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Original Article

Pregnancy-induced hypertension is an independent risk factor for meconium aspiration syndrome: A retrospective population based cohort study

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ABSTRACT

Objective: Meconium aspiration syndrome (MAS), possibly resulting from fetal hypoxia, is a respiratory distress disorder in the infant. Pregnancy-induced hypertension (PIH) can cause placental dysfunction and lead to fetal hypoxia, which may induce the development of MAS. Therefore, the aim of this study was to determine the association between PIH and MAS and to identify the predictive risk factors.

Materials and methods: This was a retrospective cohort study. We selected patients with newly diagnosed PIH and a matched cohort group from the Taiwan National Health Insurance Research Database (NHIRD), from January 1, 2000 till December 31, 2013. For each patient in the PIH cohort, 4 subjects without PIH, matched for age and year of delivery, were randomly selected as the comparison cohort. The incidence of meconium aspiration syndrome was assessed in both groups.

Results: Among the 23.3 million individuals registered in the NHIRD, 29,013 patients with PIH and 116,052 matched controls were identified. Patients who experienced PIH had a higher incidence of MAS than did those without PIH. According to a multivariate analysis, PIH (odds ratio [OR] = 1.70, 95% confidence interval [CI] = 1.49–1.93, $p < 0.0001$) was independently associated with increased risk of MAS. Additionally, age ≥30 years (OR = 1.26, 95% CI = 1.12–1.42, $p = 0.0001$), nulliparity (OR = 1.13, 95% CI = 1.01–1.27, $p = 0.0367$) and patients with diabetes mellitus (OR = 3.09, 95% CI = 1.35–7.09, $p = 0.0078$) were also independent risk factors of MAS.

Conclusion: Patients with PIH obtained higher subsequent risk for the development of MAS than those without PIH. Besides, age ≥30 years, nulliparity and patients with diabetes mellitus are the independent risk factors of developing MAS.

Introduction

Pregnancy-induced hypertension (PIH), including gestational hypertension, preeclampsia and eclampsia, is one of the major causes leading to maternal deaths worldwide [1]. Preeclampsia, which complicates 2%–8% of pregnancies [2], is characterized by the newly-onset of hypertension and proteinuria after 20-week gestation. Preeclampsia has an unpredictable course that can cause severe morbidity or even mortality for both the mother and

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the fetus [2,3]. Although the pathogenesis of preeclampsia is still unclear, the central hypothesis strongly suggests that impaired cytotrophoblast invasion of the uterus occurs during early pregnancy, which contributes to a failure in spiral artery remodeling and subsequent progressive utero-placental insufficiency. Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and causes chronic placental ischemia, leading to the release of several anti-angiogenic factors, reactive oxygen species, and inflammatory cytokines. The widespread endothelial dysfunction, microangiopathy, and vasospasm are then induced and lead to the development of the clinical symptoms of preeclampsia [4,5].

Meconium aspiration syndrome (MAS) is defined as respiratory distress in an infant born through meconium-stained amniotic fluid (MSAF) whose symptoms cannot be otherwise explained [6]. MSAF occurs in approximately 8–25% of all deliveries and MAS occurs in about 5% of these infants [7]. Aspirated meconium can interfere with normal breathing by several mechanisms, including airway obstruction, chemical irritation, activation of inflammatory mediators, infection and surfactant inactivation [6,8]. Therefore, MAS may be life threatening, complicated by respiratory failure, pulmonary air leaks and persistent pulmonary hypertension, as a leading cause of neonatal morbidity and mortality [7,9,10].

Fetal hypoxia may stimulate colonic activity, leading to the passage of meconium, and also may stimulate fetal gasping movements that result in meconium aspiration [6,11]. As mentioned above, PIH can cause chronic placental insufficiency, which may proceed fetal hypoxia. Accordingly, we hypothesized that patients with PIH was associated with increased risk of MAS. However, seldom studies were conducted to investigate the correlation between PIH and MAS. To test our hypothesis, we designed a nationwide population-based matched cohort study to assess the relationship between PIH and MAS.

Patients and methods

Data sources

The National Health Insurance program, established in 1995, has covered over 23 million residents of Taiwan, which represented more than 99% of the population in Taiwan [12–15]. We obtained data for the current study from the National Health Insurance research database (NHIRD), which owned intact health information including patients' socio-demographic data, diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, medical procedures, and drug prescriptions. The data of NHRID was encrypted to protect the privacy of individuals and the data extracted was anonymous. The study was approved by the institutional review board at Kaohsiung Veterans General Hospital (VGHKS15-EM4-01).

