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Folic acid supplementation in early pregnancy and the risk of preeclampsia, small for gestational age offspring and preterm delivery☆

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ABSTRACT

Objective: To assess whether folic acid intake during the first trimester of pregnancy is related to pregnancy outcomes preeclampsia, low birth weight or preterm birth.
Study design: Prospective cohort study of 3647 women who were followed from the first trimester of pregnancy. Detailed information on quantity of folic acid intake before and during the first three months of pregnancy was recorded. Pregnancy outcome data were abstracted from obstetric records.
Results: Lean mothers who used folic acid supplementation the month before pregnancy had a 40% reduced risk of developing preeclampsia. The adjusted odds ratio (OR) with 95% confidence intervals (95%CI) for preeclampsia in lean mothers (BMI < 25) who used folic acid supplements the month before pregnancy was 0.6 (95% CI 0.4–1.0). Obese mothers who used folic acid supplementation in the first trimester had an increased, but not statistically significant risk for preterm birth (adjusted OR 1.9 with 95% CI 0.9–4.0). There were no significant associations between folic acid supplementation and low birth weight.
Conclusion: Our study supports a possible protective effect of folate intake in early pregnancy on preeclampsia in lean mothers. There was no support for any beneficial effect of folic acid use on preterm birth or low birth weight, and we found no evidence of any harmful effects of folate use for the outcomes included in our study.

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Introduction

Fortification of nutrients with folic acid and folic acid supplementation to women of childbearing age is among the greatest modern advances in the care of pregnant women and their offspring. This implementation has been extremely important in preventing congenital birth defects, especially neural tube defects (NTD) [1]. Effects of folic acid supplementation on other adverse pregnancy outcomes have been less well-studied. Low birth weight, whether due to preterm birth or growth restriction, has a negative impact on later health and development in later life [2,3]. Preeclampsia is a potentially life-threatening condition in pregnancy that has both short- and long-term consequences for mother and baby. Questions remain if deficiencies of micronutrients during pregnancy, including folic acid, may increase risk of preeclampsia, low birth weight, or preterm birth.

Folate is essential for the synthesis of nucleic acids, amino acids, cell division, tissue growth, and DNA synthesis [4]. Requirements during pregnancy are markedly increased to cover the needs of placental and fetal growth and development. Folate deficiency may impair cellular growth of the placenta. Poor placental perfusion is

☆ The studies were conducted in New Haven, Connecticut, USA.

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associated with defective trophoblastic invasion and widespread endothelial dysfunction, as seen in preeclampsia. Following folate deficiency, circulating homocysteine may accumulate [5], which may result in endothelial dysfunction [6].

In a cohort of 3647 US women with prospective information about folic acid supplementation in the periconceptual period and the first trimester, we assessed the association of folic acid intake and the risk of preeclampsia, low birth weight birth and preterm delivery.

Materials and methods

Study population

The present analyses combine data from two prospective pregnancy cohort studies conducted in New England, USA. Pregnant women were recruited from September 1996 to January 2000 from 56 obstetric practices and 15 clinics associated with 6 hospitals in Connecticut and Massachusetts. Women were eligible if the pregnancy was before 24 weeks' gestational age at enrolment, did not have insulin-dependent diabetes mellitus, spoke English or Spanish, and did not intend to terminate their pregnancy. Of 11,267 women screened, 9576 met eligibility criteria. The eligible population was further screened to participate in either the Asthma in Pregnancy Study (AIP) [7,8] or the Nutrition in Pregnancy Study (NIP) [9].

For the AIP study after excluding refusals ($n = 531$), pregnancies that had gone beyond 24 weeks gestational age at home interview ($n = 389$), miscarriages ($n = 73$), and non-participation for other reasons ($n = 41$), 2379 women were enrolled. After delivery, 171 women were excluded because of multiple births, abortions, stillbirth, or lack of information, leaving 2208 eligible women who delivered a singleton baby.

