Long Term Maintenance of Neural Tube Defects Prevention in a High Prevalence State

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Objective To assess the efficacy of folic acid (FA) supplementation and fortification in preventing neural tube defects (NTDs) in a high prevalence region of the United States.

Study design Active and passive surveillance methods were used to identify all fetuses/infants affected with an NTD in South Carolina. Prevalence rates were compared with FA intake to determine the effects of increased intake on NTD occurrence and recurrence.

Results From 1992 to 2009, 916 NTD cases occurred in South Carolina, with isolated defects comprising 79% of cases. The NTD rate decreased 58% during this period. There was one NTD-affected pregnancy in 418 subsequent pregnancies (0.2%) in mothers with earlier NTD-affected pregnancies who consumed periconceptional FA supplements, and there were 4 NTDs in 66 pregnancies (6.1%) in which the mother did not take FA supplements. FA supplementation increased from 8% to 35% from 1992 to 2007, and knowledge of the protective benefits of FA increased from 8% to 65% in women of childbearing age.

Conclusions Increased periconceptional intake of FA appeared to reduce NTDs in a high-prevalence region. The rate of spina bifida and anencephaly in South Carolina is now essentially the same (0.69 cases per 1000 live births and fetal deaths) as the 1998 to 2005 US rate (0.69). *(J Pediatr 2011;159:143-9)*.

Neural tube defects (NTDs) are serious forms of craniospinal birth defects that result from the failure of the neural tube to close during the first month of embryonic development.[1,2] The 3 major forms of NTDs are spina bifida, anencephaly, and encephalocele. Spina bifida usually results in paralysis below the level of the spinal lesion and hydrocephaly, whereas anencephaly results in death in utero or death shortly after birth, and the effects and outcome of encephalocele are variable.[2,3] Although specific genetic and environmental causes are known for a minority of NTDs, especially those with associated malformations, most isolated NTDs are thought to have a multifactorial basis.[1] Recognized predisposing factors that may increase the risk for an NTD include maternal diabetes mellitus, maternal obesity, early prenatal exposure to anticonvulsant medication and folic acid (FA) antagonists, early amnion rupture, twin gestation, and earlier occurrence of an NTD in a first- to second-degree relative.[1,4-7]

After Smithells' observations (1982) on the protective benefits of FA against NTDs and a decade-long controversy about his findings, 2 studies were decisive in mounting a public health effort to reduce the risk of NTDs.[8-10] The first was the Medical Research Council (1991) case-control study showing 72% reduction in NTDs in high-risk pregnancies by using 4.0 mg of FA in the periconceptional period.[9] The second was the study by Czeizel and Dudas (1992) showing a similar reduction of the occurrence of NTDs by using 0.8 mg of FA in the periconceptional period.[10]

Because South Carolina had been previously identified as a region with a high prevalence of NTDs, having approximately 2 times the national prevalence rate from 1973 to 1977,[11] the South Carolina NTD Surveillance and Prevention Program was initiated to capitalize on knowledge of the protective effect of FA.[12-14] The program followed recommendations from the Centers for Disease Control and Prevention that all women of childbearing age should consume 0.4 mg of FA per day and that women with an earlier NTD-affected pregnancy consume 4 mg of FA daily in the periconceptional period.[15,16] A boost came to the prevention effort in 1996 when the US Food and Drug Administration mandated that enriched cereal grain flours be fortified with 0.14 mg FA per 100 g milled flour.[17] The rule, set to take place by January 1998, was accomplished by South Carolina flour producers by the summer of 1996. This report describes the identification and prevention of NTDs in South Carolina from 1992 through 2009.

FA	Folic acid
NTD	Neural tube defect

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Methods

Neural tube defects were defined as cases of spina bifida, anencephaly, and encephalocele.[1] Midline cranial aplasia cutis congenita and multiple vertebral malformations were included as forme fruste NTDs. Isolated NTDs had no significant anomalies in other organ systems. Hydrocephaly and club feet were considered secondary consequences of NTDs. Abdominal wall defects, diaphragmatic hernia, and holoprosencephaly were considered non-related malformations for purposes of this study.

Both active and passive surveillance methods were used to screen statewide for NTDs.[12,13] Active surveillance methods involved monitoring results of maternal α-fetoprotein laboratories, amniocentesis testing, and pregnancy ultrasound scanning programs. Passive surveillance methods included monthly reviews of medical reports from delivery hospitals and annual reviews of state birth and death certificates. All known live birth and fetal death cases from South Carolina were included. The surveillance period was October 1 through September 30 of every year from 1992 through 2009. All infants who were conceived in South Carolina, including those born out-of-state, were included. Surveillance of NTDs was coordinated by the Greenwood Genetic Center from 1992 through June 2006 and thereafter by the South Carolina Department of Health and Environmental Control.

