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Effects of folic acid fortification on the prevalence of neural tube defects

ABSTRACT

OBJECTIVE: To analyze the effect of folic acid-fortified foods on the prevalence of neural tube defects in live newborns.

METHODS: Longitudinal study with newborns from the city of Recife, Northeastern Brazil, between 2000 and 2006. Data analyzed were obtained from the *Sistema Nacional de Informações de Nascidos Vivos* (National Information System on Live Births). Neural tube defects were defined in accordance with the International Classification of Diseases, 10th revision (ICD-10): anencephaly, encephalocele, and spina bifida. Prevalences from the periods before (2000-2004) and after (2005-2006) the mandatory fortification period were compared. Time trend of three-month prevalences of neural tube defects were analyzed using Mann-Kendall test and Sen's Slope estimator.

RESULTS: Tendency towards reduction in the occurrence of outcome (Mann-Kendall test; p= 0.270; Sen's Slope estimator =-0.008) was not identified in the period studied. The difference between prevalences of neural tube defects in the periods before and after food fortification with folic acid was not statistically significant, according to maternal characteristics.

CONCLUSIONS: Even though reduction in neural tube defects after the period of mandatory food fortification with folic acid was not observed, results found do not enable its benefit to prevent malformations to be ruled out. Studies assessing longer periods and considering the level of consumption of fortified products by women of fertile age are necessary.

DESCRIPTORS: Foods for Pregnants and Breastfeeding Mothers. Food, Fortified. Folic Acid. Neural Tube Defects, prevention & control. Prenatal Nutrition. Evaluation of Results of Preventive Actions.

INTRODUCTION

Neural tube defects (NTD) are congenital malformations resulting from the neural tube closing incorrectly or incompletely between the third and fourth week of embryonic development, and comprising anencephaly, encephalocele, and spina bifida.[3,19]

Even though prevalence of these congenital defects varies according to the period in time and area, it is usually 1/1,000 live births,[1] with anencephaly and spina bifida cases predominating.[1,9,11] In Brazil, this rate is estimated to vary around 1.6/1,000 live births,[15] even though publications on this problem are still scarce.[19]

Etiology of neural tube defects has not been clarified yet, with multifactorial inheritance resulting from the interaction between genetic and environmental

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factors being considered.[1,3] The most studied genes involved in this malformation are associated with the folic acid metabolism,[3] particularly one mutation of the 5,10 metylenetetrahydrofolate reductase gene.[1,3] The following are among maternal risk factors for this anomaly: diabetes mellitus,[7] use of valproic acid during pregnancy,[5] maternal obesity,[18] hyperthermia,[14] and folic acid deficiency.[4]

Studies report the importance of folic acid to prevent NTDs, despite its functioning being little understood yet.[3] Indications of reduction of about 50% to 70%[4,8] in the occurrence of such congenital defects after periconception supplementation with this nutrient have led several health organizations to recommend its use.[4,8] In 1992, the Centers for Disease Control and Prevention (CDC) recommended the daily intake (between three months before conception and the first trimester of pregnancy) of 0.4 mg of folic acid to women of fertile age to prevent the first NTD occurrence, and of 4.0 mg to reduce the risk of recurrence.[8] In 2000, the Institute of Medicine of the National Academies, in the United States, established a dose of 0.4 g/day for adult non-pregnant women and 0.6 mg/day for pregnant women.[8] In Brazil, the *Agência Nacional de Vigilância Sanitária* (ANVISA – National Health Surveillance Agency), in its most recent publication,[a] increased the nutritional recommendations for daily intake of folic acid, as proposed by the Institute of Medicine of the National Academies.[8]

Aiming to guarantee broad coverage of the folic acid supplementation strategy in the population of pregnant women, 40 countries[19] established the folic acid fortification measure for foods consumed in great amounts to prevent NTD occurrence. Study performed in 45 US states and Washington, DC,[11] showed a 19% reduction in the occurrence of neural tube defects after the measure was established. On Newfoundland Island, Canada, a 78% reduction in NTD was observed after the mandatory folic acid fortification period.[12] In Brazil, the ANVISA made it mandatory to fortify wheat and corn flour with 150 mcg/100 g of folic acid, beginning in June 2004,[19,b] as recommended by the Pan American Health Organization (PAHO). However, there are no studies assessing the effectiveness of such measure on NTD prevalence in the country.

The present study aimed to analyze the effect of folic acid-fortified foods on the NTD prevalence in live newborns.

