Pre-eclampsia/Eclampsia as a Risk Factor of Noninfectious Uveitis Among Postdelivery Women

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• PURPOSE: **We sought to analyze the incidence and risk of noninfectious uveitis (NIU) among postdelivery women with a history of pre-eclampsia/eclampsia (PEE).**
• DESIGN: **Population-based retrospective matched cohort study.**
• METHODS: **All participant data were retrieved from the Longitudinal Health Insurance Database 2005. Two thousand seventy-three postdelivery women ≥20 years of age were diagnosed with PEE between January 1, 1997 and December 31, 2012 and were included in the study. We traced the occurrence of NIU during 5 years of follow-up. The primary outcome measure was the occurrence of NIU with the use of anti-inflammatory drugs and adjudication by an ophthalmologist.**
• RESULTS: **NIU occurred in 14 of 2073 (0.7%) postdelivery women with PEE. The incidence rate of NIU was 1.5 and 0.5 per 1000 person-years among postdelivery women with and without PEE, respectively (incidence rate ratio 2.96 [95% confidence interval 1.48–5.90]; $P = .002$). Postdelivery women with PEE demonstrated a significant increase in the cumulative incidence of NIU compared with those without PEE ($P = .001$). The risk of the occurrence of NIU was significantly higher in the PEE group than in the non-PEE group (adjusted hazard ratio 2.96 [95% CI 1.48–5.92]; $P = .002$) after adjusting for age, income, urbanization, and comorbidities.**
• CONCLUSIONS: **This is the first study to substantiate an association between PEE and NIU. Our results suggest that PEE could be a potential risk factor for the occurrence of NIU among postdelivery women. (Am J Ophthalmol 2019;198:166–173. © 2018 Elsevier Inc. All rights reserved.)**

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PRE-ECLAMPSIA, A MULTISYSTEM PREGNANCY DISORder characterized by gestational hypertension and often associated with proteinuria in the second trimester, threatens the safety of 2% to 5% of mothers and neonates worldwide.[1] The progressive stage of pre-eclampsia with convulsions is defined as eclampsia. Although the mechanism of preeclampsia/eclampsia (PEE) is incompletely elucidated, placenta-induced immune and endothelial dysfunction is considered a key role in leading to pertinent pathogenesis and complications.[2] The exquisite balance between proinflammatory and anti-inflammatory reactions in pregnancy is dramatically altered in the presence of PEE. Growing evidence shows that systemic inflammation is induced by helper T-lymphocyte immune shifting and a subsequent series of evoked cytokine response during PEE activation.[3] Even after delivery, PEE-mediated immune inflammation consistently increases the risks for systemic disorders.[4–6]

Uveitis is a generic term for intraocular inflammatory diseases of pigmented vascular uveal entities encompassing the iris, ciliary body, and choroid. The incidence rate of uveitis is from 25 to 113 per 10,000 person-years.[7–9] More attention has focused on the visual influence of uveitis because 10–20% of visual blindness worldwide is attributed to this enigmatic disorder.[10] Uveitis can be categorized anatomically into anterior, intermediate, posterior, or panuveitis, and etiologically into infectious and non-infectious. In infectious uveitis, immune responses are triggered after exposure to antigen from virus, bacteria, fungi, or protozoa. In contrast, non-infectious uveitis (NIU) is primarily elicited by immune reactions to self-antigen and is related to systemic autoimmune disorders, tumors, trauma, drugs, or surgical procedures. However, the etiology of nearly 90% of NIU cases remains unknown.[11]

Previously, hypertensive retinopathy, exudative retinal detachment, central serous chorioretinopathy, central retinal vein occlusion, and cortical blindness have been reported in women with PEE.[12] In our clinical practice, uveitis has been diagnosed in several postdelivery women without autoimmune diseases or intraocular infection but with a history of PEE. To date, no case report or study had reported the correlation between PEE and NIU. In this retrospective matched-cohort study, we aimed to investigate the risk of NIU among postdelivery women with PEE.

