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Original Article

Maternal pregnancy-induced hypertension increases the subsequent risk of neonatal candidiasis: A nationwide population-based cohort study

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ABSTRACT

Objective: Neonatal candidiasis is a leading infectious cause of significant morbidity and mortality in premature birth mainly due to impaired physical barriers and immature immune system of fetus. Maternal pregnancy-induced hypertension (PIH) has been reported to be able to disturb the neonatal immune system, which could cause the increased possibility of neonatal infection. Therefore, we hypothesized that maternal PIH may increase the risk of neonatal candidiasis and identify the predictive risk factors.
Materials and methods: Patients with newly diagnosed PIH between January 1, 2000, and December 31, 2013 were selected from the Taiwan National Health Insurance Research Database (NHIRD). 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. A Cox proportional regression model was used to estimate the risks of neonatal candidiasis 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. Patients with PIH had a higher incidence of neonatal candidiasis than did those without PIH. According to the multivariate analysis, PIH (odds ratio [OR] = 2.08, 95% confidence interval [CI] = 1.11–3.19, $p < 0.0228$), single parity (OR = 1.91, 95% CI = 1.00–3.65, $p < 0.0499$), and preterm birth (OR = 3.57, 95% CI = 1.84–6.93, $p = 0.0002$) were independent risk factors for the development of neonatal candidiasis.
Conclusion: Patients who had a history of PIH was associated with an increased risk of having infants who develop neonatal candidiasis compared with those without PIH. Additionally, preterm birth was an independent risk factor for the development of neonatal candidiasis.

Introduction

Hypertensive disorders during pregnancy, including maternal pregnancy-induced hypertension (PIH), complicate approximately 10% of pregnancies worldwide and represent one of the major causes of maternal and perinatal morbidity and mortality worldwide [1]. It is generally established that PIH is a syndrome recognized as the new-onset of hypertension during second half of pregnancy with the occurrence of substantial proteinuria [2].

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Among other clinical manifestations accompanying PIH, it has been reported that visual disturbances, headaches, epigastric pain, and the development of edema are the most common. There are several risk factors that could account for increased likelihood of developing PIH, including multiple pregnancy, maternal age younger than 20 or older than 40, diabetes and obesity [3]. Moreover, the risk of PIH is increased 2-fold in women with first-degree relative with a medical history of the disorder, and even 7-fold if PIH complicated previous pregnancy [3].

Pathogenesis of early PIH involves impaired placentation and secondary complications due to poor placentation, which are probably evoked by placental hypoxia and hypoxia reperfusion, resulting in a damaged syncytium and limited fetal growth [4]. Several mechanisms may account for the link between relatively hypoxic placenta and the maternal syndrome, including altered pro-angiogenic and anti-angiogenic factor balance, metabolic changes, increased maternal oxidative stress and endothelial dysfunction and impaired immune response. A recent meta-analysis demonstrated the association between elevated preeclampsia and elevated circulating levels of TNF-alpha, IL-6 and IL-10 in the third trimester of pregnancy [5]. Impaired inflammatory response may errand infections, including infection with *Candida* species [4], which has been associated with significant increased risk of complications, such as neurodevelopmental impairment, heart and kidney disorders, and mortality [6,7]. A recent study demonstrated that maternal PIH was one the main risk factors for candidiasis [8]. However, the small sample size limited the strength of the evidence and additional studies are needed to further investigate such potential relation. The aim on this study was to investigate the association between maternal PIH and the risk of neonatal candidiasis in a population-based retrospective cohort study.

Patients and methods

Data sources

The Taiwan National Health Insurance program was launched since 1995 and the National Health Research Institute in Taiwan established the National Health Insurance research database (NHIRD). The data for the current study were extracted from the Taiwan NHIRD, which covers more than 99% of the 23 million Taiwanese residents. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for the disease record system. The source data were encrypted to protect privacy, and the data were accessed anonymously. This study was approved by the Institutional Review Board of the Kaohsiung Veteran's General Hospital (VGHKS15-EM4-01).

