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Research Paper

Association of family history with incidence and gestational hypertension outcomes of preeclampsia

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ABSTRACT

Background: Gestational hypertension and preeclampsia are hypertensive disorders related to pregnancy that can cause maternal morbidity and fetal growth retardation. The association of these disorders with family history remains unclear.
Objectives: To examine the degree of family aggregation of preeclampsia and gestational hypertension in Taiwan.
Methods: The study was conducted using the data from the National Health Insurance Database of Taiwan. Delivery events in Taiwan from 1999 to 2013 were collected. Preeclampsia was identified based on the hospital diagnosis of index delivery. The family aggregation pattern of preeclampsia was assessed and analyzed using the relationship registered in the database with the patients.
Results: A total of 60,314 preeclampsia events were identified among 4,091,641 deliveries, accounting for 1.5% of the cohort. The incidence of preeclampsia increased with maternal age. A total of 768 preeclampsia events occurred in mothers who had a sororal history of preeclampsia (n = 20,704), accounting for 1.3% of all preeclampsia events (n = 60,314). Mothers who had a sororal history of preeclampsia had a relative risk (RR) of 2.6 (95% confidence interval [CI]: 2.41–2.80) for preeclampsia compared with mothers who did not have a sororal history of preeclampsia. The RR for gestational hypertension was 2.79 (95% CI: 2.36–3.3) in mothers with a positive sororal history of gestational hypertension.
Conclusions: Having a sororal history of preeclampsia was a strong risk factor for preeclampsia and gestational hypertension in mothers in Taiwan. The pattern of family aggregation was similar at all maternal ages.

1. Introduction

Gestational hypertension and preeclampsia are hypertensive disorders related to pregnancy. Gestational hypertension is defined as a consistent elevation of blood pressure above 140/90 mmHg in a previously normotensive woman after 20 weeks of pregnancy. Preeclampsia is characterized by maternal hypertension and proteinuria [1]. Preeclampsia can occur in previously healthy women and cause maternal morbidity and fetal growth retardation. Without proper management, preeclampsia can result in a life-threatening condition known as eclampsia, which causes maternal seizure and organ failure [2]. The incidence of preeclampsia is approximately 2%–8% in developing countries [3,4]. Preeclampsia is also associated with a relatively high incidence of

Abbreviations: RR, relative risk; CI, confidence interval; NHI, National Health Insurance NHI; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases; Ninth Revision, Clinical Modification; SD, standardized difference.

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maternal cardiovascular events after delivery, including stroke, myocardial infarction, and sudden death [5,6].

Maternal blood pressure and proteinuria are routinely monitored during pregnancy. Pregnant women with a high risk of preeclampsia are prescribed low-dose aspirin because a previous study reported that a daily aspirin dose of 150 mg can reduce the risk of preeclampsia by 62% in high-risk women [7]. However, the effect of aspirin in moderate-risk or low-risk women remains unclear. Moreover, no curative treatment is available to treat preeclampsia during pregnancy, and delivery is the only solution for preventing further damage.

The pathophysiology of preeclampsia remains poorly understood. A two-staged model that considers both placental and maternal factors is widely accepted [8–10]. The model is based on the proposition that a poorly perfused placenta (Stage 1) produces factors causing the clinical manifestations of preeclampsia (Stage 2). Several risk factors for preeclampsia have been identified, such as advanced maternal age, chronic hypertension, renal disease, diabetes mellitus, obesity, and carrying twins. However, the onset and course of preeclampsia remain unpredictable.

Studies using genome-wide scanning have identified several maternal susceptibility loci in various populations [11–14], but the clinical relevance of these genetic factors remains controversial. Because hereditary factors may contribute to preeclampsia, we hypothesized that positive family history is associated with the incidence of preeclampsia. Family-based studies are the cornerstone for identifying the familial risk and heritability of human diseases because they evaluate whether familial clustering among cases is higher than expected. The National Health Insurance (NHI) database includes the medical records, diagnoses, and treatment histories of virtually all the residents of Taiwan. We identified genealogical relationships and linked health information from this database to investigate the familial clustering of preeclampsia events by estimating the incidence of the disease among mothers with or without a sororal history of preeclampsia.