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TABLE 1. 2001 Edition of ICD-9-CM Codes of Diseases

Disease(s)	ICD-9-CM Code
Pre-eclampsia/eclampsia	642.4, 642.5, 642.6
Outcomes	
Anterior uveitis	364.0, 364.00, 364.01, 364.02, 364.04, 364.05, 364.1x, 364.2x, 364.3
Posterior/pan-uveitis	360.01, 360.02, 360.03, 360.1, 360.11, 360.12, 360.14, 360.19, 362.18, 363.0x, 363.1x, 363.2x
Exclusion	
HIV	042.x, V08
Cytomegalovirus	078.5
Herpes zoster	053, 053.0, 053.1, 053.2
Herpes simplex of the eye	054.4
Syphilis	647.0, 090-097
Tuberculosis of the eye	017.3
Histoplasmosis	115.x
Toxoplasmosis	130.x
Comorbidities	
Systemic lupus erythematosus	710.0
Multiple sclerosis	340.x
Rheumatoid and juvenile arthritis	714.x
Sarcoidosis	135.x, 321.4
Psoriasis	696.0, 696.1, 696.8
Behçet disease	136.1, 711.2
Ulcerative colitis	556.x
Crohn disease	555.x
Ankylosing spondylitis	720.x
Polyarteritis nodosa	446.0
Reiter syndrome	099.3, 711.1
Thyroid diseases	240.x-246.x
Hepatitis B and C	070.2–070.5

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

METHODS

OUR DATA ORIGINATED FROM THE NATIONAL HEALTH Insurance Research Database (NHIRD), affiliated with the National Health Insurance (NHI) program in Taiwan. The NHI program, a single-payer, mandatory, and ubiquitous health care program launched on March 1, 1995, has covered >99% of Taiwanese citizens and foreigners with an Alien Resident Certificate. The NHIRD primarily comprises registration files and original claims data providing comprehensive information for population-based research. We retrieved the data for this study from the Longitudinal Health Insurance Database 2005 (LHID2005), which selected 1 million random samples from the 2005 (January 1, 2005 to January 1, 2006) registry of beneficiaries (n = 25.68 million) of the NHIRD. The LHID2005 contains compendious and deidentified claims data from 1997 to 2013 that revealed no statistically significant difference in the distribution of age, sex, and health care costs compared with the total population. In addition, the *International Classification of Diseases, 9th Revision, Clinical Modification* was applied to diagnostic codes in LHID2005 (all diagnostic codes used in this study were recorded in Table 1). This study adhered to the Declaration of Helsinki. The institutional review board of Chang Gung Medication Foundation approved our research protocol (201800248B1) and exempted it from institutional review board review according to the regulations of the Ministry of Health and Welfare, Taiwan.

Figure 1 shows the flowchart of enrollment of the PEE and non-PEE groups. We retrieved all participants of this retrospective, matched-cohort study from the LHID2005. Postdelivery women (n = 102,182) ≥20 years of age between January 1, 1997 and December 31, 2013 were included. Postdelivery women were defined as women coded as having vaginal or caesarean delivery or management charge for newborns. All postdelivery women were traced back 300 days from the delivery date to evaluate the development of PEE. Two thousand two hundred twenty-nine women had a diagnosis of PEE during gestation. To ensure at least a 1-year follow-up duration after PEE diagnosis, we excluded 143 postdelivery women with a diagnosis of PEE after December 31, 2012. In addition, 13 women with any form of uveitis before PEE diagnosis were excluded. However, women who had a diagnosis of uveitis before 1997 could not be ruled out, as medical records could only be traced as far back as 1997 in the LHID2005. Ultimately, a total of 2073 postdelivery women were involved in the PEE group. The non-PEE group included postdelivery women without PEE. Postdelivery women with PEE were randomly matched with those without PEE by age, sex, urbanization, and income at a ratio of 1:4. All women were traced from the index date to the occurrence of NIU or censored if NIU did not occur in ≤5 years or by December 31, 2013. Considering that the development of NIU has a link with high socioeconomic status,[8] the influence of socioeconomic status should be maximally lowered through matching 2 socioeconomic indicators: urbanization and income. Urbanization in Taiwan was stratified into 4 gradient levels following the evaluation of 8 cardinal city development factors.[13] Levels 1 and 4 represent the most and the least urbanized societies, respectively. According to the income-proportioned premium of beneficiaries in NHI, the income structure was classified into 4 groups.