METHODS

A total of 161,341 live newborns were analyzed between 2000 and 2006. Their mothers lived in the city of Recife, Northeastern Brazil. Data analyzed were obtained from the *Sistema Nacional de Informações de Nascidos Vivos* (SINASC – National Information System on Live Births), which were made available by the City of Recife Department of Health.

Neural tube defects were defined in accordance with the International Classification of Diseases (ICD-10), corresponding to anencephaly (Q00.0), encephalocele (Q01) and spina bifida (Q05). NTD prevalence was analyzed according to maternal sociodemographic characteristics, number of pre-natal consultations, type of delivery, and gestational age.

NTD prevalences in the periods before (2000-2004) and after (2005-2006) mandatory food fortification, implemented by the ANVISA, were compared using Pearson chi-square and Fisher exact tests. A 5% level of significance was adopted. Excel 2000, SPSS v8.0, and Epi Info v3.3.2. software programs were used.

Time trend analysis of three-month NTD rates was performed with the sequential version of the Mann-Kendall test, as this in a non-parametric test that enables detection of trends in time series.[21] The non-parametric Sen's Slope method was used to estimate the value and confidence interval for the series slope.[20]

This study was approved by the *Comitê de Ética e Pesquisa do Instituto de Medicina Integral Professor Fernando Figueira* (Professor Fernando Figueira Institute of Comprehensive Medicine Research and Ethics Committee).

RESULTS

Between 2000 and 2006, 108 NTD cases were recorded, of which spina bifida was the most common type of anomaly (45.4%), followed by anencephaly (36.1%) and encephalocele (18.5%).

The Table shows NTD prevalences according to maternal sociodemographic characteristics, number of pre-natal consultations, type of delivery and gestational age, in the periods before and after fortification. From 2000 to 2004, the period before food fortification with folic acid, NTD prevalence was 0.72 per 1,000 live births (LB), whereas in the period after fortification, from 2005 to 2006, NTD prevalence was 0.51 per 1,000 LB, with no statistically significant difference in the event observed (χ^2= 1.96; p= 0.1596).

Stratified analysis of NTD prevalence did not detect significant reduction in NTD prevalence per maternal schooling and age, type of delivery and gestational age in the period following fortification (Table). Statisti-

[a] Agência Nacional de Vigilância Sanitária. RDC n. 269, de 22 de setembro de 2005. Aprova o regulamento técnico sobre aingestão diária recomendada (IDR) de proteína, vitaminas e minerais. Diário Oficial da União. 23 set 2005.
[b] Ministério da Saúde. Resolução RDC nº 344, de 13 de dezembro de 2002. Aprova o regulamento técnico para a fortificação das farinhas de trigo e das farinhas de milho com ferro e ácido fólico. Diário Oficial da União. 18 dez 2002.

Table. Prevalence of neural tube defects in live newborns, according to characteristics of the pregnant woman, prenatal care and delivery, in the periods before and after food fortification with folic acid. City of Recife, Northeastern Brazil, 2000-2006.

Variable	Pre-fortification (2000-2004)			Post-fortification (2005-2006)			P
	Live births	NTD		Live births	NTD		
		n	n/1,000		n	n/1,000	
Age (years)							
10 to 19	27,653	20	0.72	7,750	7	0.90	0.6119[a]
20 to 24	44,312	34	0.76	13,369	8	0.56	0.5257[a]
25 to 29	27,861	13	0.46	9,463	1	0.10	0.0959[b]
≥30	22,274	21	0.94	8,659	4	0.46	0.1815[a]
Level of education (years)							
0 to 3	11,067	8	0.72	2,341	1	0.42	0.5161[b]
4 to 7	45,423	30	0.66	12,506	5	0.40	0.2935[a]
8 to 11	62,631	30	0.79	23,739	14	0.58	0.5196[a]
Number of prenatal consultations							
0-3	15,267	18	1.18	4,973	8	1.60	0.4520[a]
4 or more	105,270	70	0.66	33,832	12	0.35	0.0408[a]
Type of delivery							
Vaginal	68,481	38	0.55	19,773	6	0.30	0.1629[a]
Cesarean	53,568	50	0.93	19,453	14	0.71	0.3882[a]
Length of gestation (weeks)							
<37	9,303	37	3.98	3,552	9	2.53	0.2203[a]
≥37	112,739	51	0.45	35,675	11	0.30	0.2459[a]
Total	122,100	88	0.72	39,241	20	0.51	0.1596[a]

Source: Sistema Nacional de Informações de Nascidos Vivos (SINASC – National Information System on Live Births), 2000-2006. City of Recife Department of Health.
NTD: Neural tube defect
[a] Pearson chi-square test
[b] Fisher exact test

cally significant reduction in the occurrence of event was observed in women who had had more than three pre-natal consultations.