Study design and participants

Using a retrospective population-based cohort study design, we identified two cohorts, PIH and matched groups, who were aged 20–50 years between January 1, 2000, and December 31, 2013. The PIH group was defined as a new diagnosis of PIH based on ICD-9-CM codes 642.3–642.6, which can be divided into gestational hypertension (ICD-9-CM codes 642.3x), mild preeclampsia (ICD-9-CM codes 642.4x), severe preeclampsia (ICD-9-CM codes 642.5x), and eclampsia (ICD-9-CM codes 642.6x). To ensure the validity of PIH diagnosis, only patients with inpatient hospitalization were included. The index date for the patients in the PIH group was the date of their first diagnosis of PIH. For each patient with PIH, four insured enrollees, who did not have a history of PIH and were matched for age and year of delivery, were randomly retrieved from the NHIRD and included as the matched group. All subjects were followed from the index date to the study endpoints, which were defined as the onset of a neonatal candidiasis (ICD-9-CM: 771.7), death within 28 days after birth, or the end of the study period. The flow chart of the study design is shown in Fig. 1.

The pregnancy and baseline characteristics, including age, parity, gestational age, gestational number, delivery mode and major comorbidities, were obtained. The major comorbidities in this study included diabetes mellitus (DM) (ICD-9-CM: 250), hypertension (HTN) (ICD-9-CM: 401–405), dyslipidemia (ICD-9-CM: 272), coronary artery disease (CAD) (ICD-9-CM: 410–414), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491.2, 493.2, 496), chronic kidney disease (CKD) (ICD-9-CM: 585, 403), and cerebrovascular disease (ICD-9-CM: 430–437).

Statistical analysis

The distributions of the pregnancy and baseline characteristics between the PIH and matched groups were compared using Student's t-test for continuous variables and the chi-squared test for categorical variables. Univariate and multivariate Cox proportional hazards regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of neonatal candidiasis. The multivariate model was adjusted for age, parity, gestational age, gestational number, cesarean section, and common comorbidities, including DM, HTN, CAD, dyslipidemia, COPD, CKD, and cerebrovascular disease. All statistical analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Inc., Cary, NC, USA). Comparisons with two-tailed p value of less than 0.05 were considered statistically significant.

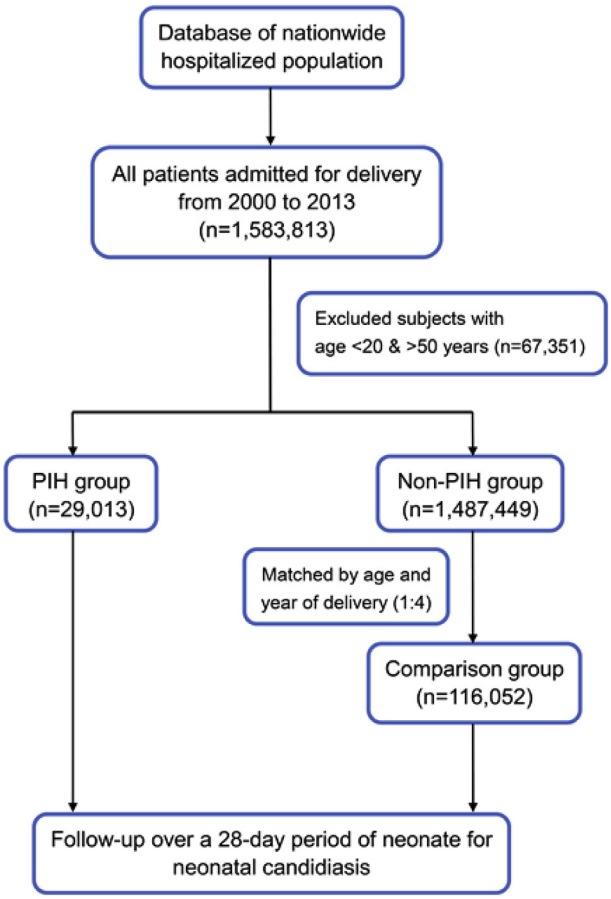

Fig. 1. Flow chart of the study design. PIH, pregnancy-induced hypertension.

Results

Characteristics of the study population

The demographic characteristics and history of comorbidities in patients with PIH and matched subjects were demonstrated in Table 1. A total of 145,065 participants were enrolled in this study, including 29,013 subjects with PIH and 116,052 subjects as a matched cohort. The corresponding average ages of the PIH and matched cohorts were 30.96 and 30.83 years, respectively. In both cohorts, most patients were aged ≥30 years (56.29%). The PIH cohort included a significantly higher percentage of single parity, preterm birth, multiple births and cesarean section than the matched cohort. Additionally, compared with the comparison group, the PIH group exhibited a higher prevalence of DM, HTN, dyslipidemia, CAD, COPD, CKD, and cerebrovascular disease.

