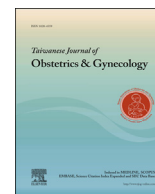




Contents lists available at ScienceDirect

## Taiwanese Journal of Obstetrics &amp; Gynecology

journal homepage: [www.tjog-online.com](http://www.tjog-online.com)

## Original Article

## Trends in the incidence of pre-eclampsia and eclampsia in Taiwan between 1998 and 2010

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## ARTICLE INFO

Article history:  
Accepted 4 June 2013Keywords:  
age  
eclampsia  
pre-eclampsia  
Taiwan

## ABSTRACT

**Objective:** The aim of our study was to determine the relationship between age and the incidence of pre-eclampsia and eclampsia.**Materials and Methods:** We analyzed data collected by the National Health Insurance Bureau between 1998 and 2010. Data were obtained from the Taiwanese Department of Health website and the Department of Internal Affairs.**Results:** The incidence of pre-eclampsia increased significantly (from 0.87% to 1.21%), but the incidence of eclampsia did not change significantly (from 0.04% to 0.05%) between 1998 and 2010. The incidence of pre-eclampsia in the 20–24-year age group was  $0.60 \pm 0.09\%$ . The relative risk of pre-eclampsia in the different age groups was as follows: aged <20 years, 1.02-fold ( $p = 1.0$ ); 25–29 years, 1.35-fold ( $p = 0.041$ ); 30–34 years, 1.79-fold ( $p < 0.001$ ); 35–39 years, 2.99-fold ( $p < 0.001$ ); and  $\geq 40$  years, 5.13-fold ( $p < 0.001$ ). The incidence of eclampsia in the 20–24-year age group was  $0.04 \pm 0.01\%$ . The incidence of eclampsia in only the  $\geq 40$ -years age group significantly increased by 2.49-fold ( $p = 0.001$ ).**Conclusion:** The incidence of pre-eclampsia was correlated with maternal age. The incidence of pre-eclampsia was the lowest in the 20–24-year age group and soared in the >35-year age groups.

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## Introduction

A number of studies have focused on the incidence of pre-eclampsia, a potentially severe complication of pregnancy, and established risk factors, such as nulliparity, family history of pre-eclampsia/eclampsia, pre-eclampsia in a previous pregnancy, obesity, increased insulin resistance, hyperlipidemia, and increased trophoblastic mass [1–4]. Pre-eclampsia occurs more frequently in women of advanced maternal age. In the past decade, Taiwan has

witnessed a significant decrease in the birth rate and an increase in maternal age at birth. It is possible that the changing perception of an appropriate timeframe for childbirth among women has had an impact on the change in the incidence of pre-eclampsia and eclampsia. Our study determined the relationship between age and the incidence of pre-eclampsia and eclampsia by analyzing six age groups (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, and  $\geq 40$  years), and defining the relative risk of pre-eclampsia and eclampsia in different age groups. We also investigated whether the incidence rate of pre-eclampsia and eclampsia had increased yearly. The analysis was based on the data obtained from the dataset of the National Health Insurance (NHI) released by the Taiwanese National Health Research Institute between 1998 and 2010. This study provided a clearer picture of the association between maternal age and the incidence of pre-eclampsia and eclampsia.

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## Materials and methods

### Participants, study design, and data source

We obtained details of pre-eclampsia and eclampsia patients for each age group (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, and  $\geq 40$  years) using data from the public dataset of the NHI released by the Taiwanese Ministry of Health and Welfare ([http://www.mohw.gov.tw/cht/DOS/Statistic\\_P.aspx?f\\_list\\_no=312&fod\\_list\\_no=2425&doc\\_no=13717](http://www.mohw.gov.tw/cht/DOS/Statistic_P.aspx?f_list_no=312&fod_list_no=2425&doc_no=13717) and [http://www.mohw.gov.tw/cht/DO\\_S/Statistic.aspx?f\\_list\\_no=312&fod\\_list\\_no=2591](http://www.mohw.gov.tw/cht/DO_S/Statistic.aspx?f_list_no=312&fod_list_no=2591)). In Taiwan, the NHI program finances health care for 99% of all residents of Taiwan (>25 million enrollees) [5]. Data were collected between January 1998 and December 2010. The data released by the NHI are generally correct and have been extensively used in different types of research. We obtained the birth numbers for each age group from the website of the Taiwanese Ministry of Internal Affairs ([http://www.ris.gov.tw/zh\\_TW/346](http://www.ris.gov.tw/zh_TW/346)). The data released by the governmental agency did not involve human participants and were deidentified; therefore, Institutional Review Board approval was not required.

Diagnoses were coded according to the International Classification of Diseases 9<sup>th</sup> Revision, Clinical Modification (ICD-9-CM). The definition of pre-eclampsia relied on ICD-9-CM discharge diagnosis codes. The incidences were calculated as cases/100 live births for both pre-eclampsia (ICD-9-CM 642.4 and 642.5) and eclampsia (ICD-9-CM 642.6). Personal information, including family history of hypertension and diabetes mellitus, lifestyle factors, and habits (e.g., smoking and alcohol consumption), was not available in the database. To calculate the relative risk ratios for pre-eclampsia and eclampsia, we used the incidence in the 20–24-year age group as the default value to compare the aforementioned six age groups. Eclampsia and pre-eclampsia ratios (EPRs) were the risk ratios for eclampsia to preeclampsia.

### Statistical analysis

Data were evaluated using SPSS software for Windows (version 20; SPSS, Inc., Chicago, IL, USA) and presented as the mean  $\pm$  standard deviation. Pearson correlation and linear regression analysis were performed to determine the relationship between the variables. All tests were two-tailed, and the significance level was defined as  $p < 0.05$ . Analysis was performed using one-way analysis of variance, followed by the Dunnett multiple comparison test.