The outcome of NIU was designated as nonpurulent uveitis with the exclusion of pertinent viral, bacterial, fungal, and protozoal infection (HIV, cytomegalovirus, herpes zoster, herpes simplex of the eye, syphilis, tuberculosis of the eye, histoplasmosis, and toxoplasmosis). To validate the diagnosis of NIU, women must show

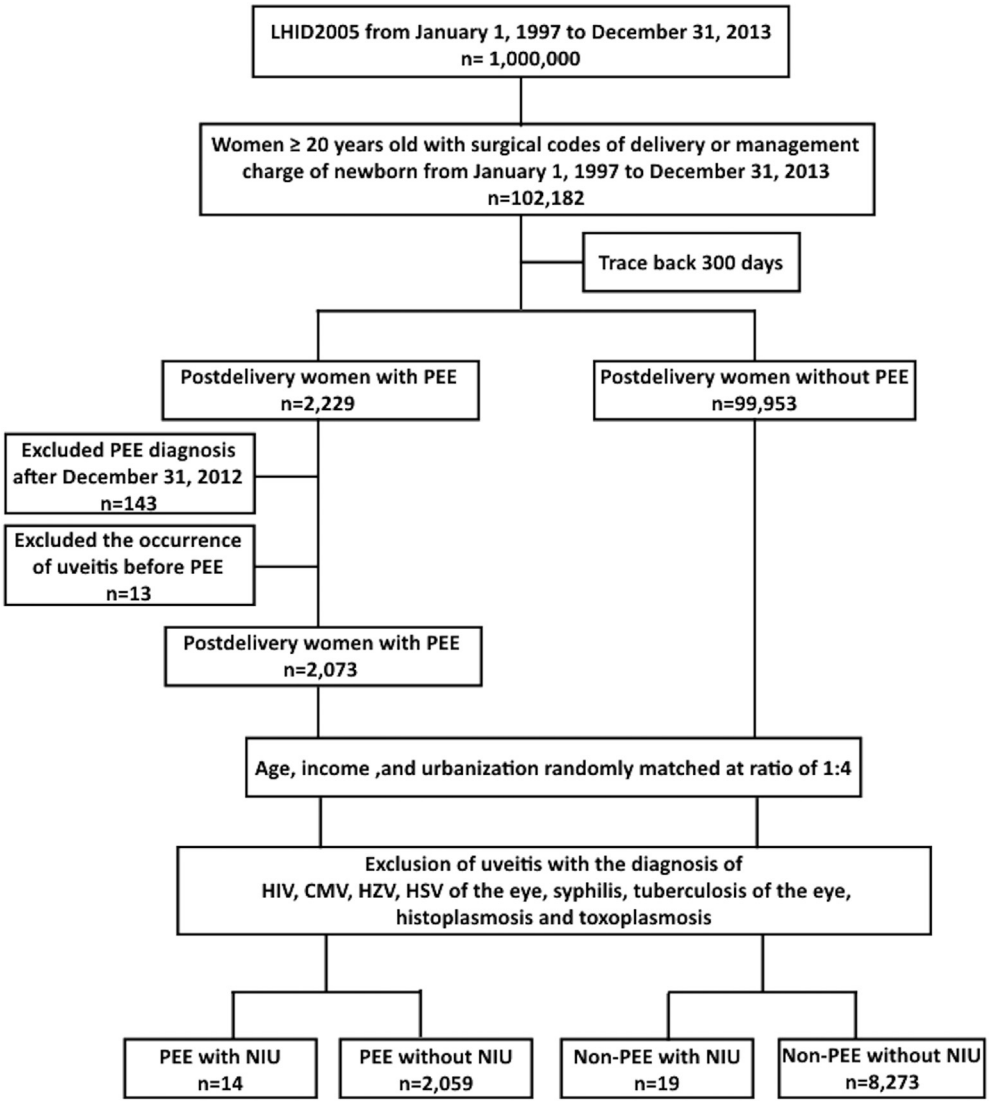

FIGURE 1. Flowchart of enrollment of the study population. CMV = cytomegalovirus, HSV = herpes simplex virus, HZV = herpes zoster virus, LHID2005 = Longitudinal Health Insurance Database 2005, NIU = noninfectious uveitis, PEE = pre-eclampsia/eclampsia.

≥1 diagnostic code of NIU with a treatment record of anti-inflammatory drugs (no-steroidal anti-inflammatory drugs, steroid, or immunomodulatory drugs) after adjudication by ophthalmologists. We collected the published comorbidities of NIU to adjust the influence of outcome: autoimmune diseases (systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, sarcoidosis, ankylosing spondylitis, psoriasis, Behçet disease, ulcerative colitis, Crohn disease, polyarteritis nodosa, and Reiter syndrome), thyroid diseases, and hepatitis B and C diseases. These comorbidities were included if they were encoded ≥1 time(s) in an inpatient visit or 3 times in ambulatory visits.

