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Evaluation of the safety of different doses of folic acid supplements in women in Brazil

ABSTRACT

OBJECTIVE: To evaluate the distribution of folic acid intake and the safety of different doses of supplements in women of childbearing age.

METHODS: Data were used from two non-consecutive days of food records of 6,837 women of childbearing age (19-40 years old) participants of the National Food Survey, a module of the Household Budget Survey 2008-2009. Means and percentiles of usual consumption of natural folate and folic acid were estimated using the National Cancer Institute method. Five scenarios were simulated by adding different daily doses of fortification (400 mcg, 500 mcg, 600 mcg, 700 mcg and 800 mcg) to folic acid derived from food consumed by the women. To define a safe dose of the supplement, the total folate (dietary + supplement) was compared with the tolerable upper intake level (UL = 1,000 mcg).

RESULTS: Women with usual intake of folic acid above the tolerable upper intake levels were observed only for doses of supplement of 800 mcg (7.0% of women). Below this value, any dose of the supplement was safe.

CONCLUSIONS: The use of supplements of up to 700 mcg of folic acid was shown to be safe.

DESCRIPTORS: Women. Folic Acid, administration & dosage. Dietary Supplements, utilization. Nutrition Surveys, utilization.

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INTRODUCTION

Folate is the generic name for the B-complex vitamin, which occurs naturally in leafy green vegetables, legumes, citrus fruit, liver and other meat. Folic acid is the synthetic form of the vitamin used in vitamin supplements and to fortify food items.[11] Adequate folic acid intake is a component of pre-pregnancy care in women of childbearing age. Deficiency may increase the risk of neural tube defects (NTD),[20] serious congenital birth defects involving part of the neural tube not closing completely, which occur in the third or fourth week of pregnancy (between the 26th and 28th day), often before the woman even knows she is pregnant.[13]

Fertile women of childbearing age should consume at least 400 mcg of folic acid per day, either in the form of fortified food items or supplements, or both, in addition to folate obtained in an ordinary diet.[16,17] In view of limited adhesion to taking supplements on the part of women of childbearing age (between 30.0% and 47.0% in American women and from 0.5% to 52.0% in women worldwide),[5,19] it was proposed that food items be fortified to prevent neural tube closure defects.[1] Around 53 countries worldwide have laws making it obligatory to fortify wheat flour with folic acid.[6] In June 2004, the Brazilian Government introduced a law obliging wheat and corn flour to be fortified with 150 µg of folic acid/100g.[a]

A review of 13 studies showed that intake of folic acid supplements of 400 mcg/day reduced the risk of NTD by around 36.0%, whereas an intake of 1 mg/day reduced the risk by 57.0% and a 5mg pill taken daily reduced the risk by 85.0%, although the latter concentration is above the daily tolerable upper intake level (UL) of folic acid (1,000 mcg/day).[24] The UL is the highest possible daily intake of a nutrient, above which it has adverse health effects. It is defined as the absolute value of usual folic acid intake from fortified foods items and supplements and is expressed in mcg of folic acid/day. Intake of foods that are sources of natural folate is not counted in the calculation of the UL.[11]

Over the last two decades, concern has grown over possible intake of folic acid in quantities above the tolerable upper intake level.[12] Excessive intake of folic acid appears to accelerate the progression of existing, undiagnosed pre-cancerous lesions, as well as possibly masking vitamin B12 deficiency anemia.[7,22]

This study aimed to assess the distribution of folic acid intake and the safety of different doses of the supplement in women of childbearing age. The simulation of different scenarios aimed to determine safe doses of this supplement, without going over the tolerable upper intake level.

METHODS

Data were taken from the *Inquérito Nacional de Alimentação* (INA – National Food Survey), part of the *Pesquisa de Orçamentos Familiares* (POF – Household Budget Survey), 2008-2009, carried out by the Brazilian Institute of Geography and Statistics (IBGE).[b]

A two-stage cluster sampling plan was adopted for the POF 2008-2009.[b] Census tracts that were stratified by geography and by mean head of household income were chosen in the first stage. These tracts were selected for sampling with a probability proportional to the number of residents in each, corresponding to the geographically based sectors in the 2000 Demographic Census. The sampling units in the second stage were permanent private residences, randomly selected, without replacement, within each of the tracts. Data collection took place in all of the geographical tracts of the study over a 12-month-period.

