의학석사 학위논문

The Association of Pregnancy-induced Hypertension with Bronchopulmonary Dysplasia - A Retrospective Study Based on the Korean Neonatal Network database

임신성 고혈압과 기관지폐이형성증의 연관성-한국신생아네트워크 데이터베이스를 기반으로 한 후향적 연구

2021년 2월

서울대학교 대학원
임상의과학과 임상의과학 전공
신 승 현

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이 논문을 의과대학 의학석사 학위논문으로 제출함

2020년 10월

서울대학교 대학원

임상의과학과 임상의과학 전공

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신승현의 석사 학위 논문을 인준함

2021년 1월

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Abstract

The Association of Pregnancy-induced Hypertension with Bronchopulmonary Dysplasia - A Retrospective Study Based on the Korean Neonatal Network database

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Background: The prevalence of preeclampsia (PE) is 2 - 4%. PIH might afect angiogenesis in preterm neonates, but its association with bronchopulmonary dysplasia (BPD) remains controversial.

Objective: This study evaluated the association between PIH and BPD in very low-birth weight infants.

Method: We retrospectively analysed the maternal, perinatal, and neonatal data of preterm infants born before 30 weeks of gestation, selected from the nationwide registry of very low-birth weight infants, between January 2013 and December 2014.

Result: As a result, 1,624 infants without maternal PIH (gestational age: 27.3±1.8 weeks) and 203 infants with maternal PIH (28.0±1.4 weeks, $p<0.001$) were included. Birth weight was higher in the non-PIH group, compared with the PIH group (1027.4±250.2 vs. 876.4±261.5g, $p<0.001$). Multivariate logistic regression showed that PIH was associated with BPD (adjusted OR 1.474, 95%

confdence interval 1.025 - 2.121), after adjusting for confounders, including small-for-gestation age (SGA).

Conclusion: The result of present study is consistent with the current concept of BPD as an early form of pulmonary vascular disease, for both PIH and BPD are attributed by abnormal vascular formation.

Keywords: Pregnancy-induced hypertension, Pre-eclampsia, Bronchopulmonary dysplasia, Preterm infant

Student Number: 2019-24702

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Introduction

Bronchopulmonary dysplasia (BPD) is a major cause of morbidity and mortality among very low-birth weight (VLBW) infants. Although the introduction of antenatal steroids and surfactant therapy has improved the neonatal outcomes of preterm infants, the incidence of BPD has not decreased, with the increased survival of pre-term infants [1-4]. These extremely preterm infants, characteristically presented with with arrested alveolar-capillary development, with larger, simplified alveoli, increased interstitial fibrosis, abnormal pulmonary vasculature with decreased branching, and pre-capillary arteriovenous anastomoses [5]. Therefore, BPD has been recently recognized as an early manifestation of pulmonary vascular disease in preterm infants, because both, angiogenesis and alveolar development in the fetal lung are associated with it [6].

Preeclampsia (PE), a specific form of pregnancy induced hypertension (PIH) affects 2-4% of pregnancies [7-10]. Although the pathophysiology of PE is not fully understood, abnormal placental implantation, vascularization, or function might influence the development of PIH [11]. Several maternal angiogenic factors and anti-angiogenic factors are associated with the regulation of placental growth and vascular development, including vascular endothelial growth factor (VEGF) in PE [12-14]. VEGF signaling also could alter vascular growth, structure, and reactivity, which could lead to neonatal pulmonary vascular disease [15]. A study with preterm infants predicted the pulmonary outcome of preterm infants, by measuring the placental growth factor [16]. Since both, PIH and BPD are associated with abnormal angiogenesis, there has been some effort to evaluate the association of PIH with BPD in preterm infants. A small prospective study showed that moderate to severe BPD was more prevalent in preterm infants born at less than 32 weeks of gestation, to mothers with PE [17]. A recent meta-analysis and international cohort study also reported that BPD was associated with BPD [18,19].

On the other hand, meta-analysis of three cohort from different period in Austria reported that PE was not associated with BPD [20]. Another large population-based study also reported that preeclampsia decreased the risk for BPD in VLBW infants [21]. This study demonstrated a negative

association between pre-eclampsia and BPD only in the group with a gestational age (GA) of more than 31 weeks. As hypertensive disorders in pregnancy are greatly associated with small-for-gestational age (SGA) infants [22], studies using birth weight-based registries should be interpreted with caution, because more mature but smaller infants could be included in the registry.

