The association between hypertensive disorders in pregnancy and bronchopulmonary dysplasia: a systematic review

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Systematic review

Background: **Whether hypertensive disorders in pregnancy (HDP) are the risk factors of bronchopulmonary dysplasia (BPD) is controversial. A systematic review was made to determine the association between HDP and BPD in preterm infants.**

Methods: **We searched PubMed, Embase, Cochrane Library, ScienceDirect, Web of Science, with no language limitation, and reviewed the reference lists of the selected articles to identify additional relevant publications and contacted the authors of relevant studies for further information. The data were extracted independently by 2 reviewers who used a predetermined data extraction form. Studies were combined with an odds ratio (OR) using a random-effects model. Meta-regression and subgroup analysis were used to explore potential confounders. Funnel plots, Egger's test and Begg's test were used to investigate the publication bias. The Trim and Fill method was used to control the publication bias.**

Results: **A total of 787 studies were identified and only 15 studies (20 779 patients) were included. The pooled unadjusted OR showed that HDP was significantly associated with BPD (*P*=0.04; OR=1.29, 95% CI=1.01-1.65). Heterogeneity was substantial (I^2=74%) and might be partially explained by different variables in maternal complications between the control groups across the studies. The pooled adjusted OR suggested the same conclusion that HDP was a risk factor for BPD (*P*=0.01; OR=1.59, 95% CI=1.11-2.26). Funnel plot and Egger's test showed that there were publication bias of unadjusted estimate of association between HDP and BPD.**

Conclusions: **Unadjusted analyses showed that the rate of BPD was slightly higher in the infants exposed to HDP, and adjusted analyses confirmed this finding. But this result should be interpreted cautiously because substantial heterogeneity and publication bias were identified in this review.**

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Key words: **bronchopulmonary dysplasia;**
hypertensive disorders in pregnancy;
preeclampsia;
pregnancy induced hypertension

Introduction

Bronchopulmonary dysplasia (BPD) was first described as a complication of prematurity by Northway et al in 1967.[1] It was considered that premature birth, respiratory failure, oxygen supplementation, and mechanical ventilation were the main causes of classic BPD.[2] Due to advances in perinatal care and new neonatal respiratory therapies, classic BPD has been replaced by a milder clinical form,[3] a new BPD which is more related to immaturity, perinatal infection and inflammation, persistent ductus arteriosus, and disrupts alveolar and capillary development.[4] The new BPD is due to the injury of the lung in the canalicular and saccular phases of lung development that alters subsequent alveolar and vascular development, resulting in simplified alveolar structures, dysmorphic capillary configuration, variable interstitial cellularity and fibroproliferation.[5]

Hypertensive disorders in pregnancy (HDP) including pregnancy-induced hypertension (PIH), preeclampsia (PE), hemolysis, elevated liver enzymes, and low platelet count (HELLP) could be seen in 7% of pregnancies and rank second as a cause of maternal mortality. The current literature showed that PE might be mediated by an altered angiogenic state such as high levels of several anti-angiogenic factors,[6] and this angiogenic state was due to decreased umbilical cord vascular endothelial growth factor (VEGF) in infants born to PE mothers.[7] It was reported that

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angiogenesis was necessary for alveolarization during normal lung development and that injury to the pulmonary circulation during a critical period of lung growth may contribute to lung hypoplasia.[8] It was suggested that VEGF receptor signaling is required for the maintenance of the alveolar that alveolar septal cell apoptosis contributes to the pathogenesis of emphysema.[9] Whether HDP is the risk factor of BPD is controversial. Studies[10-13] found that HDP was associated with an increased incidence of BPD, but one[14] reported that those born to mothers with mild hypertension had a significantly lower incidence of BPD as compared with those with severe maternal hypertension or without maternal hypertension at all.

This systematic review aimed to find the association between BPD and HDP so that we could control the risk factors and prevent BPD in the early stage.

Methods

Search strategy

We searched PubMed, Embase, Cochrane Library, ScienceDirect, Web of Science, up in February 2013 with no limitations of language or publication status. Search terms of MeSH were "maternal hypertension", "hypertensive disorders in pregnancy", "gestational hypertension", "preeclampsia", "pregnancy-induced hypertension", "bronchopulmonary dysplasia" and "chronic lung disease". We reviewed the lists of selected articles to identify additional relevant publications and contacted the authors of relevant studies.