2. Method

2.1. Data source

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number 98-4060B) and the entity responsible for the data, the NHI Administration. This study is based in part on the NHI Research Database (NHIRD) data provided by the Applied Health Research Data Integration Service of the National Health Insurance Administration. The NHI program is a government-run universal single-payer health insurance program launched in 1995 that covers over 99% of the population in Taiwan. The NHIRD contains data of all registered beneficiaries, including all claims for outpatient and inpatient services by medical providers contracted with the NHI Administration, all treatments prescribed by the providers, and all treatments dispensed by pharmacies. All registered personal information in the NHIRD is encrypted before being released to researchers but can be linked. All personal data in the database are anonymous, and thus, this study was exempt from the requirement of informed consent.

2.2. Study design, population, and outcome

We identified all women who delivered one or more singletons in Taiwan between January 1, 1999, and December 31, 2013, from the Applied Health Research Data Integration Service, provided by the NHI Administration. All live deliveries in this period were included for analysis. The NHIRD contains all records of parent–child relationships and other kinships of the entire population. All full biological siblings can be identified. Data of 4,091,641 deliveries were retrieved from the database and analyzed. Mothers with a sororal history of preeclampsia (exposure) were identified. The outcome of interest was the prevalence of preeclampsia in mothers who had a sororal history of preeclampsia compared with mothers who did not have a sororal history of preeclampsia. Associated diseases, including gestational hypertension and eclampsia, were also analyzed in the same cohort.

2.3. Ascertainment of preeclampsia and other events

Preeclampsia was identified based on medical records between delivery (day 0) and 180 days before delivery (day 180). Preeclampsia, gestational hypertension, and other associated maternal diseases were identified using the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (Supplemental Material Table 1), which were 642.4 (mild or unspecified preeclampsia), 642.5 (severe preeclampsia), 642.6 (eclampsia), 642.7 (preeclampsia/eclampsia with preexisting hypertension), 642.3 (gestational hypertension), 648.8 (gestational diabetes), 641.x (antepartum hemorrhage), and 666.x (postpartum hemorrhage). Preeclampsia has been defined in previous studies [15,16].

2.4. Statistical analysis

The Breslow–Cox proportional hazards model with a robust sandwich method was used to perform intra-familial clustering [17]. We calculated the prevalence and relative risk (RR) of preeclampsia and gestational hypertension between mothers with and without a sororal history of the disease separately. The RR was adjusted for maternal age, distribution of residence, income level quintiles, and occupational categories. Linear regression was employed to confirm the relationship between maternal age and the prevalence of preeclampsia. Furthermore, the RR of other common pregnancy-associated diseases, including gestational hypertension, gestational diabetes, antepartum hemorrhage, and postpartum hemorrhage, were calculated in both positive and negative sororal history groups. All statistical hypotheses were tested at the two-sided 5% level of significance, and all analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Incidence of preeclampsia in the cohort

A total of 4,091,641 deliveries from 1999 to 2013, including 60,314 preeclampsia events, were identified in the NHIRD. The overall incidence of preeclampsia was 1.5% in this cohort (Tables 1 and 2). Mothers with a sororal history of preeclampsia were younger than those without (27.7 vs. 29.1, standardized difference [SD] = 0.29, $p < 0.0001$). The distribution of residence differed between mothers with and without a sororal history of preeclampsia. Women with a sororal history of preeclampsia more commonly resided in suburban and rural areas compared with those without (SD = 0.11, $p < 0.001$). Maternal income level and occupation also differed slightly between the two groups (SD = 0.08, $p < 0.001$). Mothers with a sororal history of preeclampsia had lower income levels, were more often nonmanual workers and professionals, and were less often dependents of other insured individuals.

3.2. Family aggregation of preeclampsia and gestational hypertension

The RRs of preeclampsia and gestational hypertension based on sororal history and other factors are listed in Table 2. Among all 60,314 preeclampsia events in the cohort, 768 events involved mothers with a sororal history of preeclampsia, accounting for 1.3% of all events. The prevalence of preeclampsia was significantly higher among mothers with a positive sororal history (RR = 2.60, 95% confidence interval [CI]: 2.41–2.80). Furthermore, the prevalence of preeclampsia was lower in mothers with previous deliveries compared with mothers with nulliparity (P2 vs. P1, RR = 0.61; P ≥ 3 vs. P1, RR = 0.79).

