High-Dose Folic Acid Supplement Use From Prepregnancy Through Midpregnancy Is Associated With Increased Risk of Gestational Diabetes Mellitus: A Prospective Cohort Study

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Periconceptional folic acid (FA) supplementation is widely recommended for substantial benefits on preventing neural tube defects (1), but concerns regarding the potential side effects on both mothers and their infants have been raised recently (2,3). Higher plasma folate was found to be associated with higher risk of gestational diabetes mellitus (GDM) (4). A Chinese cohort had reported association between FA supplement use in early pregnancy and increased GDM risk (5). However, no details on FA doses and durations had been addressed. To further understand the safe dose and duration of FA supplement use regarding GDM risk, for the first time, we evaluated the impact of FA supplement use on GDM with consideration of both doses and durations.

Participants came from the Tongji Maternal and Child Health Cohort (TMCHC), a cohort investigating the role of maternal nutritional, environmental, and lifestyle influences on the outcomes of pregnant women and their offspring. Information on social-demographic status, reproductive factors, lifestyle factors, illnesses, and medical records was collected via questionnaire-based interviews at enrollment (<16 weeks of gestation) and follow-up visits. The study was approved by the ethics committee (Tongji Medical College of Huazhong University of Science and Technology, NO-201302).

Among 8,649 women in TMCHC, after excluding those with diabetes/glucose intolerance prepregnancy, multiple pregnancies, and abortions and without reliable FA information (unclear doses/durations or varying doses) and/or oral glucose tolerance test (OGTT), 4,353 women were eligible for final analysis. The incidence of GDM was 8.6%.

All participants were instructed to report at enrollment whether they used any FA or other supplements prepregnancy and in early pregnancy, and if so, the brand, dose, timing, and frequency were recorded. Consumer choice determined whether <400 μg, 400–799 μg, or ≥800 μg FA was taken. The same questions were repeated at follow-up visits. FA supplement use was defined as a daily intake of supplement containing ≥400 μg FA for at least 4 weeks. Duration was classified as long (continuous at least 4 weeks prepregnancy and continued for at least 16 weeks during pregnancy before OGTT) or short (continuous less than 4 weeks prepregnancy and/or less than 16 weeks during pregnancy before OGTT). Women were categorized into five groups based on FA supplement doses and durations: *1*) never used any FA supplement or used FA with a daily dose <400 μg or duration less than 4 weeks (nonusers), *2*) took FA 400–800 μg/day for short duration (FA400-S), *3*) took FA 400–800 μg/day for long duration (FA400-L), *4*) took FA ≥800 μg/day for short duration

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(FA800-S), and *5*) took FA ≥800 μg/day for long duration (FA800-L). GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Groups (2010) when any of the three plasma glucose values of a 75-g OGTT at 24–28 gestational weeks was equal to or exceeded the thresholds as follows: fasting blood glucose (FBG) 5.1 mmol/L, 1-h postprandial blood glucose (PBG) 10.0 mmol/L, and 2-h PBG 8.5 mmol/L.

By logistic regression, odds ratios (ORs) with 95% CIs of GDM were 1.23 (0.84–1.80), 1.23 (0.78–1.94), 1.37 (0.93–2.01), and 2.36 (1.51–3.69) for FA400-S, FA400-L, FA800-S, and FA800-L, respectively, compared with nonusers. After adjusting for potential confounders, those with FA800-L still had significant higher risk of GDM (adjusted OR [95% CI] 2.09 [1.30–3.36]). The FA–GDM associations were consistently observed in stratified analyses according to gestational weight gain at OGTT (Fig. 1*A*), family history of diabetes (Fig. 1*B*), and fetal sex (Fig. 1*C*). Using multivariate linear regression, women with FA800-L had higher 1-h and 2-h PBG than nonusers by 0.34 (0.14–0.54) and 0.21 (0.06–0.36) mmol/L, respectively, but there was no significant effect on FBG (Fig. 1*D*).

To the best of our knowledge, our study provides the first evidence that periconceptional FA supplement use ≥800 μg/day from prepregnancy through midpregnancy was related to elevated GDM risk in a Chinese population. FA supplement was the only source of synthetic FA for the study population, as food fortification with FA has not been implemented in China. The average dietary folate intake was 461.3 (SD 197.2) μg/day, and no statistically significant difference was found among groups. Although FA supplement use was self-reported, the information provided reliable measurements of dose and duration of FA supplement use.

In conclusion, FA supplement use ≥800 μg/day from prepregnancy through midpregnancy was found to be associated with higher GDM risk. Given periconceptionally, a FA dose of 400 μg/day has been shown to be effective in preventing neural tube defects; there is no scientific justification for long-term use of a higher dose of FA unless otherwise indicated. The potential risk of excess FA intake is a concern, which will require