Incidence and risk factors of neonatal candidiasis

The incidence of neonatal candidiasis was higher in PIH group (0.69‰) than in matched cohort group (0.29‰). Table 2 presented the univariate and multivariate Cox proportional analyses. After adjustment for age, parity, gestational age, gestational number, cesarean section and comorbidities, patients who experienced PIH exhibited a 2.08-fold higher risk of neonatal candidiasis compared to those without PIH (95% CI = 1.11–3.91, $p = 0.0228$). Furthermore, single parity (OR = 1.91, 95% CI = 1.00–3.65, $p = 0.0499$) and preterm birth (OR = 3.57, 95% CI = 1.84–6.93, $p = 0.0002$) were independently correlated with an increased risk for the development of neonatal candidiasis.

Discussion

We present a population-based, retrospective cohort study to determine the risk of neonatal candidiasis in patients with PIH by using a design of comparison cohort over a 28-day follow-up period of neonate. A higher incidence of neonatal candidiasis was observed among patients who had PIH than those in the control group. After adjustment for covariates, PIH remained independently associated with an increased risk for developing neonatal candidiasis. Moreover, preterm birth was an independent risk factor of neonatal candidiasis.

Neonatal candidiasis has emerged as one of the leading cause of late-onset infection in most neonatal intensive care units and is associated with significant morbidity and mortality in the neonates. Neonatal candidiasis developed in 2.6%–16.7% of very low birth weight infants (VLBW, less than 1500 g) and 5.5%–20% of extremely low birth weight infants (ELBW, less than 1000 g) [6,9,10]. The crude mortality related to neonatal candida infection ranged from 10% to 54% [10–12]. Long-term neurodevelopmental impairments, including cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia occurs in nearly 60% of survivors [12,13]. C. albicans was reported the most common pathogen of neonatal candidemia, followed by C. parapsilosis [10]. Extreme prematurity is the strongest risk factor for developing neonatal candidiasis. Additionally, prolonged endotracheal intubation, presence of central venous catheters, total parenteral nutrition, administration of broad-spectrum antibiotics, and prolonged antibiotic therapy duration were associated with an increased risk for the development of neonatal candidiasis [6,13,14]. However, fluconazole prophylaxis, reduced use of broad-spectrum antibiotics, empirical antifungal therapy, and improved care of central venous catheters have contributed to the decreased incidence of invasive candidiasis [15–17].

Neonatal candidiasis generally occurs after the first 2 weeks of life in the extreme prematurity of infants. Premature neonates are predisposed to develop invasive candidiasis after colonized by Candida after birth. Candida species are yeast that frequently colonize skin, the gastrointestinal tract, and the female genitourinary tract [18] Premature infants, particularly those of VLBW, have a poor skin barrier with few cornified layers and deficient dermal proteins and is characterized by less skin functionality. Those could lead to an increased risk for skin damage and increased permeability to exogenous agents and infection [19,20]. Furthermore, due to an intrinsic immaturity of the enteric nervous system, the motility of the small intestine is less organized in premature infants than in term infants. This immature motility results in impaired function of intestinal mucosal barrier and intestinal immune network, which makes premature neonates particularly susceptible to infection [21]. In addition, marked leukopenia of monocytes, granulocytes and lymphopenia of CD4+ T cells, CD8+ T cells, natural killer cells, and B cells were observed in preterm infants compared to full-term infants [22,23]. The maturation of anti-microbial responses develops asynchronously in preterm neonates [24]. These also play a pivotal role in the increased frequency of infections in these neonates. Taken together, premature neonates show an increased susceptibility to neonatal candidiasis, conceivably related to their defective physical barriers and immature immune system. Our study demonstrated that preterm neonates exhibited a 3.57-fold increase in the incidence rate of neonatal candidiasis compared to term neonates (95% CI = 1.84–6.93, $p = 0.0002$).