Inclusion criteria

The inclusion criteria of the studies should be met: (i) a control group is necessary in the studies; (ii) participants should be preterm or low BW infants; (iii) primary data could be used to detect the association between exposure to HDP and the development of BPD.

PIH is defined as blood pressure higher than 140/90 mmHg occurred after 20 weeks of postmenstrual age,[15] without evidence of PE or HELLP syndrome. PE is defined as the development of hypertension plus one of the following: proteinuria, thrombocytopenia, or pulmonary edema.[16] HELLP syndrome was defined as hemolysis, elevated serum concentration of aspartate aminotransferase (≥70 IU/L) and thrombocytopenia.[17]

We classified BPD as either a need for oxygen at the first 28 days together with a compatible chest radiograph[18] or a need for additional oxygen at 36 weeks of postmenstrual age according to the criteria of Bancalari et al.[19] Two reviewers screened the results of the searches and applied inclusion criteria using a structured form independently to identify relevant studies.

Quality assessment

The quality of the studies was independently assessed by 2 reviewers using Newcastle-Ottawa Scale (NOS)[20] for case-control or cohort studies as appropriate. The assessment considered such domains: selection bias, comparability bias, exposure bias (case-control studies) and outcome bias (cohort studies).

Data extraction

Data were extracted independently by 2 reviewers who used a predetermined data extraction forms. For each study, the following characteristics were extracted: study design; population characteristics including sample size, ethnicity, birth weight (BW), gestational age (GA), data years, definitions of BPD, type of HDP, and usage of antenatal corticosteroids. Differences were resolved by discussion and consensus of the two reviewers.

Statistical analysis

The extracted data were analyzed using RevMan 5 and STATA 11. The association was evaluated between HDP and BPD by combining the studies with an odds ratio (OR) using a random-effects model. Heterogeneity was quantified using the I^2 statistical method and the value greater than 50% was considered substantial. We conducted meta-regressions to test the effect on confounders such as GA, BW and antenatal steroid's prevalence separately. We also investigated heterogeneity by subgroup analysis according to the type of HDP, which was also considered the severity of HDP. Since this could not adequately explain the heterogeneity, post hoc analyses were conducted to assess whether the different inclusion criteria of participants, whether the definition of BPD or whether the different expoure factors of the control group could explain the heterogeneity. Forest plots were used to illustrate results from meta analyses, and unadjusted OR analyses were based on raw data for HDP and BPD. But adjusted OR analyses were based on data from multiple logistic regression analyses within the studies that adjusted for potential confounders. Funnel plots, Egger's or Begg's tests were used to investigate publication bias. The Trim and Fill method was used to control the publication bias.

Results

Identifying studies

The literature review identified 787 potentially relevant studies from PubMed, Embase, Cochrane Library, ScienceDirect, and Web of Science. Forty-three studies were identified as relevant to the review through titles or abstracts, and 15 studies[10-14,21-30] met the inclusion criteria finally (Fig. 1).

Characteristics of the studies

The 15 studies were published in the English language

between 1996 and 2013. Six studies were prospective cohort studies, 6 retrospective cohort studies and 3 case-control studies. There was great variability in the study size, from very small (n=66) to large (n=12 139). These studies were performed in a variety of countries. Not only definitions of BPD and HDP, but also the inclusion criteria varied in the studies (Table 1). Data extracted from the studies were used to measure the association between BPD and HDP, but only 6 studies provided adjusted measures of the association between BPD and HDP (Table 2).

Association between HDP and BPD

Pooled unadjusted OR showed that the rate of BPD was

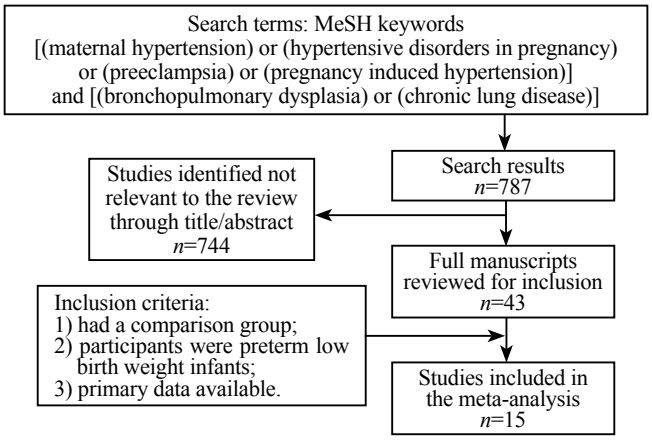

Fig. 1. The flow diagram of the literature reviewing process.

