15 mmHg[29] and sBP ≥ 145 mmHg and/or dBP ≥ 95 mmHg[38,39] after week 20 of gestation. Pre-eclampsia was defined as sBP ≥ 160 mmHg and/or dBP ≥ 110 mmHg with proteinuria, an increased creatinine level, a decreased platelet count, elevated hepatic enzyme levels, cerebral or visual symptoms (including headache), or persistent epigastric pain.[14,40] The combination of hemolysis, elevated liver enzyme levels, and low platelet count was considered to indicate hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome. Eclampsia was defined as a combination of seizures and pre-eclampsia.[14] Pre-eclampsia superimposed on chronic hypertension was defined as pre-eclampsia in women exhibiting chronic hypertension prior to pregnancy.[14] The definition of BPD varied among studies; some[16,20,22,24,25,31,37] used the National Institutes of Health consensus,[41] while others defined BPD as either oxygen dependency 28 days postnatally[18,42,43] or at 36 weeks of postmenstrual age.[8,12,18,21,23,27-30,32-36,38,39,42,44-47]

Data extraction and study quality assessment

Park HW and Lim G independently extracted data via full-text review of selected studies. We recorded first author names, year of publication, country of origin, study design, period, and population; definitions of HDP and BPD, sample size, and BPD rates in the HDP and non-

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HDP groups. We assessed study quality using the Newcastle-Ottawa Scale,[48] which has three domains: selection (four items), comparability (one item), and outcomes (three items). All eight items are awarded one point, except comparability (two points). Total scores range from 0 to 9: 0–3 points reflect low quality, 4–5 points moderate quality, and ≥ 6 points high quality. Any discrepancy in quality scoring or data interpretation was resolved via discussion with a third reviewer (Park YM).

Data synthesis and statistical analysis

We meta-analyzed the relationship between maternal HPD and BPD using Comprehensive Meta-Analysis software (version 3.3; Biostat Inc., Englewood, NJ, USA). We used a random-effects model if heterogeneity was present and a fixed-effects model if heterogeneity was absent. We used the I^2 statistic to evaluate statistical heterogeneity among studies. If $I^2 > 50\%$, significant between-study heterogeneity is present. We performed sensitivity analysis by removing each study individually from the analysis, and performed cumulative analyses to detect changes over time. We performed subgroup analyses according to the definition of pre-eclampsia. Funnel plot symmetry was assessed, and the Begg and Mazumdar rank correlation test and Egger regression test were performed to assess publication bias. We defined publication bias as funnel plot asymmetry or a P value < 0.05 in either the Begg and Mazumdar rank correlation test or Egger regression test. We also followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist of 2009 (**Supplementary Table 1**).

RESULTS

Literature search and selection

A flowchart of the study inclusion/exclusion process is shown in **Fig. 1**. Of 1,056 studies obtained via database and manual searching, 336 duplicates were removed. Of the remaining 720 studies, 622 were excluded based on title or abstract review, and a further 63 during full text review. We finally included 35 studies.

Characteristics of the included studies

The characteristics of the included studies are shown in **Table 1**.[8,12,16-39,42-47,49-51] A total of 97,399 infants were included in the meta-analysis. Based on a BPD definition of oxygen requirement at 36 weeks of gestation, the incidence of BPD was 32.0% (3,768 of 12,445 cases) in the HDP group and 29.1% (18,101 of 62,152 cases) in the non-HDP group. Based on a BPD definition of oxygen requirement at 28 days of age, the incidence of BPD was 27.6% (205 of 640 cases) in the HDP group and 25.5% (444 of 1,743 cases) in the non-HDP group. The incidence of severe BPD was 25.4% (91 of 358 cases) in the HDP group and 14.3% (144 of 1,007 cases) in the non-HDP group. The incidence of undefined BPD was 9.0% (16 of 177 cases) in the HDP group and 25.8% (64 of 248 cases) in the non-HDP group.

