

# Effect of folic acid fortification on the incidence of neural tube defects

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## Summary

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In a few countries enriched cereal grains have been fortified with folic acid to reduce the incidence of neural tube defects. The objective of this study was to analyse the effect of folic acid fortified foods on the incidence of neural tube defects in live newborns at Princess Badea Teaching Hospital, in the north of Jordan, before and after the national food fortification with folic acid was implemented. For the 7-year period from 1 January 2000 to 31 December 2006, we retrospectively extracted the total number of births at Princess Badea Hospital, as well as the number of pregnancies affected by spina bifida and anencephaly, per 1000 births during the periods before (2000–01), during (2002–04) and after (2005–06) folic acid fortification of grain products, was implemented. Neural tube defects were defined in accordance with the International Classification of Diseases, 10th revision (ICD-10): anencephaly, encephalocele and spina bifida.

A total of 78 subjects with neural tube defects were recorded among 61 447 births during the study period. The incidence of neural tube defects decreased from 1.85 per 1000 births before fortification [95% confidence interval (CI) 1.2, 2.4] to 1.07 per 1000 births during the fortification period [95% CI 0.7, 1.5], and 0.95 after full fortification [95% CI 0.5, 1.5], a 49% reduction. The difference between incidence of neural tube defects in the periods before and after food fortification with folic acid was statistically significant. We conclude that food fortification with folic acid was associated with a significant reduction in the rate of neural tube defects in north Jordan.

**Keywords:** neural tube defects, spina bifida, folic acid, food fortification.

## Introduction

Neural tube defects are relatively common birth defects. They occur in 1–2 per 1000 births<sup>1,2</sup> and result from the neural tube closing incorrectly or incompletely between the third and fourth week of embryonic development, and comprise anencephaly, encephalocele and spina bifida.<sup>3,4</sup>

Neural tube defects are strongly associated with maternal folic acid deficiency during the periconception period.<sup>3</sup> The genes involved in this malformation are associated with the folic acid metabolism<sup>3</sup>, particularly the 5,10 methylenetetrahydrofolate reductase gene mutation.<sup>1,3</sup> Known maternal risk factors for these anomalies include diabetes mellitus,<sup>5</sup> use of valproic

acid during pregnancy,<sup>6</sup> maternal obesity,<sup>7</sup> hyperthermia<sup>8</sup> and most importantly folic acid deficiency.<sup>9</sup>

The benefit of folic acid supplementation during the periconception period in reducing the risk of neural tube defects in offspring has been demonstrated both in experimental and in observational studies.<sup>10</sup> This reduction occurs both among mothers with previously affected pregnancies and among those who have no such risk factors.<sup>11</sup> A multicentre, prospective, randomised trial of folic acid supplementation in high-risk patients showed that a daily dose of 4 mg of folic acid was associated with a 71% reduction in the recurrence of open neural tube defects.<sup>12</sup> A similar reduction in the incidence of open neural tube defects was

**Table 1.** Comparison of pre-fortification, introduction period and post-fortification ratios of neural tube defects (NTDs) per 1000 live newborns; Princess Badea Teaching Hospital, north Jordan, 2000–06

Period	Years	Livebirths	NTDs	Rate per 1000	[95% CI]
Before fortification	2000–01	18392	34	1.85	[1.2, 2.4]
Introduction period	2002–04	26286	28	1.07	[0.7, 1.5]
After fortification	2005–06	16769	16	0.95	[0.5, 1.5]

demonstrated among low-risk women taking 0.80 mg of folic acid in a daily multivitamin preparation.<sup>9</sup>

Despite the benefit of folic acid, many periconceptional women still do not follow supplementation recommendations to prevent open neural tube defects. Studies showed that less than 45% of pregnant women reported having taken folic acid before conception.<sup>13,14</sup> Therefore, attention has shifted towards the effects of folic acid fortification as a means of increasing the daily intake of this vitamin.<sup>15,16</sup>

Fortification of many cereal food products has become mandatory in a few countries.<sup>17,18</sup> The goal of fortification was to increase by approximately 30–70% of the average intake of folic acid among women of childbearing age without posing a risk to the general public. Higher levels of fortification were not adopted because of concern about exceeding the recommended daily upper intake level of 1000 µg for adults.<sup>10</sup>

Flour fortification was launched at a national level in Jordan in 2002 (1.5 ppm). Termination of pregnancy for fetal anomalies is not practised in Jordan on legal grounds. The present study aimed to assess the effect of folic acid fortified foods on the incidence of neural tube defects in the north of Jordan.

## Methods

A total of 61 447 livebirths between 2000 and 2006 at Princess Badea Teaching Hospital were analysed. Neural tube defects were defined in accordance with the International Classification of Diseases (ICD-10). Neural tube defect incidence in the periods before (2000–01), during the introduction period (2002–04) and after (2005–06) folic acid mandatory food fortification was compared using Pearson chi-square and Fisher exact tests. A 5% level of significance was adopted. Statistical analysis was conducted using the SPSS 10.0 for Windows program. The hospitals approval for the conduct of the study was obtained.

## Results

Between 2000 and 2006, 78 neural tube defect cases were recorded, of which 44 were female (56.4%) and 34

were male (43.6%). Spina bifida was the most common type of anomaly (87.2%), followed by encephalocele (11.5%) and anencephaly (1.3%). The average age of mothers was 27.6 years, SD 6.2, and ranged from 17 to 41 years. There was only one twin pregnancy where one of the twins was affected by a neural tube defect.

In the period before food fortification with folic acid, the birth incidence of neural tube defects was 1.85 per 1000 livebirths, whereas during the introduction period of fortification the incidence was 1.07, and in the period after fortification it was 0.95 per 1000 livebirths (Table 1). There was a significant decline of 49% in the overall incidence of neural tube defects ( $P < 0.05$ ).

## Discussion

Fortification of food with nutrients has historically been successful in preventing such conditions as goiter with iodine, rickets with vitamin D, beriberi with thiamine, pellagra with niacin and anaemia with iron. Folic acid, sometimes called folate, is a water-soluble B vitamin (B9) found mostly in leafy green vegetables. Studies have shown that women who get 400 µg (0.4 mg) daily prior to conception and during early pregnancy, and 4 mg/day for those with a previous neural tube defect pregnancy outcome reduce the risk that their baby will be born with a serious neural tube defect.<sup>19</sup>

This study has demonstrated that food fortification with folic acid was associated with a marked reduction in rates of neural tube defects in the north of Jordan. This reduction is consistent with reductions observed in other countries that have fortified their food supplies, where mandatory fortification of basic foodstuffs was implemented,<sup>17,20–22</sup> and is inconsistent with the findings of other studies that have similar fortification programmes, but without significant reduction in the incidence of neural tube defects.<sup>23</sup>

We did not address the question of cost: benefits of fortification. Various studies from different countries produced varying ratios, the cost: benefit ratio in averting neural tube defects was approximately 40 to 1 in

the United States, 30 to 1 in South Africa, and 10 to 1 in Chile.<sup>24–26</sup>

The prevention of birth defects is a challenging goal, but current fortification measures appear to have successfully resulted in a reduction in the incidence of open neural tube defects among livebirths in the north of Jordan. For a further reduction, based on these findings, an increase in the concentration of folic acid in fortified food in Jordan is recommended.

In addition, the finding of this study should further encourage the decision to fortify food with folic acid in countries that have not yet implemented such programmes, in addition to encouraging increased use of periconceptional folic acid supplements.

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