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

First author, year (site)	Data year	Inclusion criteria	Sample size	Study design	BPD definition	HDP type	Denominator	Antenatal corticosteroids	Mean GA (wks)	Mean BW (g)	NOS
Akram, 2006 (USA)[21]	1993-2000	GA<30 wk	306	Retrospective study	Oxygen at 36 wk and chest X-ray changes	PIH	Alive at 36 wk	Hospital A 73%, Hospital B 69%	26.9	978	5
Cetinkaya, 2010 (Turkey)[22]	2006-2007	GA<37 wk	84	Case-control study	Oxygen at 28 d or 36 wk	PE	Alive at 36 wk	39%	31.5	1432	5
Gortner, 2011 (Europe)[23]	2003	24 wk<GA <32 wk	4154	Prospective study	Oxygen at 36 wk	PIH PE HELLP	Alive at 36 wk	85%	29.5	1252	7
Hansen, 2010 (USA)[11]	2006-2008	23 wk<GA<32 wk	107	Prospective study	Oxygen at 36 wk	PE	All live births	87%	29	1370	7
Kim, 1996 (USA)[14]	1991-1992	BW≤1250 g, GA<33 wk	105	Case-control study	Oxygen at 36 wk	PIH PE HELLP	Alive at 36 wk	27%	28	971	6
Klinger, 2013 (Israel)[24]	2000-2010	BW≤1500 g	12 139	Prospective study	Oxygen at 36 wk	PIH PE HELLP	Alive at 36 wk	83%	29	1200	7
Korhonen,1999 (Finland)[13]	1990-1994	BW<1500 g	192	Retrospective study	Oxygen at 28 d and chest X-ray changes	PE	Alive at 28 d	37%	28.5	1125	6
O'Shea, 2012 (Australia)[25]	1991-1992 1997 2005	BW<1000 g or GA<28 wk	753	Retrospective study	Oxygen at 36 wk	PE	Alive at 36 wk	73% 88% 89%	26.6	861	7
Ozkan, 2012 (Turkey)[12]	2009-2010	GA≤32 wk	332	Prospective study	Oxygen at 28 d or 36 wk	PE	Alive at 28 d	64%	29.2	1166	7
Park, 2012 (Korea)[26]	2003-2011	24 wk ≤GA≤32 wk, BW≤1500 g	191	Retrospective study	Oxygen at 28 d or 36 wk	PIH	Alive at 36 wk	68%	28.8	1136	6
Redline, 2002 (England)[27]	1995-1997	GA<32 wk, BW<1500 g	371	Retrospective study	Oxygen at 36 wk	PE	Alive at 36 wk	65%	27.6	1023	5
Schlapbach, 2010 (Switzerland)[28]	2002-2005	GA<32 wk	66	Case-control study	Oxgen at 36 wk	PE	All alive	66%	30	1130	5
Todd, 1997 (Australia)[29]	1986-1994	GA<32 wk	296	Prospective study	Oxgen at 36 wk	PIH	Alive at 36 wk	46%	27.5	1032	4
Bose, 2009 (USA)[10]	2002-2004	GA<28 wk	1241	Prospective study	Oxygen at 36 wk	PE	Alive at 36 wk	90%	25.6	852	5
Withagen, 2001 (Netherlands)[30]	1985-1993	24 wk<GA<31 wk	444	Retrospective case-control study	Oxygen at 28 d and chest X-ray changes	PE	Alive at 28 d	15%	31	1475	6

GA: gestational age; BW: birth weight; BPD: bronchopulmonary dysplasia; HDP: hypertensive disorders in pregnancy; PIH: pregnancy-induced hypertension; PE: preeclampsia; HELLP: hemolysis, elevated liver enzymes, and low platelet count syndrome; NOS: Newcastle-Ottawa Scale. 36 wk: 36 weeks postconceptional age for <32 gestational age; 28 d: 28 days of age for >32 gestational age.