There were 68,373 residences selected for the POF 2008-2009. The subsample for the INA was initially calculated as 25.0% of the residences sampled for the POF 2008-2009 (16,764 residences). There were 13,569 residences that responded to the study, corresponding to 33,004 individuals aged > 10. The no response rate for women in the age group in this study was 4.7%, which can be considered low. Details on the sampling and data collection are available from the IBGE.[b]

This analysis includes data on the food intake of 6,837 women of childbearing age in Brazil, in the 19 to 40 years old age group.

Food intake was collected using food records from two non-consecutive day, in which the individual recorded all food and drink consumed on a particular day, including a description of the time and quantities consumed and the method of preparation.

Tables of nutritional composition and portion sizes compiled specifically for analyzing the food items and dishes cited in the POF 2008-2009[b] were used to calculate the nutritional value of each food item consumed. The Nutrition Data System for Research from the University of Minnesota (NDSR, 2003),[c] was used in the analysis of folate intake, correcting

[a] Brasil. Resolução RDC nº 344, de 13 de dezembro de 2002. Aprova o regulamento técnico para fortificação das farinhas de trigo e das farinhas de milho com ferro e ácido fólico. *Diario Oficial da Uniao.* 18 dez 2002;Seção 1:58.
[b] Instituto Brasileiro de Geografia e Estatística. Pesquisa de Orçamentos Familiares, 2008-2009. Análise do Consumo Alimentar Pessoal no Brasil. Rio de Janeiro; 2011.
[c] University of Minnesota. Nutrition Coordinating Center. Nutrition data system for research-NDSR. Minneapolis; 2003 [cited 2012 Dec 1]. Available from: http://www.ncc.umn.edu/products/ndsr.html

the figure of 140 mcg of folic acid /100 g of wheat and corn flour (the figure used in the United States) for 150 mcg/100 g of wheat and corn flour, as is the case in Brazil.

For data quality control, partial analyses were carried out during the data collection, verifying response frequency, mean of the items consumed on the first and second day of the food record, codification of non-registered items and analysis of items not appropriately included, among others.

Details on the pretest, training, validation of the data collection instrument and data input are available from the IBGE.[b]

The distribution of intake was assessed using the National Cancer Institute method,[21] which corrects for intra-personal variation and estimates percentiles of typical consumption.

Means of intake, percentiles of distribution of usual folic acid and natural folate intake and the prevalence of inadequate folate intake were calculated for the women of childbearing age. The Estimated Average Requirement method (EAR)[11] was used as the cutoff point when calculating inadequate folate intake. The 95% confidence intervals for the means were calculated based on estimated standard error using the Balanced Repeated Replication technique with Barbosa's modification.[3]

Simulations of five scenarios in which different concentrations of folic acid supplement were added to the folic acid from the women's diet were carried out. The five scenarios were the following 1) 400 mcg of folic acid per day, as recommended by the Institute of Medicine;[11] 2) 500 mcg/day; 3) 600 mcg/day; 4) 700 mcg/day; and 5) 800 mcg/day. Safe supplement was defined as that in which none of the women ingested more than 1,000 mcg/day, the UL.

The most natural folate dense foods consumed by the women in the POF were listed in order to document the difficulty in meeting the recommended level of folic acid intake through food alone. A separate scenario was simulated using these reported foods.

The analyses were carried out using the Statistical Analysis System program (SAS), version 9.1, taking into consideration the expansion of the sample and the complex sampling design.

