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

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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.

Design, Setting, and Population National study of birth certificate data for live births to women in 45 US states and Washington, DC, between January 1990 and December 1999.

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.

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Spina bifida and anencephaly, the most common neural tube defects (NTDs), together affect approximately 4000 pregnancies resulting in 2500 to 3000 US births annually.[1,2] 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,[3] and in another randomized study, supplementation reduced the occurrence of NTDs by 100% (95% CI, 0.0-0.63).[4]

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[2,5]; however, a recent survey indicated that only 29% of US women were following this recommendation in 1998.[6] 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. The current level of fortification was expected to add approximately 100 μg of folic acid to the daily diet of the average person and to result in approximately 50% of all reproductive-aged women receiving 400 μg of folate from all sources.[7-9] In addition, other countries recently fortified their grain supplies on either a voluntary or mandatory basis,[10-12] and several more countries are considering folic acid fortification.[13-16]

Birth certificates are an important data source for monitoring national NTD trends. They are completed for all US live births, and since 1989, they include check boxes for selected congenital anomalies, including anencephaly and spina bifida.[17-19] The quality of data on birth defects from birth certificates is limited,[20-22] in particular, sensitivity is low.

See also p 3022 and Patient Page.

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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.[18] 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.[7] 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[23,24] and continuing to increase through 1998.[24] 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,[25] 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.[26] 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,[27] 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 100000 births) and 497 infants with anencephaly (11.6 per 100000 births) were reported on birth certificates from October 1995 through December 1996 (TABLE 2). The birth prevalence of spina bifida decreased to 20.2 per 100000 births during October 1998 through December 1999, representing a 23% decline (PR, 0.77; 95% CI, 0.70-0.84). The birth prevalence of anencephaly declined 11% (PR , 0.89; 95% CI, 0.78-1.01), reaching a birth prevalence of 10.3 per 100000 live births during October 1998 through December 1999. The decline in total NTDs during October 1998 through December 1999 compared with October 1995 through December 1996 was 19% (PR, 0.81; 95% CI, 0.75-0.87), from 37.8 to 30.5 per 100000 live births. The decline in spina bifida and total NTDs was similar when the entire 7-year period from 1990 to 1996 was used as the referent group; however, the decline in the 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 100000 from October 1995 through December 1996 and declined to 46.5 per 100000 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. Anen-

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

Year	No. of Infants*	Prevalence†	No. of Live Births
1990	37 861	1036	3 655 217
1991	34 808	952	3 614 929
1992	34 125	933	3 576 260
1993	33 368	913	3 522 065
1994	33 918	928	3 481 455
1995	33 761	924	3 438 898
1996	33 325	912	3 438 108
1997	33 199	908	3 435 192
1998	34 395	941	3 490 775
1999	34 419	980	3 512 327

*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*

		Spina Bifida		Anencephaly		Total NTDs	
	No. of Live Births	No. of Cases	PR (95% CI)	No. of Cases	PR (95% CI)	No. of Cases	PR (95% CI)
All live births							
10/98-12/99†	4 381 901	884	0.77 (0.70-0.84)	453	0.89 (0.78-1.01)	1337	0.81 (0.75-0.87)
10/95-12/96 (referent)	4 282 672	1123	1.00	497	1.00	1620	1.00
10/98-12/99†	4 381 901	884	0.81 (0.75-0.87)	453	0.77 (0.70-0.85)	1337	0.79 (0.75-0.84)
1990-1996 (referent)	24 726 932	6163	1.00	3329	1.00	9492	1.00
Third-trimester only or no prenatal care							
10/98-12/99†	159 322	38	0.71 (0.47-1.07)	36	1.14 (0.71-1.83)	74	0.87 (0.64-1.18)
10/95-12/96 (referent)	166 718	56	1.00	33	1.00	89	1.00
10/98-12/99†	159 322	38	0.71 (0.51-0.99)	36	0.89 (0.63-1.26)	74	0.79 (0.62-1.00)
1990-1996 (referent)	1 175 443	395	1.00	298	1.00	693	1.00

*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.