Results of pooled meta-analysis

Of the 35 eligible studies, 29[8,12,16,18,19,21-26,28-39,44-47,49,50] evaluated the relationship between HDP and BPD defined as an oxygen requirement at 36 weeks of gestation, and 8[18,20,24,25,36,37,42,43] evaluated the relationship when BPD was defined as an oxygen requirement at 28 days of postnatal age. Two studies[24,36] evaluated the relationship between HDP and severe BPD, and three[17,27,50] the relationship between HDP and undefined BPD. Five studies[18,24,25,36,37] described one or more outcomes of BPD.

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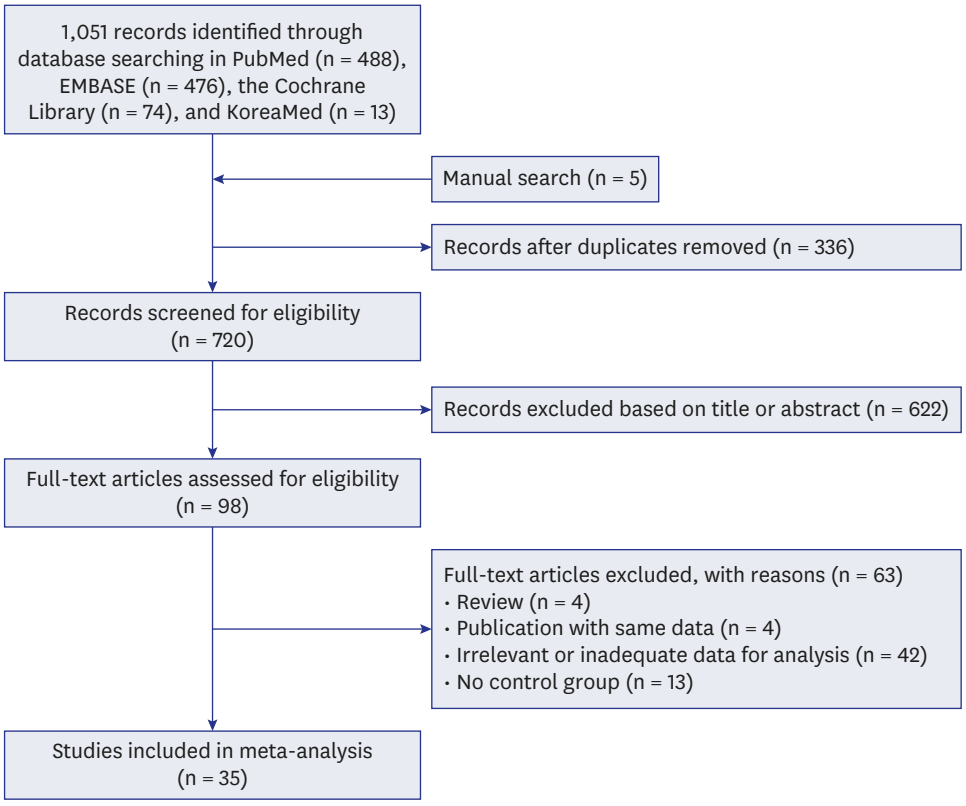

Fig. 1. Flow diagram of study selection.

Regardless of the definition of hypertension, BPD was not associated with HDP in the overall analysis (odds ratio [OR], 1.131; 95% confidence interval [CI], 0.977–1.309; P = 0.100; **Fig. 2**). Subgroups were defined according to the definition of HDP: subgroup 1, pre-eclampsia and/or eclampsia and/or HELLP; subgroup 2, other HDP except chronic hypertension; subgroup 3, HDP including chronic hypertension. BPD was not associated with any HDP subgroup (**Fig. 2**).

