



## Original Article

## Preeclampsia-eclampsia and future cardiovascular risk among women in Taiwan

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## ABSTRACT

**Objective:** This study aims to examine the long-term cardiovascular and cerebrovascular risks in a large cohort of women with past history of preeclampsia and/or eclampsia.**Materials and methods:** This is a retrospective longitudinal study using National Health Insurance Research Database from 1996 to 2010. We identified 1295 women with preeclampsia and eclampsia. The control group was 5180 pregnant women without preeclampsia/eclampsia, who were matched for age and date of delivery. The incidences of diabetes, dyslipidemia, hypertension and cardiovascular events after pregnancy were identified from medical records after the date of delivery to the date of an event or the end of the study.**Results:** The median follow-up duration was 9.8 years (interquartile 5.1–12.7 years). The incidences of diabetes, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease events were significantly greater in women with eclampsia or preeclampsia than those in controls. Eclampsia or preeclampsia increased the risk of diabetes, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease events (hazard ratio [HR] 3.84 and 5.42,  $P < 0.0001$ ; HR 2.75 and 3.40,  $P < 0.0001$ ; HR 6.52 and 7.31,  $P < 0.0001$ ; HR 9.07,  $P = 0.0060$  and 7.39,  $P < 0.0001$ ; HR 10.71,  $P < 0.0001$  and 3.47,  $P = 0.0048$ , respectively). The survival curves for the development of congestive heart failure and cerebrovascular disease in women with eclampsia/preeclampsia and in control differed significantly (Log-rank test  $P < 0.0001$ ). From the curve, we can find dramatic increases of congestive heart failure and cerebrovascular disease incidences at roughly 3 years and 10 years since the diagnosis of eclampsia/preeclampsia.**Conclusions:** Our study revealed that women with a history of preeclampsia/eclampsia were at increased risks for subsequent diagnoses of diabetes, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease. Preventive counseling, more vigilant screening and management for the modifiable risks should be provided to the affected women. Clinicians should closely monitor these patients in the first three years postpartum and continuously for up to at least a decade.© 2018 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Preeclampsia has an incidence rate of 2–8% in all pregnancy, posing as one of the leading causes of maternal and neonatal morbidity and mortality [1]. More and more evidence suggests that the harmful effects of preeclampsia/eclampsia might not be limited

to the gestation period only, but remained as an important risk for long-term cardiovascular sequelae in impacted women [2–6].

The meta-analysis done by Bellamy et al. found that women with preeclampsia history have four-fold increased risk of hypertension, two-fold risk of ischemic heart disease, stroke and venous thromboembolism later in their lives [7]. Similarly, McDonald et al. revealed a doubled risk of cardiac, cerebrovascular, peripheral arterial disease and cardiovascular mortality in women who had previous preeclampsia in their work, also a meta-analysis [8]. Dozens of other studies, mostly case controlled cohort series, reported agreeable results with associated risk ratio ranged from two

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to four folds [9–16]. However, these reports were inconsistent in study designs, patient population, sample size and length of follow up, making it difficult to generalize the conclusion to all affected women or to delineate the long-term natural course of the etiology. In the current study, we extended the observation period to approximately 10 years, using data from birth registry linked to National Health Insurance claims to examine the long-term cardiovascular and cerebrovascular risks in a large cohort of women with past history of preeclampsia and/or eclampsia.

## Materials and methods

### Study population

In Taiwan, the National Health Insurance is a single-payer program that has covered more than 98% of the population since 1995. National Health Insurance Research Database (NHIRD, [www.nhri.org.tw/nhird](http://www.nhri.org.tw/nhird)) contains information regarding patients' demographic descriptions, diagnoses, prescriptions, inpatient and outpatient claims. It is one of the largest nationwide and population-based data banks in the world. A double-scrambling protocol that encrypts original patient identification numbers is used to protect confidentiality while maintaining consistency. In this study, one million pregnant women were randomly selected from NHIRD and their medical records reviewed from January 1, 1996 to December 31, 2010.