We then assessed the RRs of gestational hypertension in the same cohort. A total of 22,976 events of gestational hypertension were identified in the cohort, including 149 events (0.65%) involving mothers with

Table 1
Baseline characteristics of pregnancies with preeclampsia in patients with a positive and negative sororal history.

Variables	With affected sister relatives		General population		Standardized difference[a]	P-value
Total participants, n	11,708		2,536,742			
Total pregnancies	20,704		4,070,937			
Age, mean (SD) (years)	27.68	(4.75)	29.08	(4.97)	0.2878	<0.0001
Preeclampsia, N (%)	768	(3.71)	59,546	(1.46)	0.1419	<0.0001
Place of residence, N (%)					0.1082	<0.0001
Urban	10,765	(51.99)	2,312,673	(56.81)		
Suburban	6631	(32.03)	1,218,276	(29.93)		
Rural	2269	(10.96)	354,820	(8.72)		
Unknown	1039	(5.02)	185,168	(4.55)		
Income levels, N (%)					0.0757	<0.0001
Quintile 1 (低)	3029	(14.63)	569,239	(13.98)		
Quintile 2	3297	(15.92)	580,993	(14.27)		
Quintile 3	5002	(24.16)	1,013,937	(24.91)		
Quintile 4	4654	(22.48)	882,381	(21.68)		
Quintile 5 (高)	4157	(20.08)	918,805	(22.57)		
Unknown	565	(2.73)	105,582	(2.6)		
Occupation, N (%)					0.0981	<0.0001
Dependents of the insured individuals	5139	(24.82)	1,152,004	(28.3)		
Civil servants, teachers, military, and personnel	1079	(5.21)	216,832	(5.33)		
Non-manual workers and professionals	8622	(41.64)	1,553,247	(38.15)		
Manual workers	3775	(18.23)	780,919	(19.18)		

[a] Standardized difference (SD) = difference in means or proportions divided by standard error. Imbalance is defined as an absolute value above 0.20.

Table 2
Relative risks for preeclampsia and gestational hypertension in patients with a positive and negative sororal history of preeclampsia or gestational hypertension.

Variable		[a]Preeclampsia		[a]Gestational hypertension	
		Sister with preeclampsia	General population	Sister with gestational hypertension	General population
No. of case		768	54,596	149	22,827
Prevalence (%)		3.71	1.46	1.67	0.56
Sister History	0	Ref.		Ref.	
	1	2.60 (2.41–2.80)[a]		2.79 (2.36–3.30)	
Age (Ref.: <20)	20–24	1.09 (1.03–1.16)		1.12 (1.02–1.24)	
	25–29	1.39 (1.31–1.47)		1.50 (1.36–1.66)	
	30–34	1.93 (1.82–2.04)		2.16 (1.96–2.38)	
	35–39	3.16 (2.98–3.36)		3.39 (3.07–3.75)	
	≥40	5.29 (4.93–5.67)		5.29 (4.71–5.94)	
Parity (Ref.: 1)	2	0.62 (0.60–0.63)		0.63 (0.62–0.65)	
	≥3	0.79 (0.77–0.82)		0.86 (0.82–0.91)	
Number of sister (Ref.: 0)	1	1.15 (1.12–1.17)		1.28 (1.23–1.32)	
	2	1.15 (1.11–1.19)		1.27 (1.21–1.34)	
	≥3	1.19 (1.13–1.25)		1.41 (1.31–1.52)	

[a] Preeclampsia and gestational hypertension were analyzed separately.

Table 3
Relative risks for different degrees of preeclampsia in patients with a positive and negative sororal history.

Variable		Mild or unspecified preeclampsia		Severe preeclampsia	
		Sister with any preeclampsia	General population	Sister with any preeclampsia	General population
No. of case		496	38,605	272	20,941
Prevalence (%)		2.4	0.95	1.31	0.51
Family history	0	Ref.		Ref.	
	1	2.53 (2.31–2.77)		2.73 (2.41–3.10)	
Age (Ref.: <20)	20–24	1.16 (1.08–1.26)		0.98 (0.89–1.08)	
	25–29	1.49 (1.38–1.61)		1.23 (1.12–1.35)	
	30–34	2.10 (1.95–2.26)		1.67 (1.52–1.83)	
	35–39	3.39 (3.14–3.66)		2.82 (2.56–3.10)	
	≥40	5.55 (5.08–6.06)		4.89 (4.37–5.47)	
Parity (Ref.: 1)	2	0.64 (0.63–0.66)		0.57 (0.55–0.58)	
	≥3	0.80 (0.77–0.83)		0.78 (0.74–0.82)	
Number of sister (Ref.: 0)	1	1.18 (1.14–1.21)		1.10 (1.06–1.14)	
	2	1.20 (1.15–1.25)		1.06 (1.00–1.12)	
	≥3	1.22 (1.15–1.30)		1.13 (1.03–1.23)	