## Results

This study included a total of 2,980,898 births between 1998 and 2010. During this period, 21,519 and 940 patients were diagnosed with pre-eclampsia and eclampsia, respectively. The incidence of pre-eclampsia increased significantly between 1998 and 2010 (from 0.87% to 1.21%,  $p < 0.001$ ; Table 1 and Fig. 1). However, the incidence of eclampsia did not change significantly with time (from 0.04% to 0.05%,  $p = 0.874$ ).

We further analyzed the incidence of pre-eclampsia and eclampsia in all age groups and found that the incidence of pre-eclampsia and eclampsia in the 20–24-year age group was the lowest ( $0.60 \pm 0.09\%$  and  $0.04 \pm 0.01\%$ , respectively; Table 2). The relative risk of pre-eclampsia increased incrementally with the increase in age, as follows: aged <20 years, 1.02-fold ( $1.02 \pm 1.70$ ;  $p = 1.0$ ); 25–29 years, 1.35-fold ( $1.35 \pm 1.54$ ;  $p = 0.041$ ); 30–34 years, 1.79-fold ( $1.79 \pm 2.21$ ;  $p < 0.001$ ); 35–39 years, 2.99-fold ( $2.99 \pm 4.20$ ;  $p < 0.001$ ); and  $\geq 40$  years, 5.13-fold ( $5.13 \pm 6.47$ ;  $p < 0.001$ ; Fig. 2A). The relative risk for eclampsia in the  $\geq 40$ -year

age group increased significantly by 2.49-fold ( $2.49 \pm 2.01$ ;  $p = 0.001$ ; Fig. 2B). The other age groups had a similar relative risk compared with the 25–29-year age group. When we further separated our data by age group to analyze the incidence of pre-eclampsia as a function of age, some interesting trends emerged (Table 1). For the under 20s group, the incidence rate of pre-eclampsia increased with yearly changes and had a negative correlation with the average age in pre-eclampsia [year,  $\beta \pm$  standard error (SE):  $0.032 \pm 0.007$ ,  $p = 0.001$ ; average age,  $\beta \pm$  SE:  $-1.437 \pm 0.354$ ,  $p = 0.002$ ]. In the 20–24- and 25–29-year age groups, the incidence of pre-eclampsia was correlated positively with the increase in average age of developing pre-eclampsia, but not with the changes with age (year,  $\beta \pm$  SE:  $-0.002 \pm 0.008$ ,  $p = 0.840$ ; average age,  $\beta \pm$  SE:  $0.819 \pm 0.327$ ,  $p = 0.031$  and year,  $\beta \pm$  SE:  $0.010 \pm 0.006$ ,  $p = 0.152$ ; average age,  $\beta \pm$  SE:  $0.585 \pm 0.248$ ,  $p = 0.040$ , respectively). The 30–34-, 35–40-, and  $\geq 40$ -year age groups showed yearly changes in the incidence of pre-eclampsia that were significant, even after the average age was controlled. The EPRs were lower in the 30–34-, 35–39-, and  $\geq 40$ -year age groups than the 20–24-year age group ( $3.63 \pm 1.11\%$ ,  $p = 0.012$ ;  $3.31 \pm 1.21\%$ ,  $p = 0.005$ ; and  $2.77 \pm 3.63\%$ ,  $p = 0.001$ , respectively), but were not significantly different in the <20- and 25–29-year age groups ( $7.33 \pm 2.63\%$ ,  $p = 0.090$ ; and  $4.35 \pm 1.36\%$ ,  $p = 0.058$ , respectively). The EPR decreased in proportion to age ( $r = -0.558$ ,  $p = 0.048$ ).

## Discussion

Maternal age is a risk factor for pre-eclampsia. Although numerous studies have established this association, the data have been based on hospital studies [1,6,7]. This study was based on data collected by the Taiwanese NHI Bureau; a comprehensive database of pregnant women at different ages because of the universal coverage of all medical institutions. Because of the cultural expectation of giving birth in a medical setting, we can be reasonably certain that the data accurately reflected the status of pre-eclampsia and eclampsia in Taiwan. Based on the data, the peak childbearing age has shifted upward. As we expected, the rates of pre-eclampsia increased significantly along with this trend. These findings are in agreement with the study by Wallis et al [6], in which the rates of pre-eclampsia increased significantly with age. In reviewing studies involving age and pre-eclampsia rates in other countries, we found that the results varied. Klungsøyr et al [1] reported that in Norway the time trends for pre-eclampsia rates increased from 1967 to 1999; however, there was a marked increase in 1999 due to the introduction of a new notification form and a significant decline in 2002 and beyond. Roberts et al [7] demonstrated that most countries, including Australia (New South Wales, Western Australia), Sweden, Scotland, Denmark, and Alberta, showed a decline in the rates of pre-eclampsia over time between 1997 and 2007, although maternal age was generally increasing. Nevertheless, the same study also showed that the incidence of pre-eclampsia increased in Massachusetts (USA) [7]. Overall, the reasons for the declining rates of pre-eclampsia in some of the abovementioned regions are not known.

It has been suggested that maternal age, possibly related to the aging of uterine blood vessels, appears to be an independent obstetric risk factor for pre-eclampsia [8]. Lamminpää et al [9] claimed that pre-eclampsia is more common in women with advanced maternal age. Our study confirmed that increasing maternal age is consistently associated with higher risks of pre-eclampsia. We determined whether or not there were any differences in the incidence of pre-eclampsia in each age group. The risk of pre-eclampsia was lowest in the 20–24-year age group; the risk of pre-eclampsia increased dramatically as maternal age increased

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