• **STATISTICAL ANALYSIS:** To examine the variation of demographic characteristics and comorbidities between the PEE and non-PEE groups, we applied the χ^2 and Student *t* tests to categorical data and continuous variables, respectively. We calculated the cumulative incidence rates of NIU in the PEE and non-PEE groups by using the Kaplan–Meier method, and evaluated the distinction between 2 curves with the log rank test. Using the multivariable Cox proportional hazard model, we adjusted the hazard ratio (HR) and 95% confidence interval (CI) of NIU occurrence for age, urbanization, income, and comorbidities. We used SAS software (version 9.4; SAS Inc., Cary, NC, USA) to analyze all statistical data, and defined statistical significance as a 2-tailed $P < .05$.

TABLE 2. Prevalence Rate of Preeclampsia/Eclampsia from 1997 to 2013 in Taiwan

Variables	PEE, n (%)	Non-PEE, n (%)	*P* Value
Total	2229 (2.2)	99953 (97.8)	
Age, y			<.001
<35	1802 (2.0)	88470 (98.0)	
≥35	427 (3.6)	11483 (96.4)	

PEE = pre-eclampsia/eclampsia.

The overall prevalence rate of preeclampsia/eclampsia in Taiwan was 2.2%. Postdelivery women ≥35 years of age had a significantly higher prevalence rate of PEE than those <35 years of age.

TABLE 3. Baseline Characteristics of Postdelivery Women

Variables	PEE (n = 2073)	Non-PEE (n = 8292)	*P* Value
NIU, n (%)	14 (0.7)	19 (0.2)	.001
Incidence[a]	1.5	0.5	.002
IRR (95% CI)	2.96 (1.48–5.90)	Reference	
Age, y, n (%)			1.00
<35	1685 (81.3)	7139 (81.3)	
≥35	388 (18.7)	1153 (18.7)	
Severity, n (%)			
Mild	1379 (66.5)		
Severe[b]	694 (33.5)		
Urbanized level, n (%)			1.00
1 (cities)	651 (31.4)	2604 (31.4)	
2	989 (47.7)	3956 (47.7)	
3	316 (15.2)	1264 (15.2)	
4 (villages)	117 (5.6)	468 (5.6)	
Income (NTD), n (%)			1.00
0	319 (15.4)	1276 (15.4)	
1–15,840	222 (10.7)	888 (10.7)	
15,841–25,000	790 (38.1)	3160 (38.1)	
≥25,001	742 (35.8)	2968 (35.8)	
Comorbidities, n (%)			
Autoimmune diseases	102 (4.9)	341 (4.1)	.104
Thyroid diseases	179 (8.6)	606 (7.3)	.041
Hepatitis B and C	63 (3.0)	260 (3.1)	.821

IRR = incidence rate ratio, NIU = noninfectious uveitis, NTD = New Taiwan dollar, PEE = pre-eclampsia/eclampsia.

[a]Per 1000 person-years.

[b]Including severe preeclampsia and eclampsia.

RESULTS

IN THIS STUDY, THE OVERALL PREVALENCE RATE OF PEE IN Taiwan was 2.2%. Postdelivery women aged <35 and ≥35 years had 2% and 3.6% of the PEE prevalence rate, respectively ($P < .001$; Table 2). In Table 3, NIU occurred in 14 of 2073 (0.7%) postdelivery women with PEE compared with 19 of 8292 (0.2%) postdelivery women without PEE ($P = .001$). The incidence rate of NIU was 1.5 and 0.5 per 1000 person-years in the PEE and non-PEE groups, respectively (incidence rate ratio 2.96 [95% confidence interval {CI} 1.48–5.90]). There was no statistical difference in autoimmune diseases and hepatitis B and C diseases between the PEE and non-PEE groups, whereas women with PEE were apt to have thyroid diseases. The cumulative incidence of NIU occurrence among postdelivery women is shown in Figure 2, and the log rank test showed that women with PEE had a significantly higher cumulative incidence of NIU occurrence than women without PEE.

