Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage

Lynn B Bailey and Robert J Berry

ABSTRACT

Key research findings relative to the question of whether maternal use of folic acid before and during pregnancy reduces the chance that offspring will be born with a congenital heart defect or an orofacial cleft are reviewed in this paper. Observational studies in general support an association between maternal use of multivitamins containing folic acid and a reduction in the occurrence of congenital heart defects and orofacial clefts. Results from one randomized controlled trial (RCT) provide the strongest evidence that multivitamins prevent congenital heart defects, but this RCT did not provide evidence that multivitamins prevent orofacial clefts. In addition, most observational and interventional studies are not designed to detect an independent effect from folic acid. Early studies suggested that periconceptional multivitamin use was associated with an increased occurrence of both miscarriages and multiple births, which has resulted in a great deal of controversy about the safety of folic acid use during pregnancy. We also review reports that were designed to answer these questions with more definitive data. When more substantial evidence about the effect of periconceptional folic acid on the occurrence of congenital heart defects and orofacial clefts is reported, we will have additional support for promoting folic acid intervention programs. All women capable of becoming pregnant should continue to consume 400 μg/d of folic acid in addition to a healthy diet as advised. Am J Clin Nutr 2005;81(suppl):1213S–7S.

KEY WORDS Folic acid, heart defects, orofacial clefts, miscarriages, multiple births

INTRODUCTION

Periconceptional consumption of folic acid, or multivitamins containing folic acid, has been shown in intervention studies to reduce the risk for neural tube defects (NTDs) (1–3). The successful translation of these scientific data related to folic acid and NTD risk reduction into public health policy provides the rationale for evaluating evidence for an association between periconceptional folic acid and other common congenital anomalies including heart defects and orofacial clefts. In this paper, key findings related to periconceptional use of multivitamins containing folic acid and a reduced occurrence of both congenital heart defects and orofacial clefts are briefly reviewed.

The controversial claims that periconceptional folic acid use will increase the occurrence of both multiple births (4–6) and miscarriages (7, 8) are of concern to women of reproductive age and their health care providers. Most of these studies analyzed data collected for other purposes which introduced many potential flaws. More recent findings from a large-scale intervention study fail to confirm an increased risk for either multiple births or miscarriages associated with maternal use of folic acid before and during early pregnancy (3).

An RCT testing whether different doses of folic acid or folic acid plus other vitamins reduce the risk for other birth anomalies including heart defects and orofacial clefts is needed before specific public health recommendations are made. The appropriate advice to women capable of becoming pregnant is to follow the current folic acid recommendation designed to reduce the occurrence of NTDs.

CONGENITAL HEART DEFECTS

Heart defects affect 1 in 110 newborns and account for a third or more of infant deaths due to birth defects, more than that for any other congenital anomaly including NTDs (9–12). In the United States alone the number of deaths attributed to heart defects is estimated to be ≈6000/y (13). There has been an extensive investigation of potential causes and risk factors for heart defects; however, only a very small percentage of cases can be definitively linked to known etiology (10).

The strongest evidence that multivitamins containing folic acid taken periconceptionally will significantly reduce the risk of congenital heart defects is supported by data from a Hungarian RCT (2) and from 2 population-based case-control (PCC) studies in the United States (14, 15). The Hungarian RCT was designed to evaluate the efficacy of a prenatal multivitamin containing 800 μg of folic acid in reducing the occurrence of NTDs (2). Further analysis of this RCT and subsequent data from Hungary showed that prenatal multivitamins were associated with an impressive overall 50% reduction in risk for a broad range of heart defects (Figure 1) (16, 17). In an Atlanta PCC study, use of periconceptional multivitamins containing folic acid was associated with a 24% reduction in the odds for congenital heart defects in general.

[odds ratio (OR), 0.76] (see Figure 1) (14). Although the observed association was less than that observed in the Hungarian RCT (2, 17), data from the Atlanta PCC study also support the conclusion that periconceptional use of multivitamins significantly reduces the occurrence of congenital heart defects (14). When evaluating the association with specific types of heart defects, the data suggest that the association may be strongest for ventricular septal defects (VSD) and some conotruncal defects (tetralogy of Fallot and D-transposition of the great arteries) (18). In both the Atlanta PCC study and the Hungarian RCT (14, 17), the occurrence of conotruncal defects was reduced ~50% (Figure 1). Data from a different PCC study (15) also support the conclusion that periconceptional multivitamins are associated with a reduction (30%) in the occurrence of conotruncal defects.

