Impact of Folic Acid Fortification of the US Food Supply on the Occurrence of Neural Tube Defects

Margaret A. Honein, PhD, MPH
Leonard J. Paulozzi, MD
T. J. Mathews, MS
J. David Erickson, DDS, PhD
Lee-Yang C. Wong, MS

Spina bifida and anencephaly, the most common neural tube defects (NTDs), together affect approximately 4000 pregnancies resulting in 2500 to 3000 US births annually. In randomized controlled trials, folic acid supplementation before conception and during the first trimester has been shown to reduce the recurrence of NTDs by 72% (relative risk, 0.28; 95% CI, 0.12-0.71) in women with a previous NTD-affected pregnancy, and in another randomized study, supplementation reduced the occurrence of NTDs by 100% (95% CI, 0.0-0.63). In 1992, the US Public Health Service issued a recommendation that all US reproductive-aged women who are capable of becoming pregnant should consume 400 µg of folic acid daily, however, a recent survey indicated that only 29% of US women were following this recommendation in 1998. In a further effort to reduce the occurrence of folate-preventable NTDs, the US Food and Drug Administration (FDA) authorized the addition of folic acid to enriched grain products in March 1996 and made compliance mandatory by January 1998.

Context Daily consumption of 400 µg of folic acid before conception and during early pregnancy dramatically reduces the occurrence of neural tube defects (NTDs). Before food fortification, however, only an estimated 29% of US reproductive-aged women were taking a supplement containing 400 µg of folic acid daily. The US Food and Drug Administration authorized addition of folic acid to enriched grain products in March 1996, with compliance mandatory by January 1998.

Objective To evaluate the impact of food fortification with folic acid on NTD birth prevalence.


Main Outcome Measure Birth certificate reports of spina bifida and anencephaly before fortification (October 1995 through December 1996) compared with after mandatory fortification (October 1998 through December 1999).

Results The birth prevalence of NTDs reported on birth certificates decreased from 37.8 per 100000 live births before fortification to 30.5 per 100000 live births conceived after mandatory folic acid fortification, representing a 19% decline (prevalence ratio [PR], 0.81; 95% confidence interval [CI], 0.75-0.87). During the same period, NTD birth prevalence declined from 53.4 per 100000 to 46.5 per 100000 (PR, 0.87; 95% CI, 0.64-1.18) for women who received only third-trimester or no prenatal care.

Conclusions A 19% reduction in NTD birth prevalence occurred following folic acid fortification of the US food supply. However, factors other than fortification may have contributed to this decline.

JAMA. 2001;285:2981-2986 www.jama.com
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Nonetheless, birth certificates represent a stable source of data that can be used for monitoring approximately 4 million births per year. The impact of universal folic acid fortification as a public health intervention was assessed by evaluating birth certificate data on NTDs to determine its effect on the US NTD birth prevalence.

METHODS
Data Source
Birth certificate information is routinely collected by state vital statistics offices and compiled by the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics (NCHS). We evaluated the prevalence of NTDs in births to US residents, specifically spina bifida and anencephaly, reported on birth certificates from 45 states and Washington, DC, from January 1990 through December 1999. Residents of Connecticut, Maryland, New Mexico, New York, and Oklahoma were excluded for the following reasons: New Mexico, New York, and Oklahoma birth certificates did not report congenital anomalies for 1 or more years during this period, and in Connecticut and Maryland, congenital anomaly status was "not stated" for more than 25% of births during several years between 1990 and 1999. To determine whether the overall sensitivity of birth certificates to birth defects varied during this period, the percentage of certificates noting 1 or more defects by year for 1990 through 1999 was calculated. Any birth certificate that did not indicate an NTD but did indicate at least 1 of 19 other congenital anomalies was included. Birth certificates with only "other" checked in the congenital anomaly list were excluded. This analysis was conducted because a decline in the sensitivity of birth certificates to other birth defects during this time period would suggest that any observed decline in NTDs would need to be viewed more cautiously.