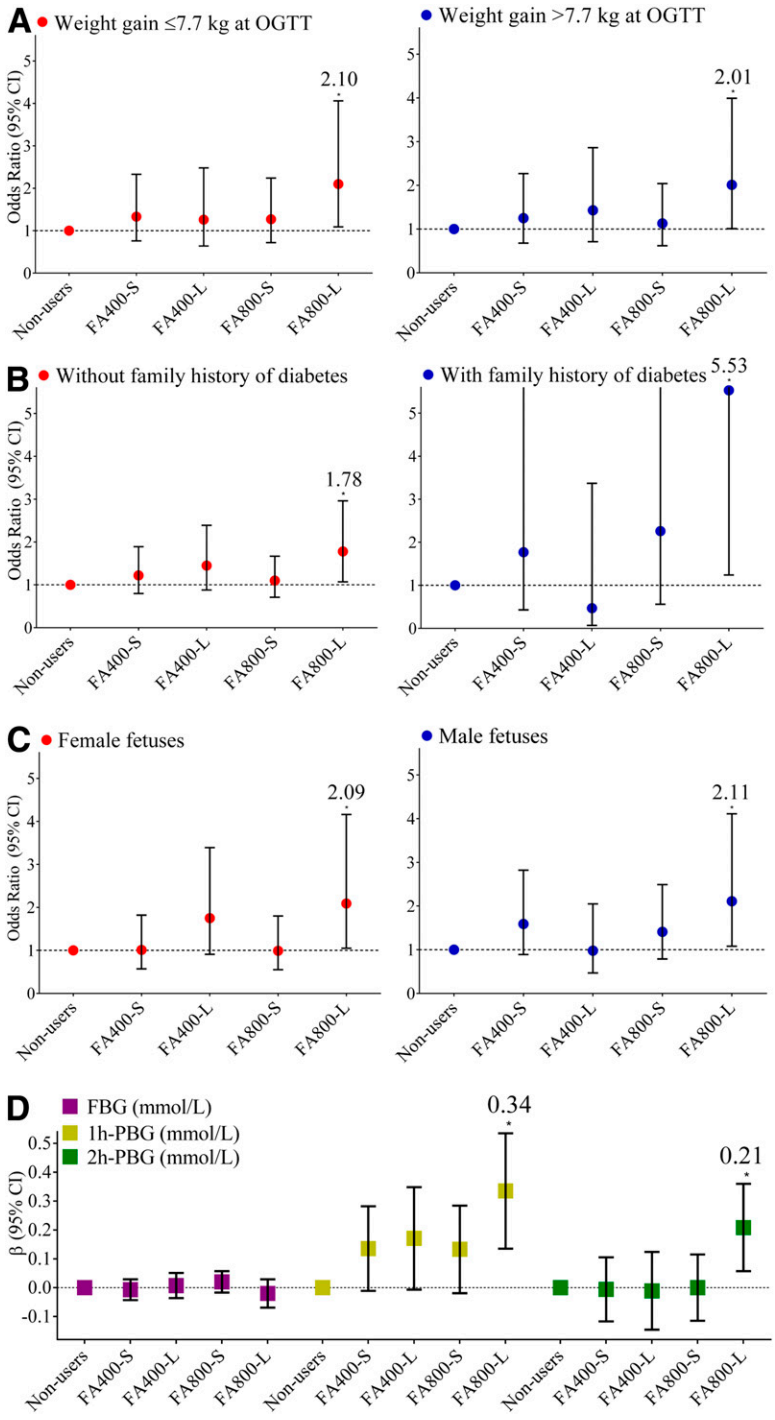

Figure 1—ORs and 95% CIs for GDM according to FA supplement use in subgroups, stratified by weight gain at OGTT (*A*), family history of diabetes (*B*), and fetal sex (*C*) and adjusted β values for FA supplement use and FBG, 1-h PBG, and 2-h PBG (*D*). *A*: Adjusted for age, education, employment, monthly income, ethnicity, primiparity, prepregnancy BMI, smoking, drinking, fetal sex, family history of diabetes, and other supplement use. *B*: Adjusted for age, education, employment, monthly income, ethnicity, primiparity, prepregnancy BMI, smoking, drinking, fetal sex, other supplement use, and weight gain at OGTT. *C*: Adjusted for age, education, employment, monthly income, ethnicity, primiparity, prepregnancy BMI, smoking, drinking, family history of diabetes, other supplement use, and weight gain at OGTT. *D*: Adjusted for age, education, employment, monthly income, ethnicity, primiparity, prepregnancy BMI, smoking, drinking, fetal sex, family history of diabetes, other supplement use, and weight gain at OGTT. Nonusers: never used any FA supplement or used FA with a daily dose <400 μg or duration less than 4 weeks. FA400-S: took FA 400–800 μg/day for short duration. FA400-L: took FA 400–800 μg/day for long duration. FA800-S: took FA ≥800 μg/day for short duration. FA800-L: took FA ≥800 μg/day for long duration. *P < 0.05.

further evaluation to examine the underlying mechanism.

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Author Contributions. Q.L. and Nianh.Y. had the original idea of this study. Q.L., C.Z., R.C., X.Zho., X.L., W.C., Q.G., S.X., M.X., G.X., H.Y., and Z.J. recruited participants from pregnant women; conducted questionnaire-based interviews at enrollment for basic information on general characteristics, dietary intake, and supplement use; and measured body weight and body height at enrollment. Y.Z., L.Hu., X.C., T.X., Y.W., X.W., G.Z., X.Zha., L.L., and D.G. were involved in the follow-up survey on dietary intake and supplement use as well as the measurement of body weight. X.Y., L.Ha., and Nianh.Y. arranged and supervised the work, trained the investigators, and controlled the progress and quality of work. Q.L., C.Z., and L.L. abstracted data from the medical records of the participants. Q.L. analyzed the data, and Nianl.Y. assisted in data analysis and explanation. Q.L. drafted the manuscript, and Nianh.Y. revised and edited the manuscript. Nianh.Y. designed the TMCHC study and made substantial contributions to the interpretation of the results in this study. All authors critically read and approved the final manuscript. Nianh.Y. is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

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