In contrast, Werler et al (19) detected no association between 2 types of congenital heart defects (VSD and outflow tract) and periconceptional multivitamin use in a hospital-based case-control study. Also, Scanlon et al (20) detected no association between outflow tract defects and periconceptional multivitamin use in the Baltimore-Washington Infant Study. The majority of evidence supports the conclusion that periconceptional multivitamins containing folic acid may reduce the risk for congenital heart defects.

Which nutrient or combination of nutrients in multivitamins that is responsible for the apparent reduction in congenital heart defects has not been established. No direct evidence that folic acid alone is responsible has been published. However, some indirect evidence does exist. Analysis of a large case-control study (21) evaluated, among women who took drugs that inhibit dihydrofolate reductase, which is required for normal DNA synthesis, whether taking these folic acid antagonists during early pregnancy increased a woman’s risk of having an infant with a congenital heart defect and whether concomitant use of multivitamins influenced this risk. The relative risk associated with the use of the folic acid antagonists when no multivitamin supplement containing folic acid was taken was 7.7 [95% confidence interval (CI), 2.8 to 21.7]. In contrast, when multivitamins were taken in addition to the drugs (trimethoprim, trimaterine, and sulfasalazine), the relative risk associated with the use of both the drugs plus supplement was reduced to 1.5 (95% CI, 0.6 to 3.8). These findings indicate that the use of folic acid antagonists in early pregnancy increases the risk of heart defects particularly among the infants of women who did not take multivitamins, but that multivitamins could attenuate this increased risk. These data support the conclusion that folic acid is the active ingredient in multivitamins, that folic acid is essential for normal fetal cardiac development during early embryogenesis, and that periconceptional folic acid use may reduce the risk for congenital cardiac anomalies.

OROFACIAL CLEFTS

Orofacial clefts including cleft lip with or without cleft palate (CLP) and cleft palate alone (CP) affect ~ 1 in 1000 and ~1 in 2500 infants, respectively (22). Studies have resulted in mixed findings related to the protective effect of maternal multivitamins containing folic acid on the occurrence of orofacial clefts. Maternal use of multivitamins was associated with a significant reduction in the occurrence of orofacial clefts in a PCC study based on an analysis of data from the California Birth Defects Monitoring Program (23). In this study, a 50% reduction in the occurrence of CLP and a 27% reduction in the occurrence of CP was associated with maternal use of multivitamins (23). A similar finding for CLP (48%) was reported by Itikala et al (22) among women who used multivitamins during the periconceptional period or who started multivitamin use during the first postconception month. In contrast, no association was observed in a hospital-based case control study in the Boston, Philadelphia, and Toronto areas (24). However, in a subsequent investigation in this same area, Werler et al (19) found significantly lower odds for CP, but not CLP, among mothers who took multivitamins containing folic acid during pregnancy and gave birth to healthy infants compared with case mothers. Recently periconceptional folic acid supplement use was reported to halve the risk of CLP (25). The findings from this investigation support the previously reported 50% reduction in occurrence of CLP with periconceptional folic acid-containing multivitamin use (22, 23). The fact that 93% of the women took supplements containing...
only folic acid strengthen the direct evidence that the association between maternal use of periconceptional folic acid and a reduction in the occurrence of CLP is true (25).

A significant protection against recurrence of CLP was reported in response to supplementation with multivitamins containing a very high dose of folic acid (10 mg) in a Hungarian study (26). In contrast, no protection against the occurrence of CLP was detected in a cohort study with lower doses (800 μg) of folic acid in a multivitamin supplement (27). In addition, data from the Hungarian RCT do not support the conclusion that periconceptional use of multivitamins containing folic acid may reduce the risk for orofacial clefts (28).

Indirect evidence that the folic acid component of multivitamins taken periconceptionally reduces the risk for orofacial clefts is supported by findings from a large case-control study in which folic acid antagonists were shown to increase the risk for orofacial clefts (21). The relative risk of orofacial clefts in infants whose mothers were exposed to dihydrofolate reductase inhibitors during early pregnancy as compared with infants whose mothers had no such exposure was 2.6 (95% CI, 1.1 to 6.1). In contrast, the relative risk of orofacial clefts associated with the use of dihydrofolate reductase inhibitors with no multivitamins containing folic acid was 4.9 (95% CI, 1.5 to 16.7). These findings support the conclusion that the folic acid component of multivitamins may reduce the risk for orofacial clefts.