Of 14 PEE women diagnosed with NIU (Table 4), the mean age of PEE diagnosis was 30.9 ± 7.3 years and the mean interval from PEE diagnosis to NIU occurrence was 1.9 ± 1.6 years. Concerning the location of uveitis, 11 of 14 (79%) NIU cases of PEE women were anterior uveitis. The mean age, the mean interval from PEE to NIU, and the incidence rate of NIU between 5 NIU cases with severe PEE and 9 NIU cases with mild PEE were 34.6 ± 7.7 versus 28.9 ± 5.6 years, 1.3 ± 1.7 versus 2.3 ± 1.2 years, and 1.61 versus 1.46 per 1000 person-years. In the survey of comorbidities, all PEE women with NIU had no history of autoimmune, thyroid diseases, or hepatitis B and C diseases.

The results of the analysis of the multivariable Cox proportional hazards model are shown in Table 5. The adjusted HR (aHR 2.96 [95% CI 1.48–5.92]) of NIU occurrence was significantly higher in the PEE group than in the non-PEE group after adjusting for age, income, urbanization, and comorbidities. In the analysis of age subgroups, PEE women ≥35 years of age had a dominantly significant risk of NIU occurrence even though PEE women <35 years of age also had a higher risk of NIU occurrence than non-PEE women after adjustment (<35 years: aHR 2.29 [95% CI 1.02–5.14]; ≥35 years: aHR 8.14 [95% CI 1.57–42.18]).

DISCUSSION

THIS IS THE FIRST STUDY TO DISCUSS AN ASSOCIATION between PEE and NIU. After adjustment for age, income, urbanization, and comorbidities, postdelivery women with PEE had a higher risk of NIU occurrence than those without PEE. NIU attributed to various autoimmune and systemic diseases has been reported in women; however, most cases are still idiopathic.[11,14] In clinical practice, we observed several cases deemed as idiopathic uveitis in women with a history of PEE. Based on the results of this study, PEE could be a potential risk factor for NIU in postdelivery women.

Immune maladaptation derived from poor placentation is a pivotal mechanism leading to systemic complications in PEE. In normal gestation, T helper 1 (T_H1) immunity that drives proinflammatory response is inhibited extensively,

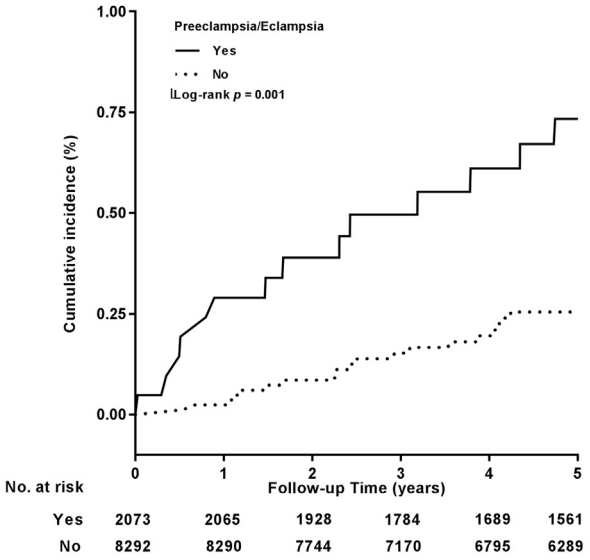

FIGURE 2. Cumulative incidence of noninfectious uveitis among postdelivery women shown by the Kaplan–Meier curve. Women with pre-eclampsia/eclampsia had a significantly higher cumulative incidence of noninfectious uveitis than women without pre-eclampsia/eclampsia.

TABLE 4. Cases of Noninfectious Uveitis Among Postdelivery Women With Pre-eclampsia/Eclampsia

No.	Age, y	Interval From PEE to NIU, y	Types of PEE	Types of NIU	Autoimmune Diseases	Thyroid Diseases	Hepatitis B and C
1	20	3.2	Mild	A	No	No	No
2	24	0.5	Severe[a]	P	No	No	No
3	24	1.5	Mild	A	No	No	No
4	25	2.4	Mild	A	No	No	No
5	26	1.7	Mild	A	No	No	No
6	27	0.9	Mild	P	No	No	No
7	27	0.8	Severe	A	No	No	No
8	31	0.5	Mild	P	No	No	No
9	33	2.3	Mild	A	No	No	No
10	37	3.8	Mild	A	No	No	No
11	37	4.3	Mild	A	No	No	No
12	38	0.4	Severe	A	No	No	No
13	40	0.0[b]	Severe	A	No	No	No
14	44	4.7	Severe	A	No	No	No

A = anterior uveitis, NIU = noninfectious uveitis, P = posterior/pan-uveitis, PEE = pre-eclampsia/eclampsia.