The research was approved by the Ethics Committee of the *Instituto de Medicina Social* (CAAE – Process no. 0011.0.259.000-11), of the *Universidade do Estado do Rio de Janeiro.*

RESULTS

The mean intakes, distribution percentiles of usual natural folate and folic acid intake for the women of childbearing age in the study can be found in the Table. The prevalence of inadequate folate intake was 40.0% (around 2,735 women did not meet the recommended EAR).

The 800 mcg supplement, in the percentiles above the 90th percentile, was over the tolerable upper intake level. The other supplements proved to be safe and did not exceed the UL (Figure).

In order for women of childbearing age to achieve the recommended additional intake of 400 mcg of folate via food, it would be necessary to include for example: three soup spoons of broccoli + three soup spoons of spinach + half a papaya + one glass (250 ml) of orange juice + one large guava + three soup spoons of cooked chicory + three soup spoons of raw beetroot + three soup spoons of raw *couve* (a cabbage-like leafy vegetable) + two small kiwis + two soup spoons of lentils in their daily diet. These foods give 900 mcg of natural folate.

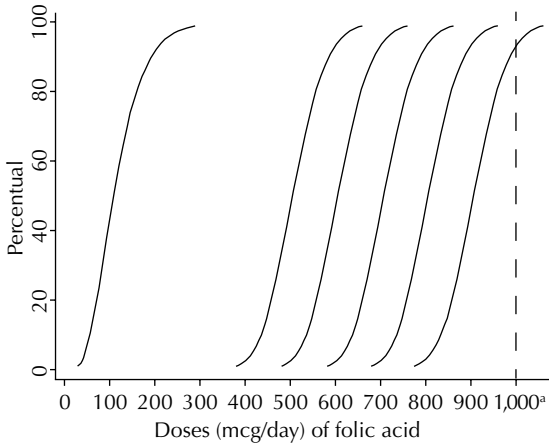
DISCUSSION

The simulations of the scenarios showed that taking supplements up to a concentration of 700 mcg does not exceed the UL.

Supplements are an essential means of preventing neural tube defects NTD. It is almost impossible for women of childbearing age to achieve the recommended additional folate intake only from 100.0% food sources of natural folate, as these women would need to drastically increase

Table. Mean, 95% confidence interval and percentiles of distribution for normal natural folate and folic acid intake in women of childbearing age. Brazil, 2008 to 2009.

Variable	Percentiles of normal intake							
	Mean (mcg/day)	5	10	25	50	75	90	95
Natural folate	195.0 190.5;199.5	86.1	102.6	135.3	181.3	239.4	305.0	351.3
Folic acid	115.7 110.2;121.2	43.9	54.3	75.7	106.3	145.5	189.0	218.8



[a] tolerable upper intake level

Figure. Simulation of the distribution of folic acid intake using different doses of supplement (in mcg/day) in women of childbearing age. Brazil, 2008 to 2009.

their intake of fruit, vegetables, legumes and pulses in their diet. The absorption of natural folate is not as efficient as that of folic acid.[11] Even taking into account the intake of fortified food products, the recommended level is not reached in Brazil.

There is no consensus concerning the correct daily dose of folic acid needed to prevent NTD.[4] The current recommendation of the US Institute of Medicine of 400 mcg of folic acid per day, adopted in various countries, appears to be sufficient to achieve the optimum cellular concentration of folate after at least eight to 12 weeks of daily intake.[15] On the other hand, with a supplement of 800 mcg of folic acid per day, the optimum cellular concentration of folate is reached, on average, four weeks after beginning to take the supplement.[d]

There has been much discussion on the role of folic acid in cancer incidence. Four of five recent meta-analyses of randomized clinical trials[9,18,23,25] showed that taking folic acid supplements had no significant effect on the incidence of any type of cancer from three to five years of treatment (the doses varied from 0.5 mg to 40 mg of folic acid/day). Incidence of cancer in six randomized clinical trials were analyzed in another meta-analysis and it was observed that the incidence of cancer was higher in the group taking supplements than in the group that did not take them.[2] Folic acid participates in a series of reactions within the organism, including DNA synthesis and the process of cell division.[11] High consumption of folic acid may stimulate the growth and division of all cells, healthy and otherwise. Folic acid supplements may intensify the progress and growth of pre-cancerous cells and subclinical cancers, common in the population.[14]

Although a dose of 700 mcg may encourage the optimum cellular concentration of folate in less time and without exceeding the UL, there is not sufficient information on long term harmful effects. A cautious recommendation would be to use 700 mcg doses in cases of planned pregnancy (beginning to take the supplement four weeks before conception). The recommendation of 400 mcg per day for women of childbearing age should be maintained.

