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Maternal pregnancy-induced hypertension increases subsequent neonatal necrotizing enterocolitis risk

A nationwide population-based retrospective cohort study in Taiwan

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Abstract

The utero-placental ischemia induced by pregnancy-induced hypertension (PIH) could lead to fetal hypoxia and proinflammatory cytokine release, which are associated with the development of neonatal necrotizing enterocolitis (NEC). However, a few studies have investigated the relationship between PIH and neonatal NEC and have produced controversial results. Therefore, we attempted to assess the relationship between PIH and the subsequent neonatal NEC risk and identify predictive risk factors.

Patients with newly diagnosed PIH were recruited from the Taiwan National Health Insurance Research Database (NHIRD). For each participant, 4 age- and delivery-year-matched participants without PIH were randomly selected. A multivariable logistic regression was performed for the identification of the predictive risk factors for neonatal NEC.

Among the 23.3 million individuals registered in the NHIRD, 29,013 patients with PIH and 116,052 matched controls were identified. For the multivariable analysis, maternal PIH was associated with an increased risk of subsequent neonatal NEC development (odds ratio [OR] 1.86, 95% confidence interval [CI] 1.08–3.21, $P = .026$). Furthermore, single parity (OR 2.06, 95% CI 1.12–3.77, $P = .019$), preterm birth (OR 5.97, 95% CI 3.49–10.20, $P < .001$), multiple gestations (OR 2.25, 95% CI 1.22–4.14, $P = .010$), and intrauterine growth restriction (IUGR) (OR 3.59, 95% CI 2.06–6.24, $P < .001$) were independent risk factors for the development of subsequent neonatal NEC.

Maternal PIH increases the risk for developing neonatal NEC. Furthermore, primiparity, preterm birth, multiple gestations, and IUGR were independent risk factors for neonatal NEC.

Abbreviations: CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, DM = diabetes mellitus, GH = gestational hypertension, HTN = hypertension, ICD = International Classification of Diseases, IL = interleukin, IUGR = intrauterine growth restriction, NEC = necrotizing enterocolitis, NHIRD = National Health Insurance Research Database, OR = odds ratio, PE = preeclampsia, PIH = pregnancy-induced hypertension.

Keywords: gestational hypertension, necrotizing enterocolitis, preeclampsia, pregnancy-induced hypertension

1. Introduction

Pregnancy-induced hypertension (PIH), estimated to affect approximately 5% to 8% of pregnant women, is one of the main causes of maternal, fetal, or neonatal morbidity and mortality.[1] PIH is classified into the following 3 categories: gestational hypertension, preeclampsia, and eclampsia.[2] Gestational hypertension is the new onset of hypertension after 20 weeks of gestation. Preeclampsia is known as a multi-organ disease process of unknown etiology characterized by the development of hypertension and proteinuria after 20 weeks of gestation. Eclampsia is defined as the development of convulsions in preexisting preeclampsia.[3] Although the precise pathogenesis of PIH remains uncertain, a pivotal hypothesis suggests that trophoblast and decidual pathology, shallow endometrial invasion, and failure of the physiologic transformation of the spiral arteries are caused by genetic and environmental factors that disrupt pregnancy-induced immunomodulation. As a consequence of placental ischemia, the release of inflammatory cytokines, type-1 angiotensin II receptor autoantibodies, angiogenic and antiangiogenic factors, and syncytiotrophoblast-derived particles into the

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maternal circulation precede the onset of symptomatic pregnancy hypertensive disorder.[4] Additionally, PIH causes vascular manifestations, endothelial damage, and oxidative stress. Therefore, PIH may disturb placental function and subsequently result in insufficient fetal perfusion and nutrition supply, leading to perinatal morbidity and mortality.[5]

Neonatal necrotizing enterocolitis (NEC) is one of the most frequent diseases encountered in neonatal intensive care units. According to a study in Sweden, the overall incidence of neonatal NEC was 3.4 per 10,000 live births.[6] Although the exact pathogenesis of neonatal NEC remains poorly understood, multiple pathogenetic mechanisms, including intestinal immaturity, enteral feeds, the intestinal microbiome, inflammation, and local ischemia or reperfusion injury, have been implicated in this disease.[7] Several well-known risk factors in newborns are associated with the development of NEC. Preterm birth is the most important risk factor associated with NEC. Furthermore, infants with asphyxia, formula feeding, sepsis, intestinal ischemic reperfusion injury, polycythemia, and intrauterine growth restriction (IUGR) are also risk factors of neonatal NEC.[8] However, the relationship between maternal characteristics and neonatal NEC has seldom been reported.[9]