All cases were classified as spina bifida, anencephaly, or encephalocele. Co-occurring anencephaly and spina bifida (24 cases) were included in the anencephaly category; co-occurring spina bifida and encephalocele (4 cases) were designated as spina bifida. The two cases of aplasia cutis congenita were designated encephaloceles, and the one case of multiple vertebral malformations was designated spina bifida. When possible, cases were examined by geneticists at the Greenwood Genetic Center, and chromosome analyses were performed to search for co-existing anomalies and determine causation.

Efforts to decrease the occurrence of NTDs were targeted at health care professionals and the general public. Prevention alerts on FA and annual newsletters were distributed to obstetricians, family physicians, pediatricians, and health department clinics. A FA representative visited physician offices and health clinics to reinforce the FA message and provide patient literature and vitamins.

A public awareness campaign focused on women of childbearing age by using billboards, television and radio announcements, newspaper releases, fact sheets, and brochures. The FA prevention message was included in continuing education courses for high school science teachers and in materials distributed at bridal fairs, sports events, and community festivals.

Once notified of an NTD-affected pregnancy, South Carolina Birth Defects Prevention Program personnel obtained permission from the primary physician to contact the mother. With such permission, a letter and a packet explaining recurrence prevention with FA were sent to the mother. The mother was contacted by telephone a week later to see whether she was willing to participate in a behavioral risk survey and recurrence prevention program. Folic acid intake of 0.4 mg daily was recommended for women who were not actively attempting to get pregnant, and 4.0 mg FA daily was recommended for women who were actively trying to get pregnant. Enrolled women were continually monitored for FA supplement use and their reproductive plans. Women who were not actively trying to get pregnant were contacted by telephone every 3 months. Women who were pregnant or were actively trying to get pregnant were contacted every month and reminded of the recommended amount of FA intake.

During the initial 5 years of this project, the level of knowledge and use of FA supplementation was determined with interviews of a group of women (n = 287) who had pregnancies that were not affected with an NTD. From 1997 to 2007, telephone surveys were made that included approximately 1000 women each year who were in the childbearing years (ages 15-45 years). Among other questions, they were asked whether they knew of the health benefits of FA, whether they took FA supplements, and, if so, how often.

Prevalence rates of NTDs were recorded as the total number of NTD cases per 1000 live births and fetal deaths. χ^2 or two-tailed Fisher exact tests were performed with Epi Info software version 3.4.3 (Centers for Disease Control and Prevention, Atlanta, Georgia). Two-sided Cochran-Armitage trend tests were run with SAS software version 9.2 (SAS Institute, Cary, North Carolina).

Results

The annual prevalence rates for the 17 years of surveillance are shown in **Table I**, with a graphic representation of the rates of isolated NTDs, NTDs with other anomalies, and total NTDs for years 1 to 17 (**Figure 1**). There were statistically significant declines in overall NTDs ($P < .0001$) and in isolated NTDs ($P < .0001$), but not for NTDs with associated anomalies ($P = .2803$) from 1992 through 2009. **Table I** also shows the rates of spina bifida, anencephaly, and encephalocele for 17 years of surveillance. The rates of spina bifida ($P < .0001$) and anencephaly ($P < .0001$) declined significantly during this period, and the decrease in the rate of encephalocele ($P = .0586$) was near significance. The number of NTD cases totalled 916 of the 945 685 livebirths and fetal deaths during the 17-year period.

Ultrasound scanning was the most frequent means of NTD detection in all years of surveillance, accounting for 55% of identification of cases in the first 5 years and for 78% in the last 5 years (**Table II**; available at www.jpeds.com). Maternal serum screening for alpha fetoprotein became a progressively less-frequent source of initial case identification. Only 13% of NTD cases reached delivery without earlier detection. Three sources—medical records, genetics clinics/autopsy records, and obstetric offices/clinics—accounted for 76% of case notifications to the surveillance program (**Table III**; available at www.jpeds.com).