Among 14 PEE women diagnosed with NIU, the mean age of PEE diagnosis was 30.9 years and the mean interval from PEE to NIU occurrence was 1.9 years; 11 NIU cases of PEE women were anterior uveitis. There were no NIU cases with a history of autoimmune diseases, thyroid diseases, or hepatitis B and C diseases.

[a]Including severe preeclampsia and eclampsia.

[b]12 days.

whereas dominant T_H2 immunity that secretes immunosuppressive cytokines modulates the balance of maternal inflammation. Therefore, T_H1–immune-mediated autoimmune diseases, such as rheumatoid arthritis and juvenile idiopathic arthritis are ameliorated in gestation.[15,16] Moreover, Rabiah and Vitale reported that flare-up of NIU is lowered in midpregnancy compared with the prepregnancy and postpartum periods, and both studies of Kump and associates and Chiam and associates proved this tendency.[17–19] In PEE, however, a distinctive shift from T_H2 to T_H1 immune response was noticed resulting from the increase of T_H1 cells and the decrease of T_H2 cells in maternal circulation.[3] Dominance of T_H1 immunity yields a great amount of proinflammatory cytokines and suppresses the expression of T_H2-related cytokines. Augmentation of T_H1 immunity that manifests in PEE is similar to the T lymphocyte–mediated immune reaction in NIU. In a rodent model of experimental autoimmune uveitis (EAU), EAU was induced by polarization of T_H1 immunity and was resistant to T_H2 immunity. In contrast, induction of EAU in immunized mice during pregnancy was interrupted compared with nonpregnant mice, because of suppression of T_H1 immunity, which may imply that maternal immunity during pregnancy has an impact on the reaction of ocular immunity.[19] Patients with idiopathic uveitis also display robust T_H1 immunity that T_H1-mediated cytokines are predominant, while T_H2-modulated cytokines are inhibitory in the aqueous humor and serum.[20]

T regulatory (Treg) cells play a decisive role in self-tolerance of semiallogeneic fetus and suppression of excessive inflammatory response during pregnancy. It is akin to ocular immune privilege that Treg cell activation curtails immune rejection and provides a better tolerance for allografts, autoantigen, or tumor implants in the eye. Recent evidence showed that while Treg cells were diminished, simultaneous conversion from Treg to T_H17 cells was detected in women with PEE.[21] Increased T_H17 cells produce substantial proinflammatory cytokines, such as interleukins (ILs)-6 and -17 and tumor necrosis factor–α, which, in turn, stimulate natural killer cells and process systemic inflammation with augmented T_H1 immunity. Upregulation of T_H17 cells was also confirmed in an EAU rodent model and in patients with uveitis.[22,23] IL-17 elicited by T_H17 cells displays vigorous activity and, in synergy with T_H1 immunity, induces various autoimmune diseases and idiopathic uveitis. PEE and NIU exhibit similar immune responses of T_H1 and T_H17 dominance; nonetheless, advanced clinical and laboratory research are still needed to assess whether the upregulated T_H1 and T_H17 immunity in PEE can contribute to analogous immune response in the eyes.

Molecules of human leukocyte antigen (HLA), a cell-surface glycoprotein expressed on human white blood cells, are strongly correlated with NIU. For instance, nearly half of acute anterior uveitis cases are concomitant with the expression of the HLA-B27 haplotype. Moreover, Vogt-Koyanagi-Harada syndrome is considered to be closely

TABLE 5. Multivariable Cox Proportional Hazard Model for the Associations of Pre-eclampsia/Eclampsia With Noninfectious Uveitis

Variables	Crude HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Postdelivery women				
Non-PEE	1.0		1.0	
PEE	2.96 (1.48–5.90)	.002	2.96 (1.48–5.92)	.002
<35 years of age				
Non-PEE	1.0		1.0	
PEE	2.22 (0.99–4.97)	.054	2.29 (1.02–5.14)	.045
≥35 years of age				
Non-PEE	1.0		1.0	
PEE	8.39 (1.63–43.33)	.011	8.14 (1.57–42.18)	.001

CI = confidence interval, HR = hazard ratio, NIU = noninfectious uveitis, PEE = pre-eclampsia/eclampsia.

Among postdelivery women, PEE was significantly associated with a higher incidence of NIU. For the analysis of age subgroup, PEE women aged ≥ 35 years had a convincingly increased risk of NIU occurrence although both of PEE women aged < 35 and ≥ 35 years had a significant risk of NIU occurrence compared with non-PEE women.