significantly higher in the HDP group (P=0.04; OR=1.29, 95% CI=1.01-1.65), although heterogeneity was substantial (I^2=74%) (Fig. 2). The effect of HDP on BPD seems to be related to the severity of HDP according to the pooled OR of the PE+HELLP subgroup (P=0.05; OR=1.33, 95% CI=1.00-1.76). Six studies[11-13,23-25] reported adjusted OR and four of them[11,13,23,24] showed that HDP was a significant risk factor for BPD. The pooled adjusted OR also suggested that HDP was a risk factor for BPD (P=0.01; OR=1.59, 95% CI=1.11-2.26), although the heterogeneity was also substantial (I^2=58%) (Fig. 3, Table 2).

Heterogeneity

BW and GA were always considered the symbol of maturation for the preterm infant, and antenatal steroid given was considered an effective treatment to promote fetal lung maturity. Thus, BW, GA and antenatal steroid prevalence are thought to be the most important confounders. Meta-regression was conducted to test the effect on GA, BW and antenatal steroid prevalence separately, and the result showed that none of them was the source of heterogeneity (GA, P=0.446; BW, P=0.149; antenatal steroid, P=0.715). Subsequently, subgroup analysis was conducted according to the type of HDP to explore the heterogeneity, and the association was not significant in both subgroup analyses (PIH: P=0.64, OR=1.14, 95% CI=0.65-2.00; PE and HELLP: P=0.05, OR=1.33, 95% CI=1.00-1.76) (Fig. 2). Moreover, post

Table 2. Studies that provided adjusted measures of the association between BPD and HDP

First author, year	Type of HDP	Unadjusted measure, OR (95% CI)	Adjusted measure, OR (95% CI)	Variables controlled for in adjusted model
Gortner, 2011[23]	PIH, PE, HELLP	1.72 (1.29-2.30)	1.60 (1.1-2.4)	GA, gender, PROM, SGA, apgar score, site
Hansen, 2010[11]	PE	2.96 (1.17-7.51)	18.70 (2.44-144.76)	Clinical chorioamnionitis, GA, BW z score, gender, maternal tobacco use
Klinger, 2013[24]	PIH, PE, HELLP	0.96 (0.84-1.09)	1.28 (1.07-1.52)	SGA, delivery room resuscitation, sepsis
Korhonen, 1999[13]	PE	0.62 (0.28-1.36)	6.75 (1.22-37.3)	BW, age, ventilator therapy, SP, PDA, hyperoxia
O'Shea, 2012[25]	PE	0.72 (0.49-1.05)	1.14 (0.71-1.81)	PROM, cesarean delivery, gender, GA, BW, BW z score
Ozkan, 2012[12]	PE	2.57 (1.56-4.25)	1.97 (0.74-2.1)	GA, BW, duration of mechanical ventilation, duration of total oxygen

BW: birth weight; GA: gestational age; SGA: small for gestational age; PROM: premature rupture of the membranes; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; HDP: hypertensive disorders in pregnancy; OR: odds ratio; CI: confidence interval.