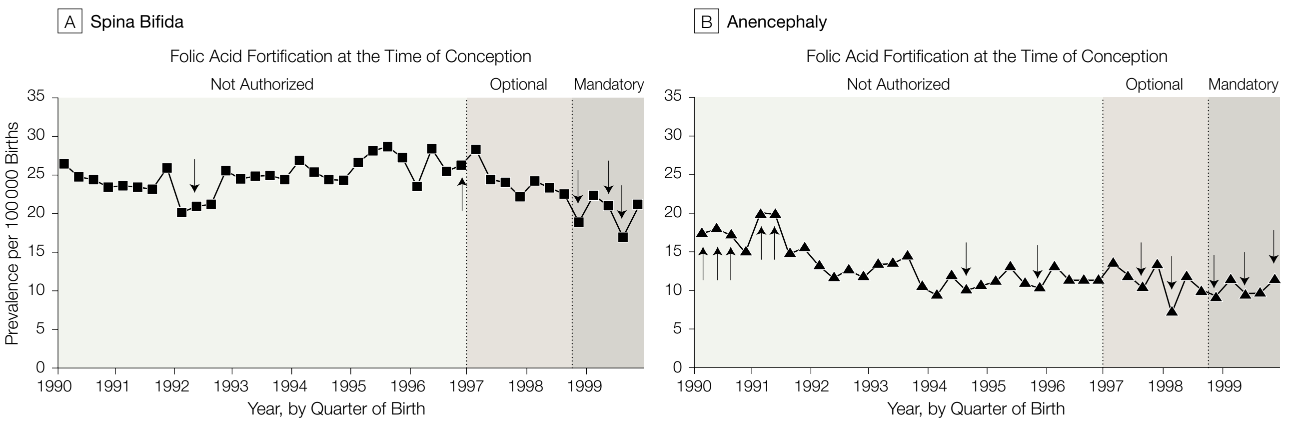
cephaly prevalence was higher in 1990 to 1991, declined from late 1991 through 1994, remained relatively stable from 1995 to 1997, and showed a further slight decline in 1998 to 1999. For anencephaly, the EWMA analysis indicated 5 statistically significant increases in 1990 to 1991 and 3 statistically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

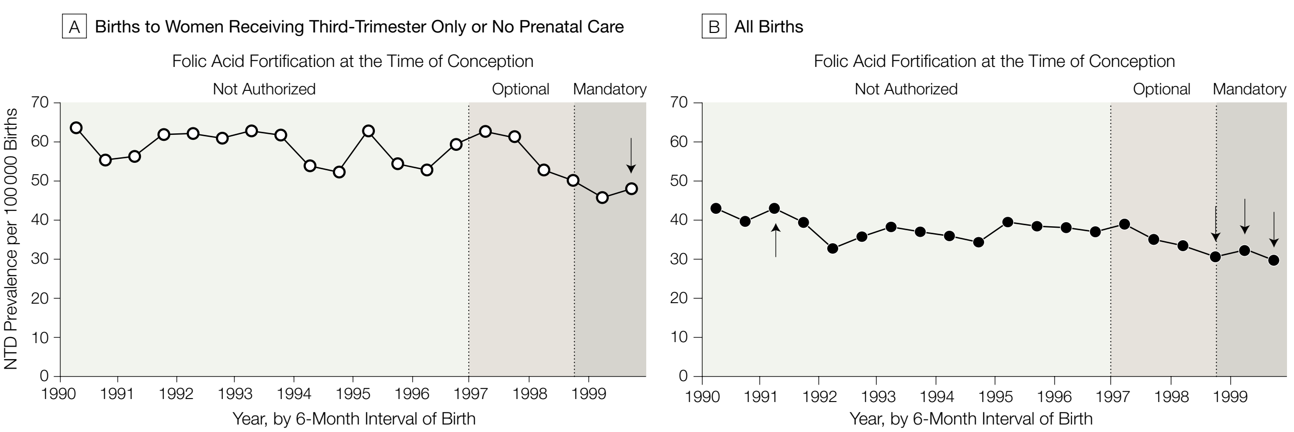
Data from US birth certificates indicate a 19% decline in the birth prevalence of NTDs and a 23% decline in spina bifida prevalence among births conceived after mandatory folic acid fortification (October 1998 through December 1999) compared with the NTD prevalence before folic acid fortification (October 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



