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High dose of maternal folic acid supplementation is associated to infant asthma

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ABSTRACT

Maternal folic acid supplementation had a positive effect on preventing neural tube defects (NTDs), but its effects in infant asthma remained unclear. A hospital-based case–control study was conducted with outpatients between March 2010 and March 2011 including 150 onset infant asthma cases and 212 controls, together with a meta-analysis involving 14 438 participants, was performed. The association between maternal folic acid supplementation and the risk of infant asthma was not significant either in the meta-analysis (*OR* = 1.06, 95% *CI* = 0.99–1.14) or in the case–control study (*OR* = 0.72, 95% *CI* = 0.37–1.39). However, quantitative analysis of the supplementation dose demonstrated that the risk of infant asthma significantly increased for the infants whose mother were with high-dose supplementation (>72 000 μg•d; *OR* = 3.16, 95% *CI* = 1.15–8.71) after adjusting for confounding factors in the case–control study. Meanwhile, the risk of infant asthma significantly decreased for the infants whose mother were with low-dose supplementation (<36 000 μg•d; *OR* = 0.36, 95% *CI* = 0.17–0.77). A high dose of folic acid supplementation for mother during pregnancy was associated with an increased risk of infant asthma, whereas supplementation with a relatively low-dose was associated with a decreased risk of infant asthma. These findings should be further investigated in a large population.

1. Introduction

Asthma is a most common chronic respiratory allergic disease, and the incidence is on the rise. The international study of asthma and allergies in childhood (ISAAC) investigated children aged 13–14 years old from 155 centres in 56 countries and children aged 6–7 years old from 91 centres in 38 countries, and the prevalence of childhood asthma was 1.6%–36.8% (The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, 1998). The ISAAC study showed that asthma was a disease of high prevalence and impact in children and adolescents and should be seen as a public health problem. In China, the result of third nationwide survey of childhood asthma in urban areas showed that the total asthma prevalence of childhood asthma aged 0–14 years old was 3.02% (National Cooperative Group on Childhood Asthma et al., 2013). Although the prevalence of childhood asthma in China is not the highest in the world, the harm to society and people should be considered seriously.

Folic acid, an essential vitamin, is required for many basic cellular processes. Since the 1990s, it had been reported that folic acid supplementation during pregnancy has a protective effect against neural tube defects (NTDs) in newborn infants (Botto et al., 1999; Czeizel and Dudas, 1992; Wald et al., 1991). Women of reproductive age are advised to use folic acid or multivitamin containing folic acid, in many countries (Hewitt et al., 1992). In addition, mandatory folic acid fortification of flour was introduced to substantially improve the folate status in women of childbearing age (Hertrampf et al., 2003; Zhao et al., 2009).

As we all know, necessary levels of nutrients maintain our body structure and function, but the supplementation beyond the necessary levels may not have a more beneficial effect. In humans, high blood concentrations of folate may be related to a decrease in natural killer cell cytotoxicity (Troen et al., 2006), and to an increase in the breast cancer risk (Stolzenberg-Solomon et al., 2006) and in the atopic dermatitis risk in the offspring (Kiefte-de Jong et al., 2012). In addition, development was inhibited in mice that provided with

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a higher dose of folic acid (Pickell et al., 2011). Another animal experiment in mice showed that supplementation with a methyl-rich diet during gestation induced methylation changes that were associated with decreased transcriptional activity and increased the risk of allergic airway disease in the offspring (Hollingsworth et al., 2008). Folic acid is one of the most important methyl donors. More importantly, some studies have suggested that folic acid supplementation for women during pregnancy could increase the risk of wheezing (Håberg et al., 2009) and asthma in the offspring (Whitrow et al., 2009), while others (Magdelijns et al., 2011; Miyake et al., 2011) did not find the same phenomenon. Unfortunately, none of the studies had showed the data about the relationship between the dose of maternal folic acid supplementation during pregnancy and the risk for asthma on their offspring.

Taken together, we hypothesised that different doses of maternal folic acid supplementation during pregnancy would have different effects on infant asthma. To address the questions, we conducted a meta-analysis and a case–control study to assess the association between different doses of maternal supplementation and the risk of infant asthma.

2. Methods

2.1. Meta-analysis

2.1.1. Search strategy

A search was performed for relevant available articles published in English or Chinese from five databases: PubMed, Medline, China National Knowledge Infrastructure, the China Biology Medical Literature Database, and the Database of Chinese Scientific and Technical Periodicals from the earliest available date to May 16th, 2013. The keywords ('folic acid' or 'folate') and ('pregnancy') and ('asthma') were used in combination to retrieve the relevant literature in all of the above databases. Moreover, we reviewed the references of the relevant studies and review articles to identify additional studies. This systematic review was planned, conducted, and reported in adherence to standards of quality for reporting meta-analyses (Stroup et al., 2000).