a positive sororal history. The prevalence of gestational hypertension was significantly higher in mothers with a positive sororal history than in those with a negative history (RR = 2.79, 95% CI: 2.36–3.30).

Table 3 lists the RRs of various degrees of preeclampsia. Severe preeclampsia accounted for 35% (272/768) of all preeclampsia events. The RRs for mild or unspecified preeclampsia and severe preeclampsia were 2.53 and 2.73, respectively, in mothers with a sororal history of any degree of preeclampsia compared with mothers without a sororal history. The degree of family aggregation was similar in both groups.

3.3. Effect of maternal age on preeclampsia

Fig. 1 presents the age-specific incidence of preeclampsia, determined using a cross-sectional analysis of the cohort. The incidence increased gradually with maternal age in both the positive and negative sororal history of preeclampsia groups. Linear regression analysis (maternal age of <20 and ≥ 40 years were excluded in the calculation) revealed that the prevalence of preeclampsia increased by 0.2% per year of maternal age in the group with a positive sororal history (R^2 = 0.97) and increased by 0.1% per year in the group without (R^2 = 0.90). Mothers aged over 40 years had a 3.7-fold RR of preeclampsia in the group with a positive sororal history and 4.4-fold RR of preeclampsia in the group without compared with mothers aged younger than 20 years. The pattern of family aggregation was similar at all maternal ages.

3.4. Association between the sororal history of preeclampsia and other maternal disorders

The analysis of the relationship between the sororal history of preeclampsia and other maternal diseases is presented in Table 4. The prevalence of both eclampsia (RR = 1.84, 95% CI: 1.25–2.71) and gestational hypertension (RR = 2.0, 95% CI: 1.76–2.26) was higher in the

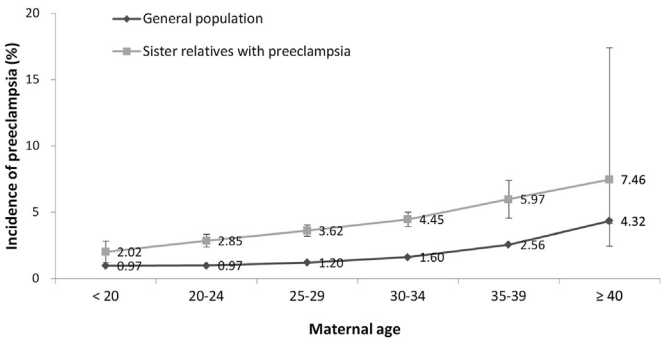

Fig. 1. Age-Specific Incidence of Preeclampsia in Mothers with a Positive and Negative Sororal History of Preeclampsia. The risk of preeclampsia increased with maternal age in both groups, and the pattern of family aggregation remained similar at all maternal ages.

Table 4
Relative risks of other maternal diseases in patients with a positive and negative sororal history of preeclampsia.

Associated conditions	Sister relative with preeclampsia		General population		Relative risks
	Case	Prevalence (%)	Case	Prevalence (%)	
Eclampsia	25	0.12	2837	0.07	1.84 (1.25–2.71)
Gestational diabetes	1063	5.13	164,268	4.04	1.09 (1.02–1.16)
Gestational hypertension	247	1.19	22,827	0.56	2.00 (1.76–2.26)
Antepartum hemorrhage	549	2.65	99,187	2.44	1.06 (0.97–1.15)
Postpartum hemorrhage due to atony	178	0.86	28,684	0.7	1.13 (0.97–1.32)
Postpartum hemorrhage not due to atony	89	0.43	16,150	0.4	0.93 (0.74–1.15)
Severe postpartum hemorrhage	28	0.14	7114	0.17	1.02 (0.70–1.48)

group with a positive sororal history of preeclampsia than that in the group without. The risk for gestational diabetes was mildly elevated (RR = 1.09, 95% CI: 1.02–1.16). No significant differences were observed in the prevalence of antepartum hemorrhage and postpartum hemorrhage between the two groups.