The PIH reduces placental perfusion, which can cause fetoplacental hypoxia.[10,11] Fetal hypoxia could lead to a hypoxic-ischemic state in the intestine or in its mucosa in the antenatal period, resulting in neonatal NEC.[10] In addition, utero-placental ischemia induced by PIH can cause the production of inflammatory cytokines.[4] Multiple factors, including hypoxia and inflammatory mediators, have been regarded as important causes of neonatal NEC.[12] Therefore, we proposed that maternal PIH may be associated with the neonatal NEC development. However, only a few studies have investigated whether maternal PIH is associated with the risk of developing neonatal NEC. Moreover, conflicting relationships between maternal PIH and neonatal NEC have been observed.[9,10,13–17] Therefore, we designed a nationwide, population-based, matched cohort study to determine the risk of neonatal NEC in patients who have experienced PIH.

2. Patients and methods

2.1. Data source

The National Health Insurance (NHI) program has covered nearly 98% of the entire population (23 million residents) of Taiwan since 1995. We obtained data for the present study from the National Health Insurance Research Database (NHIRD) established by the National Health Research Institute (NHRI). The NHIRD protects the privacy of individuals and provides data to researchers who have obtained ethical approval. We obtained anonymous data from the NHIRD without disclosure of the identities of the patients. The Kaohsiung Veterans General Hospital Institutional Review Board approved this study (VGHKS15-EM4-01).

2.2. Study design and patients

The patients with PIH aged between 20 and 50 years were assessed according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes for the following conditions: gestational hypertension (ICD-9-CM code 642.30, 642.31, 642.32, 642.33, 642.34), mild preeclampsia (ICD-9-CM code 642.40, 642.41, 642.42, 642.43, 642.44), severe preeclampsia (ICD-9-CM code 642.50, 642.51, 642.52, 642.53, 642.54), and eclampsia (ICD-9-CM code 642.60, 642.61, 642.62, 642.63, 642.64). Only patients diagnosed with PIH requiring inpatient hospitalization were selected to ensure diagnostic validity and to avoid any potential misclassifications.

The data for this study was from the period between January 1, 2000 and December 31, 2013. In total, 29,013 patients with PIH were assessed. For each patient, 4 age- and delivery-year-matched patients without a history of PIH were randomly selected from the NHIRD and 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 endpoint was defined as the date of neonatal NEC diagnosis (ICD-9-CM code 777.5) within 28 days after birth. The pregnancy characteristics of the patients, including age, parity, gestational age, gestational number, gestational diabetes, IUGR (ICD-9-CM code 656.5, 764), and comorbidities, were obtained. The following conditions are the comorbidities in our study: diabetes mellitus (DM) (ICD-9-CM code 250), hypertension (HTN) (ICD-9-DM code 401-405), coronary artery disease (CAD) (ICD-9-CM code 410-414), dyslipidemia (ICD-9-CM code 272), chronic kidney disease (CKD) (ICD-9-CM code 585, 403), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 491.2, 493.2, 496), and cerebrovascular disease (CVD) (ICD-9-CM code 430-437).

2.3. Statistical analysis

The study groups were compared using the Chi-squared test for categorical variables and independent *t* tests for continuous variables. A multivariable logistic regression model was used to identify the risk factors for NEC. Control variables, such as PIH, age, parity, gestational age, gestational number, gestational diabetes, and IUGR, and common comorbidities, including DM, HTN, CAD, dyslipidemia, COPD, CKD, and CVD, were included as covariables in the univariable model. Variables examined in the univariable analysis that displayed a P-value $< .1$ were included in the multivariable analysis. Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc, Cary, NC) was used for data analysis. Comparisons with a $P < .05$ were considered significant.

3. Results

3.1. Patient characteristics

Table 1 presents the demographic and comorbidity data for the patients with PIH and the matched controls. In total, a cohort of 29,013 patients with PIH (7573 for gestational hypertension, 20,527 for preeclampsia, and 913 for eclampsia) and a matched cohort of 116,052 controls were assessed in this study. The mean age of patients with PIH was 30.96 years. Most of the patients in both cohorts were aged over 30 years (56.29%). The prevalence of single parity, preterm birth, gestational diabetes, IUGR, and multiple pregnancies was higher in the PIH cohort than in the control cohort. Compared to the controls, the patients with PIH also exhibited a higher prevalence of the following comorbidities: DM, HTN, dyslipidemia, CAD, COPD, CKD, and CVD.