Folic acid fortification was first authorized in March 1996 and was mandatory by January 1998. Information on the estimated time from grain production to consumption or on the proportion of the grain supply that was fortified before the mandatory deadline was not obtainable. In at least some US regions, evidence of substantial folic acid fortification was shown by increasing serum folate levels beginning in 1997 and continuing to increase through 1998. From this evidence, we assumed that nearly all births from October 1998 through December 1999 (conceptions from approximately January 24, 1998, to April 23, 1999) were exposed to folic acid fortification periconceptionally. (The dates of conception are estimated assuming a 38-week gestation because this is the mean gestation for NTD-affected pregnancies reported on birth certificates.) The birth prevalence of NTDs from October 1995 through December 1996 (5 quarters of births before folic acid fortification) was compared with the birth prevalence of NTDs from October 1998 through December 1999 (5 quarters of births conceived after mandatory folic acid fortification). In addition, the postfortification NTD prevalence (October 1998 to December 1999 births) was compared with the mean prevalence from 1990 to 1996 as the reference group to assess if any reduction in NTDs observed was dependent on our choice of comparison group. Differences between these periods were expressed as prevalence ratios (PRs) and 95% confidence intervals (CIs), which were calculated using Epi Info (version 6; CDC, Atlanta, Ga). Furthermore, these estimates were calculated for spina bifida and anencephaly birth prevalences (defined as the number of infants whose birth certificates indicated that they had either spina bifida or anencephaly, with the denominator as the total number of live births during the same period).

To examine trends unaffected by changes in the use of prenatal diagnosis or termination of affected pregnancies, the prevalence of NTDs among women who began prenatal care in the third trimester or had no prenatal care at all was evaluated. Although some states are increasing restrictions on and decreasing access to pregnancy termination services, second-trimester elective terminations are legal in the United States. However, in the practice of obstetrics in the United States today, third-trimester terminations are rare, even with a prenatal diagnosis of an NTD. Therefore, affected pregnancies without obstetric oversight in the first 2 trimesters are unlikely to be terminated. As a result, the birth prevalence of NTDs in women receiving only third-trimester or no prenatal care should be relatively unaffected by changes or trends in the use of prenatal diagnosis and termination. This group of women also may be less likely to be affected by any changes in patterns of vitamin supplement use. The birth certificate has a field to indicate what month prenatal care began. The trimester that prenatal care began was dichotomized to “first or second trimester prenatal care,” meaning that the mother began prenatal care in the first 6 months of pregnancy, and “third trimester/no prenatal care,” meaning that the mother either received no prenatal care or began prenatal care in the seventh month of pregnancy or later. The percentage of women who received third-trimester or no prenatal care decreased from 6.4% in 1989 to 3.9% in 1998, limiting the number of births for subgroup analysis to approximately 150,000 births in 1998.

Data Analyses
The exponential weighted moving average (EWMA) method (using SAS; SAS Institute, Cary, NC) was used to determine the timing of statistically significant changes from a baseline mean, that is, the timing and occurrence of any statistically significant changes during the entire 10-year period. This method sets a boundary that is analogous to upper and lower confidence limits using the baseline SD. The baseline mean and SD were based on the 1990 through 1996 data. Observed values above and below the baseline mean increase the value of the EWMA statistic. When the EWMA statistic is large enough to cross the boundary (an out-of-control point), it means an increase or decrease beyond the limits of the model has occurred. The EWMA statistic was reset to the 1990 to 1996 baseline mean after each out-of-control point. The α level was set at .01.
and the weight was set at 0.075 to yield an average run length of 25 years, meaning that only 1 false out-of-control signal should occur in every 25 years of data analyzed.28 The EWMA method was used to detect the timing of statistically significant shifts from the overall mean quarterly spina bifida and anencephaly prevalence. Among women receiving third-trimester only or no prenatal care, the total NTD birth prevalence was analyzed for 6-month intervals instead of quarters because of the limited numbers in this subgroup. Also examined for ease of comparability was the total NTD prevalence among all births by 6-month intervals.

RESULTS

The percentage of infants whose birth certificate indicated the presence of at least 1 congenital anomaly other than an NTD was highest in 1990 and was relatively stable from 1991 through 1999, with slight increases noted in 1998 and 1999 (Table 1). Approximately 1% of all birth certificates indicated at least 1 congenital anomaly other than an NTD.