4. Discussion

4.1. Family aggregation pattern of preeclampsia

The NHIRD contains all the medical records, diagnoses, and treatment histories of the Taiwanese population from 1995 to the present [18]. Findings from these data indicated a 2.6-fold increase in the risk of preeclampsia among women with a sororal history of preeclampsia in Taiwan. A survey that used data from Washington, USA birth certificates linked to hospital discharge records demonstrated family clustering of preeclampsia between sisters in a small population [15], with women with preeclampsia being 2.3 times (95% CI: 1.8–2.9) more likely to have a sororal history of preeclampsia and women with gestational hypertension being 1.6 times (95% CI: 1.3–2.0) more likely to have a sororal history of gestational hypertension. Another single-center study reported that a family history of preeclampsia was associated with a 4-fold increased risk of severe preeclampsia (RR = 4.3, p = 0.02) [19]. A Swedish study published in 2004 (data from 1987 to 1997) determined that a family history of preeclampsia through full sister or mother–daughter relationships (RR = 3.3 and 2.6, respectively) was a larger risk factor for preeclampsia compared with maternal or paternal half-sister relationships (RR = 1.4 and 1.0, respectively) [20]. Our study analyzed data from the NHIRD and thus involved a much larger cohort size and longer follow-up period than previous studies, which have been town- or center-based.

In our cohort, gestational hypertension (RR = 2.79) as preeclampsia (RR = 2.60) displayed a similar family aggregation pattern. Moreover, mothers with a sororal history of preeclampsia exhibited a higher prevalence of eclampsia, gestational hypertension, and to a lesser degree, gestational diabetes. A cohort study reported that preeclampsia and gestational hypertension share similar risk factors, such as maternal obesity [21]. The similarity of risk factors and patterns of family aggregation may indicate similarities in the genetic or environmental mechanisms underlying these diseases.

4.2. Preeclampsia and maternal cardiovascular events

In this study, mothers with a sororal history of preeclampsia had a higher risk of both preeclampsia and gestational hypertension. Hypertensive disorders in pregnancy are one of the major causes of maternal morbidity and mortality [22–24]. A cohort study in Norway determined that 22% of maternal deaths were related to hypertensive disorders [25]. Our previous report using NHIRD data from 1999 to 2003 revealed that women with preeclampsia or eclampsia had a significantly higher risk of stroke, both during pregnancy and in the first year postpartum [5]. The adjusted RRs for hemorrhagic and ischemic stroke within 3 months antepartum were 10.68 (95% CI: 3.40–33.59) and 40.86 (95% CI: 12.14–137.47), respectively. Another NHIRD study indicated that women with preeclampsia or eclampsia had a 13-fold higher incidence of myocardial infarction and an 8-fold higher incidence of heart failure during pregnancy, and the risk of major cardiovascular events remained elevated for up to 3 years after delivery [6].

4.3. Hereditary and environmental factors affecting preeclampsia

Although preeclampsia and eclampsia are a global threat to the health of pregnant women, the pathogenesis remains under researched. Abnormal placentation caused by inadequate cytotrophoblast invasion into the inner myometrium and impaired formation of spiral arteries may play crucial roles in the disease's development [26]. Genetic problems affecting endothelial function or angiogenesis may be hereditary factors in the development of preeclampsia.

Possible genetic polymorphisms linked to preeclampsia were reviewed and summarized by Mütze et al., in 2008 [27]. The most widely studied genes have been those that encode angiotensinogen, angiotensin-converting enzyme, angiotensin II type I receptor, and endothelial nitric oxide synthase. Although several genetic polymorphisms have been identified, the Results from various reports are inconsistent, with more non-confirming studies than confirming studies. The incidence of preeclampsia is higher among women with systemic lupus erythematosus (SLE) [28]. Pregnant women with SLE carry a 20% risk of preeclampsia, which is approximately 10 times higher than in the general population. No direct causative genetic defects have been identified to which preeclampsia or eclampsia can be attributed.

Furthermore, environmental factors that are common among family members may contribute to the family aggregation pattern of preeclampsia and gestational hypertension. Sisters may have similar lifestyles in terms of activities, such as cooking, dining, hobbies, and sports, because these habits develop in childhood and may persist into adulthood despite the sisters no longer living together.