This retrospective cohort study selected and analyzed infants born at less than 30 weeks of gestation, from a nationwide registry database of VLBW infants in Korea, to investigate the association between PIH and BPD.

Material & Methods

The Korean Neonatal Network(KNN) is a national prospective registry of VLBW infants (birth weight < 1,500g) born In the Republic of Korea, covering more than 70% of the overall births of VLBW infants in Korea. [23] Informed consent was obtained from the parents of all infants for registration within the database and the definitions of the data were guided by the manual of operation of the KNN. The data registered in the KNN database comprises the antenatal and perinatal histories, postnatal morbidities, and clinical outcomes evaluated during the hospital stay using a standardized electronic case-report form. A total of 3,507 VLBW infants were born and registered with the KNN database from January 2013 to December 2014 and 2,276 infants who were born at less than 30 weeks of gestation were enrolled in the study. Infants with congenital anomalies, those born to mothers with chronic hypertension, infants without BPD data, and infants who died before 36 weeks of post-menstrual age (PMA) were excluded from the study.

PIH was defined as newly diagnosed hypertension in a pregnant woman after 20 weeks of gestation, where systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥90 mmHg. BPD was defined as the need for supplemental oxygen or positive pressure support at 36 weeks of PMA. This corresponds with moderate or severe BPD, according to the severity-based definition for BPD provided by the National Institute of Health consensus [24]. Respiratory distress syndrome (RDS) was defined by clinical diagnosis and required surfactant therapy. Intraventricular hemorrhage (IVH) was defined by the Papile criteria, using cranial ultrasonography [25]. Necrotizing enterocolitis (NEC) was defined according to Bell's criteria (stage 2 or higher) [26]. Retinopathy of prematurity (ROP) was defined according to the international classification of ROP [27]. SGA was defined as birth weight lower than the third percentile, according to the sex-specific international reference curves for GA. The need for approval was waived by the Institutional Review Board of Seoul National University Hospital.

The Chi-squared test was used for comparing categorical variables and Student's t-test was used for analyzing the continuous variables between

the groups. Univariate and multivariate logistic regression analyses were used to investigate the association between PIH and BPD, after adjusting for potential confounders. Adjusted odds ratios, with a 95% confidence interval (CI) were obtained, to assess the magnitude of the association between various factors and BPD. Statistical analyses were performed with STATA 11.0 (Stata Corp, College Station, Tex., USA)

Results

Of the 3,507 infants registered with the KNN database during the study period, 1,231 infants were born at or more than 30 weeks of gestation, 28 infants were born to mothers with chronic hypertension, 65 infants had a congenital anomaly, the BPD status of 9 infants was not documented, and 347 infants who died before 36 weeks of PMA, were excluded (Figure 1). Of the remaining 1,827 infants, 203/1827 (11.1%) infants were born to mothers with PIH and 1,624 (89.3%) infants were born to mothers without hypertension.

The GA of the PIH group was higher than that of the non-PIH group (27.3±1.8 versus 28.0±1.4 weeks, $p<0.001$) (Table 1). Birth weight was lower in the PIH group than that in the non-PIH group (876.4±261.5 versus 1027.4±250.2 g, $p<0.001$). Infants who were SGA were more common in the PIH group than the non PIH group (1.4% vs. 9.9%, $p<0.001$). Infants in the PIH group received more prenatal steroid therapy and were mostly delivered through a cesarean section. On the other hand, multiple births, histologic chorioamnionitis (hCAM), and preterm premature rupture of the membrane were more prevalent in the non-PIH group.

Severe IVH (≥grade 3) was significantly lower in the PIH group (10.6% versus 5.4%, $p=0.018$) and the duration of total parenteral nutrition (TPN) was significantly longer in the PIH group (33.9±28.6 versus 38.5±28 days, $p=0.031$). There were no differences in the duration of invasive ventilation and hospital stay between the non-PIH and PIH groups. The incidence of BPD (41.4% versus 44.8%) was not significantly different between the two groups(Table 2).

Univariate and multivariate logistic regression analyses were performed, to evaluate the risk factors for BPD. In the univariate analysis, lower GA at birth, SGA, RDS, male sex, hCAM, and treated patent ductus arteriosus (PDA) were associated with BPD (Table 3). Although PIH was not independently associated with BPD on the univariate analysis, PIH was associated with moderate to severe BPD (adjusted OR 1.474, 95% CI 1.025-2.121) along with GA, SGA, male sex, hCAM and treated PDA on the multivariate analysis.