Not all cases of NTD are preventable by increasing folate consumption. NTD are, from an etiological and pathological point of view, a heterogeneous group of congenital deformities and it is probable that not all cases could be avoided even with large doses of folic acid.[11] The relative decrease depends on the initial number of NTD. With greater decreases in population groups with higher prevalence at the baseline. In a systematic review, which assessed the beneficial effects of different levels of folic acid on the prevalence of NTD, it was concluded that, irrespective of the number of cases before taking supplements began, all of the groups in the study showed a residual prevalence of around five cases of NTD per 10,000 births.[16] Data from the Brazilian public health system – *Sistema Único de Saúde* database (DATASUS)[e] indicate that, between 2004 (when fortifying of flour began) and 2006 (post-fortifying), there was a decrease of around 23.5% in the prevalence of NTD and a 39.0% decrease in the prevalence of Spina bifida in particular. However, there was a slight increase in the prevalence of NTD from 2006 until 2009, before becoming relatively stable in 2010, with a mean 8.8 NTD cases per 10,000 births. This shows that the mandatory fortifying of flour led to a slight decrease in NTD, although not sufficient for Brazil to achieve the so-called "floor effect", of five cases of NTD per 10,000 births.[10] It is necessary to search for actions that will decrease the prevalence of such anomalies in this country.

One alternative for lowering the number of NTD cases in Brazil would be to create a program of folic acid supplements specifically for women of childbearing age. What currently exists is the National Iron Supplement Program, from the Brazilian Ministry of Health, which encourages pregnant women to take iron (60 mg) and folic acid (5 mg) supplements in order to reduce anemia. This program does not include reducing NDT as it includes pregnant women from 20 weeks onwards, by which time the neural tube has already closed, and therefore missing the possible protective effect of folic acid. The pregnant women are provided

[d] Pietrzik K, Prinz-Langenohl R, Lamers Y, Wintergerst ES, Bramswig S. Randomized, placebo-controlled, doubleblind study evaluating the effectiveness of a folic acid containing multivitamin supplement in increasing erythrocyte folate levels in young women of child-bearing age. In: Poster at the 18th International Nutrition Congress, Durban, South Africa; 2005.

[e] Ministério da Saúde. Departamento de Informática do SUS. Brasília (DF); 2011 [cited 2013 Jan 10]. Available from: http://www.datasus.gov.br

with high levels (5 mg) of folic acid (five times the UL). Thus, pregnant women benefitting from this program are at risk of exposure to excessive concentrations of folic acid for a relatively long period (from week 20 of the pregnancy to the 3rd month after the birth).

Additional strategies for reducing the prevalence of these anomalies include family planning. Including family planning campaigns in public health care service routines could avoid the high number of pregnancies in which the mother is unaware of conception, enabling them to start taking supplements before pregnancy and during maternity. This measure would prevent folic acid deficiencies during the most critical period of embryogenesis.

The limitations of this study are the same as those of any study based on reported data on consumption, in particular, underreporting of intake. There are not, however, any biomarkers of folic acid intake capable of estimating what the underreporting in the population might be. Even with a high percentage of underreporting, the absolute value would not be significant for the study's conclusions, given the population's low dietary folate intake.

In Brazil, the use of supplements of up to 700 mcg of folic acid, together with intake of folic acid and natural folate from food, was shown to be safe in the pre-conception period. The use of supplements of this dosage should be restricted to this period in order to prevent possible adverse effects from long term use.

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