

OBSTETRICS

Folic acid supplementation in early second trimester and the risk of preeclampsia

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OBJECTIVE: The objective of the study was to evaluate the association between folic acid supplementation in early second trimester and the risk of developing preeclampsia.

STUDY DESIGN: We carried out a prospective cohort study between October 2002–December 2005. We recruited women who had their prenatal care visit (12–20 weeks' gestation) at the Ottawa Hospital and Kingston General Hospital. All charts for participants with a diagnosis of preeclampsia were audited and blindly adjudicated by 4 study investigators to validate the diagnosis.

RESULTS: A total of 2951 pregnant women were included in the final analysis. Supplementation of multivitamins containing folic acid was associated with increased serum folate (on average 10.51 $\mu\text{mol/L}$), decreased plasma homocysteine (on average 0.39 $\mu\text{mol/L}$), and reduced risk of preeclampsia (adjusted odds ratio, 0.37; 95% confidence interval, 0.18–0.75).

CONCLUSION: Supplementation of multivitamins containing folic acid in the second trimester is associated with reduced risk of preeclampsia.

Key words: 5, 10-methylenetetrahydrofolate reductase, folic acid, homocysteine, preeclampsia, supplementation

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Preeclampsia is hypertension and proteinuria that develop during pregnancy, affecting at least 5% of pregnancies worldwide.¹ It is a leading cause of maternal and neonatal morbidity and mortality.¹ Women with a history of preeclampsia are at increased risk of cardiovascular disease in later life.² Preeclampsia may also increase the risks of

cardiovascular disease and diabetes in the offspring of the affected mothers through fetal origins of adult diseases.³

The current hypothesis for the pathogenesis of preeclampsia is that factors produced by the poorly perfused placenta enter the systemic circulation and alter vascular sensitivity to circulating pressors, activate coagulation, and re-

duce vascular integrity, resulting in the pathophysiologic changes of preeclampsia.⁴ However, which factors produced by the poorly perfused placenta are responsible for the development of preeclampsia and how they interact with maternal predisposing factors to induce the clinical syndrome of preeclampsia remain elusive.⁴

Recent studies have found that supplementation of multivitamins containing folic acid was associated with reduced risk of preeclampsia.⁵ Folic acid may reduce the risk of preeclampsia by improving placental and systemic endothelial functions and directly or indirectly by lowering blood homocysteine levels.^{6–10} The objective of this study was to comprehensively evaluate the association between folic acid supplementation, serum folate, homocysteine, and 5, 10-methylenetetrahydrofolate reductase (MTHFR) thermolabile variant gene with the risk of preeclampsia.

MATERIALS AND METHODS

The Ottawa and Kingston (OaK) Birth Cohort recruited nontransferred, consenting women between 12–20 weeks' gestation during their prenatal visit at

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the Ottawa Hospital and Kingston General Hospital. The current analysis included subjects from phase I of the OaK Birth Cohort, which started in October 2002 and ended in December 2005. The research nurses explained to pregnant women the purpose of the study, what would be expected from them, and what they could expect from the study. For participants who gave signed informed consent, blood was drawn for genetic and biochemical analyses. Twins or higher order of multiples or subjects with missing information on gestational age or birth weight were excluded.

Demographic and clinical data were collected by structured interview and chart review. Additional chart review or participant contact was performed if ambiguities or missing data were encountered. Information on supplementation of folic acid and other vitamins, including brand name, date of initiation, and date of discontinuation, was collected both at recruitment and at delivery. Participants were told that this study was observation only and that during the study we did not want them to change anything regarding their daily life or health care. Only women with regular (daily) supplementation were counted. These same questions were asked again at the time of delivery to determine whether there was any change in supplementation.

Laboratory testing was performed to determine serum folate levels and plasma homocysteine levels and for the presence of the MTHFR thermolabile variant gene. Blood for MTHFR genotyping and homocysteine measurement was collected in K₂EDTA Vacutainer tubes (Becton Dickinson, Lincoln Park, NJ). Homocysteine specimens were put on ice immediately after collection, transported to the laboratory within 30 minutes, and centrifuged at 4°C for 10 minutes at 3000 g. Plasma was removed and stored at -20°C until analysis. Samples were assayed in batches. Blood for serum folate was collected in serum separator tubes (SST; Becton Dickinson). The specimens were allowed to clot and then be centrifuged for 10 minutes at 3000 g to separate serum, which was stored at -20°C until analysis. Serum fo-

late was measured on the Beckman Coulter Access II using manufacturer's reagents (Beckman Coulter Inc, Fullerton, CA). Homocysteine was measured on the Abbott Ax Sym II (Abbott Laboratories, Abbott Park, IL) using fluorescence polarization immunoassay technology. MTHFR genotyping was conducted using the method of Donnelly and Rock.¹¹

Preeclampsia was defined as having a blood pressure of 140/90 mm Hg or 30/15 mm Hg above baseline with proteinuria of 2+ on dipstick or 300 mg in 24-hour urine collection in women greater than 20 weeks' gestation. All charts for participants with a diagnosis of preeclampsia were audited and blindly adjudicated by 4 study investigators (S.W.W., M.R., R.W., and M.W.) to validate the diagnosis.

The patterns of supplementation of folic acid and other vitamins in pregnancy and the distribution of maternal demographic and clinical characteristics of the study participants were ascertained. The effects of folic acid supplementation on serum folate and plasma homocysteine levels was then determined overall and stratified by gestational age at recruitment and by MTHFR genotype. Finally, the effect of folic acid supplementation on preeclampsia was determined. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for folic acid supplementation were estimated by multiple logistic regression analysis, with no supplementation as the reference.

Potential confounding variables included in the regression models were maternal age, ethnic background, educational level, parity, previous preeclampsia, chronic hypertension, diabetes, prepregnancy body mass index, household income, gestational age at recruitment, and cigarette smoking during pregnancy. The effects of low serum folate, hyperhomocystinemia, and the presence of the MTHFR thermolabile variant gene on preeclampsia were also examined. Low serum folate was defined as folate concentration below the 10th percentile, and hyperhomocystinemia was defined as concentration higher than the 90th percentile of the study popula-

tion, after stratification by gestational week at which the blood sample was taken.

Additional analyses assessing the effect of supplementation initiation time (before vs after conception) and discontinuation of supplementation in the third trimester (yes vs no) were conducted. All analyses were performed using SAS (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

A total of 4024 women were approached to participate in the study; 3134 (78%) agreed and were recruited. Among them, 70 women were excluded because of twin births and 113 women were excluded because of missing information such as gestational age at delivery, birthweight, or sex (59) and lost to follow-up because of the participant's relocation outside the study center (54), leaving 2951 subjects for final analysis.

Ninety-two percent of the study subjects were taking folic acid supplementation in the early second trimester, most by taking multivitamins containing folic acid at a dose of 1.0 mg or higher (Table 1). More than half of the women initiated supplementation before conception and approximately 20% discontinued supplementation in the third trimester partly or completely (Table 1).

The majority of the study participants were white with high socioeconomic status. Women with no supplementation were more likely to be younger, multiparous, non-whites; to have lower education level and household income; and to smoke cigarettes during pregnancy than women with supplementation (Table 2).

Folic acid supplementation was associated with increased serum folate and decreased plasma homocysteine (Table 3). The association between supplementation and serum folate and plasma homocysteine was stronger in blood samples taken at later gestation and (especially) in participants with MTHFR thermolabile variant genes (Table 3).

The rate of preeclampsia was lower in the supplementation group than in the no supplementation group, with an aOR of 0.37 and 95% CIs 0.18-0.75 (Table 4). Women with supplementation of folic

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