### MULTIPLE BIRTHS

A number of reports have suggested the possibility of a significant increase in the occurrence of multiple births among women who take multivitamins containing folic acid during early pregnancy (4–6). Since multiple births result in more pregnancy complications, are more likely to result in preterm delivery and are associated with an estimated sevenfold increase in mortality compared with singleton pregnancies (29–32), these reports warrant careful evaluation. An analysis of data from an RCT by Czeizel et al indicated a 40% increase in the number of infants resulting from multiple births among women who received multivitamins containing 800 μg folic acid compared with the number of infants resulting from multiple births of women who received only trace elements (4). In this study ovarian stimulating drugs were used by 6.5% of the women from whom 42% of the multiple pregnancies were produced. Among these women the rate of multiple pregnancies was 10.92%, 11 times higher than the rate of 1.03% among women who did not use ovarian stimulation. When women who used ovarian stimulation are excluded, and the appropriate comparison is made, the increased risk estimate is unchanged, but the statistical significance disappears [risk ratio (RR), 1.45; 95% CI, 0.78 to 2.67]. In 1997, Werler et al retrospectively analyzed data on multiple and singleton births collected from 3 separate birth defect programs and reported a nonsignificant 30% to 60% greater prevalence of periconceptional vitamin supplementation among mothers of multiple births (5). Information about supplement use in these studies was collected retrospectively by interview and did not differentiate among types of vitamin supplements used. Only 2 programs could evaluate the occurrence of multiple births among women who delivered normal infants. Among these women, those who took multivitamins any time during pregnancy showed no increase in the rates of twinning when compared with those who did not take multivitamins, both in Atlanta (OR, 0.92; 95% CI, 0.46 to 1.45) and in California (OR, 0.80; 95% CI, 0.22 to 2.82).

Recently, Ericson and colleagues described an increase in the occurrence of dizygotic twin deliveries among women reporting the use of folic acid during early pregnancy in Sweden, compared with the rate of twin births in the entire Swedish population (OR, 2.13; 95% CI, 1.64 to 2.74) (6). The overall rate of reported folic acid consumption in this study was < 1% which is markedly different from the consumption in the United States, where ~40% of women of childbearing age take multivitamins containing folic acid (33). In addition, the authors state that their results were highly confounded by increasing maternal age and the length of involuntary childlessness, which raises questions about whether most of the women who reported folic acid use in this study were also using assisted reproductive technologies.

If the occurrence of multiple births were influenced by consumption of folic acid, the effect might be expected to be greater with increasing folic acid dose; however, this has not been observed. In 1999, Mathews et al analyzed data from the United Kingdom Medical Research Council (MRC) Vitamin Study (1) in which women consumed a multivitamin containing 4000 μg folic acid per day and did not detect a significant difference in the rates of multiple birth between supplemented and unsupplemented women (34).

Most of the reports suggesting that the periconceptional use of multivitamins containing folic acid increased the occurrence of multiple births have focused on the use of folic acid as the purported cause of the increase despite the fact that most women in these studies took folic acid combined with multivitamins, not folic acid alone. For example, the multivitamins taken by women in the Hungarian study (4) contained 10 other components, including 4000–6000 international units (IU) of vitamin A, which has been reported to be associated with an increased rate of twin births in a randomized controlled trial in Nepal (35, 36).

Evaluation of data from a large-scale (~250,000 women) intervention study in China where women took 400 μg/d of folic acid daily before and during early pregnancy to prevent NTDs (3) provides strong evidence that periconceptional folic acid use does not increase the occurrence of multiple births (37). Overall, the rate of multiple births was not different among women who took folic acid daily compared with those who did not (0.59% and 0.65%, respectively). This study has important strengths including the fact that the results were not confounded by other factors that may have increased occurrence of multiple births. For example, other studies have been conducted in populations where the rates of multiple births may have been affected by increasing maternal age and the use of ovarian stimulation or assisted reproductive technologies (4, 6). In the China study, the study population comprised a cohort of young women, most of whom were experiencing their first pregnancy, and in whom the treatment for subfertility was extremely low. For this reason, the young Chinese women represented an excellent group for studying the occurrence of multiple births because it was not necessary to control for the presence of these factors. Another strength of the China study was that precise records of supplement-taking were collected prospectively, before the outcome of pregnancy was known, minimizing the potential for recall bias. Possibly the most important aspect of this study was that unlike others, the women consumed a supplement containing only 400 μg of folic acid. This large population-based study provided strong evidence that consumption of 400 μg of folic acid alone before and
during early pregnancy did not increase a woman’s likelihood of having a multiple birth.

In the United States, the rate of multiple births has been recently evaluated before and following the mandatory introduction of folic acid fortification in 1998. After adjusting for both increasing maternal age and use of assisted reproductive technology, no evidence that multiple births have increased since the start of folic acid fortification was detected (38–40).

