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Effect of folic acid supplementation on preterm delivery and small for gestational age births: A systematic review and meta-analysis

Qian Zhang[a,b,c], Yuanyuan Wang[b], Xiaona Xin[b,c], Ya Zhang[b], Dujia Liu[b,c], Zuoqi Peng[b], Yuan He[b], Jihong Xu[b], Xu Ma[b,c,*]

[a] Beijing University of Chinese Medicine, Bei San Huan East Road, Chaoyang District, Beijing 100029, People's Republic of China
[b] National Research Institute for Family Planning, 12 Da Hui Temple Road, Haidian District, Beijing 100181, People's Republic of China
[c] Graduate School of Peking Union Medical College, Dongdan San Tiao, Dongcheng District, Beijing 100730, People's Republic of China

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ABSTRACT

Objective: To investigate the effect of folic acid (FA) supplementation on the risks of preterm delivery (PTD) and small for gestational age births (SGA).
Data sources: Cohort studies were identified from MEDLINE, EMBASE, the Cochrane Library, CINAHL, and CBM from inception to January 2015.
Participants and included studies: Healthy women who want to get pregnancy or being pregnant.
Main outcome measures: PTD and SGA.
Results: The association of FA and PTD was significant when supplement initiated after pregnancy (RR = 0.68, 95%CI, 0.52–0.90), whereas no effect was founded if the initiation time was before conception (RR = 0.89, 95%CI, 0.80–1.01). The results for the association between FA supplementation and SGA showed significant protective effect: initiated before conception (RR = 0.70, 95%CI, 0.57–0.85) and initiated after conception (RR = 0.84, 95%CI, 0.81–0.89).
Conclusion: Folic acid supplementation is associated with a significant reduction on the risk of PTD when initiated after conception. It can also protect fetus from SGA.

1. Introduction

Folic acid (FA) is an oxidized synthetic water-soluble member of the vitamin B complex family, but does not exist in nature [1]. FA has a preventive effect on the occurrence of neural tube defects (NTDs) which has been shown by large randomized trials [2–4]. Folate plays an essential role in one-carbon metabolism, and facilitates the transfer of one-carbon units in reactions required for the synthesis of purine and pyrimidine precursors of nucleic acids, for metabolism of methionine, serine, glycine, and histidine, and for formation of methylating agents required for normal metabolism and gene regulation [1]. During pregnancy, increased folate intake is required for rapid cellular proliferation and tissue growth in the uterus and the placenta, growth of the fetus, and expansion of maternal blood volume [5,6]. Currently, the importance of adequate supplementation of folic acid for human health is well recognized. In many countries, women planning for pregnancy are recommended to use folic acid, and some countries have even adopted the policy of mandatory food folate fortification [7–9]. Although the relation between maternal folate status with NTDs has been established, the association between maternal folate status with other adverse pregnancy outcomes is still unclear.

Preterm delivery (PTD) is defined as birth occurring before 37 weeks of gestation by the World Health Organization [10]. Born small for gestational age (SGA) indicates that a weight threshold or percentile (typically the 10th or 5th percentile) for a specific gestational age (GA) is not achieved [11]. Infants of PTD or SGA are both at risk for increased long-term morbidity, growth impairment, and birth adaptation complications, including prenatal acidosis, hypoglycemia, hypothermia, coagulation abnormalities, and selected immunological deficiencies [12]. Currently, approximately 5–25% of births are affected by preterm birth and fetal growth restriction [13]. Although PTD and SGA are thought to have distinct pathogeneses, risk factors are complex. Maternal age, preterm delivery history, education level, smoking, nulliparity, BMI and intrauter-

* Corresponding author at: Beijing University of Chinese Medicine, 11 Bei San Huan, East Road, Chaoyang District, Beijing 100029, China. Tel.: +86 013371771198; fax: +86 01064287519.
E-mail address: maxupumc@163.com (X. Ma).

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ine hormone status are common risk factors [14,15]. However, the underlying factors involved in such births and the potential effects of preventive interventions remain poorly understood [16]. Modern obstetrics are still not able to predict, prevent, or treat PTD and SGA [17]. In the past decades, increasing interest and studies of the possible effects of FA supplementation used before and during pregnancy on PTD and SGA have emerged. However, the results of these studies are inconsistent, making it difficult to draw conclusions about whether FA supplementation may influence fetal growth.