Table I. Neural tube defect numbers and rates* per 1000 live births and fetal deaths in South Carolina, by project year† and type, 1992 to 2009

Type of NTD	1992-93	1993-94	1994-95	1995-96	1996-97	1997-98	1998-99	1999-2000	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08‡	2008-09	Total
Isolated spina bifida	14	37	30	23	28	18	16	20	16	16	13	14	19	18	20	18	17	337
	0.85	0.69	0.57	0.44	0.54	0.33	0.28	0.34	0.27	0.27	0.22	0.23	0.30	0.29	0.31	0.29	0.29	0.36
Spina bifida with anomalies	2	4	2	2	4	2	1	5	8	6	8	5	3	3	8	1	7	71
	0.12	0.08	0.04	0.04	0.08	0.04	0.02	0.09	0.13	0.10	0.13	0.08	0.05	0.05	0.13	0.02	0.12	0.08
Total spina bifida	16	41	32	25	32	20	17	25	24	22	21	19	22	21	28	19	24	408
	0.97	0.77	0.61	0.48	0.61	0.36	0.30	0.43	0.40	0.37	0.35	0.31	0.35	0.34	0.44	0.31	0.40	0.43
Isolated anencephaly	7	27	17	24	30	13	15	23	17	13	11	19	14	18	15	27	14	304
	0.42	0.51	0.32	0.46	0.58	0.24	0.26	0.39	0.28	0.22	0.18	0.31	0.22	0.29	0.24	0.44	0.24	0.32
Anencephaly with anomalies	4	3	4	4	1	8	6	1	5	9	3	3	0	3	2	8	1	65
	0.24	0.06	0.08	0.08	0.02	0.15	0.11	0.02	0.08	0.15	0.05	0.05	0.00	0.05	0.03	0.13	0.02	0.07
Total anencephaly	11	30	21	28	31	21	21	24	22	22	14	22	14	21	17	35	15	369
	0.66	0.56	0.40	0.54	0.59	0.38	0.37	0.41	0.37	0.37	0.23	0.36	0.22	0.34	0.27	0.57	0.25	0.39
Isolated encephalocele	3	3	9	7	5	7	8	4	4	2	3	3	6	5	7	6	4	86
	0.18	0.06	0.17	0.13	0.10	0.13	0.14	0.07	0.07	0.03	0.05	0.05	0.10	0.08	0.11	0.10	0.07	0.09
Encephalocele with anomalies	1	6	4	4	2	4	2	1	3	5	4	2	2	3	3	3	4	53
	0.06	0.11	0.08	0.08	0.04	0.07	0.04	0.02	0.05	0.08	0.07	0.03	0.03	0.05	0.05	0.05	0.07	0.06
Total encephalocele	4	9	13	11	7	11	10	5	7	7	7	5	8	8	10	9	8	139
	0.24	0.17	0.25	0.21	0.13	0.20	0.18	0.09	0.12	0.12	0.12	0.08	0.13	0.13	0.16	0.15	0.13	0.15
Isolated NTDs	24	67	56	54	63	38	39	47	37	31	27	36	39	42	42	51	35	728
	1.45	1.26	1.07	1.03	1.21	0.69	0.69	0.80	0.62	0.53	0.45	0.59	0.62	0.69	0.66	0.83	0.59	0.77
NTDs with anomalies	7	13	10	10	7	14	9	7	16	20	15	10	5	8	13	12	12	188
	0.42	0.24	0.19	0.19	0.13	0.25	0.16	0.12	0.27	0.34	0.25	0.16	0.08	0.13	0.20	0.20	0.20	0.20
Total NTDs	31	80	66	64	70	52	48	54	53	51	42	46	44	50	55	63	47	916
	1.87	1.50	1.26	1.22	1.34	0.95	0.85	0.92	0.88	0.87	0.70	0.75	0.70	0.82	0.86	1.03	0.79	0.97

*The decrease in the rate ratio over the 17 years is significant for spina bifida ($P < .0001$), for anencephaly ($P < .0009$), for isolated NTDs ($P < .0001$), and for total NTDs ($P < .0001$), but not for encephalocele ($P < .0586$) or NTDs with associated anomalies ($P < .2803$).
†Project years are October through September, year 1 ending September 1993, year 17 ending September 2009.
‡Anencephaly numbers for this period include 6 terminations in Georgia that we are not able to confirm.

At the outset of this study, spina bifida was the most common of the NTDs, accounting for 52% of the total number. Anencephaly was intermediate in prevalence, and encephalocele was least common, accounting for 35% and 13% of the total number, respectively.

Prevalence rates for spina bifida and anencephaly decreased significantly during the 17-year period, with the prevalence rate for anencephaly exceeding the rate for spina bifida in some years (**Table I**). The prevalence rate for encephaloceles and for NTDs with associated anomalies did not decrease significantly. Of the 916 total NTDs identified, 728 (79%) were isolated defects.