Maternal age is a well-established risk factor for preeclampsia. Our study identified a linear relationship between maternal age and the prevalence of preeclampsia in both women with and without a sororal history of preeclampsia. In our analysis, the degree of family aggregation

remained similar in each age group. However, the group with a positive sororal history was younger but had a 2.6-fold higher risk of preeclampsia compared with those with a negative sororal history. These findings indicate that although maternal age affects the risk of preeclampsia, it does not affect the pattern of family aggregation. Women with a sororal history of preeclampsia were at higher risk of preeclampsia at all ages.

The distribution of residence differed between groups. Mothers without a sororal history were more likely to live in urban areas and less likely to live in suburban and rural areas, which may be a shared environmental factor related to preeclampsia. City life may involve more exposure to stress, pollution, and factors that prevent healthy sleep, all of which may contribute to more sporadic cases of preeclampsia. Women in suburban and rural areas live more frequently with their parents and siblings. Therefore, sisters in this group may tend to have similar habits and lifestyles, and thus, this cohabitation effect may contribute to familial cases of preeclampsia.

In our study, the absolute differences in income level and occupation were small and the effects were limited because all women in the cohort were equally covered by NHI, regardless of income level or occupation.

4.4. Similarities and differences in epidemiology

Incidences of preeclampsia are reported in approximately 3%–6% of pregnancies, with a 1.5- to 2-fold higher incidence during the first pregnancy [3,29,30]. In our analysis, the prevalence of preeclampsia was also higher in mothers having their first delivery. This finding can be explained by the characteristics of the disease and psychological factors. Mothers who experienced preeclampsia during their first delivery are less willing to become pregnant again compared with mothers with uneventful deliveries.

According to Chan et al., the prevalence of preeclampsia in Taiwan increased from 0.87% in 1998 to 1.21% in 2010 [31], which is close to the identified prevalence of 1.5% in our study. The overall incidence of preeclampsia was 2.8% between 1980 and 2010 in Japan [32] and 3% between 2006 and 2015 in China [33]. A study in Norway determined that the incidence of preeclampsia increased gradually from 1967 to 1999 and decreased thereafter, with an overall incidence of approximately 3% [34], and the strength of the age–disease relationship decreased in the 21st century. The RR of preeclampsia between older and younger mothers was 2.4 between 1967 and 1976 and 1.2 between 1999 and 2008. In the United States, the overall incidence of preeclampsia was 3.4% in 1980 and 3.8% in 2010, with a considerable increase in the incidence of severe preeclampsia, from 0.3% to 1.4% [35]. Women born more recently have a higher risk of severe preeclampsia compared with women born in the 1970s.

The reported incidence of preeclampsia varies between countries and areas, which may be related to various factors, including genetic variation, lifestyle, and public health policy. The NHI system covers approximately 99.9% of the Taiwanese population. Routine pregnancy checkups can identify maternal and fetal problems at an early stage, allowing maternal hypertension to be well controlled.

4.5. Clinical perspectives

Having a positive sororal history is a strong risk factor for both gestational hypertension and preeclampsia in mothers. The degree of family aggregation was similar at all maternal ages. Taking a detailed family history of gestational hypertension and preeclampsia and closely monitoring mothers with positive sororal history may identify the diseases at early stage. Further studies are required to confirm whether aspirin prophylaxis or more aggressive follow-up can improve maternal outcomes in the group with a positive sororal history.

4.6. Study limitations

The present study has several limitations. First, information on the diagnosis and severity of preeclampsia was based on the medical records in the NHIRD. However, because the diagnostic criteria for preeclampsia and gestational hypertension are clear and well-established, the chance of misdiagnosis is low. Second, detailed personal information, laboratory data, and accurate onset timing of preeclampsia were unavailable. Therefore, we could not analyze whether family-associated preeclampsia tended to occur earlier or later during pregnancy. Third, the NHI program in Taiwan started in 1995; therefore, epidemiological data on preeclampsia before 1995 were not available.

