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Original Research – Quantitative

## Folic acid supplement use and the risk of gestational hypertension and preeclampsia

Maria P.G. De Ocampo<sup>a,c,\*</sup>, Maria Rosario G. Araneta<sup>a</sup>, Caroline A. Macera<sup>c</sup>,  
John E. Alcaraz<sup>c</sup>, Thomas R. Moore<sup>b</sup>, Christina D. Chambers<sup>a</sup>

<sup>a</sup> Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, USA

<sup>b</sup> Department of Reproductive Medicine, University of California, San Diego, La Jolla, CA, USA

<sup>c</sup> Division of Epidemiology and Biostatistics, San Diego State University, San Diego, CA, USA

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### ABSTRACT

**Background:** Hypertensive disorders of pregnancy are among the leading causes of maternal morbidity and mortality. Studies suggest that the use of folic acid may lower the risk of hypertensive disorders in pregnant women.

**Aim:** The aim of this study was to assess the effects of timing and duration of folic acid-containing supplement use on the risk for gestational hypertension and preeclampsia.

**Methods:** Exposures and outcomes data were obtained through interviews and review of participant's medical records from the MotherToBaby cohort studies across the United States and Canada. Demographics, medical history, lifestyle factors, substance use, and fetal sex were assessed as potential confounders. Unadjusted and adjusted risks for gestational hypertension and preeclampsia were examined using odds ratios and 95% confidence intervals.

**Findings:** 3247 women were included in the study. Compared to non-supplement use, early and late supplement use were not significantly associated with the development of gestational hypertension or preeclampsia. The odds of developing gestational hypertension and preeclampsia were significantly reduced as the duration of folic acid-containing supplement use increased.

**Conclusion:** Findings from this study suggest that the use of folic acid-containing supplements may mitigate the risk for gestational hypertension and preeclampsia.

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### Statement of significance

#### Problem

Preeclampsia and gestational hypertension are major contributors to maternal morbidity and mortality.

#### What is already known

The use of folic acid may reduce the risk for hypertensive disorders of pregnancy. Better understanding of how timing

of folic acid use during and before pregnancy may provide greater insight in optimizing benefits for women.

#### What this paper adds

This paper examined how timing and duration of folic acid use influence the risk for preeclampsia and gestational hypertension.

### 1. Introduction

The benefits of taking folic acid supplements during pregnancy to prevent birth defects, such as neural tube defects and cleft palate, are well documented.<sup>1,2</sup> Some evidence have indicated that folic acid-containing supplements may also lower the risk for hypertensive disorders of pregnancy.<sup>3–11</sup> Hypertensive disorders of pregnancy, such as preeclampsia (PE) and gestational hypertension

\* Corresponding author at: Department of Family Medicine and Public Health, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0725, USA. Fax: +1 858 246 1793.

E-mail address: [mdeocampo@ucsd.edu](mailto:mdeocampo@ucsd.edu) (M.P.G. De Ocampo).

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(GH), affect as many as 81.4 per 1000 births in the United States (US), and are common causes of maternal morbidity and mortality.<sup>12,13</sup>

It has been suggested that folic acid and folic acid-containing multivitamins may reduce the risk of GH and PE by lowering plasma homocysteine concentrations in pregnant women.<sup>14,15</sup> Hyperhomocysteinemia induces maternal endothelial dysfunction leading to the development of hypertensive disorders.<sup>16</sup> Several studies that have examined the association between the use of folic acid and risk for GH and PE observed significantly lowered risk for women who took folic acid supplements or had high dietary folate intake in pregnancy.<sup>3–11</sup> However, some of these studies only used maternal self-reports to confirm the outcomes.<sup>6,9</sup> In addition, many were conducted outside the US making generalizations to the US population problematic due to possible differences in dietary folate intake and variations in food fortification policies.<sup>3,5,7,9–11</sup> Yet, other studies have also indicated that folate alone is ineffective in preventing PE.<sup>3</sup> Previous studies that have used larger samples of women to examine the effects of folic acid and folate on hypertensive disorders, including studies that examined exposure to folic acid food fortification, also showed no significant risk reduction.<sup>17–20</sup>

To our knowledge, only four studies have examined supplement use at the periconception and postconception time periods with respect to risk for hypertensive disorders of pregnancy.<sup>3,4,7,8</sup> The effect of when women initiated supplement use on risk for disease development varied in these studies. One study did not show significant difference between beginning folic acid-containing multivitamins before or after conception.<sup>8</sup> Other studies showed significantly reduced risk with supplement use at the periconceptional period, with one indicating significant findings only in women with body mass index (BMI) less than 25 kg/m<sup>2</sup>.<sup>3,4,7</sup> These studies mainly focused on the effects of supplement use on PE, and not GH. Given the inconsistent findings in the literature, our study sought to examine the effects of using folic acid and folic acid-containing supplements on the development of GH and PE. Our study expanded on previous work by examining whether there were varying effects in timing and duration of supplement use on the risk for GH and PE.

