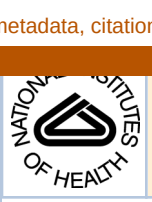

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Periconceptional use of folic acid and risk of miscarriage – Findings of Oral Cleft Prevention Program in Brazil

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Abstract

We report on the risk of miscarriage due to high dosage periconceptional folic acid (FA) supplementation from a double blind randomized clinical trial for prevention of orofacial clefts in Brazil. The miscarriage rate was 14.2% in the low dose FA group (0.4 mg per day) and 11.3% for the high dose (4 mg per day) group (p=0.4877); the population miscarriage rate is 14%. These results indicate that high dose FA does not increase miscarriage risk in this population and add further information to the literature on the safety of high FA supplementation for prevention of birth defect recurrence.

Keywords

risk of miscarriage; folic acid supplementation; orofacial clefts

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Disclosure of interests

The authors have no conflicts of interest to declare.

Contribution to authorship

JCM and GLW developed the concept and study design. The data was gathered by CVN, FQ, TMF, LL, and CP. CVN, GLW, and FQ were responsible for the overall drafting of the article. HC and GLW conducted the analysis and contributed to the interpretation of the data along with JM, CVN, FQ, NG, EV, and CP. All authors had final approval of the article to be published.

Details of ethics approval

The study was approved by the Brazilian National Council of ethics in research (Comissão Nacional de Ética em Pesquisa – CONEP) on September 20, 2001 (ref. no. 1130/2001).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Maternal characteristics by Treatment.

Introduction

Periconceptional use of folic acid (FA) is well known to reduce the occurrence and recurrence risk of Neural Tube Defects (NTDs). NTDs are common and burdensome congenital malformations that occur during the development of the neural tube until the first 28 days after conception. FA supplementation is recommended worldwide for prevention of NTD occurrence. The World Health Organization (WHO) recommends that women of reproductive age regularly take FA supplements.[1] Some studies have suggested that periconceptional use of FA may also prevent other common congenital anomalies such as occurrence of orofacial clefts (OFC) at low doses and recurrence at higher doses.[2] OFC are widely considered the most common birth defects affecting about 1 infant per 700 live births worldwide with incidence varying by ancestry, socioeconomic status, and demographic region.[3]

In parallel to the evidence on preventive effects, some studies have raised concerns about the safety of FA supplementation including an increased risk of miscarriage.[1] Even though many studies find no increased miscarriage risk, the literature may still be considered mixed on this topic particularly for high FA doses, requiring further investigation.[1,4] Specifically, there is still limited knowledge about the effects of FA doses ≥1.0 mg per day on miscarriage rates as most studies of FA supplementation involved low doses (<1.0 mg per day).[1]

We had been conducting a double blind randomized clinical trial, the Oral Cleft Prevention Program (OCPP), designed to investigate the effect of high versus low dose FA on preventing the recurrence of OFC in a Brazilian population. The treatment involved FA supplementation during the pre-conceptional period until the end of the first trimester of gestation at a dose of 4.0 mg per day compared to a control group taking 0.4mg per day during the same period. The study participants included women at risk for recurrence of non-syndromic OFC (i.e. without other birth defects) who had OFC themselves or have had a child with OFC. This study provides a unique setting to evaluate the effects of high-dose FA supplementation on miscarriages based on a randomized design. Most previous studies of FA effects on miscarriages were based on non-randomized designs that may suffer from confounding. Therefore, given its double blinded randomized design, our study provides strengths over most previous studies. In this paper, we report on the miscarriage risks in the high and low FA supplementation groups in the OCPP.

Methods

The OCPP was conducted in six different sites in Brazil in the cities of Bauru, Curitiba, Lajeado, Porto Alegre, Recife, and Salvador, between 2001 and 2010. Each site was part of a center that provides comprehensive care to patients with OFC including surgery, speech therapy, dental care, and other needed treatments. These sites were chosen because they are referral centers for patients with OFC in Brazil. Subjects were women 16 to 45 years of age who were themselves affected with non-syndromic OFC or have had a previous child with non-syndromic OFC and who have attended the study centers for their own or their children's treatment. Exclusion criteria were: permanent sterilization; history of epilepsy/seizure and use or antiepileptic drugs; syndromic OFC; planning to move outside of the study state; consanguineous couples; pregnancy at baseline; and B12 level < 174 pg/ml. Women were enrolled regardless of whether they were planning on having a child in the future or not. Study subjects were randomized into two groups: low FA dose of 0.4 mg per day, and high FA dose of 4.0 mg per day. A low dose FA supplementation was used as the control group instead of a placebo-control group given the established evidence that low dose FA reduces NTD occurrence. After screening for eligibility, qualified subjects provided

consent and were randomized. The 0.4 and 4.0mg study pills were identical in shape and color. The investigators and subjects were blinded to the group assignment. The protocol was approved by the local Institutional Review Board (IRB) of all sites, the National Committee in ethical research in Brazil, and the University of Iowa IRB.