A total of 1123 infants with spina bifida (26.2 per 100 000 births) and 497 infants with anencephaly (11.6 per 100 000 births) were reported on birth certificates from October 1995 through December 1996 (TABLE 1). The birth prevalence of anencephaly was greater when this alternative comparison group was used.

The NTD birth prevalence for women who received third-trimester only or no prenatal care was 53.4 per 100 000 from October 1995 through December 1996 and declined to 46.5 per 100 000 for October 1998 through December 1999 (PR, 0.87; 95% CI, 0.64-1.18). Comparing data from October 1998 through December 1999 with the entire period from 1990 through 1996 yielded a similar result (PR, 0.79; 95% CI, 0.62-1.00) (Table 2).

Among all women, data are presented by quarter of birth for spina bifida and anencephaly separately (Figure 1). Spina bifida prevalence has been declining since early 1997. The EWMA statistical analysis demonstrated a statistically significant increase in spina bifida prevalence in the fourth quarter of 1996, and statistically significant decreases in spina bifida prevalence in the second quarter of 1992, the fourth quarter of 1998, and the second and third quarters of 1999.

Table 1. Prevalence of at Least 1 Congenital Anomaly Reported on the Birth Certificate in 45 US States and Washington, DC, January 1990 to December 1999

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Infants*</th>
<th>Prevalence†</th>
<th>No. of Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>37 861</td>
<td>1036</td>
<td>3 665 217</td>
</tr>
<tr>
<td>1991</td>
<td>34 808</td>
<td>952</td>
<td>3 614 929</td>
</tr>
<tr>
<td>1992</td>
<td>34 125</td>
<td>933</td>
<td>3 576 260</td>
</tr>
<tr>
<td>1993</td>
<td>33 608</td>
<td>913</td>
<td>3 522 065</td>
</tr>
<tr>
<td>1994</td>
<td>33 918</td>
<td>928</td>
<td>3 481 455</td>
</tr>
<tr>
<td>1995</td>
<td>33 761</td>
<td>924</td>
<td>3 438 989</td>
</tr>
<tr>
<td>1996</td>
<td>33 325</td>
<td>912</td>
<td>3 438 108</td>
</tr>
<tr>
<td>1997</td>
<td>33 199</td>
<td>908</td>
<td>3 435 192</td>
</tr>
<tr>
<td>1998</td>
<td>34 395</td>
<td>941</td>
<td>3 490 775</td>
</tr>
<tr>
<td>1999</td>
<td>34 419</td>
<td>980</td>
<td>3 512 327</td>
</tr>
</tbody>
</table>

* Excluding infants with neural tube defects.† Prevalence per 100 000 live births.

Table 2. Effect Estimates for the Observed Decline in NTDs Following US Folic Acid Fortification of the Grain Supply, January 1990 to December 1999

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Live Births</th>
<th>No. of Cases</th>
<th>Spina Bifida PR (95% CI)</th>
<th>Anencephaly PR (95% CI)</th>
<th>Total NTDs PR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1996 (referent)</td>
<td>24 726 932</td>
<td>6163</td>
<td>1.00</td>
<td>3232</td>
<td>1.00</td>
</tr>
<tr>
<td>10/98-12/99†</td>
<td>4 381 901</td>
<td>884</td>
<td>0.77 (0.70-0.84)</td>
<td>453</td>
<td>0.89 (0.78-1.01)</td>
</tr>
<tr>
<td>10/95-12/96 (referent)</td>
<td>4 282 672</td>
<td>1123</td>
<td>1.00</td>
<td>497</td>
<td>1.00</td>
</tr>
<tr>
<td>10/98-12/99†</td>
<td>4 381 901</td>
<td>884</td>
<td>0.81 (0.75-0.87)</td>
<td>453</td>
<td>0.77 (0.70-0.85)</td>
</tr>
<tr>
<td>10/95-12/96 (referent)</td>
<td>24 726 932</td>
<td>6163</td>
<td>1.00</td>
<td>3232</td>
<td>1.00</td>
</tr>
<tr>
<td>10/98-12/99†</td>
<td>159 322</td>
<td>38</td>
<td>0.71 (0.47-1.07)</td>
<td>36</td>
<td>1.14 (0.71-1.83)</td>
</tr>
<tr>
<td>10/95-12/96 (referent)</td>
<td>166 718</td>
<td>56</td>
<td>1.00</td>
<td>33</td>
<td>1.00</td>
</tr>
<tr>
<td>10/98-12/99†</td>
<td>159 322</td>
<td>38</td>
<td>0.71 (0.51-0.99)</td>
<td>36</td>
<td>0.89 (0.63-1.26)</td>
</tr>
<tr>
<td>10/95-12/96 (referent)</td>
<td>1 175 443</td>
<td>395</td>
<td>1.00</td>
<td>298</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Includes birth certificate data from 45 US states and Washington, DC. NTD indicates neural tube defect; PR, prevalence ratio; and CI, confidence interval.
†Births conceived after mandatory folic acid fortification.