Study design and participants

We performed a retrospective cohort study of patients newly diagnosed with PIH between January 1, 2000 and December 31, 2013. PIH patients between 20 and 50 years of age were assessed based on 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.

We enrolled a total of 29,013 PIH subjects. For each patient in PIH cohort, four subjects without PIH matched for age and year of delivery were randomly selected from the NHIRD and were included as the comparison cohort. MAS was identified using the ICD-9-CM code: 770.6. The index date for the patients in the PIH cohort was the date of the initial PIH diagnosis. Participants were followed from the index date until the date of a MAS diagnosis, death within 28 days after birth, or the date of the end of the study period. The flow chart of the study design is shown in Fig. 1. Patients characteristics, including age, parity, gestational age, gestational number, experiencing cesarean section or not, and having major comorbidities or not, were obtained. The major comorbidities in this 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 chi-square test was used for comparison of categorical variables. The independent *t*-tests was utilized for the comparison of continuous variables. The Cox proportional hazard model was

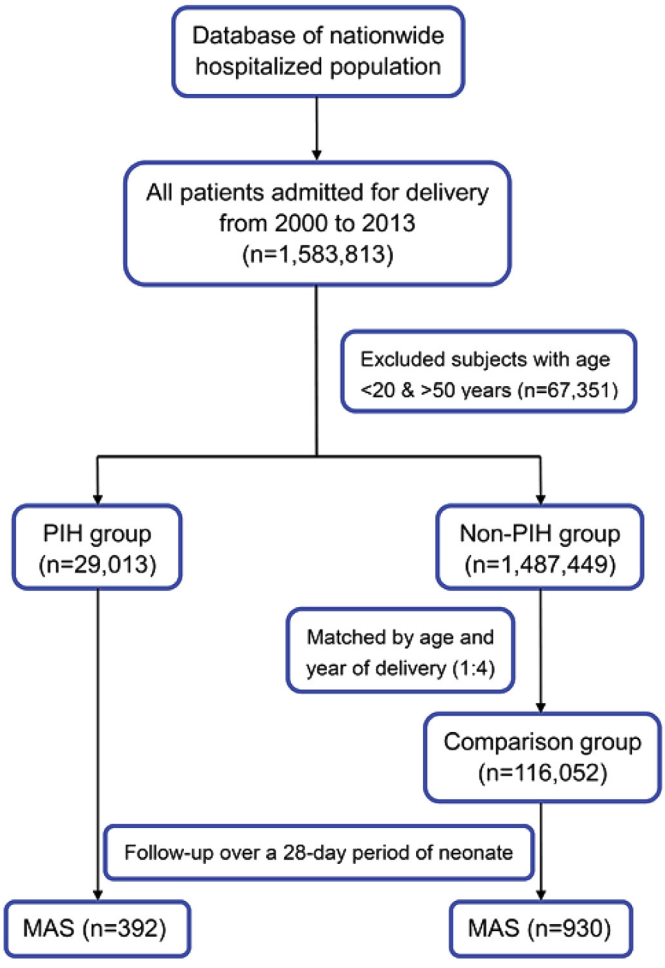

Fig. 1. Flow chart of the study design. PIH, pregnancy-induced hypertension; MAS, meconium aspiration syndrome.

used to estimate the odds ratio (OR) and the accompanying 95% confidence interval (CI) of MAS with adjustment for confounders. The variables, including PIH, age, parity, gestational age, gestational number, cesarean section, and common comorbidities, were included as covariates in the univariate and multivariate model. The 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

The demographic characteristics and comorbidities of the study subjects are demonstrated in Table 1. We identified 29,013 patients with PIH and 116,052 matched subjects, matched for age and year of delivery, as the control group. The mean patient ages were 30.96 and 30.83 years in the PIH and matched cohort groups, respectively. Most patients (56.29%) in both the PIH and matched cohort groups were aged more than 30 years. PIH patients had higher nulliparity (61.42% vs 58.11%, p < 0.0001), higher preterm birth (22.27% vs 4.70%, p < 0.0001), higher multiple birth (5.85% vs 1.81%, p < 0.0001), and higher cesarean section rates (74.36% vs 36.44%, p < 0.0001) compared to the matched cohort. Furthermore, patients with PIH had higher prevalence of DM, HTN, dyslipidemia, COPD, CKD, and cerebrovascular disease than patients in the matched cohort group.