Figure 1. Flow chart of the study population.

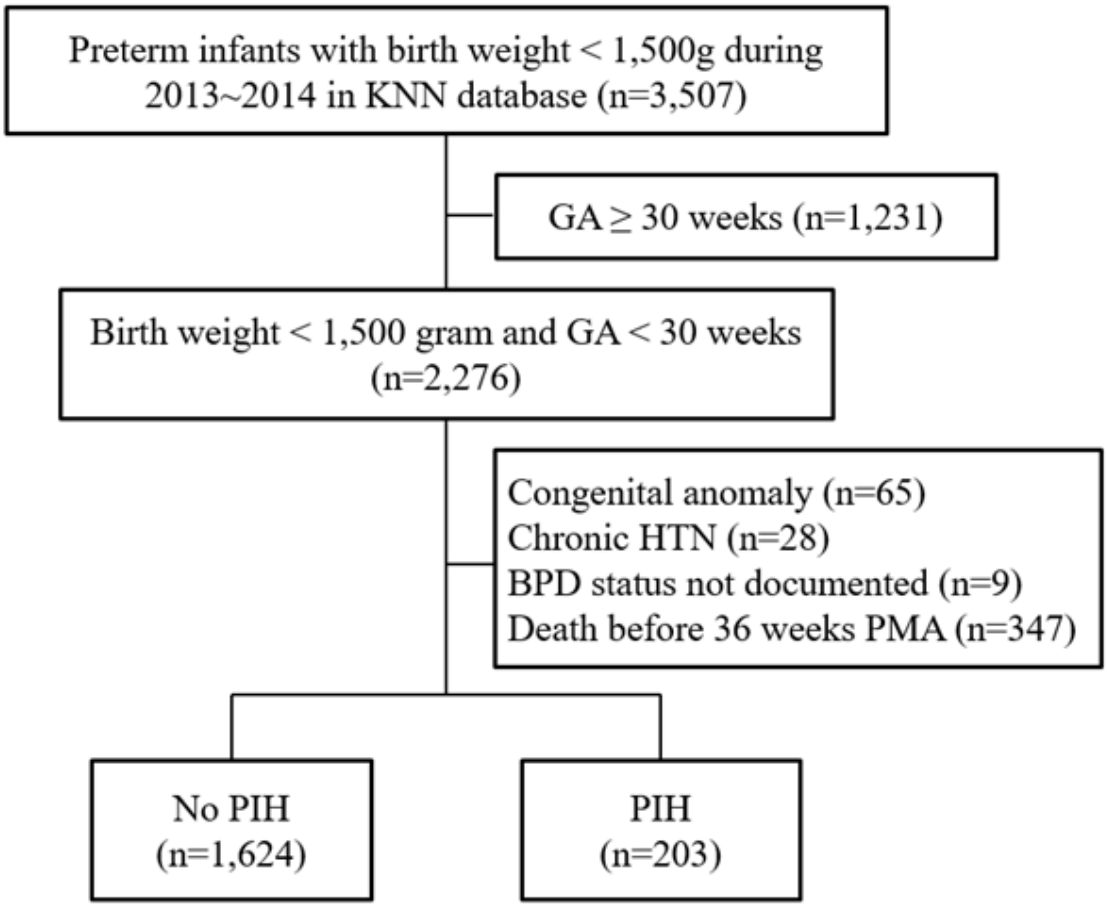

Table 1. Demographics of study population

	non-PIH (n=1,624)	PIH (n=203)	p value
GA (weeks)	27.3±1.8	28±1.4	<0.001
Birthweight (grams)	1027.4±250.2	876.4261.5	<0.001
Prenatal steroid	1294 (81)	176 (87.6)	0.026
SGA	23 (1.4)	20 (9.9)	<0.001
C/S	1084 (66.8)	191 (94.1)	<0.001
Male	850 (52.3)	94 (46.3)	0.118
AS 1 min	4.3±1.9.	4±1.8	0.011
AS 5 min	6.5±1.7.	6.5±1.7.	0.948
Oligohydramnios	197 (13.4)	21 (10.9)	0.366
hCAM	614 (44.9)	22 (12.3)	<0.001
Multiple birth	551 (33.9)	26 (12.8)	<0.001
PPROM	785 (48.7)	15 (7.4)	<0.001