Arrows indicate statistically significant increases and decreases by the exponential weighted moving average analyses with parameters of α=.01 and weight=0.075.

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



Arrows indicate statistically significant increases and decreases by the exponential weighted moving average analyses with parameters of α=.01 and weight=0.075. NTD indicates neural tube defects.

a statistically significant decline in spina bifida prevalence occurred in the fourth quarter of 1998 and the second and third quarters of 1999. These declines were observed despite no apparent decline in sensitivity of the birth certificate during this time. Due to the public health importance 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 anencephaly prevalence that preceded folic acid fortification makes it difficult to interpret the 11% decline following fortification. In particular, the mean anencephaly prevalence from 1990 through 1996 was heavily influenced by the high prevalence observed in 1990 to 1991 and may have resulted from reporting differences in those years. The check box format for reporting birth defects was introduced on the birth certificate in 1989, and anencephaly was the first check box on the congenital anomaly list. It is unclear why the EWMA analysis showed 5 statistically significant increases and 2 statistically significant decreases in anencephaly prevalence from 1990 to 1996, complicating the interpretation of the 4 significant decreases observed in 1998 and 1999.

Among infants whose mothers received 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 reference group, but the decline was not statistically significant when the 5 quarters just before fortification were used as the reference group. There was a statistically 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 prenatal diagnosis or termination. While the NTD prevalence was higher among women receiving third-trimester only or no prenatal care, the trend was very similar to that for all births.

The 1999 National Health and Nutrition Examination Survey data documented dramatic increases in serum and red blood cell (RBC) folate levels among reproductive-aged women in the US population following folic acid fortification of enriched grain products.[30] This increase confirms the findings of 2 earlier studies of selected US populations that noted increases in serum folate levels beginning in 1997 that also may have been due to folic acid food fortification.[23,24] It is not known whether the increase in serum folate levels observed is sufficient to maximize NTD prevention,[31] but measurements of RBC folate 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 prevalence of a magnitude similar to that observed in our study if fortification added 100 µg of folic acid to the average daily diet of reproductive-aged women.[33,34] Daly et al[34] estimated that folic acid levels equivalent to the current level of fortification in the United States would result 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 al[33] extended these analyses and predicted 18%, 35%, and 53% reductions from 100, 200, and 400 µg, respectively. These estimates of 22% and 18% bracket the 19% decline observed in our study. However, recent data suggest that women may be getting more folic acid from fortification than was originally 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 originally made or due to differences in lab techniques for measuring RBC folate levels 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 defects 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% sensitivity 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 anencephaly and 40% for spina bifida and the positive predictive value was 100% for both defects.[20] A recent unpublished evaluation that indicated a sensitivity for anencephaly is closer to the Tennessee study than to the Atlanta study (written communication, L. Miller, MD, September 16, 1999). However, despite their limited sensitivity, the positive predictive value of NTDs reported on birth certificates is high. The high positive predictive 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 reported on birth certificates should represent actual declines in the birth prevalence of these defects. The percentage of all birth certificates with 1 or more defects other than NTDs remained relatively 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. However, 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 pregnancies 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 being born alive. There has been some debate 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 spontaneously aborted has not changed over time.

The proportion of NTD-affected pregnancies 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.[39,40] 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%.[41-44] However, the Hawaii study,[44] 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 is it 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.

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