By analyzing the NTD prevalence coefficients per trimester, an increasing or decreasing trend in the occurrence of malformation was not observed (Mann-Kendall test; p=0.270; Sen's Slope=-0.008) (Figure).

DISCUSSION

The NTD prevalences found in the city of Recife, 0.72 and 0.51:1,000 LB, in the pre- and post-fortification periods respectively, were lower than the rates found in previous surveys in Brazil, which varied between 0.83:1,000 and 1.87:1,000 LB,[10,15] and in Latin American countries, where prevalences of 1.5:1,000 LB[10] were observed. NTD prevalence varies according to period in time and area; it is very low in Finland (0.4/1,000 LB), high in Mexico (3.3/1,000) and very high in southern Wales (up to 12.5/1,000).[6,10] In addition, there is the possibility of these frequencies being underestimated when considering the fact that many pregnancies are naturally or deliberately interrupted.[10]

As regards the type of anomaly, the distribution was found to follow the pattern described in the literature,[1,9,11] with cases of spina bifida and anencephaly predominating. According to data from the 2003 WHO World Atlas of Congenital Malformations,[19] in terms of anencephaly and spina bifida prevalence, Brazil comes in fourth place among 41 countries surveyed.

A reduction in the occurrence of neural tube defects was not observed after food fortification with folic acid was established in the population studied, both in the global NTD prevalences between the pre- and post-fortification periods and in the trend of event reduction throughout the study period. Likewise, reduction in post-fortification NTD rates was not observed, when age and maternal schooling were considered, thus avoiding the possibility that one of these groups had benefited from the fortification.

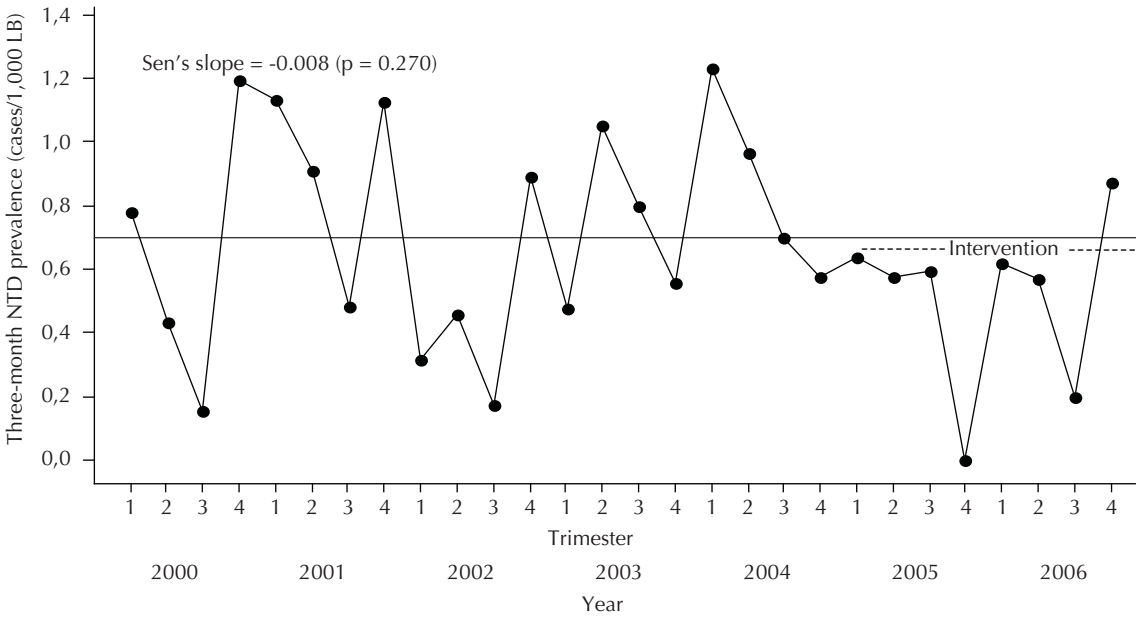

Figure. Three-month prevalence of neural tube defects in live newborns. City of Recife, Northeastern Brazil, 2000-2006.