Since prenatal FA supplementation is almost universally recommended for women who want to become pregnant and who are already pregnant [18], conducting a randomized controlled trial (RCT) without FA in a control group would not be ethical. Consequently, few RCTs investigating the association between FA and PTD/SGA have been published. As a result, a cohort study design has become the optimal choice for researchers. Although the level of evidence for cohort study is slightly lower than a RCT, it is still regarded as a good research methodology for determining the relationship between FA and PTD/SGA in a large population [19].

The objective of this systematic review and meta-analysis was to summarize the evidence from cohort studies, and to assess the relationships of FA supplementation with PTD and SGA neonates.

2. Material and methods

2.1. Identification of studies and inclusion criteria

Electronic searches were carried out in MEDLINE (PubMed), EMBASE, the Cochrane Library, CINAHL, and CBM from inception to January 2015. The search strategies for each database were different according to their search characteristics. We also searched reference lists of retrieved articles, especially those searched from systematic reviews in the Cochrane Library. We manually searched for unpublished data, such as postgraduate theses and conference proceedings. Inclusion criteria included the following:(1) healthy women who had the intention to become pregnant or being pregnant; (2) any supplement containing FA provided before or during pregnancy as an exposure; (3) supplement not containing FA is applied in the reference group; (4)report the occurrence of PTD or SGA; and (5)cohort studies that were prospective or historical. PTD was defined as birth occurring before 37 weeks of gestation. SGA was defined as less than the 10th percentile or the 5th percentile for a specific gestational age.

2.2. Data collection and extraction

Two independent reviewers screened the titles and abstracts for inclusion. For the studies that met the inclusion criteria, reviewers extracted the data describing population characteristics, study design, exposure specifics, and outcome effects using a standardized inclusion/exclusion form. For the articles in doubt, studies were discussed among the review team before extracting the data. All the other studies that did not meet the above-mentioned criteria were excluded. Records were kept and managed by Note Express 2.7.1 reference manager (http://www.inoteexpress.com/CompanyWeb/). Studies in any language other than English were translated. Related data were entered into the Review Manager ([a computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for outcome measurement.

2.3. Evaluation on the quality of included studies

Assessment of the quality of the cohort studies and risk of bias existed in those studies were carried out independently by two reviewers using the Newcastle–Ottawa Scale (NOS) [20]. Evaluation content included population selection, comparability, exposure and outcome assessment. All eight entries could obtain a maximum of nine points. Disagreement among researchers was resolved by discussion or consultation with a third researcher.

2.4. Data synthesis

Dichotomous data are expressed as risk ratios (RRs) with 95% confidence intervals (CIs). The I^2 test was applied to analyze statistical heterogeneity among studies. In situations of high heterogeneity, causes were explored and random effect models were applied. Subgroup analyses were carried out for different exposure of studies. All analyses were conducted using the software Review Manager 5.3.

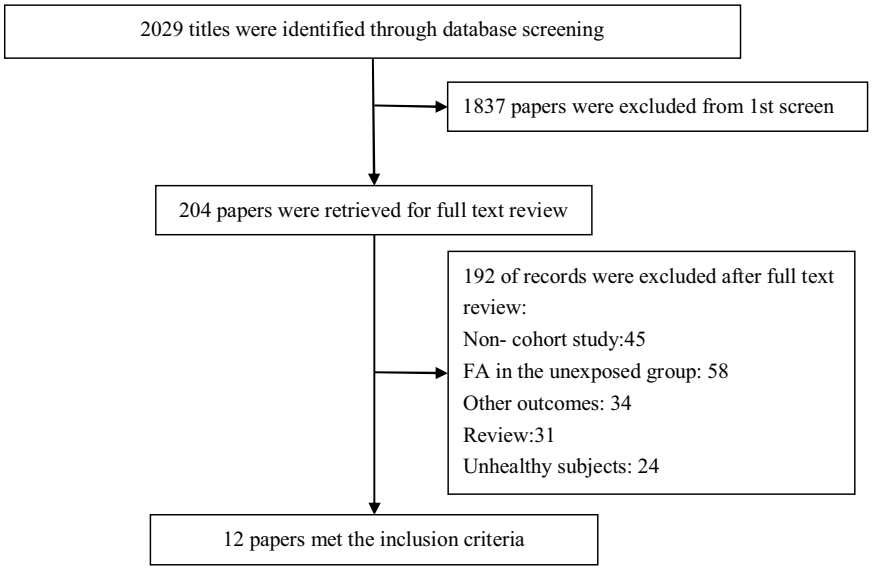

Fig. 1. Flow diagram of the systematic literature search.