After randomization, subjects were asked to take one FA pill per day beginning at enrollment and continuing until the end of the first trimester of pregnancy. Every two months, and until the end of their participation in the study, participants were followed-up either in person or by phone to gather information about pregnancy occurrence and health status. Compliance with the intervention was based on counting returned pills or on self-reports of used pills when unused pillboxes were not returned. The sample for the analysis presented here included all women who became pregnant during their participation in the OCPP and who were followed to evaluate the pregnancy outcome. Pregnancy was reported by subjects and was confirmed by the study as needed using pregnancy tests. Pregnant women were followed bimonthly to inquire about healthy conditions and pregnancy progress and for pillbox dispensing. Miscarriage was recorded based on subjects' self-report of spontaneous abortion at/before 20 weeks of gestation and confirmed in most cases through an interview with the subject's healthcare provider. Women who delivered a live born child were interviewed by the study staff in person with the child. Data were collected at each site using the same questionnaires and study procedures. All data were transmitted regularly to the study's Data Coordinating Center (DCC) at the Research Triangle Institute (RTI) International (North Carolina, USA), which maintained the data. The study was also monitored by a Data Safety and Management Board (DSMB) involving experts in perinatology, medicine, and statistics selected by the National Institute of Dental and Craniofacial Research.

We compared miscarriage rates between the two FA groups using a Fisher's exact test in order to test the hypothesis that miscarriage rate did not vary between the two FA doses. We also compared the miscarriage rates in each sample to the Brazilian population miscarriage rate of 14% using a one sample proportion test. We compared the mean of gestational age at miscarriage between the two FA groups for the subset that had a miscarriage using a t-test. All null hypotheses were tested at a 0.05 level of significance. We used the software SAS 9.2 to perform statistical analyses.

Results

Of 273 pregnancies in the study, 268 completed the study protocol: 141 in the 4.0 mg group and 127 in the 0.4 mg group. There were 5 lost-to-follow-up pregnancies (1.8%) because of address and telephone number changes. Given the randomized design of the study, there were no statistically significant differences between the two FA groups in baseline characteristics that have been associated with miscarriage risk in previous studies such as alcohol consumption, cigarette smoking, maternal age, marital status, education, employment, parity, multivitamin use, and frequency of gynecological visits. Detailed descriptive statistics for these characteristics are reported in supplementary Table S1. Also, use of multivitamin during pregnancy and baseline levels of vitamin B12, serum and red blood cells folate did not differ between the two groups. Compliance with the study pills was overall comparable between the two FA groups; average compliance was 72.5 (SD = 28.2) in the 0.4 mg group and 79.6 (SD=34.0) in the 4.0 mg group (p=0.0681).

Table 1 shows the miscarriage rates in the two FA groups. From a total of 268 pregnancies, 34 (12.7%) ended in a miscarriage. Occurrence of miscarriage did not differ statistically between the FA groups; miscarriage rate was 14.2% (18/127) in the 0.4 mg group and 11.3% (16/141) in the 4.0 mg FA group (p=0.4877). Also, these miscarriage rates are not

significantly different from the miscarriage rate in the Brazilian population, estimated to be around 14% (p=0.311) for the 4 mg FA group and 0.949 for the 0.4 mg FA group.[5] The mean gestational age at miscarriage was 11.2 (SD =5.1) weeks for the 0.4 mg group and 8.6 (SD=3.1) weeks for the 4.0 mg group; the difference was not statistically significant (p=0.0963). As described in the literature, we observed that more than three quarters of miscarriages in both study groups occurred at the first trimester of pregnancy. However, occurrence of miscarriage in the first trimester of pregnancy did not differ statistically between groups; first trimester miscarriage rate was 11.0 % (14/127) in the 0.4 mg group and 10.0% in 4.0 mg group (p=0.7851).