Maternal HDP was not significantly associated with BPD defined as an oxygen dependency at 36 weeks of gestation (OR, 1.162; 95% CI, 0.991–1.362; P = 0.064; **Fig. 3**). In the meta-analysis of the relationship between maternal HDP and BPD based on oxygen dependency at 36 weeks of gestation, significant between-study heterogeneity was evident (P < 0.001; I^2 = 86.07%) so a random-effects model was used. The Begg and Mazumdar rank correlation test (P = 0.302), Egger regression test (P = 0.494) and funnel plot (**Supplementary Fig. 1**) showed no evidence of publication bias. The data did not change when each study was sequentially removed or added (**Supplementary Fig. 2**).

Maternal HDP was not significantly associated with BPD defined as oxygen dependency at 28 days of age (OR, 1.084; 95% CI, 0.660–1.780; P = 0.751; **Fig. 4**). In the meta-analysis of the relationship between maternal HDP and BPD defined as oxygen dependency at 28 days of age, significant heterogeneity was evident among the studies (P < 0.001; I^2 = 78.92%) so a random-effects model was used. Both the Begg and Mazumdar rank correlation test (P = 0.035) and Egger regression test (P = 0.011) revealed evidence of publication bias.

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Table 1. Characteristics of studies included in this meta-analysis

Studies	Population	Definition of HDP (after the 20th week of gestation)	Definition of BPD (oxygen dependency)	NOS
Spinillo et al.[17] (1993)	IUGR and/or preterm	BP > 140/90 mmHg ± proteinuria	NA	6
Kim et al.[18] (1996)	Bwt ≤ 1,250 g	BP > 140/90 mmHg plus persistent proteinuria	At 28 day PNA or 36 wk PMA	8
Todd et al.[19] (1997)	GA 24–32 wk	Diastolic BP ≥ 90 mmHg	At 36 wk of PMA	7
Korhonen et al.[42] (1999)	Bwt < 1,500 g	NA	At 28 day PNA and 36 wk PMA with radiologic changes	8
Redline et al.[44] (2002)	GA < 32 wk	NA	At 36 wk of PMA	6
Cunha et al.[20] (2003)	Bwt < 1,500 g	BP > 140/90 mmHg	NICHD workshop, 2001	6
Hernández-Ronquillo et al.[43] (2004)	Preterm	NA	At 28 PNA with radiologic changes	5
Akram Khan et al.[21] (2006)	GA < 30 wk	BP > 140/90 mmHg plus proteinuria and nondependent edema	At 36 wk of PMA and radiologic changes	7
Cetinkaya et al.[22] (2010)	GA < 37 wk	BP > 140/90 mmHg plus proteinuria	NICHD workshop, 2001	10
Hansen et al.[8] (2010)	GA 23–32 wk	BP > 140/90 mmHg plus proteinuria	At 36 wk of PMA	6