3.2. Risk factors for neonatal NEC

The incidence of NEC was higher in the PIH cohort (0.16%) than in the matched control cohort (0.03%). As demonstrated in the multivariable analysis (Table 2), PIH (odds ratio [OR] 1.86, 95%

Table 1

Baseline characteristics of the patients in the pregnancy-induced hypertension and matched cohorts.

Parameters	PIH (n = 29,013)		Matched cohort (n = 116,052)		P
	n	%	n	%	
Age, y, mean ± SD	30.96 ± 5.04		30.83 ± 5.01		1.000
<30	12,681	43.71	50,724	43.71	
≥30	16,332	56.29	65,328	56.29	
Parity, n					<.001
1	17,819	61.42	67,437	58.11	
≥2	11,194	38.58	48,615	41.89	
Gestational age					<.001
Term	22,553	77.73	110,597	95.30	
Preterm	6460	22.27	5455	4.70	
Gestational number					<.001
Singleton	27,316	94.15	113,949	98.19	
Multiple	1697	5.85	2103	1.81	
Gestational diabetes					<.001
Yes	1368	4.72	1147	0.99	
No	27,645	95.28	114,905	99.01	
IUGR					<.001
Yes	3147	10.85	1195	1.03	
No	25,866	89.15	114,857	98.97	
Comorbidities					
Diabetes mellitus	112	0.39	69	0.06	<.001
Hypertension	266	0.92	85	0.07	<.001
Dyslipidemia	99	0.34	90	0.08	<.001
CAD	26	0.09	71	0.06	.094
COPD	36	0.12	66	0.06	<.001
CKD	187	0.64	158	0.14	<.001
CVD	54	0.19	87	0.07	<.001

CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, IUGR = intrauterine growth restriction, PIH = pregnancy-induced hypertension, SD = standard deviation.

confidence interval [CI] 1.08–3.21, $P = .026$), single parity (OR 2.06, 95% CI 1.12–3.77, $P = .019$), preterm birth (OR 5.97, 95% CI 3.49–10.20, $P < .001$), multiple gestations (OR 2.25, 95% CI 1.22–4.14, $P = .010$), and IUGR (OR 3.59, 95% CI 2.06–6.24, $P < .001$) were independent risk factors for the subsequent development of neonatal NEC.

We further investigated the women in the PIH group and divided them into 2 groups (preeclampsia/eclampsia vs gestational hypertension) based on disease severity. In the PIH group, the incidences of neonatal NEC were 0.12% in the gestational hypertension subgroup, and 0.17% in the preeclampsia/eclampsia subgroup. In the multivariable analysis (Table 3), preterm

Table 2

Analyses of the risk factors for neonatal necrotizing enterocolitis in the pregnancy-induced hypertension and matched cohorts.

Parameters	Necrotizing enterocolitis			
	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
PIH				
Yes vs no	6.01 (3.78–9.54)	<.001	1.86 (1.08–3.21)	.026
Age, y				
≥30 vs <30	1.65 (1.02–2.68)	.043	1.12 (0.68–1.85)	.660
Parity				
1 vs ≥2	3.06 (1.71–5.46)	<.001	2.06 (1.12–3.77)	.019
Gestational age				
Preterm vs term	15.07 (9.53–23.82)	<.001	5.97 (3.49–10.20)	<.001
Gestational number				
Multiple vs singleton	9.33 (5.29–16.44)	<.001	2.25 (1.22–4.14)	.010
Gestational diabetes				
Yes vs no	4.06 (1.64–10.06)	.003	1.84 (0.71–4.76)	.212
IUGR				
Yes vs no	12.66 (7.64–20.98)	<.001	3.59 (2.06–6.24)	<.001

The OR is adjusted for age, parity, gestational age, gestational number, gestational diabetes, IUGR, diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and cerebrovascular disease.

CI = confidence interval, IUGR = intrauterine growth restriction, OR = odds ratio, PIH = pregnancy-induced hypertension.