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cephaly prevalence was higher in 1990 to 1991, declined from late 1991 through 1994, remained relatively stable from 1995 to 1997, and showed a further slight decline in 1998 to 1999. For anencephaly, the EWMA analysis indicated 5 statistically significant increases in 1990 to 1991 and 3 statistically significant decreases from 1994 through 1997. There were also statistically significant decreases in anencephaly in the first and fourth quarters of 1998 and the second and fourth quarters of 1999.

Among women receiving third-trimester only or no prenatal care, data are presented in 6-month intervals (Figure 2). While the data are unstable, the point estimates for the last half of 1998 and all of 1999 are the 3 lowest points on the figure. A statistically significant decline in total NTDs was detected by the EWMA analysis in the second half of 1999 among women who received only third-trimester or no prenatal care. For comparability purposes, total NTDs among all births also are presented by 6-month intervals. The EWMA analysis for NTDs among all births showed 1 statistically significant increase (January to June 1991) and 3 statistically significant decreases in the last 3 time periods (July to December 1998, January to June 1999, and July to December 1999).

**COMMENT**

Data from US birth certificates indicate a 19% decline in the birth prevalence of NTDs and a 23% decline in spina bifida prevalence among births conceived after mandatory folic acid fortification (October 1998 through December 1999) compared with the NTD prevalence before folic acid fortification (October 1995 through December 1996). This decline was temporally associated with the fortification of the grain supply with folic acid: the EWMA analysis indicated that

![Figure 1. Trends in Spina Bifida and Anencephaly Among All Births, National Center for Health Statistics Vital Statistics Data, 1990-1999, for 45 US States and Washington, DC](image1)

![Figure 2. Trends in Total NTDs (Anencephaly and Spina Bifida) Among All Births and All Births to Women Receiving Third-Trimester Only or No Prenatal Care, National Center for Health Statistics Vital Statistics Data, 1990-1999, for 45 US States and Washington, DC](image2)
a statistically significant decline in spina
dibida prevalence occurred in the fourth
quarter of 1998 and the second and third
quarters of 1999. These declines were ob-
served despite no apparent decline in sen-
sitivity of the birth certificate during this
time. Due to the public health impor-
tance of the NTD declines observed in
our study, a brief announcement was
published on the CDC’s NCHS Web site
in December 2000.29

The long-term downward trend in an-
encephaly prevalence that preceded fo-
lolic acid fortification makes it difficult to
interpret the 11% decline following for-
tification. In particular, the mean anen-
cephaly prevalence from 1990 through
1996 was heavily influenced by the high
prevalence observed in 1990 to 1991 and
may have resulted from reporting dif-
fences in those years. The check box
format for reporting birth defects was in-
troduced on the birth certificate in 1989,
and anencephaly was the first check box
on the congenital anomaly list. It is un-
clear why the EWMA analysis showed
5 statistically significant increases and
2 statistically significant decreases in an-
encephaly prevalence from 1990 to
1996, complicating the interpretation of
the 4 significant decreases observed in