[a]Adjusted for age, income, urbanization, autoimmune diseases, thyroid diseases, and hepatitis B and C.

linked with HLA-DR4[24]; tubulointerstitial nephritis and uveitis syndrome is genetically susceptible to HLA-DRB1.[25] In pregnant women with PEE, Small and associates identified that HLA-DRB1 expression increased in the placenta and HLA-A was upregulated in the peripheral maternal circulation.[26] Furthermore, the endoplasmic reticulum aminopeptidase 2 (ERAP2) gene, which modulates the trimming of antigenic epitopes presented by HLA class I, plays a crucial key in systemic immune reaction and proinflammatory cytokine production. The mutation of ERAP2 gene has been confirmed the close relationship with immunologic disorders such as PEE, ankylosing spondylitis, psoriasis, and birdshot chorioretinopathy.[27,28] It is rather likely that the interaction between ERAP2 gene and HLA class I orchestrates similar pathogenesis in PEE and intraocular immune reaction.

Systemic inflammation caused by PEE was still detected in postdelivery women. Proinflammatory markers including tumor necrosis factor–α and IL-6 remained elevated even at 12 to 14 weeks postdelivery.[29] In addition, women with PEE showed a greater ratio of IL-6/IL-10 at 20 years postdelivery than those with normal gestation.[30] C-reactive protein is a powerful indicator of inflammatory disorders, and elevated C-reactive protein level is well recognized in patients with anterior uveitis.[31] In the study by Kvehaugen and associates, blood tests revealed significantly higher concentrations of high-sensitivity C-reactive protein in women with PEE at 5 to 8 years postdelivery.[32] Persistence over years of inflammatory response in postdelivery women with PEE corroborates higher risks on cardiovascular diseases, autoimmune diseases, and end-stage renal disease after delivery.[4–6] In this study, >46% of NIU cases occurred within 1 year of PEE diagnosis, which explained nearly half of the cases of NIU in the acute PEE-mediated inflammatory phase. Given that long-term chronic inflammation could persist for ≥5 years after PEE exposure, we decided on a follow-up of 5 years to trace the incidence of NIU. Compared with 9 NIU cases with mild PEE, 5 NIU cases with severe PEE had an older mean age, a shorter interval from developing PEE to NIU, and a higher incidence rate of NIU. These data implied that PEE severity could affect the development of NIU. Nearly 80% of cases of NIU were anterior uveitis that could be associated with the interaction between ERAP2 and HLA among women with PEE. Of 14 NIU cases among PEE women, there was no case with a previous history of related comorbidities. It can possibly be inferred that PEE can be independently associated with the occurrence of NIU. PEE and NIU are considered age-dependent diseases. In this study, the results confirmed that women at advanced maternal ages (≥35 years) are susceptible to the development of PEE.[33] For age analysis, PEE women aged ≥35 years had a more convincing hazard of NIU occurrence, notwithstanding that both subgroups of PEE women aged <35 and ≥35 years had a significantly increased risk of NIU occurrence compared with non-PEE women after adjustment. This suggested that PEE women at advanced maternal ages could evoke prominent inflammatory reaction and comorbidities.

This cohort study had several limitations. First, the diagnosis of PEE and NIU thoroughly depended on *International Classification of Diseases, 9th Revision, Clinical Modification* codes in the LHID2005. Clinical course, severity, and manifestations could hardly be observed and accurately evaluated. To compensate, we included the use of medication and adjudication by specialists to enhance the validation. Also, we could not identify ethnic origin in the LHID2005, although this database was primarily based on the Taiwanese population. Second, women without delivery were not recruited for comparison with women with PEE for the risk of NIU. Third, it is difficult to differentiate nulliparous or multiparous women in this study because the records of delivery before 1997 could not be traced. Besides,

the medication used for PEE management was not evaluated; however, the common drugs—namely antihypertensive drugs, aspirin, and magnesium sulfate applied for controlling PEE—have not been reported to induce uveitis. Finally, a retrospective study might present some selection or exposure bias compared with a prospective study. Therefore, it is necessary to elucidate the causal relationship between PEE and NIU through larger prospective clinical and laboratory investigations.

In conclusion, this is the first study to show the association between PEE and NIU. The results suggest that PEE could be a potential risk factor for NIU. This finding raises awareness that a history of PEE should be considered when women develop NIU.

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