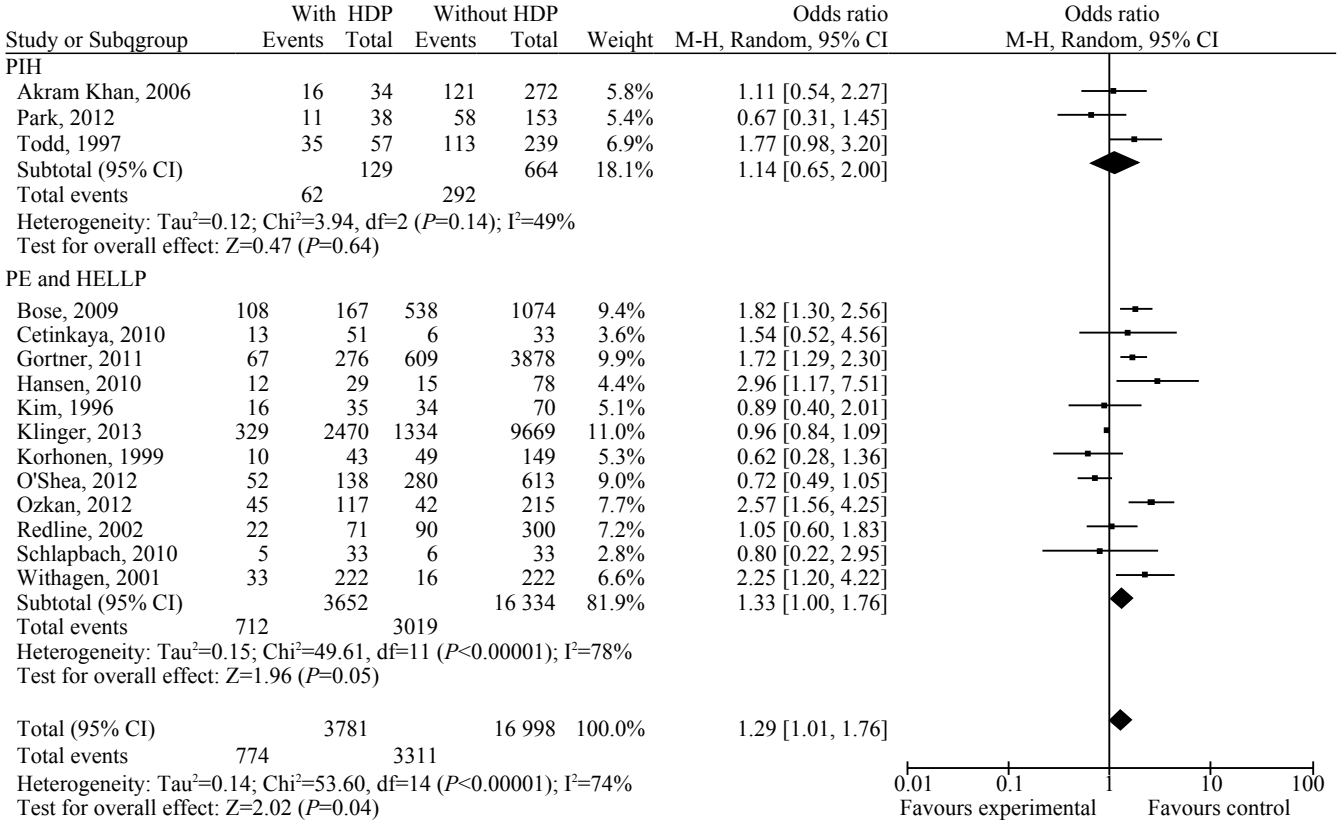

Fig. 2. Forest plot showing the unadjusted association between HDP and BPD by type of HDP. BPD: bronchopulmonary dysplasia; HDP: hypertensive disorders in pregnancy; CI: confidence interval.

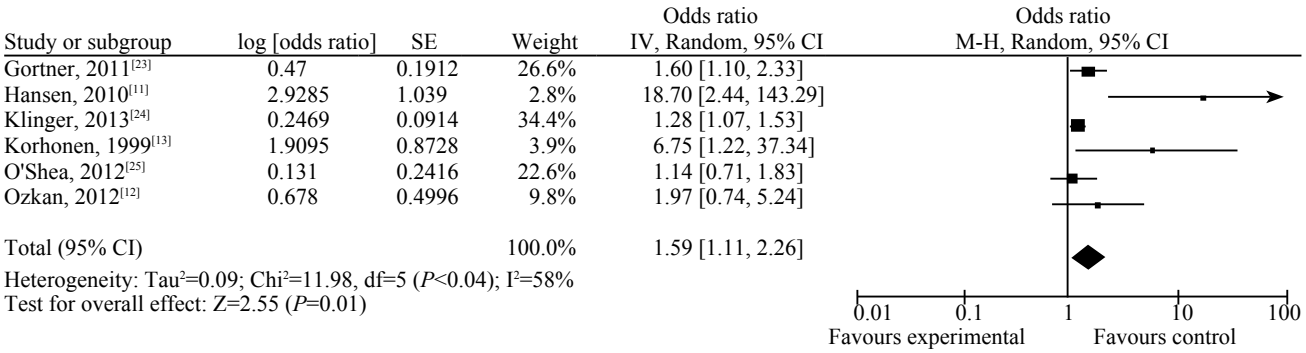

Fig. 3. Forest plot showing the adjusted association between bronchopulmonary dysplasia and hypertensive disorders in pregnancy.