Among infants whose mothers re-
ceived third-trimester or no prenatal care,
the magnitude of the decline in NTDs
was similar when the entire period from
1990 through 1996 was used as the ref-
ence group, but the decline was not sta-
tistically significant when the 5 quar-
ters just before fortification were used as
the reference group. There was a statis-
tically significant decline in this group
during the last half of 1999 by the EWMA
analysis. We expected that the birth
prevalence of NTDs in this subgroup
would be unaffected by changes in pre-
natal diagnosis or termination. While the
NTD prevalence was higher among
women receiving third-trimester only or
no prenatal care, the trend was very simi-
lar to that for all births.

The 1999 National Health and Nu-
trition Examination Survey data docu-
mented dramatic increases in serum and
red blood cell (RBC) folate levels among
reproductive-aged women in the US
population following folic acid forti-
cation of enriched grain products.30 This
increase confirms the findings of 2 ear-
erlier studies of selected US populations
that noted increases in serum folate lev-
els beginning in 1997 that also may have
been due to folic acid food forti-
cation.23,24 It is not known whether the in-
crease in serum folate levels observed is
sufficient to maximize NTD preven-
tion,31 but measurements of RBC fo-
late levels taken early in pregnancy have
shown a dose-response relation to the
risk for having an infant with an NTD,
with the lowest risk among those women
with the highest RBC folate levels.32

The authors of a study conducted in
Ireland predicted a decline in NTD preva-
lence of a magnitude similar to that ob-
served in our study if fortification added
100 µg of folic acid to the average daily
diet of reproductive-aged women.33,34
Daly et al35 estimated that folate acid lev-
equivalent to the current level of for-
tification in the United States would re-
sult in a 22% reduction in the NTD risk.
They also estimated that 200 µg would
lead to a 41% reduction, and 400 µg
would lead to a 47% reduction in NTD
risk. Wald et al36 extended these analy-
eses and predicted 18%, 35%, and 53% re-
ductions from 100, 200, and 400 µg, re-
spectively. These estimates of 22% and
18% bracket the 19% decline observed in
our study. However, recent data sug-
gest that women may be getting more fo-
lolic acid from fortification than was origi-
nally projected.35 Despite these possibly
higher levels of folic acid in fortified
foods, we may have observed only a 19% decline due to differences between the
US population and the Irish population
on which these predictions were origi-
nally made or due to differences in lab
techniques for measuring RBC folate le-
vels in the Irish vs US studies.

A major concern is the validity of birth
defect data from birth certificates. The
sensitivity of birth certificates is low for
total birth defects, but it is higher for de-
fects that are usually diagnosed at birth.
An evaluation of 1989 birth certificate
data on birth defects in Tennessee found
that the birth certificate had a 67% sen-
sitivity to detect anencephaly and an 89%
positive predictive value.21 One study
found that of all 1989 and 1990 births in
metropolitan Atlanta the sensitivity of
the birth certificates was 86% for anen-
cephaly and 40% for spina bifida and
the positive predictive value was 100% for
defects.20 A recent unpublished evalu-
ation that indicated a sensitivity for an-
encephaly is closer to the Tennessee
study than to the Atlanta study (written
communication, L. Miller, MD, Septem-
ber 16, 1999). However, despite their
limited sensitivity, the positive predic-
tive value of NTDs reported on birth cer-
tificates is high. The high positive pre-
dictive value indicates that trends in true
NTD cases are being observed rather than
false positives.

If the sensitivity and specificity of birth
certificates have remained stable over
time, then observed declines in NTDs re-
ported on birth certificates should rep-
resent actual declines in the birth preva-
lence of these defects. The percentage of
all birth certificates with 1 or more de-
fects other than NTDs remained rela-
tively stable from 1991 through 1999 and
even increased slightly in 1998 and 1999.
Therefore, a variation in reporting of all
defects on the birth certificate over time
does not explain the decline observed in
NTDs after folic acid fortification. How-
ever, we cannot rule out the possibility
that subtle changes in the sensitivity of
NTD reporting on birth certificates have
contributed to the observed trends.