A slight majority (106 of 188; 56%) of NTDs with other structural anomalies constituted recognizable patterns of malformations (**Table IV**). Chromosome aberrations were found in 43 cases, with trisomy 18 (21 cases) being most common, and triploidy (6 cases) being second most common. Other syndromes included amniotic bands (33 cases), Meckel syndrome (12 cases), OEIS (Omphalocele, Exstrophy of the bladder, Imperforate anus, and Sacral meningomyelocele; 7 cases), NTD-holoprosencephaly (6 cases), limb-body wall complex (2 cases), and Goldenhar syndrome (3 cases).

Eighty-two NTD cases with co-occurring anomalies did not appear to constitute recognizable syndromes or there was insufficient documentation to make a syndrome diagnosis (**Table V**; available at www.jpeds.com). The co-occurring anomalies ranged from mild and trivial (eg, abnormal palmar creases, bifid scrotum) to severe and lethal (eg, conjoined twinning, sirenomelia). Certain defects (eg, diaphragmatic hernia, omphalocele) were placed in this category, although they might also have reasonably been classified as defects caused by the NTDs.

Maternal diabetes mellitus has long been recognized as a risk factor for NTDs.[4] We had information on the diabetes status of mothers in 704 pregnancies that resulted in infants born with an NTD. Twenty-eight of these (4.0%) had pre-existing diabetes mellitus, and 27 (3.8%) had gestational diabetes mellitus. The percentage of NTD-associated pregnancies with pre-existing diabetes mellitus (4.0%) was 4-fold the background rate of pre-existing diabetes mellitus in South Carolina (0.9%). The percentage of NTD-associated pregnancies with gestational diabetes mellitus (3.8%) was not significantly different from the background rate of gestational diabetes mellitus (4.0%).[18] After fortification, the rates of NTDs in infants of mothers with pre-existing diabetes mellitus decreased from 3.5 to 2.7 per 100 000 live births and fetal deaths. The rate of NTDs in infants of mothers with gestational diabetes mellitus decreased from 6.4 per 100 000 to 1.4 per 100 000 after fortification.

NTDs (66 spina bifida, 55 anencephaly, and 19 encephalocele) occurred in pregnancies in which the mother reported the use of FA during the periconceptional period (**Table VI**; available at www.jpeds.com). The dose of FA used by the mothers varied from 0.4 mg to 1.8 mg. A slightly higher, but non-significant ($\chi^2 = 0.94$, $P = .3321$) percentage (23.6%) of these NTD pregnancies had associated anomalies, as compared with the percentage of infants with

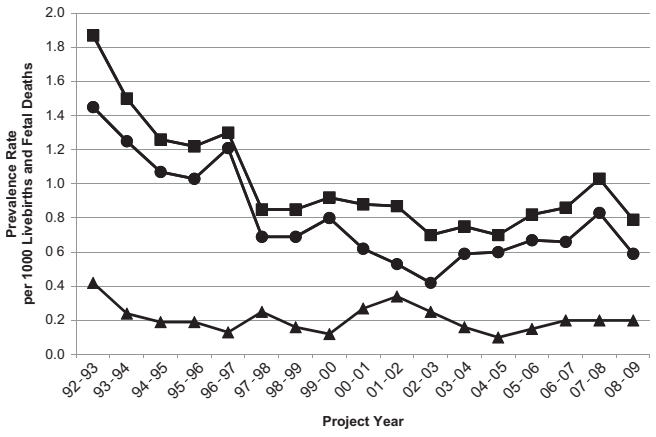

Figure 1. Rates of total NTDs (*squares*), isolated NTDs (*circles*), and NTDs with other anomalies (*triangles*) per 1000 live births and fetal deaths for 1992 through 2009. Project years run from October to September of the next year. Two-sided Cochrane-Armitage trend test results were significant for total NTDs (P = .0001) and isolated NTDs (P = .0001), and the change in rates of NTDs with other anomalies was not significant (P = .2803).

NTD-associated anomalies (20.0%) born to mothers not taking FA.

Pregnancies (n = 484) occurred in women with a child with an NTD. Of 418 pregnancies in which the mother took periconceptional FA supplements, there was one recurrence (0.2%), a recurrent anencephaly with a 13q deletion. Of 66 pregnancies in which the mother did not use FA supplements, there were 4 recurrences (6.1%; a recurrent Meckel/encephalocele, a recurrent anencephaly, a recurrent encephalocele, and a situation in which the first child had spina bifida and the second had craniorachischisis). These proportions are significantly different (P = .0014) with a two-tailed Fisher exact test. Two of the recurrences (1.2%) occurred in 173 pregnancies before fortification, and the other 3 recurrences (1.0%) occurred in 311 post-fortification pregnancies. These proportions are not significantly different (P = 1.0000) with a two-tailed Fisher exact test.