hoc analyses were conducted to assess the source of heterogeneity, but the different inclusion criteria of participants, the different definitions of BPD, and the different exposure factors of the control group in the studies cannot adequately explain the heterogeneity (data not shown). We found that the objectives of the studies varied, and their control groups were not matched for GA, BW, antenatal steroid therapy, maternal complications (maternal diabetes mellitus, intra-uterine growth restriction, chorioamnionitis), pulmonary surfactant and mechanical ventilation. It was recognized that intra-uterine growth restriction (IUGR) is a complication of HDP,[31] and that more mature growth-restricted infants with similar birth weight may be protected by more advanced gestation and therefore less likely to develop BPD. This is why some studies[13,24,25] came to a false conclusion that HDP was protective against BPD, but adjusted OR showed that HDP was still a risk factor increasing the rate of BPD. Above all, without consistently controlling GA in the individual studies, HDP might be falsely associated with a decreased incidence of BPD based on the assessment of preterm infants with similar birth weight.

In addition, failure to control other antenatal and postnatal risk factors of BPD between the study and control groups, such as chorioamnionitis, neonatal sepsis, patent ductus arteriosus requiring intervention, and use of mechanical ventilation, may also contribute to substantial heterogeneity in the studies.

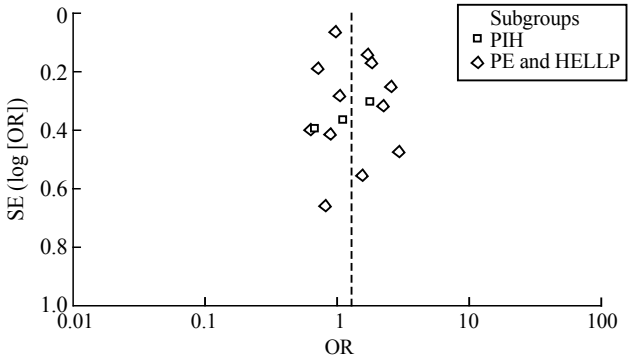

Fig. 4. Funnel plot showing publication bias of unadjusted estimate of association between bronchopulmonary dysplasia and hypertensive disorders in pregnancy. PIH: pregnancy-induced hypertension; PE: preeclampsia; HELLP: hemolysis, elevated liver enzymes, and low platelet count syndrome; OR: odds ratio.

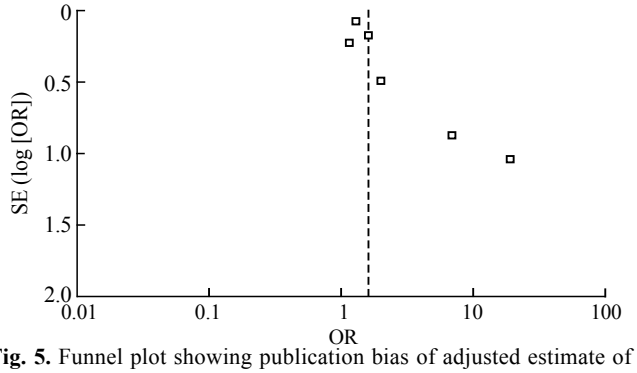

Fig. 5. Funnel plot showing publication bias of adjusted estimate of association between bronchopulmonary dysplasia and hypertensive disorders in pregnancy; OR: odds ratio.

Publication bias

We investigated the publication bias by using funnel plots, Egger's test and Begg's test. The asymmetry funnel plot (Fig. 4) and the result of Egger's test showed that there were publication bias of unadjusted estimate of association between HDP and BPD (P=0.026, based on Egger's test; P=0.16, based on Begg's test). We then used the Trim and Fill method to adjust the publication bias, and no trimming was performed and the data were not changed. There were also publication bias for the adjusted estimate (Fig. 5), but the pooled OR after use of the Trim and Fill method was not significant (OR=1.324, 95% CI=0.885-1.981).