## 2. Methods

### 2.1. Study population

All participants in this study were recruited from the Mother-To-Baby (MTB) network, a program of the Organization of Teratology Information Specialists that provides free health counseling and pregnancy risk assessment across 13 sites in North America. The MTB network serves approximately 80,000 pregnant women and healthcare providers annually. Women who contacted the MTB network were screened for inclusion in the ongoing cohort studies, including MTB US and Canada and MTB California. MTB US and Canada includes pregnancy studies on asthma, autoimmune diseases, and vaccines. Women were eligible for these studies if they were US or Canadian residents, were no more than 20 weeks in gestation, and had no prior diagnosis of any major birth defects in their current pregnancy. Informed consent and all data collection were conducted in the MTB research center based in the University of California, San Diego.

Semi-structured phone interviews were conducted at intake, every three months until the end of pregnancy, and once after pregnancy. Data collected at these interviews include demographics, previous pregnancy history and outcomes, women's medical history, and family medical history. Information on the following were also updated at each interview: lifestyle factors, prenatal tests, complications in the current pregnancy, and

pregnancy exposures, including prenatal and folic acid supplement use, medication use, and substance use. An outcome interview, conducted after the birth of the child, collected data on exposures in the last weeks of pregnancy as well as data on pregnancy outcomes and the newborn. In addition to interviews with the mothers, information from medical records was also obtained from the obstetrician, birth hospital and child's pediatrician. These medical records were used to validate maternal reports of study outcomes, medical history, ultrasounds, pregnancy complications, prenatal tests, delivery outcomes, and newborn complications.

Women were included in the current study if they provided informed consent, enrolled and completed an outcome interview for the MTB US and Canada or MTB California cohort studies from January 1, 2004 to June 30, 2014, had a live singleton birth, had no pre-existing chronic hypertension, were not aspirin users during their pregnancy, and had available data on the study outcomes and the exposure of interest.

This study was approved by the Human Research Protections Program of the University of California, San Diego.

### 2.2. Exposures

Information on folic acid and folic acid-containing supplements were obtained at intake, follow-up, and outcome interviews. Data included supplements used, start and stop times, and dosage. For this study, the timing of supplement use was categorized into 3 levels: early users (women who reported starting use of supplements prior to or up to 4 weeks after their last menstrual period), late users (women who reported starting use of supplements only after 4 weeks after their last menstrual period), and nonusers (women who did not report using supplements at any time during pregnancy). These cutoffs were determined based on critical time windows for implantation and placentation linked to the pathogenesis of hypertensive disorders of pregnancy.<sup>16</sup> Women were also grouped in quartiles to examine duration of supplement use by length of time of exposure in weeks.

### 2.3. Outcomes

In this study, the outcomes were self-reported by participants at any interview after 20 weeks of gestation. Reported outcomes were validated using medical records from the obstetrician or delivery hospital. GH was defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg on two or more occasions after 20 weeks of gestation without the presence of proteinuria, and PE was defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg on two or more consecutive readings 4 or more hours apart with proteinuria of 0.3 g during 24 h or more after 20 weeks of gestation. Women who had both GH and PE were classified in the PE group for the multinomial logistic regression models. Data validation using medical records was conducted to confirm the outcomes for both cases and non-cases. For women without available medical records (19%), self-reports were the only source of data for the outcomes. Information regarding data validation procedures was included in a previous publication.<sup>21</sup>

### 2.4. Covariates

The following variables were assessed as possible confounders: maternal age and pre-pregnancy BMI (both continuous); education, race/ethnicity, parity, previous spontaneous abortion or stillbirth, gravidity, current asthma status, diabetes status, autoimmune disease status, alcohol use during pregnancy, cigarettes smoked per day at conception, antidepressant use

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