On the basis of the 1992 prevalence rates of 1.87 cases per 1000 live births and fetal deaths, approximately 1738 NTD-affected pregnancies would have been expected in the subsequent 16 years; however, there were only 885 NTD-affected pregnancies during this period. This represents a reduction of 853 NTD cases prevented with FA supplementation and other unknown factors (**Table I** and **Figure 2**; available at www.jpeds.com). Since 1992 to 1993, there has been a decrease in the number of spontaneous abortions with NTDs (67% decrease), terminations of NTD-affected pregnancies (54% decrease), and live-born infants with NTDs (54% decrease). Of the total 982 NTD-affected pregnancies in 17 years (**Figure 2**), 124 (12.6%) were lost to spontaneous abortion and fetal death, 430 (43.8%) were prenatally diagnosed and the pregnancies interrupted, and 428 (43.6%) were live-born infants with NTD.

The distribution of male and female children with NTDs that had other associated anomalies was equal (87 male, 87 female, 14 with unknown sex), and the sex ratio of isolated NTDs showed significantly more female (47.5%) than male children (39.7%, P = .003). There was a slightly higher prevalence rate of total NTD conceptions or births in Hispanic mothers (1.2 per 1000 live births and fetal deaths) than any other racial group (non-Hispanic whites, 1.1; non-Hispanic blacks, 0.7). Although Hispanic conceptions or births had the highest rate of anencephaly, non-Hispanic white NTD conception or birth had the highest rate of encephalocele and the highest rate of spina bifida. Hispanic conception or birth had the highest rate of isolated NTDs, and all races had near equal rates of NTDs with other anomalies.

During the first year of this project (1992), 8% of the women of childbearing age knew of the health benefits of FA, and 8% took FA. These percentages increased to 33% in year 5. These percentages were based on interviews of small numbers (year 1 = 38, year 5 = 60) of women of childbearing years who completed pregnancies not associated with an infant with an NTD. From 1997 to 2007, knowledge and use of FA was based on telephone interviews of approximately 1000 women of childbearing age. The percentage of women having knowledge of FA increased from 32% to 65% and the

Table IV. Neural tube defects with co-occurring anomalies

Type of defect	n of cases	Sex			Race			
		M	F	U	W	B	H	O
Syndromes	106 (56.4%)	49 (26.1%)	48 (25.5%)	9 (4.8%)	62 (33.0%)	38 (20.2%)	6 (3.2%)	0 (0.0%)
Chromosome aberrations	43 (22.9%)	20	21	2	27	15	1	0
Amniotic bands/cranial defects	33 (17.5%)	17	14	2	15	13	5	0
Meckel syndrome	12 (6.3%)	7	3	2	8	4	0	0
OEIS syndrome	7 (3.7%)	2	3	2	4	3	0	0
NTDs/holoprosencephaly	6 (3.2%)	2	4	0	5	1	0	0
Goldenhar syndrome	3 (1.6%)	1	2	0	2	1	0	0
Limb-body wall complex	2 (1.1%)	0	1	1	1	1	0	0
Other associated anomalies not recognized as a syndrome	82 (43.6%)	38 (20.2%)	39 (20.7%)	5 (2.7%)	53 (28.2%)	21 (11.2%)	4 (2.1%)	4 (2.1%)
Total	188 (100%)	87 (46.3%)	87 (46.3%)	14 (7.4%)	115 (61.2%)	59 (31.4%)	10 (5.3%)	4 (2.1%)

M, Male; *F,* female; *U,* unknown; *W,* non-hispanic white; *B,* non-hispanic black; *H,* hispanic; *O,* other; *OEIS,* Omphalocele, Exstrophy of the bladder, Imperforate anus, and Sacral meningomyeocele.

Table VII. Outcome of neural tube defect-affected pregnancies

Outcome	1992-93*	1993-94	1994-95	1995-96	1996-97	1997-98	1998-99	1999-2000	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08†	2008-09	Total
Live births	9	27	20	14	27	21	15	20	12	13	16	15	15	16	26	20	16	302
Live births (died)	3	7	7	9	3	4	3	6	5	7	3	5	8	8	12	5	6	101
Terminations	12	40	36	38	34	20	20	18	26	24	16	18	16	23	11	32	18	402
Fetal demise	4	1	1	2	1	0	0	0	1	2	0	0	0	1	0	0	0	13
Still births	2	3	1	0	4	6	10	9	7	3	5	7	5	2	5	5	6	80
Spontaneous abortion	1	2	1	1	1	1	0	1	2	2	1	0	0	0	0	1	1	15
Unknown	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	3
Total NTDs	31	80	66	64	70	52	48	54	53	51	42	46	44	50	55	63	47	916

*Project years are October through September, year 1 ending September 1993, year 17 ending September 2009.
†Anencephaly numbers for this period include 6 terminations in Georgia that we are not able to confirm.

percentage of women using FA ≥4 times a week increased from 25% to 35% during this period.