Table 3

Analyses of risk factors for neonatal necrotizing in the pregnancy-induced hypertension cohort.

	Necrotizing enterocolitis	
	Multivariable analysis	
Parameters	**OR (95% CI)**	***P***
PIH severity		
PE/eclampsia vs GH	1.03 (0.48–2.18)	.947
Age, y		
<30 vs ≥30	1.37 (0.71–2.66)	.355
Parity		
1 vs ≥2	2.04 (0.92–4.50)	.079
Gestational age		
Preterm vs term	4.23 (2.22–8.07)	<.001
Gestational number		
Singleton vs multiple	1.82 (0.82–4.04)	.145
Gestational diabetes		
Yes vs no	2.18 (0.82–5.84)	.120
IUGR		
Yes vs no	2.81 (1.47–5.36)	.002

The OR is adjusted for age, parity, gestational age, gestational number, gestational diabetes, IUGR, PIH severity, diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and cerebrovascular disease.

CI = confidence interval, GH = gestational hypertension, IUGR = intrauterine growth restriction, OR = odds ratio, PE = preeclampsia, PIH = pregnancy-induced hypertension.

birth (OR 4.23, 95% CI 2.22–8.07, $P < .001$) and IUGR (OR 1.81, 95% CI 1.47–5.36, $P = .002$) were independent risk factors for developing neonatal NEC in the PIH group. However, preeclampsia/eclampsia did not significantly increase the risk of neonatal NEC compared to gestational hypertension (OR 1.03, 95% CI 0.48–2.18, $P = .947$). It seemed that PIH severity was not associated with the development of neonatal NEC.

4. Discussion

A higher incidence of subsequent neonatal NEC was observed in patients with PIH (0.16%) than in patients without PIH (0.03%) in this study. As demonstrated in the multivariable analysis, we found that maternal PIH is an independent risk factor for neonatal NEC. In addition, single parity, preterm birth, multiple gestations, and IUGR are crucial risk factors for neonatal NEC development. There was one NEC hospitalization per 1000 live births in the year 2000 in the United States.[18] Furthermore, population studies estimate the incidence of NEC to be between 0.3 and 2.4 per 1000 live births in the United States annually.[19] The incidence of neonatal NEC in our study was consistent with previous studies. However, the incidence of neonatal NEC among preterm births was relatively high. The retrospective study conducted by Jelin et al showed that the incidence of NEC was 2.55% among preterm infants with preeclamptic mothers and 4.68% among preterm infants without preeclamptic mothers.[14] In the study of Çetinkaya et al, a total of 51 premature infants born to preeclamptic mothers at <37 weeks of gestational age were compared with 33 gestational age-matched premature infants born to normotensive mothers; the incidence of NEC was 45.1% among preterm births with preeclamptic mothers and 30.3% among preterm births with normotensive mothers.[15] Another prospective study performed by Çetinkaya and colleagues revealed that the incidence of NEC (stages II and III) was 14.3% in preterm infants with preeclamptic mothers and 5.3% in preterm infants with normotensive mothers.[10] The variations in the incidence of NEC may be due to different study populations, different study designs or different NEC stages.

A lower birthweight or gestational age is known to correspond to a higher risk of developing neonatal NEC.[6] The mortality rate of neonatal NEC has been reported to be approximately 20% to 30%.[12] The exact pathogenesis of neonatal NEC remains poorly understood. However, multiple factors have been proposed to cause neonatal NEC, including hypoxia, sepsis, abnormal bacterial colonization of the bowel, enteral feeding, and inflammatory mediators stimulated by an ischemic injury of an immature bowel.[12,20]

Although the pathogenesis of PIH has not been elucidated, the principal theory suggests that impaired spiral artery remodeling contributes to utero-placental ischemia, which is characterized by the production of angiogenic or anti-angiogenic factors, reactive oxygen species, and inflammatory cytokines.[4,21] Uteroplacental insufficiency could lead to fetal hypoxia,[22] which may induce a hypoxic-ischemic state in the intestine or in its mucosa in the antenatal period.[10] If the hypoxic-ischemic state persists, it may modulate the development of motor, secretory, and mucosal functions. Therefore, the intestine is more susceptible to stasis, abnormal colonization, and bacterial invasion after birth, which are associated with the development of neonatal NEC.[23]

Elevated levels of proinflammatory cytokines, such as interleukin (IL)-6, are found in the maternal blood of patients with PIH.[24] Tosun et al found that an elevated level of IL-6 in the maternal and umbilical serum plays a significant role in the pathogenesis of PIH.[25] In addition, an increased concentration of IL-6 in the umbilical blood has been associated with a significantly increased risk for neonatal NEC.[26–28] Therefore, the release of proinflammatory cytokines from the placenta into the fetal circulation in mothers with PIH may lead to neonatal NEC.

