Folic Acid Supplement Intake in Early Pregnancy Increases Risk of Gestational Diabetes Mellitus: Evidence From a Prospective Cohort Study

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Folic acid (FA) is well known for its preventive effect on neural tube defects, and recommendations for FA supplement before and during pregnancy have been well established all over the world. Since increased consumption of FA has been prevalent, concerns about its negative consequences have been raised. Diverse adverse effects of FA have been identified, ranging from an increased risk of oral cleft malformations, asthma/respiratory tract infections, and small-for-gestational-age infants to the more serious effect of a potential increased risk of cancers.

Previous studies have suggested that a high maternal folate concentration is associated with an increased risk of insulin resistance in children and gestational diabetes mellitus (GDM) (1). In addition, animal experiments have reported that maternal high-FA supplement promotes glucose intolerance and insulin resistance in male mouse offspring fed a high-fat diet (2). However, whether FA supplement consumption preconception and during pregnancy increases the risk of GDM has not yet been investigated. We used data from a prospective cohort study to explore the association between FA supplement consumption and risk of GDM.

The China-Anhui Birth Cohort Study (C-ABCS) is a population-based study that recruited pregnant women (n = 3,474) from Ma'anshan City in the Anhui province of China between May 2013 and September 2014. Women underwent a 75-g oral glucose tolerance test at approximately 28 weeks of gestation, and diagnosis of GDM was made when any of the following criteria were met: fasting plasma glucose ≥5.1 mmol/L, at 1 h ≥10 mmol/L, and at 2 h ≥8.5 mmol/L, according to current guidelines from the American Diabetes Association. We used multivariable logistic regression to evaluate the effect of FA supplement consumption on risk of GDM and further assessed the interactions between prepregnancy BMI, a family history of diabetes, and FA supplement consumption. Only women who had either used FA supplements or never used any vitamin supplements (n = 1,938) were included in the analysis. GDM was diagnosed in 249 of the 1,938 (12.8%) women. We found that daily FA supplement consumption in the first trimester was associated with an increased risk of GDM (adjusted odds ratio [OR] 2.25 [95% CI 1.35–3.76]). Women with a prepregnancy BMI ≥25 kg/m^2 and taking FA supplements daily in the first trimester had a much higher risk of GDM (OR 5.63 [95% CI 2.77–11.46]) compared with women with a prepregnancy BMI <25 kg/m^2 and not taking any FA supplements. An increased risk of GDM was not apparent for women using FA before pregnancy alone or in the second trimester alone.

The underlying mechanism of this adverse effect is unclear. There are at least two possible explanations. The first may be an imbalance between vitamin B_{12} and folate. High folate status could exaggerate the metabolic effects of vitamin B_{12} deficiency (3) and might participate in the pathogenesis of GDM through worsening insulin resistance. The second possible explanation may be the harmful effects of unmetabolized plasma FA. Unmetabolized plasma FA has been reported to be related to decreased natural killer cell cytoactivity (4), which has also been suggested to be involved in the pathogenesis of GDM (5).

In conclusion, our study, for the first time, suggests that daily FA supplement consumption in early pregnancy increases the risk of GDM, and further larger cohort studies are warranted to examine this adverse effect.

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