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Original Article

Maternal pregnancy-induced hypertension increases the subsequent risk of transient tachypnea of the newborn: A nationwide population-based cohort study

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ABSTRACT

Objective: To determine the association between pregnancy-induced hypertension (PIH) and transient tachypnea of the newborn (TTN) and to identify the predictive risk factors.

Materials and Methods: Pregnant women with a newly diagnosed PIH (between 2000 and 2013) from the Taiwan National Health Insurance Research Database (NHIRD) were compared with a matched (with respect to age and year of delivery) cohort of pregnant women without PIH. The occurrence of TTN was evaluated in both cohorts.

Results: Among the 23.3 million individuals registered in the NHIRD, 29,013 patients with PIH and 116,052 matched controls were identified. According to a multivariate analysis, PIH (odds ratio [OR] = 1.85, 95% confidence interval [CI] = 1.69–2.03, $p < 0.0001$), age ≥ 30 years (OR = 1.38, 95% CI = 1.26–1.51, $p < 0.0001$), primiparity (OR = 1.37, 95% CI = 1.24–1.5, $p < 0.0001$), preterm birth (OR = 3.4, 95% CI = 3.09–3.75, $p < 0.0001$), multiple births (OR = 2.54, 95% CI = 2.24–2.89, $p < 0.0001$), and cesarean section (OR = 1.71, 95% CI = 1.56–1.88, $p < 0.0001$) were independent risk factors for the development of TTN.

Conclusion: Women with PIH have an increased risk of having infants who develop TTN compared with those without PIH. Additionally, age ≥30 years, primiparity, preterm birth, multiple births, and cesarean section were independent risk factors for the development of TTN.

Introduction

Pregnancy-induced hypertension (PIH), including gestational hypertension, preeclampsia, or eclampsia, is a major cause of maternal morbidity and mortality [1–5]. Preeclampsia is a complication in approximately 3–5% of pregnancies [6,7] and is associated with a higher risk of neonatal death [8–10]. It is characterized by the de novo development of hypertension and proteinuria that arise after 20 weeks of gestation [11–14]. Although the exact pathogenesis of preeclampsia has not been fully elucidated, the main hypothesis is that abnormal cytotrophoblast invasion of

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spiral arterioles results in reduced uteroplacental perfusion and causes placental ischemia, followed by the release of several anti-angiogenic factors, reactive oxygen species (ROS), and inflammatory cytokines, which then lead to the onset of the clinical symptoms of preeclampsia [15–18].

Transient tachypnea of the newborn (TTN) is a respiratory disorder characterized by tachypnea that develops immediately after birth but resolves within 2–5 days [19]. Delayed reabsorption of the fetal lung fluid has been reported to be a critical mechanism underlying the development of TTN [20]. Amiloride-sensitive sodium (Na+) channels play an important role in fetal pulmonary fluid clearance [21], and dysfunction of those channels may result in TTN [22].

B-type natriuretic peptides (BNP), which play a role in the maintenance of extracellular fluid volume, seem to be able to reduce amiloride-sensitive Na + transport [23,24]. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been shown to be significantly higher in neonates with TTN [25]. In addition, patients with preeclampsia have been shown to have higher levels of BNP and NT-proBNP [26,27]. Therefore, it is reasonable to hypothesize that BNP and NT-proBNP, induced by PIH, may be released into the fetal circulatory system and may be involved in the development of TTN. To test this hypothesis, we designed a nationwide population-based matched cohort study to assess the relationship between PIH and TTN.

Materials and Methods

Data sources

The National Health Insurance program has covered almost 98% of the population (23 million residents of Taiwan) since 1995 [28–31]. We obtained data for the current study from the National Health Insurance research database (NHIRD), which was established by The National Health Research Institute (NHRI). The NHRID protects the privacy of individuals and provides data to researchers who have the necessary ethical approvals. We obtained anonymous data from the NHRID that did not include information regarding individuals' identities.

