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Review Article

Folic acid supplementation during the preconception period: A systematic review and meta-analysis

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ABSTRACT

Guidelines recommend that women take folic acid supplements in the preconception period to prevent neural tube defects (NTDs) in their offspring. Estimates of adherence to this recommendation across different countries worldwide have not been synthesized. Medline, CINAHL, and EMBASE were systematically searched to identify studies reporting the prevalence of preconception folic acid supplementation. Pooled prevalence estimates for each country (where data were available) were calculated; and differences based on demographic, methodological, and study quality characteristics were examined. Of 3372 titles and abstracts screened, 722 full-texts were reviewed and 105 articles that reported 106 estimates of preconception folic acid supplementation in 34 countries were included. Pooled prevalence estimates were 32–51% in North America, 9–78% in Europe, 21–46% in Asia, 4–34% in the Middle East, 32–39% in Australia/New Zealand, and 0% in Africa. No South American studies were identified. Higher supplementation prevalence was observed in studies that had more highly educated samples, were conducted in fertility clinics, and assessed folic acid use via self-report. Of note, only 32% and 28% of studies reported timing of folic acid use and adherence to folic acid, respectively. Preconception folic acid supplementation is highly variable worldwide and many women may not achieve sufficient folate levels to prevent NTDs. To better understand non-adherence, recommendations for future research include: more explicit reporting of methodology, more detailed assessment of folic acid use, assessment of variables potentially relevant to folic acid use, and surveillance of folic acid use in a greater diversity of countries, especially in the developing world.

1. Introduction

Neural tube defects (NTDs) result from failure of the neural tube to close at approximately 3–4 weeks gestation, and can result in infant mortality or long-term disability (Greene and Copp, 2014; Flores et al., 2015). Most NTDs are preventable by sufficient intake of folate or its synthetic form, folic acid (Greene and Copp, 2014; Czeizel et al., 2013). Although the exact mechanisms are unclear, folate may play an important role in neural tube closure by regulating processes such as nucleotide biosynthesis and methylation reactions (Greene and Copp, 2014). Evidence from observational studies indicated lower rates of NTDs in offspring of women who supplemented with folic acid before pregnancy (Mulinsky et al., 1989; Mulinare et al., 1988). Subsequently, randomized controlled trials (RCTs) indicated meaningful reductions in NTDs following folic acid supplementation (Wald and Sneddon, 1991; Czeizel and Dudas, 1992). For example, a 72% protective effect of folic acid was reported by a seven-country study (Wald and Sneddon, 1991). Based on this evidence, the United States (US) government has recommended since 1992 that all women of childbearing age should supplement with 0.4 mg of folic acid daily (MMWR., 1992; Crider et al., 2011). The World Health Organization (WHO) similarly recommends that all women attempting to become pregnant supplement with 0.4 mg of folic acid daily (World Health Organization, 2017). Supplementation is recommended before conception, rather than after confirmation of pregnancy, because neural tube closure may occur before many women are aware of their pregnancy (Greene and Copp, 2014; Government of Canada, 2016).

Many countries (e.g., Canada, the US) have mandated fortification of grain products with folic acid (Centers for Disease Control and Prevention, 2010), resulting in increased levels of serum folate and

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decreased incidence of NTDs (Crider et al., 2011; Canfield et al., 2005). However, large scale studies of reproductive aged women suggest that folic acid supplementation remains necessary even in countries with mandatory grain fortification (e.g., 22% in Canada have sub-optimal blood serum folate concentrations for NTD prevention (Colapinto et al., 2011) and 22% in the US do not meet folate requirements from diet alone (Bailey et al., 2010)). Ultimately, mandatory fortification has not changed the recommendation for folic acid supplementation before pregnancy (Crider et al., 2011; World Health Organization, 2017).

Despite recommendations, there is considerable room for improvement in uptake of folic acid supplements. Among studies from countries with 'very high human development' (designated by the United Nations' human development index (United Nations Development Programme, 2015)), the prevalence of any preconception folic acid supplementation varies considerably and can be < 10% (Toivonen et al., 2017). Even in a population-based study of 35,351 US women planning a pregnancy within the next year, only 54.3% reported taking folic acid supplements daily (Chuang et al., 2011).