Incidence of and risk factors for meconium aspiration syndrome

A total of 392 patients from the PIH group and 930 from the matched cohort group developed MAS during the follow-up period. The incidence of MAS was higher in the PIH group (1.35%) than in the matched cohort group (0.80%). As shown in the cox proportional-hazard model analysis (Table 2), PIH was independently associated with increased risk for the development of MAS (OR = 1.70, 95% CI = 1.49–1.93, $p < 0.0001$). Moreover, three other independent risk factors of developing MAS were identified, including age ≥30 years (OR = 1.26, 95% CI = 1.12–1.42, $p = 0.0001$), nulliparity (OR = 1.13, 95% CI = 1.01–1.27, $p = 0.0367$) and DM (OR = 3.09, 95% CI = 1.35–7.09, $p = 0.0078$).

Discussion

In this population-based, retrospective cohort study, we assessed the risk of MAS with PIH by using a design of matched cohort over a 28-day follow-up period of neonate. A greater incidence of MAS was found among patients who had PIH than those who did not undergo PIH. Using the multivariate analysis, we identified that PIH was an independent risk factor of MAS. In addition, age ≥30 years, nulliparity, patients with diabetes mellitus were independently associated with an increased risk for developing MAS.

MAS is the complication of perinatal aspiration of meconium stained liquor. The presence of meconium in the amniotic fluid at birth is not uncommon. Some studies disclosed that regular defecation in fetus is a normal physiological process rather than a pathological event [16,17]. However, fetal hypoxia could not only stimulate colonic activity but also impair normal clearance ability of meconium in amniotic fluid, which prolonged the presence of meconium stained in amniotic fluid [11,18]. Therefore, fetal hypoxia may play a role in the development of MAS. Hypoxia is the major stimulus of erythropoietin (EPO) synthesis in both the fetus and adult. Elevated EPO levels in amniotic fluid and in fetal cord serum imply chronic or subchronic hypoxia of fetus and can be used as markers for antepartum fetal hypoxia [19–22]. Studies showed that term fetuses complicated by MSAF had significant high levels of cord blood EPO in comparison to those with clear amniotic fluid [23,24]. Moreover, the study conducted by Jazayeri and colleagues revealed that meconium passage was independently associated with elevated fetal EPO levels [25]. Richey et al. also demonstrated that EPO levels were significantly elevated in newborns with MSAF [26]. Accordingly, above-mentioned studies support the fact that fetal hypoxia is implemented in the development of MAS.

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 ± SD	30.96 ± 5.04		30.83 ± 5.01		1
<30	12,681	43.71	50,724	43.71	
≥30	16,332	56.29	65,328	56.29	
Parity, n					<0.0001
1	17,819	61.42	67,437	58.11	
≥2	11,194	38.58	48,615	41.89	
Gestational age					<0.0001
Term	22,553	77.73	110,597	95.30	
Preterm	6460	22.27	5455	4.70	
Gestational number					<0.0001
Singleton	27,316	94.15	113,949	98.19	
Multiple	1697	5.85	2103	1.81	
Cesarean section					<0.0001
Yes	21,574	74.36	42,288	36.44	
No	7439	25.64	73,764	63.56	
Comorbidities					
Diabetes mellitus	112	0.39	69	0.06	<0.0001
Hypertension	266	0.92	85	0.07	<0.0001
Dyslipidemia	99	0.34	90	0.08	<0.0001
Coronary artery disease	26	0.09	71	0.06	0.0176
Chronic obstructive pulmonary disease	36	0.12	66	0.06	0.0005
Chronic kidney disease	187	0.64	158	0.14	<0.0001
Cerebrovascular disease	54	0.19	87	0.07	<0.0001

PIH, pregnancy-induced hypertension; SD, standard deviation.

Table 2
Analyses of risk factors for meconium aspiration syndrome among the patients with pregnancy-induced hypertension and comparison cohort.

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	[a]OR (95% CI)	*p* value
PIH				
Yes vs. No	1.70 (1.51–1.91)	<0.0001	1.70 (1.49–1.93)	<0.0001
Age				
≥ 30 vs. < 30	1.30 (1.16–1.45)	<0.0001	1.26 (1.12–1.42)	0.0001
Parity				
1 vs. ≥ 2	1.21 (1.08–1.36)	0.0008	1.13 (1.01–1.27)	0.0367
Gestational age				
Preterm vs. Term	1.17 (0.97–1.41)	0.0988	0.95 (0.78–1.15)	0.5705
Gestational number				
Singleton vs. Multiple	1.05 (0.74–1.49)	0.7828	1.28 (0.90–1.83)	0.1748
Cesarean section				
Yes vs. No	1.23 (1.10–1.37)	0.0002	1.04 (0.92–1.17)	0.5213
Diabetes mellitus				
Yes vs. No	3.74 (1.66–8.46)	0.0015	3.09 (1.35–7.09)	0.0078

PIH, pregnancy-induced hypertension; OR, odds ratio; CI, confidence interval.
[a] OR is adjusted for group differences in age, parity, gestational age, gestational number, cesarean section, diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and cerebrovascular disease.