Schlapbach et al.[23] (2010)	GA 25–32 wk	dBP > 90 mmHg plus proteinuria and/or acute spiral artery atherosis on placental histology	At 36 wk of PMA	10
Gortner et al.[45] (2011)	GA 24–31 wk	NA	At 36 wk of PMA	6
O'Shea et al.[12] (2012)	GA < 28 wk or Bwt < 1,000 g	Hypertension and proteinuria or nondependent edema	At 36 wk of PMA	7
Ozkan et al.[24] (2012)	GA < 32 wk	BP > 140/90 mmHg plus proteinuria	NICHD workshop, 2001	5
Klinger et al.[38] (2013)	Bwt ≤ 1,500 g	BP ≥ 145/95 mmHg plus proteinuria with/without proteinuria	At 36 wk of PMA and clinical findings	6
Shima et al.[25] (2013)	GA < 32 wk	BP > 140/90 mmHg	NICHD workshop, 2001	7
Yen et al.[26] (2013)	Bwt < 1,500 g	BP > 140/90 mmHg plus proteinuria	At 36 wk of PMA	7
Morsing et al.[27] (2014)	GA < 30 wk	dBP > 90 mmHg plus proteinuria	NA	7
Çetinkaya[46] (2015)	GA ≤ 32 wk	NA	At 36 wk of PMA	10
Regev et al.[39] (2015)	GA 24–32 wk Bwt ≤ 1,500 g	BP ≥ 145/95 mmHg	At 36 wk of PMA and clinical & radiologic findings	7
Gemmell et al.[28] (2016)	GA 24–28 wk	BP > 140/90 mmHg	At 36 wk of PMA	8
Matić et al.[29] (2017)	GA < 29 wk	BP > 140/90 mmHg or rise in sBP ≥ 25 mmHg and/or dBP ≥ 15 mmHg	At 36 wk of PMA	7
Morrow et al.[49] (2017)	GA ≤ 34 wk, Bwt 500–1,250 g	NA	NICHD workshop, 2001	6
Soliman et al.[30] (2017)	GA < 32 wk	BP > 140/90 mmHg	At 36 wk of PMA	6
Xu et al.[50] (2017)	Bwt < 1,500 g	NA	NA	7
Anwar et al.[47] (2018)	GA ≤ 32 wk	NA	At 36 wk of PMA	5
Kim et al.[31] (2018)	GA < 32 wk, singleton	BP > 140/90 mmHg plus proteinuria	NICHD workshop, 2001	7
Lu et al.[32] (2018)	GA < 34 wk	BP > 140/90 mmHg	At 36 wk of PMA or at discharge	6
Mao et al.[51] (2018)	GA 28–31 wk	NA	NICHD workshop, 2001	5
Razak et al.[33] (2018)	GA < 33 wk	BP > 140/90 mmHg plus proteinuria	At 36 wk of PMA	9
Rocha et al.[34] (2018)	GA 24–30 wk	BP > 140/90 mmHg plus proteinuria	At 36 wk of PMA	6
Strouss et al.[16] (2018)	Bwt < 1.500 g	ACOG 2002	NICHD workshop, 2001	7
Yusuf et al.[35] (2018)	GA < 29 wk	BP ≥ 140/90 mmHg	At 36 wk of PMA	7
Tagliaferro et al.[36] (2019)	GA 23–28 wk	BP > 140/90 mmHg plus proteinuria and/or thrombocytopenia, impaired liver function, pulmonary edema and new onset cerebral or visual disturbance	At 36 wk of PMA	7
Wilmink et al.[37] (2019)	GA 24–31 wk	BP ≥ 140/90 mmHg plus or maternal organ dysfunction or fetal growth restriction	NICHD workshop, 2001	7