5. Conclusions

A sororal history of preeclampsia is a strong risk factor for preeclampsia in Taiwan. This pattern was also observed in gestational hypertension. The degree of family aggregation was similar at all maternal ages. The main findings are summarized in the graphic abstract. To our knowledge, this study is the first nationwide family-based study to confirm that a sororal history of preeclampsia or gestational hypertension is a strong risk factor for these diseases. Intensive blood pressure monitoring is crucial for high-risk mothers because studies have demonstrated that approximately 60% of preeclampsia-related deaths are preventable [36]. Further studies are required to confirm whether aspirin prophylaxis or more aggressive follow-up can improve clinical outcomes in the group with a positive sororal history. Furthermore, identifying possibly modifiable environmental risk factors is another crucial research field to control and reduce preeclampsia.

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Disclosures

Dr. Chia-Tung Wu has nothing to disclose. Dr. Chang-Fu Kuo has nothing to disclose. Dr. Chia-Pin Lin has nothing to disclose. Dr. Yu-Tung Huang has nothing to disclose. Dr. Shao-Wei Chen has nothing to disclose. Dr. Hsien-Ming Wu has nothing to disclose. Dr. Pao-Hsien Chu has nothing to disclose.

Declaration of competing interest

The authors all have not any conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2021.100084.

References

[1] E. Eiland, C. Nzerue, M. Faulkner, Preeclampsia 2012, J Pregnancy 2012 (2012) 586578.
[2] N. Al-Jameil, F. Aziz Khan, M. Fareed Khan, H. Tabassum, A brief overview of preeclampsia, J. Clin. Med. Res. 6 (2014) 1–7.