Taken together, we hypothesized that patients with PIH are at a higher risk of neonatal NEC because of possible placental insufficiency, fetal hypoxemia, and an elevated proinflammatory cytokines level, resulting in increased fetal intestinal susceptibility. In our study, we observed that PIH increased the risk of neonatal NEC. However, the finding of a correlation between infants born to mothers with PIH and the development of NEC is controversial. In a study of 211 cases, Bashiri et al reported that maternal hypertensive disorders are independent risk factors for the development of NEC in very low birthweight infants, with a 5.2-times higher incidence of stages II and III NEC development in these infants.[9] Cetinkaya and colleagues studied 501 patients and showed that preeclampsia is associated with an increased risk of neonatal stages II and III NEC in preterm infants.[10] Perger et al demonstrated a study of 9993 cases and concluded that maternal preeclampsia is an independent risk factor for all stages neonatal NEC.[17] In contrast, some studies have shown that maternal PIH or preeclampsia does not significantly increase the risk of NEC of preterm neonates.[13–16] Therefore, more studies are necessary to clarify the relationship between maternal PIH and neonatal NEC risk.

More than 90% of neonatal NEC cases occur in preterm infants. Therefore, preterm birth is the most critical risk factor of NEC.[20] An increased risk for neonatal NEC was observed in preterm infants in our study. Preterm infants have been proposed to have poorly developed gut motility and digestion, intestinal circulatory regulation, gut barrier function, and immune defense than term infants. These factors may predispose preterm infants to an increased risk of intestinal injury.[29] Immature intestinal

functions, such as reduced integrity of epithelial tight junctions, impaired peristalsis, and deficiencies in the components of the mucus lining, may contribute to the development of neonatal NEC.[30] Furthermore, immunologic host defences, including intraepithelial lymphocytes and secretory IgA, are markedly impaired in preterm infants.[31] The immature intestine is thought to respond to injury with excessive inflammation, which may serve as the final common pathway in the pathogenesis of neonatal NEC.[20]

In this study, we also found that IUGR increased the risk of neonatal NEC. Several studies revealed that IUGR would increase the risk of NEC.[8,32,33] Pregnant women with IUGR usually accompanied with poor placental perfusion, which could reduce fetal oxygen and nutrients transferred from the mother.[33] The development of NEC may result from hypoxic-ischemic injury of the bowel which could be caused by impaired fetal mesenteric circulation and fetal hypoxia. Short gastrointestinal tract length, small size of intestinal villi and liver are other possible factors contributing to NEC in IUGR infants.[34] Moreover, persistent abnormalities in the superior mesenteric artery blood flow velocity in IUGR infants were detected during the first days of life.[35] Neonates with increased resistance patterns of blood flow velocity in the superior mesenteric artery on the first day of life are at a higher risk of neonatal NEC.[36]

Insurance databases are usually involved in some limitations, as follows: First, the ICD-9-CM codes were used to identify the PIH group. We could not get information such as blood pressure, proteinuria, symptoms, and maternal medications from the database. Second, the diagnosis of the infants' condition in the NHIRD was also based on ICD-9-CM codes. More detailed information such as gestational age, Apgar scores, birthweight, feeding pattern, umbilical end-diastolic flow status, postnatal day of NEC diagnosis, NEC stage, and surgical requirements was not available. Third, several maternal demographic variables, such as socioeconomic status, body mass index, lifestyle, smoking status, and family medical history, were not recorded in the database. Despite these limitations, our study was conducted using information from a nationwide database that included nearly all the residents of Taiwan. Our results may reflect a trend in the relationship between maternal PIH and neonatal NEC.

In conclusion, maternal PIH may increase the risk of developing of neonatal NEC. Babies born to mothers with PIH require a more cautious feeding strategy and monitoring of abdominal conditions. Furthermore, women with primiparity, preterm birth, multiple gestations, and IUGR are also at an increased risk of neonatal NEC.

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