Birth certificates are completed for live
births only; any NTD-affected pregnan-
cies ending in induced or spontaneous
abortions are not recorded. Any observed
changes in the birth prevalence of NTDs
may actually be due to changing patterns
in the percentage of affected fetuses be-
ing born alive. There has been some de-
bate on the possible role of folic acid in
increasing or decreasing the likelihood of
a spontaneous abortion of an NTD-
affected pregnancy,36-38 however, in the
absence of evidence to the contrary, we
have assumed that the proportion of NTD-
affected pregnancies that are spontane-
ously aborted has not changed over time.

The proportion of NTD-affected preg-
nancies that are electively terminated
may be influenced by many factors, including the proportion of pregnant women receiving prenatal care, insurance reimbursement for prenatal diagnostic tests, availability of termination services, and improvements in the prognosis of the affected fetus. Termination is more likely to occur among pregnancies affected by anencephaly than among pregnancies affected by spina bifida. Techniques, such as α-fetoprotein screening and ultrasound, now are often used during the second trimester of pregnancy to detect fetal defects. In concert with pregnancy termination, these techniques have had a substantial impact on the prevalence of NTDs in live births as measured by surveillance systems. Several recent studies show that the percentage of NTD-affected pregnancies that were prenatally diagnosed and terminated ranged from 39% to 48%. However, the Hawaii study, which included cases from 1987 through 1996, suggested that the proportion of fetuses prenatally diagnosed with NTDs and terminated has remained relatively stable during that time, and no other evidence indicates that the percentage of affected pregnancies that are terminated has changed since 1990 in the United States. Indeed, spina bifida prevalence for 1990 to 1996 was relatively stable. It seems unlikely that a substantial increase in use of prenatal diagnosis and termination of pregnancies affected by an NTD occurred between 1996 and 1999.

The decline in NTDs observed among infants born to women who received only third-trimester or no prenatal care was similar to that observed for all women, but this was only statistically significant when the entire period from 1990 to 1996 was used as the reference group. This may be due to the limited number of women obtaining only third-trimester or no prenatal care. Our analysis comparing postfortification with prefortification births only had 40% power to detect a 20% decline in NTDs among women in this subgroup, but the analysis did have more than 90% power to detect a 40% decline in NTDs for these women. This difference in power means that it is unlikely that a large decline occurred that was not detected in our analysis. It seems implausible that increased use of prenatal diagnosis and termination caused the reduction in NTDs among total live births because the declines in women receiving third-trimester or no prenatal care were of similar magnitude to those observed among all births. We will continue to monitor the birth prevalence of NTDs to further evaluate the impact of folic acid fortification on the occurrence of NTDs.


REFERENCES

**Comment.** Our data suggest that oral care may improve the swallowing reflex and the ability to perform ADLs among elderly patients. The elevated SP levels in the oral care group suggest that daily brushing stimulates sensory nerves in the oral cavity by enhancing release of neuropeptides, through afferent or efferent pathways of the swallowing reflex. Oral care may reduce the risk of pneumonia by improving the swallowing reflex and by improving overall functional status.

Akiko Yoshino, MD
Takae Ebihara, MD, PhD
Satoru Ebihara, MD, PhD
Hidetoshi Fuji, DD
Hidetada Sasaki, MD, PhD
Department of Geriatric and Respiratory Medicine
Tohoku University School of Medicine
Sendai, Japan


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**CORRECTION**

Incorrect Data in Table: In the Original Contribution titled “Impact of Folic Acid Fortification of the US Food Supply on the Occurrence of Neural Tube Defects” published in the June 20, 2001, issue of THE JOURNAL (2001;285:2981-2986), incorrect data appeared in Table 1 on page 2983. The column labeled “Prevalence” should have read as follows: 1036, 963, 954, 947, 974, 982, 969, 966, 985, 980. The corrected data still indicate that birth certificate reporting of congenital anomalies other than neural tube defects has been stable from 1991 through 1999, as was stated in the article.

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**Better incur the trouble of testing and exploding a thousand fallacies than by rejecting stifle a single beneficent Truth.**
—Horace Greeley (1811-1872)