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Review

Folic acid supplementation in pregnancy to prevent preterm birth: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Folic acid (FA) may have a role in the prevention of pregnancy complications. However, the efficacy of FA supplementation in reducing the risk of preterm birth (PTB) is still unclear. The aim of this systematic review with meta-analysis was to evaluate the efficacy of folic acid supplementation during pregnancy to prevent preterm birth (PTB). The research protocol was designed a priori, defining methods for searching the literature in electronic databases, including and examining articles, and extracting and analyzing data. We included all randomized trials (RCTs) of asymptomatic singleton gestations without prior PTB who were randomized to prophylactic treatment with either FA supplementation or control (placebo or no treatment). The primary outcome was the incidence of PTB <37 weeks. Five randomized trials including 5,332 asymptomatic singleton gestations without prior PTB were included in the analysis. Women who received FA supplementation had a similar rate of PTB <37 weeks (22.6% vs 22.9%; RR 0.99, 95% CI 0.82–1.18), PTB < 34 weeks (7.1% vs 8.7%; RR 0.77, 95% CI 0.55–1.09) and of preterm premature rupture of membranes (2.4% vs 2.9%; RR 0.81, 95% CI 0.44–1.50) compared with control group. Regarding neonatal outcome we found no significant differences in birth weight (mean difference 85.58 g, 95% CI -55.17–226.34), low birth weight (21.0% vs 15.1%; RR 0.79, 95% CI 0.49 to 1.28) and perinatal death (2.9% vs 2.4%; RR 0.90, 95% CI 0.60–1.34). In summary, FA supplementation during pregnancy does not prevent PTB <37 weeks. Daily FA supplementation remains the most important intervention to reduce the risk of neural tube defects.

Contents

Introduction

Preterm birth (PTB) remains the number one cause of perinatal mortality in many countries, including the US [1]. Prior PTB is one of the most important risk factors for PTB; however, most of these PTBs occur in women without a prior PTB [2].

Folic acid (FA) is a water-soluble vitamin of the B group. Data from observational studies showed that FA, which is commonly used to prevent neural tube defects (NTDs) [3], may have a role in the prevention of pregnancy complications such as PTB, small for gestational age, preeclampsia and may lead to prolongation of pregnancy [4–7], However, the efficacy of FA supplementation in reducing the risk of PTB is still unclear [4–33].

The aim of this meta-analysis was to evaluate the efficacy of FA in decreasing the incidence of PTB in asymptomatic singleton gestations without prior PTB.

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1. Materials and methods

The research protocol was designed a priori, defining methods for searching the literature, including and examining articles, and extracting and analyzing data. Searches were performed in MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, Scielo and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to "micronutrients supplementation," "folic acid," "pregnancy," "folate" and "preterm birth" from inception of each database to October 2015. No restrictions for language or geographic location were applied.

We included all randomized trials (RCTs) of asymptomatic singleton gestations who were randomized to prophylactic treatment with either FA supplementation or control (either placebo or no treatment). Only trials on singleton gestations without prior PTB were included. Exclusion criteria included quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation); trials in women with multiple gestations; prior PTB; FA given also to controls; trials with only biochemical outcomes available; and trials evaluating other micronutrient supplementation in addition to FA.

Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42014013874). The meta-analysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [34].

Data abstraction was completed by two independent investigators (GS, VB). Each investigator independently abstracted data from each study and analyzed data separately. Differences were reviewed, and further resolved by common review of the entire data. All authors were contacted for missing data if possible.

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [35]. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias [35].Risk of bias was assessed by authors independently (GS, VB). Differences were resolved by consensus.

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome was the incidence of PTB <37 weeks. Secondary outcomes were PTB <34 weeks, spontaneous PTB (sPTB) <37 weeks, sPTB <34 weeks, gestational age (GA) at delivery, latency, preterm premature rupture of membranes (PPROM) and neonatal outcomes including birth weight, low birth weight (LBW), admission to neonatal intensive care unit (NICU), neonatal respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), neonatal sepsis and perinatal death. We planned subgroup analysis including RCTs with FA supplementation of more than 1 mg daily.

The data analysis was completed independently by authors (GA, VB) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistic. In case of statistically significant heterogeneity ($I^2 \geq 0\%$), the random effects model of DerSimonian and Laird was used to obtain the pooled relative risk (RR) estimate, otherwise in case of no inconsistency in the risk estimates ($I^2 = 0\%$) a fixed effect model was performed [35]. The summary measures were reported as RR with 95% confidence interval (95% CI). Potential publication biases were statistically assessed by using Begg's and Egger's tests [35]. p-value <0.05 was considered statistically significant.

Results

We initially identified 26 trials on FA supplementation during pregnancy [8–33]. No similar systematic reviews were found during the search process.

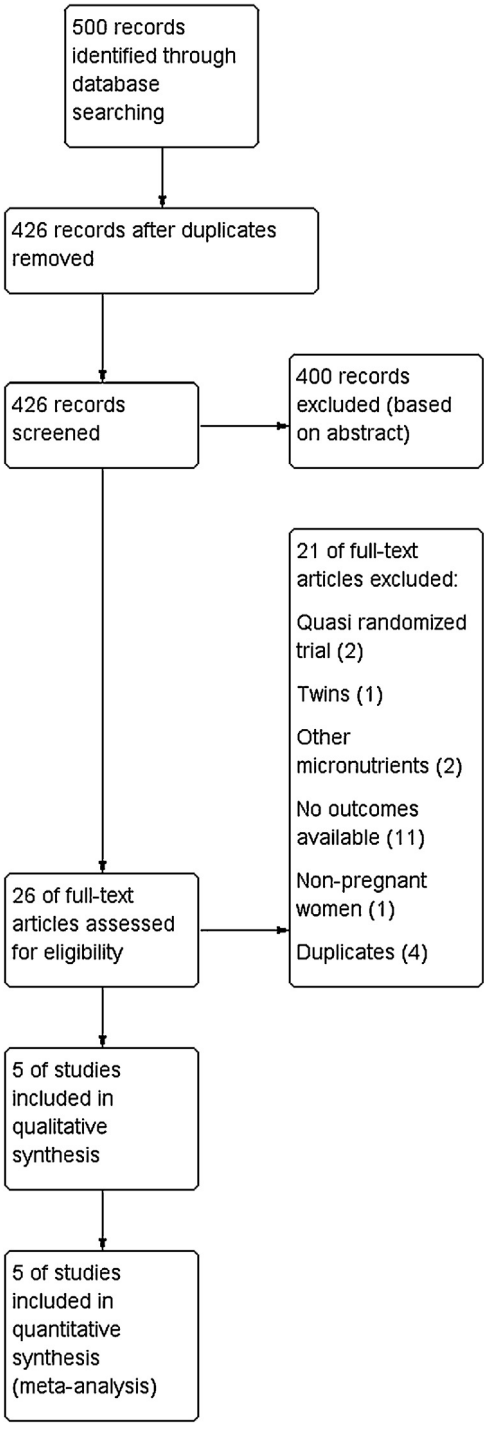

Fig. 1. Flow diagram of studies identified in the systematic review.