HDP = hypertension during pregnancy, BPD = bronchopulmonary dysplasia, NOS = The Newcastle-Ottawa Scale, IUGR = intrauterine growth restriction, BP = blood pressure, NA = not available, Bwt = birth weight, PNA = postnatal age, PMA = postmenstrual age, GA = gestational age at birth, NICHD = National Institute of Child Health and Human Development, dBP = diastolic blood pressure, sBP = systolic blood pressure, ACOG = American College of Obstetricians and Gynecologist.

Thus, we performed trim and fill adjustments and the results did not change (OR, 1.084; 95% CI, 0.660–1.780) (**Supplementary Fig. 3**). No changes were seen in the sensitivity (**Supplementary Fig. 4A**) or cumulative (**Supplementary Fig. 4B**) analysis.

Maternal HDP was significantly associated with severe BPD (OR, 2.341; 95% CI, 1.726–3.174; $P < 0.001$; **Fig. 5**). There was no significant between-study heterogeneity ($P = 0.963$; $I^2 = 0\%$)

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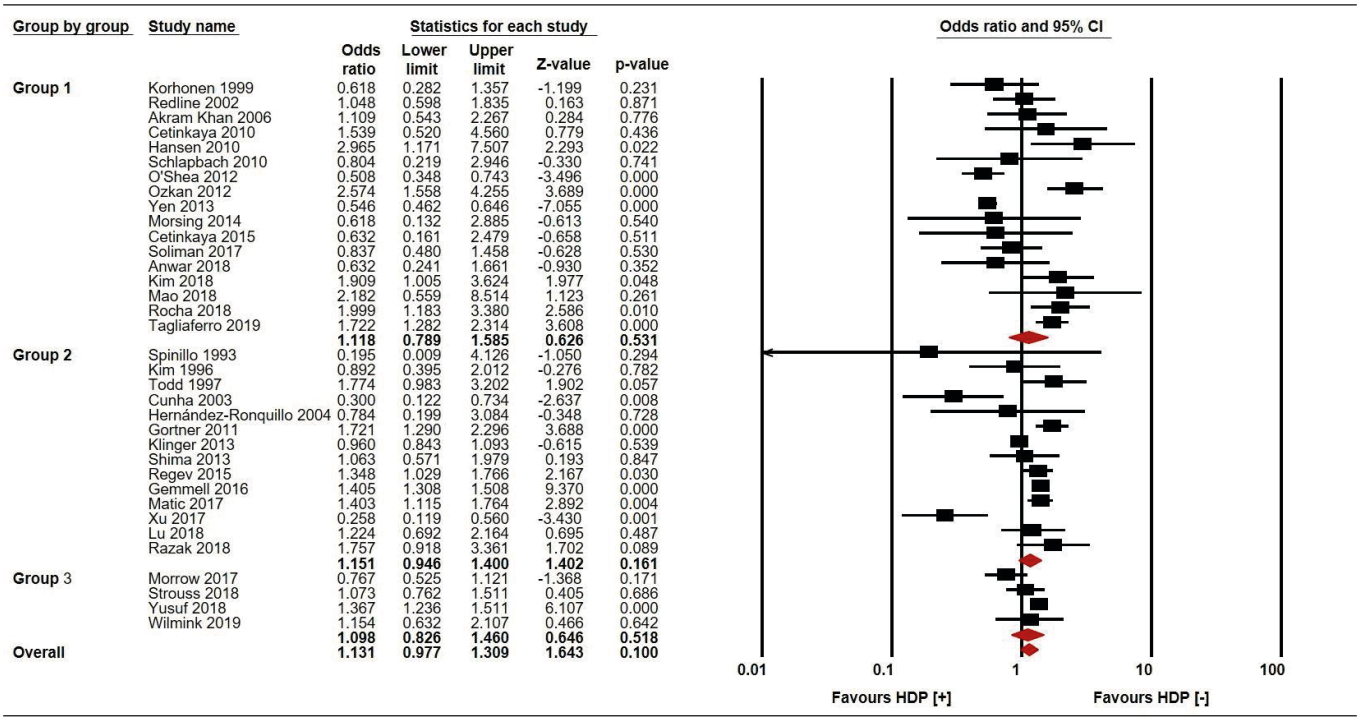

Fig. 2. Meta-analysis of the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia: subgroup analysis based on the definition of HDP. Subgroups were defined according to the definition of HDP: subgroup 1, pre-eclampsia and/or eclampsia and/or HELLP; subgroup 2, other HDP except chronic hypertension; subgroup 3, HDP including chronic hypertension.
HDP = hypertension during pregnancy, HELLP = hemolysis, elevated liver enzymes, and a low platelet count, CI = confidence interval.