MISCARRIAGE

In 1997, Hook and Czeizel analyzed data from the Hungarian RCT (2) and concluded that periconceptional use of a multivitamin containing 800 μg folic acid was associated with a significant 16% increase in miscarriage rates compared with women who received trace elements (7). In addition, these investigators analyzed data from the MRC (1) study including all women assigned periconceptional folic acid treatment (4000 μg) and reported a nonsignificant 15% increase in miscarriage rates (7). Based on an analysis of these data by MRC study researchers including only data from women who became pregnant, there was no association between periconceptional folic acid supplementation and an increase in miscarriage rates (RR, 1.06; 95% CI, 0.79 to 1.43, P = 0.70) (41). More recently, Windham et al (8) reported that data from a prospective study of women in California interviewed during their first trimester of pregnancy supported the conclusion of Hook and Czeizel (7) that periconceptional vitamins increased the occurrence of miscarriage. In this study, a nonsignificant increase in the occurrence of miscarriage among women who took vitamins during the prenatal period (RR, 1.14; 95% CI, 0.96 to 1.35) was observed and attributed to periconceptional folic acid use although the supplements taken were a mixture of vitamins not folic acid alone (8). Other investigators, however, disagreed that this report provided evidence that folic acid increased the occurrence of miscarriage (42).

Data from a large-scale folic-acid intervention study conducted in China provided strong evidence that periconceptional folic acid use does not increase miscarriage rates (43). In this study, the miscarriage rate was 9.0% for women who took folic acid alone (400 μg) and 9.3% for women who did not take folic acid during early pregnancy (RR, 0.97; 95% CI, 0.84 to 1.12). The strengths of this study include the fact that the investigation was larger than all of the previous studies combined (6, 8); the study population was confined to women who were registered in the program before they became pregnant for the first time (avoiding confounding by previous miscarriages); supplement-taking data were obtained during pregnancy (avoiding recall bias); and supplements contained folic acid alone.

The association between folate status and the occurrence of miscarriage was further evaluated in a recent large PCC study in Sweden (44). Cases were women who had spontaneously aborted a fetus with a gestational age of 6–12 wk and controls were women matched for gestational age of the fetus. Women with low plasma folate concentrations (≤4.9 nmol/L) were more likely to have had a miscarriage than women with plasma folate concentrations between 5.0 and 8.9 nmol/L. The occurrence of miscarriage was not increased in women with higher plasma folate concentrations (≥14.0 nmol/L) relative to women with plasma folate concentrations between 5.0 and 8.9 nmol/L. Supplement use was not associated with an increased occurrence of miscarriage. A major strength of this study was the adjustment for confounders (eg, maternal age, cigarette smoking, previous miscarriages) providing data that further supports the conclusion that a folate deficiency significantly increases the occurrence of miscarriage as previous studies had suggested (45–47).

APPLICATION AND FUTURE DIRECTION

Research findings to date suggest that periconceptional use of multivitamins containing folic acid is associated with a reduction in the occurrence of congenital heart defects and a possible reduced occurrence of orofacial clefts, although the data are less convincing for orofacial clefts. Efforts to draw definitive conclusions from these studies are hampered by the difficulties in interpreting and drawing conclusions due to heterogeneity between studies including factors such as classification of the types of defects and variation in exposure to numerous environmental factors, including maternal use of multivitamins containing folic acid (11, 18). The evolution of science related to folic acid and NTD risk reduction required the careful evaluation of similar types of complex and often conflicting data (48). Resolution of the NTD/folic acid controversy was a direct result of RCTs, which highlights the need for similar large well-designed studies to specifically address whether maternal periconceptional use of other vitamins or higher doses of folic acid will reduce the occurrence of other congenital anomalies, and, if so, whether the protective effect of folic acid is limited to specific types of defects. Collaborative multidisciplinary research endeavors that address the complexities of these research issues are needed before definitive public health recommendations can be implemented (11).

The appropriate medical advice is that all women capable of becoming pregnant should consume 400 μg/d of synthetic folic acid in addition to a healthy diet (49). Although NTD risk reduction is the goal of this existing public health recommendation, if future research confirms that periconceptional folic acid supplementation also reduces the risk for other birth defects, this would augment the benefit to a proven effective way to prevent infant mortality and disability (18). It is reassuring that data do not support the reports that folic acid supplements increase the occurrence of miscarriage or multiple births because women of childbearing age in many countries are advised to take folic acid supplements daily to prevent NTDs. Women of reproductive age and their health care providers can support the periconceptional folic acid supplementation policy without concern that this practice will increase the occurrence of multiple births or miscarriages.

The authors have no conflict of interest.

REFERENCES