Values are expressed as N (%) or Mean±SD; PIH, pregnancy induced hypertension; GA, gestational age; SGA, small for gestational age; C/S, Cesarean section; AS, Apgar score; hCAM, histologic chorioamnionitis; PPROM, preterm premature rupture of membrane

Table 2. Neonatal morbidities of study population

	non-PIH (n=1,624)	PIH (n=203)	p value
RDS	1522 (93.7)	191 (94.1)	1.000
Treated PDA	828 (51)	107 (52.7)	0.656
IVH ≥grade 3	172 (10.6)	11 (5.4)	0.018
PVL	182 (11.2)	16 (7.9)	0.187
NEC	100 (6.2)	19 (9.4)	0.095
Treated ROP	254 (22)	34 (25.2)	0.385
BPD	673 (41.4)	91 (44.8)	0.366
Postnatal steroid	608 (37.4)	70 (34.5)	0.441
Sepsis	427 (26.3)	58 (28.6)	0.500
Ventilator duration (days)	24.1±31.9	25.6±36	0.547
TPN duration (days)	33.9±28.6	38.5±28	0.031
Hospital days	87±38.3	90.8±42.4	0.185

Values are expressed as N (%) or Mean±SD; PIH, pregnancy induced hypertension; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; TPN, total parental nutrition .

Table 3. Univariate and multivariate conditional logistic regression analysis of BPD

	OR	95% CI	p-value	aOR¶	95% CI	p-value
GA (week)	0.646	[0.608 , 0.686]	<0.001	0.673	[0.627 , 0.722]	<0.001
SGA	5.454	[2.600 , 11.441]	<0.001	5.647	[2.417 , 13.194]	<0.001
RDS	3.392	[2.093 , 5.499]	<0.001	1.617	[0.961 , 2.719]	0.070
Male	1.256	[1.042 , 1.513]	0.017	1.393	[1.111 , 1.747]	0.004
hCAM	1.597	[1.301 , 1.962]	<0.001	1.528	[1.206 , 1.936]	<0.001
Treated PDA	2.788	[2.298 , 3.382]	<0.001	2.299	[1.823 , 2.898]	<0.001
PIH	1.148	[0.856 , 1.540]	0.357	1.474	[1.025 , 2.121]	0.036

BPD, bronchopulmonary dysplasia; GA, gestational age; SGA, small for gestational age; RDS, respiratory distress syndrome; hCAM, histologic chorioamnionitis; PDA, patent ductus arteriosus; PIH, pregnancy induced hypertension; ¶ adjusted for GA, SGA, RDS, sex, hCAM, treated PDA and PIH

Table 4. Subgroup analysis of association of pregnancy induced hypertension and BPD

	non-PIH	PIH	p-value	aOR¶	95% CI	p-value
GA < 27 weeks	385/637 (60.4)	27/43 (62.8)	0.872	1.054	[0.495 , 2.243]	0.892
GA 27-29 weeks	288/987 (29.2)	64/160 (40)	0.007	1.626	[1.075 , 2.460]	0.021

BPD, bronchopulmonary dysplasia; PIH, pregnancy induced hypertension; GA, gestational age; ¶ adjusted for gestational age, respiratory distress syndrome, sex, histologic chorioamnionitis, treated patent ductus arteriosus and PIH

Discussion

In this study, PIH was associated with BPD in the VLBW infants, who were born at less than 30 weeks of gestation, after adjusting for other risk factors. Impaired pulmonary vascular growth by altered signaling of angiogenic or antiangiogenic factor derived from mother with hypertension may play a role in the pathogenesis of BPD [28]. Although the mechanisms the maternal angiogenic and anti-angiogenic factors influencing the development of the fetal lungs are not fully understood, elevation in anti-angiogenic factors, including soluble fms-like tyrosine kinase-1 and soluble endoglin in the placenta and cord blood of a mother with PE might affect angiogenesis in the fetal lung presented with low VEGF and placental growth factor [29,30]. Earlier studies also demonstrated that increased soluble endoglin (an antiangiogenic factor) in cord blood was associated with the development of BPD in preterm infants born to mothers with PE [31]. Although PIH was recorded regardless of proteinuria in this registry, most of the PIH cases might be accompanied by proteinuria, given that infants were born less than 30 weeks of GA.