The effect of PIH could be involved in the fetus because the bioactive factors induced by placental ischemia might cross the placental barrier into the fetal circulation [25,26]. It seems likely that maternal PIH could cause significant fetal immune system derangements. CD4/CD8 T-cell ratio is significantly lower in fetuses born to PIH mothers than fetuses born to healthy mothers [27–29]. Neonates born to PIH mothers had decreased percentage of regulatory T cells and CD 8 + 28+ T cells (cytotoxic) lymphocytes and increased percentage CD 8 + 28 − T cells (suppressor) lymphocytes

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

Parameters	PIH (n = 29,013)		Comparison cohort ($n = 116,052$)		p value
	n	%	n	%	
Age, years, mean ± SD	30.96 ± 5.04		30.84 ± 5.01		–
<30	12,681	43.71	50,724	43.71	
≥30	16,332	56.29	65,328	56.29	
Parity					<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	0.0938
COPD	36	0.12	66	0.06	<0.0001
Chronic kidney disease	187	0.64	158	0.14	<0.0001
Cerebrovascular disease	54	0.19	87	0.07	<0.0001

COPD, chronic obstructive pulmonary disease; PIH, pregnancy-induced hypertension; SD, standard deviation.

Table 2
Analyses of risk factors for neonatal candidiasis among the patients with pregnancy-induced hypertension and comparison cohort.

	Univariate analysis		Multivariate analysis[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
PIH				
Yes vs. No	2.36 (1.36–4.09)	0.0024	2.08 (1.11–3.91)	0.0228
Age, years				
≥30 vs. <30	1.69 (0.95–3.00)	0.0733	1.46 (0.81–2.63)	0.2145
Parity				
1 vs. ≥2	2.21 (1.19–4.13)	0.0126	1.91 (1.00–3.65)	0.0499
Gestational age				
Preterm vs. Term	4.71 (2.63–8.45)	<0.0001	3.57 (1.84–6.93)	0.0002
Gestational number				
Singleton vs. Multiple	3.80 (1.51–9.54)	0.0045	2.02 (0.73–5.56)	0.1744
Cesarean section				
Yes vs. No	1.14 (0.67–1.97)	0.6273		

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

in comparison with neonates born to healthy women [27,28]. In addition, maternal PIH is associated with a higher percentage of NK cells in umbilical cord blood of babies compared to normotensive mothers [27,30]. Neonates born to mothers with PIH have a higher alternative complement pathway activity and monocyte activation than those born to mothers without PIH [31,32]. The alterations in the immunological parameters of neonates born to PIH mothers can be associated with fetal hypoxia [33] induced by placental ischemia. Taken together, impairment of fetal immune system induced by maternal PIH may result from fetal hypoxia induced by placenta ischemia and may result in the increased possibility of neonatal infection. The present study showed that a 2.08-fold increase in the incidence rate of neonatal candidiasis in the patients with PIH compared to those without PIH (95% CI = 1.11–3.91, $p = 0.0228$). An 8-year retrospective study conducted by Celebi et al. showed that presence of maternal pre-eclampsia was one of the main predisposing factors for neonatal candidemia with C. parapsilosis [8]. However, further studies are needed to confirm the results.

This study showed that single parity seemed to be an independent risk factor for developing neonatal candidiasis. The study conducted by Fievet et al. revealed that maternal parity influenced the absolute numbers and activation status of cord blood antigen-presenting cells which is associated with neonatal innate immune responses [34]. However, no other literature proposed the similar result. Therefore, more studies are required to verify this finding.

Several limitations related to the use of insurance claims databases should be considered. First, the diagnosis of PIH in the NHIRD was based on the ICD-9 codes. Information on blood pressure, proteinuria, and symptoms were not available in the database. Second, we did not identify early or late PIH and whether patients with PIH underwent treatment. Third, the diagnosis of neonatal candidiasis in the NHIRD was also according to the ICD-9 codes. Information on birth weight, Apgar score, neonatal complications and management were not available in the database. Furthermore, we did not identify the candida species and severity and outcomes of neonatal candidiasis in this study. Fourth, some demographic variables were not available in the database, such as body mass index, smoking status, lifestyle, socioeconomic status, and family medical history. Fifth, the diagnostic criteria for PIH have changed over time, which could result in heterogeneous patient populations. Regardless of 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 neonatal candidiasis with minimal selection biases.

In conclusion, this study showed that maternal PIH significantly increase the incidence of neonatal candidiasis. Moreover, preterm birth is another important independent risk factor for neonatal candidiasis.

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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