### Study design

A cohort of one million pregnant women with or without preeclampsia/eclampsia was sampled from NHIRD for analysis of their long-term cardiovascular or cerebrovascular risks. All diagnoses were made and coded according to the ninth edition of International Classification of Diseases, Clinically Modification (ICD-9-CM) system. We identified 1295 women with preeclampsia using ICD-9-CM codes 642.4–642.5 and eclampsia 642.6–642.7. We excluded those with previous history of myocardial infarction (ICD-9-CM codes 410.x–412.x), congestive heart failure (ICD-9-CM codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x), peripheral vascular diseases (ICD-9-CM codes 093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4), cerebrovascular diseases (ICD-9-CM codes 362.34, 430.x–438.x), diabetes mellitus (ICD-9-CM code 250), dyslipidemia (ICD-9-CM code 272) and hypertension (ICD-9 code 401–405). Patients with medical data entry, as inpatient or outpatient, at least 12 months prior to delivery were included. The control group of 5180 pregnant women without preeclampsia/eclampsia diagnoses was matched for age and date of delivery. The follow up period was defined starting from the date of delivery to the date of an event or to the end of the study. Three or more inpatient and/or outpatient insurance claims submitted for diabetes mellitus, dyslipidemia, hypertension, congestive heart failure, and cerebrovascular diseases were considered confirmed diagnoses and thus used for analysis. Ethical concerns of this study protocol were approved by the institutional review board of Kaohsiung Medical University Hospital.

### Statistical analysis

Parametric continuous data were compared across groups using *t*-test and categorical data were compared across groups using chi-square test or Fisher's exact test as appropriate. Survival time was calculated from the date of delivery with preeclampsia/eclampsia occurrence to the onset date of hypertension, congestive heart

failure, cerebrovascular diseases or the end of the study (December 31, 2010). The Kaplan–Meier method was used to plot the survival curves for each group, and the log-rank test was used to test the homogeneity between survival curves. The hazard ratios (HRs) and 95% confidence interval were calculated for diabetes, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease events using Cox proportional hazards model. Study subjects were further classified into E–/H–, E+/H–, E–/H+, E+/H+ (E: eclampsia/preeclampsia, H: hypertension) groups to examine which factor might play a greater role in the disease pathophysiology. Relative risks (RR) were estimated by Cox proportional hazards model. Adjusted RRs were calculated after standardizing age, diabetes mellitus and dyslipidemia using Cox proportional hazards regression model. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC), and the significant level was set at  $p < 0.05$ .

## Results

The median follow up period last 9.8 years (interquartile 5.1–12.7 years). A total number of 1295 women with preeclampsia or eclampsia history was properly matched by age to 5180 controls ( $p = 0.4541$ ; Table 1). The majority them aged between 26 and 35 years old (63.3%), averaged at 29.7 years old. Eighty-six percent of the women were having their first pregnancies. Patients with preeclampsia or eclampsia had significantly higher rates of receiving surgical delivery, acquiring diabetes mellitus, dyslipidemia, hypertension, congestive heart failure, and cerebrovascular diseases than those in the control group (75.1% v.s. 37.3%, 8.4% v.s. 2.1%, 12.1% v.s. 3.9%, 28.3% v.s. 4%, 1.0% v.s. 0.1%, 1.0% v.s. 0.2%, respectively;  $p < 0.0001$ ). When these figures were converted to incidence per 1000 person-years, the results remained significant (Table 2). The incidences of eclamptic/pre-eclamptic women suffering from diabetes, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease per 1000 person-years were higher than those in the controls: 7.30/11.27 v.s. 2.45, 12.18/15.05 v.s. 4.44, 42.39/40.31 v.s. 4.62, 1.40/1.12 v.s. 0.15, 2.81/0.92 v.s. 0.26, respectively). Hazard ratio can then be derived from the above findings, attributing the risks of acquiring subsequent diabetes mellitus, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease from eclampsia/preeclampsia by factor of 3.84/5.42, 2.75/3.40, 6.52/7.31, 9.07/7.39, and 10.71/3.47, respectively;  $p < 0.0060$ . When cerebrovascular diseases were further classified into subtypes, it was found that eclampsia was associated with hemorrhagic stroke (HR 19.74,  $p < 0.0001$ ) and preeclampsia was associated with ischemic stroke (HR 4.76,  $p = 0.0274$ ).

In order to capture the temporal changes of the disease courses, Kaplan–Meier curves were adopted to examine the incidence of developing hypertension, congestive heart failure and cerebrovascular diseases over the years since the diagnosis of eclampsia/preeclampsia, with the follow up period lasting 16 years. As illustrated by the divergent lines in Fig. 1, the cumulative incidences of hypertension, congestive heart failure and cerebrovascular diseases were significantly higher than those in age-matched controls (Log-rank test  $p < 0.0001$ ). For the cumulative incidence of hypertension, steady increases over the years with constant slopes were observed for both eclampsia and preeclampsia groups. On the contrary, dramatic increases of congestive heart failure incidence at roughly 3 years and 10 years since the diagnosis of eclampsia/preeclampsia were noted. Similar patterns were also seen in the cumulative incidence rates for cerebrovascular diseases. To further test the validity of the figures despite of its small sample sizes, actual incidence rates were grouped into follow up periods less than 2 years, 2–9 years and longer than 9 years (Table 3). Statistical significances were found at time periods less than 2 years and at more

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