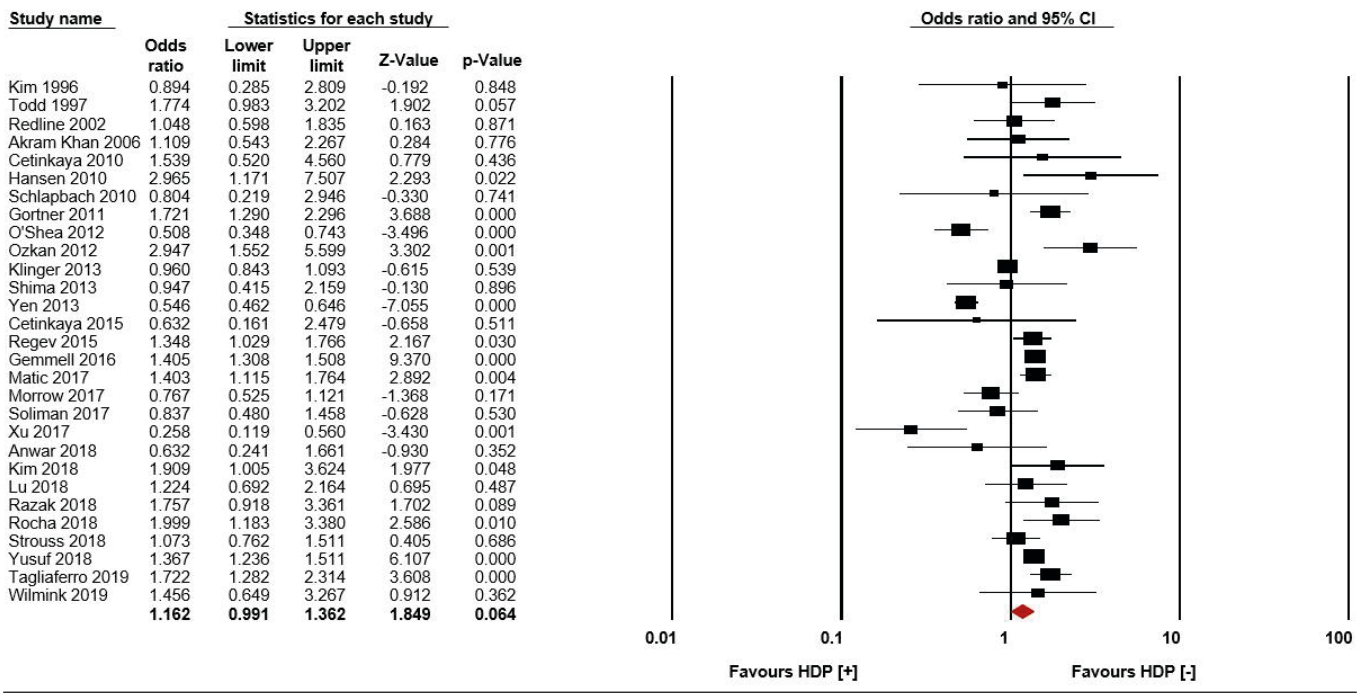

Fig. 3. Meta-analysis of the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia defined as an oxygen requirement at 36 weeks of gestational age.
HDP = hypertension during pregnancy,, CI = confidence interval.

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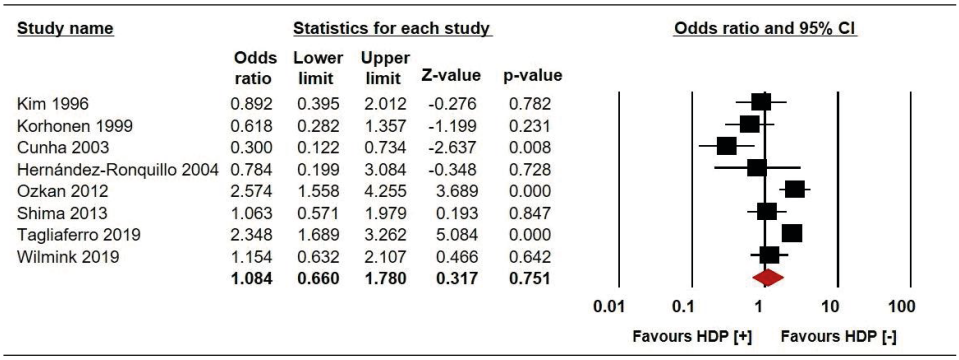

Fig. 4. Meta-analysis of the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia defined as an oxygen requirement at 28 days of postnatal age.
HDP = hypertension during pregnancy, CI = confidence interval.