[3] A.F. Saftlas, D.R. Olson, A.L. Franks, H.K. Atrash, R. Pokras, Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986, Am. J. Obstet. Gynecol. 163 (1990) 460–465.
[4] M.V. Bobic, D. Habek, J.C. Habek, Perinatal epidemiological risk factors for preeclampsia, Acta Clin. Croat. 54 (2015) 9–13.
[5] C.H. Tang, C.S. Wu, T.H. Lee, S.T. Hung, C.Y. Yang, C.H. Lee, et al., Preeclampsia-eclampsia and the risk of stroke among peripartum in Taiwan, Stroke 40 (2009) 1162–1168.
[6] Y.S. Lin, C.H. Tang, C.Y. Yang, L.S. Wu, S.T. Hung, H.L. Hwa, et al., Effect of pre-eclampsia-eclampsia on major cardiovascular events among peripartum women in Taiwan, Am. J. Cardiol. 107 (2011) 325–330.
[7] D.L. Rolnik, D. Wright, L.C. Poon, N. O'Gorman, A. Syngelaki, C. de Paco Matallana, et al., Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, N. Engl. J. Med. 377 (2017) 613–622.
[8] C.W. Redman, I.L. Sargent, Placental stress and pre-eclampsia: a revised view, Placenta 30 (A) (2009) S38–S42.
[9] C.W. Redman, I.L. Sargent, Immunology of pre-eclampsia, Am. J. Reprod. Immunol. 63 (2010) 534–543.
[10] J.M. Roberts, C.A. Hubel, The two stage model of preeclampsia: variations on the theme, Placenta 30 (A) (2009) S32–S37.
[11] A.M. Lachmeijer, R. Arngrimsson, E.J. Bastiaans, M.L. Frigge, G. Pals, S. Sigurdardottir, et al., A genome-wide scan for preeclampsia in The Netherlands, Eur. J. Hum. Genet. 9 (2001) 758–764.
[12] L. Zhao, E.W. Triche, K.M. Walsh, M.B. Bracken, A.F. Saftlas, J. Hoh, et al., Genome-wide association study identifies a maternal copy-number deletion in PSG11 enriched among preeclampsia patients, BMC Pregnancy Childbirth 12 (2012) 61.
[13] M. Johnson, S. Brennecke, A.C. Iversen, C. East, G. Olsen, J. Kent, et al., OS046. Genome-wide association scans identify novel maternalsusceptibility loci for preeclampsia, Pregnancy Hypertens 2 (2012) 202.
[14] L. Zhu, R. Lv, L. Kong, H. Cheng, F. Lan, X. Li, Genome-wide mapping of 5mC and 5hmC identified differentially modified genomic regions in late-onset severe preeclampsia: a pilot study, PloS One 10 (2015), e0134119.
[15] E. Nilsson, H. Salonen Ros, S. Cnattingius, P. Lichtenstein, The importance of genetic and environmental effects for pre-eclampsia and gestational hypertension: a family study, BJOG 111 (2004) 200–206.
[16] D.B. Carr, M. Epplein, C.O. Johnson, T.R. Easterling, C.W. Critchlow, A sister's risk: family history as a predictor of preeclampsia, Am. J. Obstet. Gynecol. 193 (2005) 965–972.
[17] A.J. Barros, V.N. Hirakata, Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio, BMC Med. Res. Methodol. 3 (2003) 21.
[18] K.T. Lee, A.L. Hour, B.C. Shia, P.H. Chu, The application and future of Big database studies in cardiology: a single-center experience, Acta Cardiol. Sin. 33 (2017) 581–587.
[19] R.B. Cincotta, S.P. Brennecke, Family history of pre-eclampsia as a predictor for pre-eclampsia in primigravidas, Int. J. Gynaecol. Obstet. 60 (1998) 23–27.
[20] S. Cnattingius, M. Reilly, Y. Pawitan, P. Lichtenstein, Maternal and fetal genetic factors account for most of familial aggregation of preeclampsia: a population-based Swedish cohort study, Am. J. Med. Genet. 130A (2004) 365–371.
[21] H.S. Ros, S. Cnattingius, L. Lipworth, Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study, Am. J. Epidemiol. 147 (1998) 1062–1070.
[22] M. Dreyfus, P. Weber, L. Zieleskiewicz, [Maternal deaths due to hypertensive disorders. Results from the French confidential enquiry into maternal deaths, 2010-2012], Gynecol Obstet Fertil Senol 45 (2017) S38–S42.
[23] J.O. Lo, J.F. Mission, A.B. Caughey, Hypertensive disease of pregnancy and maternal mortality, Curr. Opin. Obstet. Gynecol. 25 (2013) 124–132.
[24] J. Moodley, Maternal deaths due to hypertensive disorders in pregnancy, Best Pract. Res. Clin. Obstet. Gynaecol. 22 (2008) 559–567.
[25] L.T. Nyflot, L. Ellingsen, B.M. Yli, P. Oian, S. Vangen, Maternal deaths from hypertensive disorders: lessons learnt, Acta Obstet. Gynecol. Scand. 97 (2018) 976–987.
[26] J. Uzan, M. Carbonnel, O. Piconne, R. Asmar, J.M. Ayoubi, Pre-eclampsia: pathophysiology, diagnosis, and management, Vasc. Health Risk Manag. 7 (2011) 467–474.
[27] S. Mutze, S. Rudnik-Schoneborn, K. Zerres, W. Rath, Genes and the preeclampsia syndrome, J. Perinat. Med. 36 (2008) 38–58.
[28] M.E. Clowse, Lupus activity in pregnancy, Rheum. Dis. Clin. N. Am. 33 (2007) 237–252.
[29] A.F. Saftlas, R.J. Levine, The interval between pregnancies and preeclampsia, N. Engl. J. Med. 346 (2002) 1831–1832, author reply -2.
[30] R. Skjaerven, A.J. Wilcox, R.T. Lie, The interval between pregnancies and the risk of preeclampsia, N. Engl. J. Med. 346 (2002) 33–38.
[31] T.F. Chan, Y.C. Tung, S.H. Wang, C.H. Lee, C.L. Lin, P.Y. Lu, Trends in the incidence of pre-eclampsia and eclampsia in Taiwan between 1998 and 2010, Taiwan. J. Obstet. Gynecol. 54 (2015) 270–274.
[32] A. Shiozaki, Y. Matsuda, S. Satoh, S. Saito, Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan, J. Reprod. Immunol. 89 (2011) 133–139.
[33] Yi YJ. Yang, Gang Zhong, Weiwei Xu, Potential risk factor of pre-eclampsia among healthy Chinese women: a retrospective case control study, Biomed. Res. 28 (2017) 1183–1188.
[34] K. Klungsoyr, N.H. Morken, L. Irgens, S.E. Vollset, R. Skjaerven, Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival, Paediatr. Perinat. Epidemiol. 26 (2012) 190–198.
[35] C.V. Ananth, K.M. Keyes, R.J. Wapner, Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis, BMJ 347 (2013) f6564.
[36] E.K. Main, C.L. McCain, C.H. Morton, S. Holtby, E.S. Lawton, Pregnancy-related mortality in California: causes, characteristics, and improvement opportunities, Obstet. Gynecol. 125 (2015) 938–947.