Discussion

Main findings

Previous studies have examined the relationship between intrauterine exposure HDP and the risk of the infant developing BPD, but whether HDP is the risk factor of BPD is still controversial. Some of these

studies reported that HDP would increase the incidence of BPD, others reported the contradictory results, and still others found no changes.

The meta-analysis of unadjusted data (PIH+PE +HELLP) showed a significant association between HDP and BPD. Heterogeneity was substantial and could be partially explained by different variables in maternal complications between the control groups in the studies.

Pooled analysis (PIH+PE+HELLP), not subgroup analysis (either PE+HELLP or PIH alone), revealed that HDP was significantly associated with the increased incidence of BPD. The loss of association between HDP and BPD in subgroup analysis probably was due to the reduction of sample size, when the whole group of HDP was divided into PE+HELLP and PIH. In addition, we found that substantial HDP (PE+HELLP) tended to be associated with the increased incidence of BPD (P=0.05), whereas modest HPD (PIH) was not associated with BPD (P=0.64). Our finding suggests that the severity of HDP is positively correlated with an increased incidence of BPD.

The adjusted estimates suggested that the same result and strength of the association between BPD and HDP. We tried to find the source of heterogeneity, but none of GA, BW, antenatal steroids' prevalence, different types of HDP, different inclusion criterias of participants, different definitions of BPD, and different exposure factors of the control group in the studies could adequately explain the heterogeneity. We could not identify any single and consistent source to explain the heterogeneity. But we found the altered OR after multivariable analysis in some studies,[13,24,25] we inferred that the heterogeneity was due to the different variables in maternal complications between the control groups in the studies.

There were publication bias in both unadjusted and adjusted estimates of association between HDP and BPD, the visual plots of asymmetry suggested that small studies deomonstrating no effect between HDP and BPD were less likely to be published. BPD was considered a multifactor disease, and the main risk factors included preterm birth, lower BW and GA, supplemental oxygen and ventilatory support, oxygen toxicity, decreased host antioxidant defenses, perinatal infection and inflammation, persistent ductus arteriosus, disrupted alveolar and capillary development.

Studies[11,32] reported that impaired lung development and mechanical ventilation duration was significantly longer in preterm infants born to PE mothers. Our analysis supported the results of the studies.

A recent study[33] found that impaired angiogenesis was due to the altered angiogenic state in PE mothers who shared with the fetus such antiangiogenic factors as soluble VEGF receptor 1 and soluble endoglin. The low levels of angiogenic factors including free maternal VEGF and PIGF were detected in PE mothers. Maniscalco et al[34] reported that VEGF and membrane-bound fms-like tyrosine kinase 1 (FLT-1) were decreased in BPD and suggested that disruption of VEGF and FLT-1 was likely to be the mechanism of abnormal alveolar microvessels development in BPD. Gien et al[35] reported that VEGF was critical for normal lung development, and if the expression of VEGF was disrupted, it would result in impairment of vascular development and alveolarization of the lung. This finding may explain the increased incidence of BPD in preterm infants born to HDP mothers compared with those born to normotensive mothers.

Limitations

There are several limitations in this study. First, the prevalences of GA, BW and antenatal steroids are not the main source of heterogeneity through meta-regression, but we cannot control the difference in GA, BW and antenatal steroids' prevalence between exposure and non-exposure groups because most of the studies cannot provide the data on GA and BW between the two groups. We cannot get a more accurate pooled adjusted OR, which eliminates the effect of such confounders. Second, we cannot explore other important confounders because we did not have complete information about the studies.

Conclusions

In this review, unadjusted analyses revealed that the rate of BPD was slightly higher in the infants exposed to HDP. This result should be interpreted with caution because of heterogeneity and publication bias. Unadjusted OR seems to suggest that HDP is a protective factor for BPD in some studies, but adjusted OR after multivariable analysis suggested that HDP is still a risk factor, and the pooled adjusted OR can support this conclusion. Thus heterogeneity may be partially explained by different variables in maternal complications between the control groups in the studies. On the other hand, publication bias may be due to heterogeneity according to the result of controlling publication bias by the Trim and Fill method. Also, the effect of HDP on BPD seems to be potentially related to the severity of HDP according to the subgroup analysis.

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Ethical approval: Not needed.

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Contributors: Bi GL wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version.

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