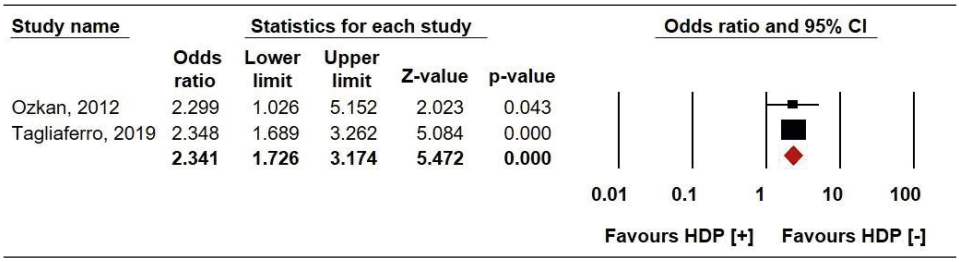

Fig. 5. Meta-analysis of the relationship between maternal pre-eclampsia and severe bronchopulmonary dysplasia.
HDP = hypertension during pregnancy, HELLP = hemolysis, elevated liver enzymes and low platelet, CI = confidence interval.

so a fixed-effects model was used. Publication bias could not be evaluated because of the small number of studies. Sensitivity and cumulative analyses revealed no significant changes.

DISCUSSION

The incidence of HDP is 2–8%.[9,13,14] HDP can cause maternal and fetal complications including preterm birth, intrauterine growth restriction, and fetal death.[13] Early onset (before 33 weeks of gestation) and severe disease are associated with increased risks of maternal and perinatal morbidity.[13,14] HDP includes gestational hypertension, pre-eclampsia/eclampsia, pre-eclampsia superimposed on chronic hypertension, and chronic hypertension.[52,53] Pre-eclampsia is defined by the American College of Obstetricians and Gynecologists as hypertension with proteinuria, or new-onset thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms.[53] Among the 35 studies included in this meta-analysis, 10 did not define HDP.[22,38,42-44,47,49-51,54] HDP was diagnosed based on BP and proteinuria in 15 studies[8,12,16,18,21-24,26,27,31,33,34,36,37] and on the basis of BP only in 10.[17,19,20,25,28-30,35,39]

BPD is a chronic lung disease requiring oxygen or ventilator support; many antenatal and postnatal factors, and preterm birth, affect BPD development.[1,2] Pre-eclampsia, one of several antenatal factors, is characterized by impaired lung alveolar and vascular development.[2,55] Changes in the levels of several anti-angiogenic and angiogenic factors have been reported in women with pre-eclampsia.[8,15,31,56-60] Angiogenic factors affect fetal lung development (especially pulmonary vascular growth and alveolarization) in animal models.[56,59,61] It has