2.1.2. Inclusion criteria

The inclusion criteria were as follows: (1) the exposure was maternal folic acid supplementation during pregnancy; (2) the outcome was infant asthma; (3) analytical study (case–control studies or cohort studies); (4) available multivariate-adjusted relative risks (*RRs*), hazard ratios (*HRs*) or odds ratios (*ORs*) with 95% confidence intervals (*CIs*); (5) unrelated case and control groups or exposed and unexposed groups in a cohort study and all subjects from the same temporally and geographically defined underlying population. If the data were presented in more than one study, we chose the most complete and recent article. The study quality was assessed using the 9-star Newcastle–Ottawa Scale (Wells et al., 2011). Two authors (Yang and Jiang) reviewed all of the studies independently to identify whether an individual study was eligible for inclusion. Disagreements between the two authors were resolved by consensus with a third reviewer (Wang).

2.1.3. Data extraction

The following information was extracted from each study: the first author; publication year; country; sample size; multivariate-adjusted *RRs, HRs*, or *ORs* (we presented all results as *ORs* for simplicity) with their *95% CIs*; the stage of folic acid supplementation; the definition of cases and the study design.

2.2. Hospital-based case–control study

2.2.1. Study design

A hospital-based case–control study was conducted in the Department of Pediatrics Outpatients, Jinan Central Hospital Affiliated with Shandong University between March 2010 and March 2011. The case inclusion criteria were as follows: (1) the diagnosis of asthma was based on the criteria for infant asthma established by the Chinese Medical Association of Respiratory Diseases (Respiratory Section of Pediatric Branch in Chinese Medical Association, Editorial Board of Chinese Journal of Pediatrics, 2008); (2) onset asthma case; (3) aged under 2.5 years old, boy or girl; (4) outpatients. The inclusion criteria for the controls were as follows: (1) non-asthmatic infants from the same hospital in the same period and the same age period as the cases, boy or girl; (2) children with traumatic diseases, such as epidermis injuries, fractures, etc. from paediatric surgery outpatients, and congenital dysplasia of bone and skeletal deformities were excluded. The exclusion criterion for the cases was duplicate cases, and for the controls were subjects with respiratory, neural, or cardiovascular diseases or immune deficiency.

2.2.2. Sample size estimation

The estimated mother folic acid exposure rates of the cases and controls were 60% and 43% (Wang et al., 2010), respectively, and the *OR* was 2, the two-sided α was 0.05, and the β was 0.10. Based on the formula for a non-matched case–control study, the numbers of cases and controls were 128 and 180, respectively.

2.2.3. Definition of the variables

Folic acid supplementation during pregnancy: supplementation with 400 μg or above of folic acid every day for one month or more in peri-pregnancy.

The total dose of maternal folic acid supplementation during pregnancy: 400 μg folic acid per tablet multiplied by the total supplementation days (μg•d). The doses were divided into four categories: zero (no supplementation in peri-pregnancy), low (supplementation dose <36 000 μg•d), middle (supplementation dose was 36 000–72 000 μg•d), and high (supplementation dose >72 000 μg•d).

Environmental tobacco smoke exposure: the time of environmental tobacco smoke exposure was 15 min per day or more. Tobacco exposure three times or more per week was defined as frequent exposure, and less than three times per week was defined as occasional exposure or no exposure. This variable was divided into maternal exposure during pregnancy and infant exposure after birth.

Intentional diet adjustment during pregnancy: the mother supplemented nutrition actively, regularly and scientifically during the 3 months before pregnancy and during the first trimester.

Feeding pattern: full breastfeeding, mixed-feeding (breastfeeding, milk and milk products), and bottle-feeding (milk and milk products) according to the feeding pattern for the first 6 months after birth.

2.2.4. Data collection

A questionnaire was designed for data collection. The questionnaire was designed based on literature review, panel discussions, check and approval by experts, and modified through pilot study. The research contents in the questionnaire included maternal information and infant information. Maternal information included maternal age at childbirth, gestational age, mode of delivery, occupation, education degree, maternal tobacco smoke, maternal environmental tobacco smoke exposure, family income and family size. Maternal diet type and food supplement (including folic acid supplementation) during pregnancy. When the mother answered she had taken folic acid during pregnancy, the time beginning to