Discussion

This study suggests no association between FA supplementation in high or low doses before and during first trimester of pregnancy and miscarriage risk. The observed miscarriage rates were not significantly different between the two FA groups and from the miscarriage rate of 14% observed in the Brazilian population.[5] Our study results are consistent with and complement the findings of several previous studies. For instance, Czeizel *et al.* (1994) found no significant difference in miscarriage rates between periconceptional multivitamin supplementation (including 0.8 mg FA) and placebo groups (10.8% versus 9.4%, respectively) in a randomized study of about 5,502 pregnancies.[4] Also, there was no statistically significant difference in miscarriage rates in a large study comparing 0.4 mg FA supplementation versus no supplementation in China (9.0 % and 9.3%).[6] The OCPP's randomized design significantly reduces the chance of confounding due to unobserved characteristics between women in the two FA groups as previously highlighted. Despite the small sample, there was no trend for a higher miscarriage risk with supplementation with a high dose of FA. Using 4.0 mg of FA per day during periconceptional period has been demonstrated to reduce the recurrence of NTDs. Our study suggests that this dose does not affect miscarriage rates. Such high doses have also been suggested for preventing OFC recurrence, although there is no evidence yet from a double-blinded randomized design. Our study suggests no concern for elevated miscarriage rates in future studies of the effectiveness of 4.0 mg FA per day in preventing the recurrence of birth defects.

Conclusion

We found that high dosage of periconceptional FA supplementation (4.0 mg per day) did not increase miscarriage risk compared to low dosage (0.4 mg), and that miscarriage rates in either group were not different from the population rate of miscarriages. As a whole, the results suggest that high dosage FA can be used to prevent the recurrence of NTDs in clinical practice and tested for its effectiveness in preventing OFC recurrence without concern about increased miscarriage risks. Obviously, FA in both low and high doses may affect other aspects of pregnancy and fetal health, which require further studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Miscarriage status by Treatment.

Variable	Folic Acid Group		Total	P-Value
	0.4 mg N=127	4.0 mg N=141	N=268	
Miscarriage	127	141	268	0.4877
Yes	18 (14.2)	16 (11.3)	34 (12.7)	
No	109 (85.8)	125 (88.7)	234 (87.3)	
Gestational Age				
N	18	15	33	
Mean (Std)	11.2 (5.1)	8.6 (3.1)	10.0 (4.4)	0.0963
Compliance				
N	18	15	33	
Mean (Std)	76.0 (27.0)	77.5 (13.2)	76.7 (21.6)	0.8428
First Trimester Miscarriage	127	140	267	0.7851
Yes	14 (11.0)	14 (10.0)	28 (10.5)	
No	113 (89.0)	126 (90.0)	239 (89.5)	
Gestational Age				
N	14	14	28	
Mean (Std)	9.1 (2.8)	8.1 (2.4)	8.6 (2.6)	0.3237
Compliance				
N	14	13	27	
Mean (Std)	74.9 (29.9)	78.7 (12.6)	76.7 (22.9)	0.6715

Table 2

Miscarriage status by Treatment.

Variable	Folic Acid Group			
	0.4 mg N=127	4.0 mg N=141	Total N=268	P-Value
Miscarriage	127	141	268	0.4877
Yes	18 (14.2)	16 (11.3)	34 (12.7)	
No	109 (85.8)	125 (88.7)	234 (87.3)	
Gestational Age				
N	18	15	33	
Mean (Std)	11.2 (5.1)	8.6 (3.1)	10.0 (4.4)	0.0963
Compliance				
N	18	15	33	
Mean (Std)	76.0 (27.0)	77.5 (13.2)	76.7 (21.6)	0.8428
First Trimester Miscarriage	127	140	267	0.7851
Yes	14 (11.0)	14 (10.0)	28 (10.5)	
No	113 (89.0)	126 (90.0)	239 (89.5)	
Gestational Age				
N	14	14	28	
Mean (Std)	9.1 (2.8)	8.1 (2.4)	8.6 (2.6)	0.3237
Compliance				
N	14	13	27	
Mean (Std)	74.9 (29.9)	78.7 (12.6)	76.7 (22.9)	0.6715

Note: P-values computed using a Chi-square or Fisher's Exact Test for categorical variables and a T-Test for continuous variables.