For the NIP study a total of 3631 women were invited of whom 2478 were enrolled, 639 declined, 424 were lost to follow-up, 72 miscarried prior to enrollment, and 20 were not eligible at enrollment interview. Among the enrolled women, 2288 delivered a singleton infant.

Data from the two studies were combined for the current analyses. We further excluded participants where complete obstetric information was missing ($n = 849$), leaving 3647 participants (1710 from the AIP study and 1937 from the NIP study).

Data collection in pregnancy

Pregnant women were interviewed, usually at home, before 24 weeks of gestational age. A standardized questionnaire included information on demographic and household characteristics including marital status, family income, health risk factors, medical conditions, and obstetric history. The two study questionnaires were identical for the background information, but differed for the different research focus of each study (asthma and coffee intake, respectively). Information on the use of vitamins and supplements were the same for both studies and could be used for the present analyses.

Information on folic acid, iron and vitamin use was obtained before 24 weeks of gestation from the following questions in the prenatal exposure questionnaire. "Have you used any of the following vitamin or mineral supplements: prenatal vitamins, multivitamin, Vitamin A, Vitamin C, Vitamin E, Iron/Ferrous Sulfate, Folic Acid/Folate Calcium, or Other; specify." If a respondent answered yes, she was specifically asked how often each item had been used (not at all, about once a month, 2–3 times a month, once a week, twice a week, 3–4 times a week, 5–6 times a week, once a day, or two or more times a day). This information was collected by month, from the month before through the third month of pregnancy.

Folic acid exposure

We collected information on folic acid content (micrograms (mcg)) in each of the different vitamin supplements. Using the detailed frequency information from the pregnancy questionnaire, we calculated each respondent's mean daily intake of folic acid supplements for each month from the month before through the third month of pregnancy. Mean folic acid intake in first trimester was defined as the average intake over these four months. For each month and for the first trimester overall, daily folic acid intake was divided into a dichotomous variable of use (no use: <200 mcg daily and use: >200 mcg average use). To test for a dose–response relationship, daily intake was also divided into three categories (<200 mcg, $200 < 600$ mcg, ≥ 600 mcg).

Outcome information

Pregnancy outcome data, which included prenatal, labor and delivery information, and information about the newborn, were abstracted from obstetric records associated with the delivery hospitalization onto a structured form of pregnancy outcome. Data abstractors were blind to exposure status. Preterm birth was defined as a birth before 37 completed gestational weeks, based on information from the obstetric records. Preference was given to sonography estimates of gestational age (61.2% of pregnancies) and based on the first day of the last menstrual period when this was unavailable.

We defined low birth weight as small for gestational age (SGA), and included infants who had a birth weight less than the 10th percentile for gestational age. As reference we used an external standard of birth weight for gestational age, adjusted for gender and ethnicity that we developed from all singleton births in the United States in 1999, as appropriate for the two cohorts [10]. Birth weights were obtained within 24 h of delivery.

We defined preeclampsia according to the National Heart, Lung and Blood Institute (NHLBI) guidelines (Working group) Report on high blood pressure in pregnancy [11]. Blood pressure and urinary protein readings from the prenatal period through the delivery hospitalization were abstracted from the medical records. A woman was classified as having preeclampsia if she met *both* of the following criteria: 1) de novo hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic on two or more occasions at least 6 h apart beginning after the 20th week of gestation; and 2) accompanying proteinuria, defined as urinary protein concentrations of 30 mg/dl or greater (equivalent to a dipstick value of 1+ from two or more specimens collected at least 4 h apart, or one or more urinary dipstick values of 2+ near the end of pregnancy, or one or more catheterized dipstick values of 1+ during delivery hospitalization, or 24-h urine collection with protein of ≥ 300 mg.

We excluded women for whom pre-existing hypertension could not be ruled out (e.g., no readings available prior to 20 weeks' gestation or physician notes indicating a patient with chronic hypertension) or who met partial criteria for preeclampsia (e.g., pregnancy-induced hypertension or proteinuria with no hypertension).

Study ethics

The Human Investigation Committee of Yale University Medical School (New Haven, Connecticut) approved the study and all respondents provided informed consent prior to participation.

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