Discussion

A substantial decrease in the prevalence rates of spina bifida, anencephaly, and encephalocele in South Carolina has accompanied the increased consumption of FA by women of childbearing age. Overall, the NTD rate has decreased 58% since 1992, a period during which FA supplement use has increased 4-fold (from 8% to 35% of women of childbearing age). In addition, many breakfast cereals have been fortified with 400 mcg FA per serving, and enriched cereal grain flours have been fortified with 140 mcg FA per 100 g milled flour, the latter occurring between 1996 and 1998.

The latest rate for NTDs from the National Birth Defects Prevention Network covers the period from 1998 (fourth quarter) to 2005 (fourth quarter). The "national" rate for spina bifida and anencephaly during this 7-year period was 0.69 cases per 1000 live births and fetal deaths.[19,20] The average rate for spina bifida and anencephaly in South Carolina during these same years was 0.69 cases per 1000 live births and fetal deaths. The rate for the most recent year (2009) for South Carolina was 0.65 cases per 1000 live births and fetal deaths, but the national rates for this period are not yet available.

For occurrent NTDs, we also make these observations. First, the birth prevalence in our population has fallen to a level indistinguishable from the national NTD birth prevalence, suggesting that regional differences in NTD occurrence rates are either attributable to FA consumption patterns or that the variability is confined to folate-responsive etiologic pathways. Second, the reduction in the occurrence rates of spina bifida and anencephaly were more dramatically influenced by folate supplementation than the rate for encephalocele. Becaues of the very high efficacy of FA in recurrence rates for subsequent pregnancies, we infer possible dosage response differences in different types of NTDs. Third, we can infer very little about racial differences in the rates for NTDs and whether those differences reflect primarily genetic or environmental-cultural differences caused by actual folate-consumption patterns. Finally, we did observe a relatively dramatic reduction in NTD rates that coincided with the introduction of FA in wheat flour spread over the interval from 1996 to 1998, when our population of mothers consumed different sources of wheat flour. This was preceded by a decline that mirrors the increasing use of folate supplements that were likely attributable to the public health awareness campaign.

At the outset of the study, expectations were that FA supplementation might be approximately 70% efficacious in the prevention of recurrent NTDs.[8,9] There has been one recurrence of NTDs in 418 prospectively ascertained subsequent pregnancies (0.2%) to mothers with an earlier conception or birth affected with an NTD who used FA in the periconceptional period of the subsequent pregnancy; the recurrence was an encephalocele associated with a 13q deletion. Thus, for isolated NTDs, we observed 0.0% recurrence. The 4

recurrences in the 66 high-risk pregnancies (6.1%) in which FA was not used emphasizes the importance of FA in recurrence prevention.[8,9] In the absence of folate supplementation, the recurrence rate of NTDs in families with an earlier NTD conception or birth is generally stated to be 3% to 5%, with areas of higher prevalence having recurrence on the high end of that range.[21] For South Carolina, the recurrence risk without folate use would be at the high end, and thus we might have expected approximately 21 cases of NTD in the 418 cases receiving folate supplements were folate not efficacious for prevention of NTDs, and approximately 3 cases of NTD in the 66 cases not receiving folate supplements. The number of pregnancies available for study is still fairly limited. However, we feel that our study and other studies[21] have shown that recurrence prevention is quite effective. Because only approximately one-third of states have or have had NTD recurrence prevention projects,[22] more public health agencies need to provide the funding and personnel to prevent the recurrence of NTDs in this very high-risk population.

Because FA fortification appears to have been effective in decreasing the NTD rate in infants of mothers with gestational diabetes mellitus to the population rate, the NTD rate in infants of mothers with pre-existing diabetes mellitus remained high after fortification. A greater effort to control pre-existing diabetes mellitus may be necessary to further reduce the NTD rate in this high-risk group. The probability that a higher-dose FA supplementation might be protective for infants of mothers with pre-existing diabetes mellitus deserves further study.