The period of time of observation may have not been enough to observe the trend towards reduction of this fetal anomaly after folic acid fortification. In previous studies, which assessed the NTD reduction trend, the post-fortification follow-up period was not longer than two years.[11,16,22]

On the other hand, Honein et al[11] found a 19% reduction in NTD prevalence in the United States, one year after the measure for food fortification with folic acid was established. In this case, it is important to consider the delay in time between the establishment of the resolution and its effective implementation in Brazil, as the regulation on folic acid fortification of corn and wheat flour by ANVISA in 2004 does not prevent products manufactured before this date and within their expiration date to have been sold until they were out of stock, without necessarily being fortified.

Likewise, due to the event's low frequency in the population studied, which did not enable temporal analysis of NTD prevalence in certain population strata, the possibility that some specific group of pregnant women could have benefited from the measure cannot be ruled out.

Another possibility is that the strategy of folic acid fortification of foods consumed in large amounts is not enough to guarantee the adequate levels of 400 µg/day of folic acid intake for pregnant women to prevent NTDs, when consumed without the associated periconceptional supplementation. Tanya et al,[22] while analyzing the changes in folate intake level during the mandatory fortification period, in the United States, observed an increase of only 100 µg/day in folate intake in the population. Moreover, in this same study, there was an increase of between 26% and 38% in the number of women of fertile age with a minimum consumption of 400 µg/day of folate necessary to prevent NTDs, even though it did not reach the estimated percentage of 50% of women with the desired limit of daily folic acid consumption during the mandatory fortification period. Mean reduction between 20% and 32% in NTD prevalence has been observed after the adoption of a fortification policy,[11,22] despite the known potential of 50% to 70%[4,13] to prevent these malformations with an adequate folate intake. These data suggest a possible limitation of the strategy of food fortification with folic acid, as an independent measure to prevent the anomaly. In view of these findings, some authors[16,19] have reflected that, despite the evidence of reduction in NTD occurrence, the protective effect of food fortification with folic acid to prevent such defects is still far from being achieved. In addition, they point to the importance of adopting different strategies to promote the increase in folate intake during pregnancy, such as the establishment of peri-conceptional supplementation, food fortification and promotion of consumption of natural sources of folic acid to reduce the occurrence of this malformation.

Another factor to be considered in the analysis of possible determinants of non-reduction of NTDs in the population studied could be the consumption of inadequate amounts of fortified foods by part of this population, resulting from local diet habits characterized by low consumption of wheat and corn flour or by the low socioeconomic level of a considerable portion of the population. *Pesquisa de Orçamento Familiar*

(POF – Family Budget Survey, 2002-2003)[19] showed an average acquisition of 144 g/day of flour, corresponding to 270 µg/day of folic acid, in the Brazilian Southern region, whereas this acquisition was 70 g/day in the Northern and Center-West regions, corresponding to less than 100 µg/day of folic acid, when considering the regulated fortification.

Despite its lower likelihood, higher prevalence of diseases and other factors equally associated with NTD occurrence in the population studied should be considered, such as diabetes mellitus,[6] use of valproic acid[5] and maternal obesity,[18] which could have contributed to the non-reduction in the anomaly prevalence. Studies[17,22] show the variation of folate level in the population, according to sex, age and ethnicity, throughout the mandatory fortification period. Moreover, they could not confirm whether the cause of such disparities was associated with different levels of folic acid consumption or if it was a distinct individual response to its intake, the latter being influenced by genetic factors which have not been clarified or by the presence of associated diseases.

As regards the higher number of pre-natal consultations being associated with the reduction in NTD occurrence, this may be attributed to the greater awareness of the need for adequate gestational follow-up when given the diagnosis of intra-uterine malformation or to the fact that these women had been referred to high risk prenatal care, where closer attention is provided.

In conclusion, even though a trend towards reduction in NTD occurrence was not observed, results from this study do not enable the benefit of such public health measure to prevent this malformation in the population living in the city of Recife to be ruled out. It is believed that the association between food fortification measures and peri-conceptional supplementation with folic acid can meet the requirements of this micronutrient and avoid possible flaws caused by these strategies being used separately for NTD prevention. Further studies assessing the effect of folic acid fortification in foods, in a higher number of cities and with longer periods of measure implementation, and verifying the level of consumption of fortified products by women of fertile age, are necessary.

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