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been suggested that increased levels of anti-angiogenetic factors and/or inhibition of the angiogenic pathway in women with pre-eclampsia could inhibit fetal vascular or alveolar lung development[56]; this is the "new BPD" described by Jobe[1] and Abman.[62] However, the strength of the relationship between HDP and BPD varied among previous reports.[8,26,63,64] The BPD risk of infants born to mothers with pre-eclampsia was elevated (unadjusted OR, 1.29; adjusted OR, 1.59) in the studies of Hansen et al.[8] and Bi et al.[9] (unadjusted OR, 2.96; adjusted OR, 18.7). On the contrary, HDP reduced the risk of BPD in the study of Yen et al.[26] and had no association with BPD of preterm infants in other reports.[12,22,23] Although HDP overall was associated with BPD in the study of Bi et al.,[9] pre-eclampsia was not and pre-eclampsia/HELLP (pooled result) was only marginally associated with BPD in the unadjusted model. We found that maternal HDP was not significantly associated with BPD defined as an oxygen dependency at either 36 weeks of gestation (OR, 1.162; 95% CI, 0.991–1.362; $P = 0.064$; **Fig. 3**) or 28 days of age (OR, 1.132; 95% CI, 0.743–1.724; $P = 0.563$; **Fig. 4**), unlike previous studies.[8,9] Moreover, the incidence of BPD and duration of mechanical ventilation did not differ between the pre-eclampsia and non-pre-eclampsia groups in the study of Shin et al.[65] It is possible that we found no association between HDP and BPD (other than severe BPD) because the clinical definitions of BPD were inconsistent. The risk of BPP in the HDP group without fetal growth restriction did not differ from that of the group without HDP, and maternal HDP was associated with BPD in cases exhibiting antenatal fetal growth restriction.[10] Dravet-Gounot et al.[11] explored the association between fetal growth restriction and BPD in neonates born to mothers with pre-eclampsia. Pre-eclampsia onset before 34^{+0} weeks of gestation (early onset), which causes fetal growth restriction, constituted only 5–20% of all pre-eclampsia cases, most of which were late-onset and thus did not cause fetal growth restriction or changes in umbilical artery blood flow.[66] As early onset pre-eclampsia increases the risk of neonatal morbidity, pre-eclampsia during a critical phase of development and/or the prolonged actions of anti-angiogenetic and/or angiogenic factors may be associated with BPD.[13,14] We assume that continued and severe pre-eclampsia causing fetal growth restriction compromises lung development and causes BPD.

We found that maternal HDP was significantly associated only with severe BPD (OR, 2.341; 95% CI, 1.726–3.174; $P < 0.001$; **Fig. 5**). Bi et al.[9] reported an association between HDP severity and BPD but the duration of ventilator support and oxygen administration are likely to vary by clinician and medical unit[66]; mild-to-moderate BPD does not reflect lung status. However, severe BPD always requires respiratory assistance or high concentrations of oxygen. BPD can be diagnosed without additional testing based on the physiologic definition of BPD if an infant requires over 30% oxygen or positive pressure ventilation (invasive or non-invasive).[66] Severe BPD has been further subclassified based on the need for invasive mechanical ventilation (or not).[67] Clinically, type 2 severe BPD is defined as a need for invasive mechanical ventilation, and is associated with poorer outcomes (including death, pulmonary hypertension, and neurodevelopmental impairment) than is type 1 BPD (defined as a need for oxygen or non-invasive mechanical support[68]).

Our work had certain limitations. First, data on the time of HDP onset were unavailable, and we did not evaluate the associations of changes in the levels of anti-angiogenic and angiogenic factors with HDP or neonatal BPD. It was inevitable because of limitations of a meta-analysis based on only the results of previously reported studies. Second, this meta-analysis showed an association between maternal HDP and severe BPD. However, only a small number of studies have described the BPD severity. Additional clinical studies are needed to verify the relationship between maternal HDP and severe BPD.

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In conclusion, we found no association between maternal HDP and neonatal BPD, other than severe BPD. Further studies should evaluate the relationships of HDP onset and/or changes in the levels of HDP-associated anti-angiogenetic and angiogenic factors with neonatal BPD.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2009 checklist

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Supplementary Fig. 1

Funnel plot for the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia defined as an oxygen requirement at 36 weeks of gestation.

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Supplementary Fig. 2

Sensitivity analysis (**A**) and cumulative analysis (**B**) for the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia defined as an oxygen requirement at 36 weeks of gestation.

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Supplementary Fig. 3

Funnel plot the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia defined as an oxygen requirement at 28 days of age. An asymmetrical funnel plot indicated possible publication bias, thus, we performed a trim and fill adjustment.

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Supplementary Fig. 4

Sensitivity analysis (**A**) and cumulative analysis (**B**) for the relationship between maternal pre-eclampsia and neonatal bronchopulmonary dysplasia defined as an oxygen requirement at 28 days of age.

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