To better understand how preconception folic acid supplementation rates compare to recommendations, there is a need to synthesize estimates of supplementation and examine potential factors associated with use. Ray et al. (2004) systematically reviewed preconceptional/periconceptional folic acid use worldwide but did not provide estimates by country or region. They observed a slight increase in use over time; reported greater likelihood of use among women with higher education, older age, non-immigrant status, partners, and planned pregnancies; but characterized overall use as generally suboptimal. Peake et al. (2013) published a systematic review and meta-analysis of periconceptional folic acid use among women of different ethnicities within the United Kingdom (UK), concluding that supplementation was nearly three times as prevalent among Caucasians relative to non-Caucasians. However, their meta-analytic estimates were based on only three studies for which adequate data were available (Peake et al., 2013). A scoping review by Toivonen et al. (2017) examined several preconception health behaviours, including folic acid use, however they only included countries with "very high human development" and did not synthesize prevalence estimates through meta-analysis. The present systematic review and meta-analysis provides an update to the review conducted by Ray et al. (2004), and is the first known study to provide national prevalence estimates of any preconception folic acid use where available. Potential sources of heterogeneity such as sample characteristics, methodology, and country fortification policy were examined. Additionally, the impact of study quality indicators on supplementation rates was investigated because low methodological quality can impact internal validity and bias the results (Stroup et al., 2000).

Because significant heterogeneity in supplementation estimates was expected among different countries, a single global prevalence estimate would not be meaningful. Therefore, the primary aim of this review was to estimate preconception folic acid supplementation prevalence by country. Secondary aims included: (1) examining supplementation prevalence by country grain fortification policies; (2) determining whether supplementation prevalence differed before and after implementation of mandatory grain fortification, among countries with mandatory fortification; and (3) examining supplementation prevalence by participant characteristics (e.g., maternal age), methodological factors (e.g., self-reports vs interviews), and study quality factors (e.g., whether inclusion/exclusion criteria were explicitly reported). This review defines the preconception period as any time before conception (among studies of women who retrospectively reported while pregnant or after a live birth), or the current time period (among women planning pregnancy within six months). Given the scarcity of data on objectively measured serum folate levels, and the inaccuracy of folate levels estimated from self-reported diet, the outcome of interest was use of folic acid supplementation as opposed to serum folate or estimated folate intake from food.

2. Methods

The present systematic review was performed according to a predetermined protocol (PROSPERO registration ID: CRD42016052774) and in accordance with MOOSE (Meta-Analyses of Observational Studies in Epidemiology) reporting guidelines (Stroup et al., 2000).

2.1. Search strategy

The databases Medline, CINAHL, and EMBASE were systematically searched in October 2016. The search was limited to publication dates after 1990 to align with introduction of the earliest recommendations for folic acid supplementation (Crider et al., 2011). No language restrictions were used as part of the search; however, only articles that included at minimum an abstract written in English, French, or German, were considered for inclusion in the study selection phase. Electronic databases were searched with two comprehensive themes surrounding folic acid use (using the medical subject heading [MeSH] term "Folic Acid" and keywords such as "folic acid", "folate", and "multivitamin") and the time period before conception (using the MeSH term "Preconception Care" and keywords such as "preconception", "periconception", and "pre-pregnancy"). Terms were combined using the Boolean operator OR and themes were combined using AND (see Appendix A for detailed search strategy). Both full text articles and conference abstracts were considered for inclusion, and a sensitivity analysis was conducted to examine whether full-text articles and abstracts could be combined in analyses.

2.2. Study selection

In the first phase of screening, KT and EL independently examined abstracts for eligibility using purposefully liberal inclusion/exclusion criteria. At this stage, only abstracts that did not assess folic acid or any multivitamin use, did not examine the preconception period, or did not include original data were excluded. In the second phase of screening, KT and EL examined records to determine whether they met inclusion criteria. Records were excluded if: (1) they did not provide data on the percentage of women who engaged in any folic acid supplementation for the preconception period specifically (e.g., studies that described the entire periconception period but did not provide preconception-specific data; studies of women considering pregnancy in the next year, rather than planning within six months), (2) they did not provide information about folic acid supplementation specifically (e.g., broadly described multivitamin use without explicitly assessing folic acid use, reported serum folate levels only), (3) they were experimental or case-control studies, (4) they focused on populations of women with diabetes, epilepsy, or prior NTD-affected births (because these populations have different folic acid recommendations and may be more closely monitored by healthcare providers surrounding pregnancy), (5) if reported data were insufficient to obtain a prevalence estimate, (6) original data was not reported (e.g., review articles), or (7) if full-texts or abstracts were not written in English, French, or German. Any full-text written in a language other than English, French, or German that had an abstract written in English, French, or German was treated as an abstract. Some records presented duplicate data (i.e., data which appeared, based on sample name or participant characteristics, to be drawn from the same participants, or a subset of the same participants). When duplicate data were encountered (e.g., data drawn from a large national database of participants) in a full-text article and a conference abstract, only the full-text was retained. If duplicate data were encountered within the same article type the record with the largest number of participants was retained. In cases where the number of participants was identical, we retained whichever record provided more detail. When articles reported separate information for a specific subgroup that fit the inclusion criteria (e.g., a study of reproductive-aged women, a portion of whom were planning pregnancy within the

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