Study design and participants

PIH patients between 20 and 50 years of age were assessed based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 642.3–642.6 for the following conditions: gestational hypertension (ICD-9-CM codes 642.30, 642.31, 642.32, 642.33, and 642.34), mild preeclampsia (ICD-9-CM codes 642.40, 642.41, 642.42, 642.43, and 642.44), severe preeclampsia (ICD-9-CM codes 642.50, 642.51, 642.52, 642.53, and 642.54), and eclampsia (ICD-9-CM codes 642.60, 642.61, 642.62, 642.63, and 642.64). Only patients with a diagnosis of PIH and who had experienced an inpatient hospitalization were selected for the study to ensure diagnostic validity and to avoid any potential misclassifications.

The data for this study were obtained from January 1, 2000, to December 31, 2013. A total of 29,013 PIH patients were assessed. For each patient with PIH, four patients who were matched with respect to age and year of delivery and who did not have a history of PIH were randomly selected from the NHIRD and were included in the comparison cohort. The index date for the patients in the PIH cohort was the date of their initial PIH diagnosis. The study endpoints were defined as the date of a TTN diagnosis (ICD-9-CM: 770.6), death within 28 days after birth, or the date of the end of the study period. Pregnancy characteristics of the patients were obtained, including age, parity, gestational age, gestational number, whether they had a cesarean section, and any comorbidities. The comorbidities in our study were as follows: diabetes mellitus (DM) (ICD-9-CM: 250), hypertension (HTN) (ICD-9-DM: 401–405), coronary artery disease (CAD) (ICD-9-CM: 410–414), dyslipidemia (ICD-9-CM: 272), chronic kidney disease (CKD) (ICD-9-CM: 585 and 403), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491.2, 493.2, and 496), and cerebrovascular disease (ICD: 430–437).

Statistical analysis

The study groups were compared using the chi-square test for categorical variables and independent *t*-tests for continuous variables. The Cox proportional hazards model [32–35] was used to identify risk factors for TTN. Control variables, such as PIH, age, parity, gestational age, gestational number, whether patients had a cesarean section, and common comorbidities, including DM, HTN, CAD, dyslipidemia, COPD, CKD, and cerebrovascular disease, were included as covariates in the univariate and multivariate model. Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for the data analysis. Comparisons with a p value of less than 0.05 were considered statistically significant.

Results

Participant characteristics

A total of 29,013 patients with PIH and a matched cohort of 116,052 subjects were identified and included in this study. Table 1 shows the demographics and comorbidities of the PIH patients and the matched subjects. The mean patient ages were 30.96 and 30.83 years in the PIH and matched cohort groups, respectively. The majority of patients in both the PIH (56.29%) and matched cohort (56.29%) groups were older than 30 years of age. Patients with PIH had lower parity but higher preterm birth, higher multiple births, and higher cesarean section rates than patients in the comparison

Table 1
Baseline characteristics of patients with pregnancy-induced hypertension and matched cohort.

Parameters	PIH (n = 29,013)		Matched cohort (n = 116,052)		*p* value
	n	%	n	%	
Age, years, mean	30.96		30.83		
< 30	12,681	43.71	50,724	43.71	1
≥ 30	16,332	56.29	65,328	56.29	
Parity, n					
1	17,819	61.42	67,437	58.11	<.0001
≥ 2	11,194	38.58	48,615	41.89	
Gestational age					
Term	22,553	77.73	110,597	95.30	<.0001
Preterm	6,460	22.27	5,455	4.70	
Gestational number					
Singleton	27,316	94.15	113,949	98.19	<.0001
Multiple	1,697	5.85	2,103	1.81	
Cesarean section					
Yes	21,574	74.36	42,288	36.44	<.0001
No	7,439	25.64	73,764	63.56	
Comorbidities					
Diabetes mellitus	112	0.39	69	0.06	<.0001
Hypertension	266	0.92	85	0.07	<.0001
Dyslipidemia	99	0.34	90	0.08	<.0001
Coronary artery disease	26	0.09	71	0.06	0.0938
Chronic obstructive pulmonary disease	36	0.12	66	0.06	0.0001
Chronic kidney disease	187	0.64	158	0.14	<.0001
Cerebrovascular disease	54	0.19	87	0.07	<.0001

PIH, pregnancy-induced hypertension.