Although several of the NTD cases with other anomalies may represent previously reported associations, there were no compelling reasons (known inheritance pattern, specificity of the association, confirmatory laboratory testing) to designate them as such. Among these previously reported associations are facial duplication-anencephaly association,[23] anophthalmia-NTD association,[24] colobomamicrophthalmia-clefting syndrome,[25] laterality syndrome,[26] schisis association,[27] anterior encephalocele-anophthalmia syndrome,[28] and others. Hunter has made an extensive listing of the numerous syndromes and associations of NTDs and other anomalies.[2] Specific recurrence risks are available for the NTD syndromes, but not for most of the entities with NTDs and other anomalies that do not constitute a specific syndrome.

Fifteen percent of NTDs occurred in pregnancies in which the mothers used FA in the periconceptional period. A slightly higher rate of syndromal NTDs was found in this group, suggesting that FA protection is more effective against isolated NTDs.

An increasing number of pregnant mothers receive birth defect screening through ultrasound scanning and blood testing, resulting in an increasing number of NTDs that are diagnosed prenatally (**Table III**). Consequently, although termination of pregnancies affected with NTDs accounts for some fraction of the reduction of NTDs, it is the lower number of NTD-affected pregnancies conceived and not an increasing termination rate that is the driving force in the dramatic reductions we describe (**Figure 2** and **Table VII**).

Having now passed through the excitement that accompanied the dramatic discovery of the preventive efficacy of FA, we should be concerned about sustaining an awareness of the importance of FA consumption periconceptionally and consider new mechanisms for increasing passive FA intake to maintain the ground we have gained in the fight to eliminate preventable birth defects. The gap between the percentage of women who know about FA (65%) and the percentage who take FA (35%) offers an opportunity to convert knowledge into action through educational means. Our finding that fortification does not appear to reduce recurrent NTDs, calls for public health agencies to focus greater efforts and resources on this identifiable high-risk group of pregnancies. Similarly, the failure of fortification to compensate for the influence of pre-existing diabetes mellitus in the mother calls for greater attention to diabetes control in the mothers and for a case-control study of the effectiveness of higher-dose folate supplementation in this high-risk group. Finally, the possibility of increasing the amount of FA in enriched cereal grain flours, although remote, deserves further examination. ■

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Table II. Methods of detection of neural tube defects in South Carolina, 1992 to 2009

	Anencephaly	Encephalocele	Spina bifida	Total	% of total
Ultrasound scanning	270	95	236	601	65.6%
Maternal serum α-fetoprotein screen*	79	13	78	170	18.6%
Amniotic fluid α-fetoprotein screen	4	6	15	25	2.7%
Delivery	17	27	76	120	13.1%
Total	370	141	405	916	100%

*This was the first postive screening test result that indicated the possibility of an NTD-affected pregnancy in these cases.

Table III. Methods of notification for the surveillance program from 1992 through 2009

Methods of notification	Number (%)
Hospital medical records surveillance	227 (25%)
Genetics clinics/autopsy	266 (29%)
Obstetric office or clinic	206 (22%)
Fetal boards	84 (9%)
Maternal serum screening program	70 (8%)
Vital records	26 (3%)
Patient initiated	11 (1%)
Spina bifida clinic	11 (1%)
CDC surveillance verification	10 (1%)
Health department prenatal clinic	4 (0.4%)
Children's rehabilitative services clinic	1 (0.1%)
Total	916 (100%)

CDC, Centers for Disease Control and Prevention.

Table V. Eighty-two cases of co-occurring anomalies with neural tube defects that do not appear to constitute a recognizable syndrome

Anomaly	n
Facial clefting	
Cleft lip/cleft palate	4
Cleft lip/cleft palate with other anomalies	8
Cleft lip	2
Cleft palate	2
Cleft palate with other anomalies	3
Facial cleft with other anomalies	3
Total facial clefting	22 (27%)
Cardiac defects	
Cardiac defects	14
Cardiac defects with other anomalies	13
Total cardiac defects	27 (33%)
Limb defects	
Limb defects	1
Limb defects with other anomalies	5
Total limb defects	6 (7%)
GI defects	
GI tract defects with other anomalies	2
Ventral wall defects	5
Ventral wall defects with other anomalies	9
Total GI tract defects	16 (20%)
GU defects	
Renal agenesis	1
Renal agenesis with other defects	9
Other GU tract anomalies	2
Other GU tract anomalies with other defects	11
Total GU tract defects	23 (28%)
Other anomalies*	
Diaphragmatic hernia	9
Situs inversus	3
Conjoined twins	2
Microphthalmia	2
Dandy-Walker	2
Laryngeal defects	2
Atelencephaly-aprosencephaly	1
Craniosynostosis	1
Cystic lungs	1
Sirenomelia	1
Total other anomalies	24 (29%)

GI, Gastrointestinal; *GU*, genitourinary.
*Other findings like single umbilical artery and abnormal palmar creases are not included in the tabulation.