However, the results of several studies on the association of PIH or PE with BPD are conflicting. A population-based study analyzing 5,753 VLBW infants by Yen et al. reported that fetal exposure to maternal PE was associated with a reduced risk of BPD [21]. A meta-analysis of 1,268 infants from three Victorian Infant Collaborative Study cohorts showed that PE did not influence the risk of BPD in extremely low-birth weight infants [20]. Results from these studies should be interpreted with caution due to several reasons. In the study by Yen et al., the study population included VLBW infants and was not defined according to the GA. Therefore, relatively smaller, mature babies were mostly included in the study population, especially in the PE group with a higher prevalence of SGA (73.3%). The protective effect of PE on BPD was shown only in the subgroup with GA of 31~34 weeks, while the number of mature babies with SGA as a confounder would be higher in the VLBW population.

Studies with a GA-based population have yielded results that are different from earlier studies. An international cohort study comprising 6 international neonatal (iNeo) database based on GA analyzed 28,092

preterm neonates born at 24 to 28 weeks of gestation and reported that the risk for BPD increased in infants born to mothers with hypertensive disorders of pregnancy [18]. A meta-analysis by Razak et al. reported that PIH was associated with BPD in the subpopulation of neonates born at < 29 weeks' gestation [19].

PIH is associated with babies that are small for the (advanced) GA at birth [32,33]. The baby's size and GA a significant inverse relationship with BPD [34]. These associations were demonstrated in the present study as well. Therefore, the "size for age" should be adjusted or GA-based population determination should be considered, while analyzing the association between PIH and BPD, similar to the iNeo study or the study by Razak et al [18,19]. To elucidate the association of BPD and PIH, amidst these confounders, infants with a GA of 30 weeks or more were excluded from the study population, where SGA babies would be included in the weight-based registration.

Conclusion

In conclusion, PIH was associated with BPD in VLBW infants, who were born before 30 weeks of gestation. The utilization of a nationwide registration database of VLBW infants in Korea was a strength of this study. This study's results are consistent with the current concept that BPD is an early manifestation of pulmonary vascular disease.

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요약 (국문 초록)

임신성 고혈압과 기관지폐이형성증의 연관성-한국신생아네트워크 데이터베이스를 기반으로 한 후향적 연구

목적

임신성 고혈압과 전자간증은 전체 임신에서 각 5-10%, 2-4%를 차지하는 질병으로, 미숙아의 혈관신생에 영향을 미칠 것으로 생각되나 기관지폐이형성증과의 관계는 여전히 논란 중에 있다. 이 연구는 국가차원의 데이터베이스를 통해 임신성 고혈압과 기관지폐이형성증의 관계를 밝히고자 하였다.

대상 및 방법

본 저자는 한국신생아네트워크 데이터베이스에 등록된 미숙아중 2013년 1월부터 2014년 12월까지 재태주수 30주 이전에 출생한 극소저체중 출생아를 분석하였고, 산모 정보 및 주산기, 출생 후 신생아 정보를 수집하였다.

결과

그 결과 총 1,827명이 분석에 포함되었으며, 임신성 고혈압을 앓은 산모에게서 출생한 신생아(고혈압군)가 1,624명 (출생 시 재태주수: 27.3 ± 1.8 weeks), 임신성 고혈압을 앓지 않은 산모에서 출생한 신생아(비고혈압군)가 203명 (출생시 재태주수: 28 ± 1.4 weeks, $p<0.001$) 에 해당하였으며, 비고혈압군의 출생시 재태주수가 더 높았다. 출생체중 역시 비고혈압군이 더 컸다. (1027.4 ± 250.2 vs. 876.4 ± 261.5 g, $p<0.001$)

다변량 회귀분석을 시행하였을 때, 임신성 고혈압은 신생아의 기관지폐이형성증의 발생에 영향을 미치는 것으로 알려진 부당경량아 여부 등의 교란변수를 모두 보정한 후에도 기관지폐이형성증의 발생과 유의한 연관이 있음이 확인되었다. (adjusted OR 1.474, 95% confidence interval 1.025-2.121)

결론

산모의 임신성 고혈압은 신생아의 기관지폐이형성증의 발생 위험을 증가시킨다. 이는 미숙아의 기관지폐이형성증을 폐혈관질환의 일종으로 간주하는 현대의 질병 관념과도 일치하는 결과로 산모의 혈관질환인 임신성 고혈압이 태아의 폐혈관형성 및 발달에 영향을 미쳤음을 시사하는 결과라 볼 수 있다.