The primary cause of PIH is the abnormal cytotrophoblast differentiation and shallow invasion in the beginning of the implantation, which could result in placenta insufficiency by several mechanisms, including increased placental bed apoptosis [27], active autophagy [28] and increased vascular abnormalities [29]. In addition, several studies showed that amniotic fluid and cord plasma EPO levels were significantly higher in patients with PIH than in control pregnancies [30–32]. That is, PIH induced placenta insufficiency could lead to intrauterine fetal hypoxia.

Taken together, placenta insufficiency in patients with PIH contributes to fetal hypoxia, which is involved in the development of MAS. Therefore, we hypothesized that PIH patients was associated with increased risk of MAS. This study supported the hypothesis and displayed patients who experienced PIH exhibited a 1.70-fold increase in the incidence rate of MAS compared to the comparison cohorts (95% CI = 1.49–1.93, $p < 0.0001$). There were some articles, which support the correlation between PIH and MAS. A prospective observational study conducted by Mundhra and Agarwal enrolled a total of 355 pregnant women who had completed more than 37 weeks of gestation with singleton pregnancies. Pregnancies complicated with pregnancy induced hypertension had statistically significant higher rates of meconium staining than those with healthy pregnancies (16.97% versus 7.89%, $p < 0.05$) [33]. Another prospective observational study enrolled 80 term pregnancies with meconium stained liquor as a study group and 80 ones without meconium stained liquor as a control group. Compared to the control group, term pregnancies with meconium stained liquor was associated with significant higher incidence of PIH (13.8% versus 3.8%, $p < 0.05$) [34]. However, more studies are required to confirm the result.

Additionally, maternal diabetes mellitus was the independent risk factor for subsequent MAS. In a study of murine model of gestational diabetes mellitus, Li et al. demonstrated that gestational diabetes induced excessive chronic hypoxia stress and inflammatory response in placentas and impacted the placental vascular development [35]. Several studies have shown that diabetic pregnancies or gestational diabetes pregnancies were associated with chronic fetal hypoxia, as indicated by high amniotic fluid EPO levels [36–38]. Moreover, the study carried out by Teramo et al. revealed that EPO concentrations in amniotic fluid correlate directly with maternal HbA1c levels. Besides, antenatal high amniotic fluid EPO levels in diabetic pregnancies were at increased risk of severe perinatal complications, including neonatal hypoglycaemia, hypertrophic cardiomyopathy and admission to the neonatal intensive care unit [36]. However, fetal hypoxia plays an important role on the development of MAS. Therefore, maternal diabetes mellitus or gestational diabetes mellitus may be at increased risk of MAS. This study displayed that patients with DM exhibited a 3.09-fold increase in the incidence rate of MAS compared to those without DM (95% CI = 1.35–7.09, $p = 0.0078$). However, we need more studies to validate the result.

This study was a longitudinal, large population-based design. Nonetheless, several limitations inherent to the use of insurance claims databases must be considered. First, the diagnosis of PIH and MAS in the NHIRD were based on the ICD-9-CM code. Information on blood pressure, proteinuria, symptoms, and laboratory examinations were not available in the database. Furthermore, data on Apgar score at birth, the severity of MAS, the management, and neonatal outcomes could not be obtained from the database. Second, some demographic variables were not present in the database, such as prenatal maternal hemoglobin level, prenatal check-up information, socioeconomic status, body mass index, lifestyle, smoking status, and family medical history. These factors could have been useful for evaluating as other factors that may be associated with PIH or MAS. Third, we cannot identify the intrapartum care and the initial neonatal intervention in the database. These procedures may influence the diagnosis and outcomes of MAS. Finally, the diagnostic criteria for PIH have changed over the years, which could lead to heterogeneous populations. Even with these limitations, our study was based on a nationwide, population-based database that included nearly all of Taiwan's residents. The large sample size in our study contributed to its substantial statistical power and revealed an obvious association between PIH and MAS with minimal selection biases.

In conclusion, the present study suggested that maternal PIH was associated with the development of MAS. Besides, mothers with diabetes mellitus was another independent risk factor of developing MAS.

Conflicts of interest statement

None.

Submission declaration and verification

All the authors declare that we have not submitted this work for publication elsewhere.

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