Table VI. Neural tube defects occurring in pregnancies in mothers who took folic acid

Type of defect	n cases	Sex			Race			
		Male	Female	Unknown	White	Black	Hispanic	Other
Isolated	107 (76.4%)	46 (32.9%)	43 (30.7%)	18 (12.9%)	89 (63.6%)	15 (10.7%)	2 (1.4%)	1 (0.7%)
Spina bifida	50 (35.7%)	26	17	7	40	9	1	0
Anencephaly	46 (32.9%)	16	22	8	41	4	1	0
Encephalocele	11 (7.9%)	4	4	3	8	2	0	1
Associated anomalies	33 (23.6%)	14 (10.0%)	16 (11.4%)	3 (2.1%)	28 (20.0%)	5 (3.6%)	0 (0.0%)	0 (0.0%)
OEIS	3 (2.1%)	3	0	0	3	0	0	0
Trisomy 18	7 (5.0%)	4	3	0	7	0	0	0
Amniotic bands/cranial defects	3 (2.1%)	2	1	0	1	2	0	0
Goldenhar	1 (0.7%)	0	1	0	1	0	0	0
Chromosome aberrations	5 (3.6%)	1	4	0	4	1	0	0
Other anomalies	14 (10.0%)	4	7	3	12	2	0	0
Total	140 (100%)	60 (43.0%)	59 (42.0%)	21 (15.0%)	117 (83.6%)	20 (14.3%)	2 (1.4%)	1 (0.7%)

OEIS, Omphalocele, Exstrophy of the bladder, Imperforate anus, and Sacral meningomyeocele.

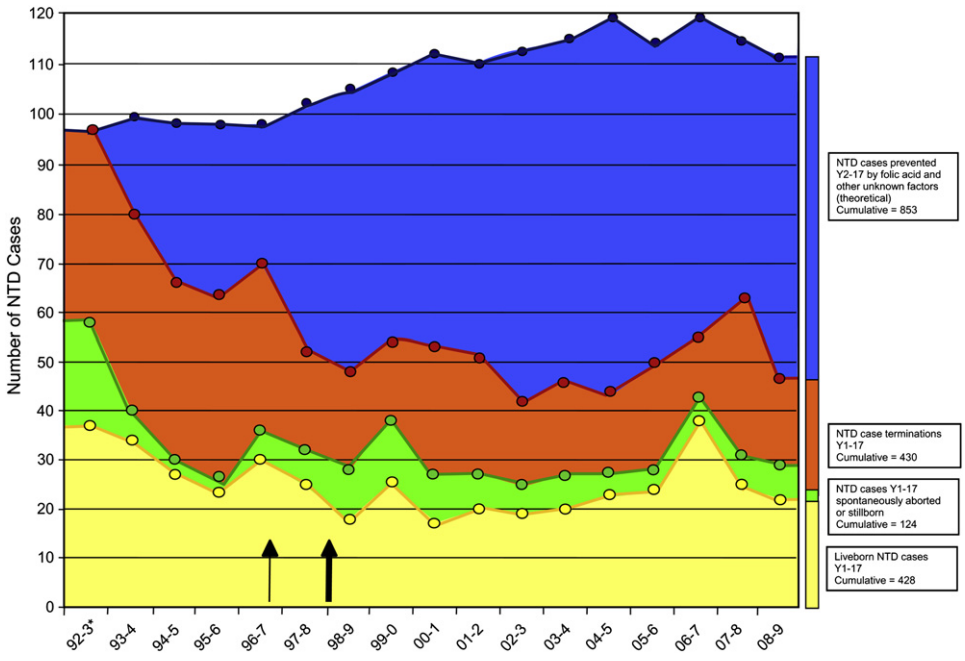

Figure 2. The combined affect of prenatal diagnosis and FA use on the number of NTDs. The top line of this **Figure**, calculated from 1992 prevalence rates, gives an estimate of the NTD cases that would have occurred without FA supplementation, fortification, and other unknown factors. *Statewide numbers for this year (1992-1993) were extrapolated from surveillance in a 14-county area. All other years are actual statewide surveillance numbers. The outcome of 3 NTD-affected pregnancies is not known. The *thin arrow* represents the fortification in South Carolina; the *thick arrow* represents mandatory fortification in the United States.