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Original Article

Neural tube defects in Australia: Trends in encephaloceles and other neural tube defects before and after promotion of folic acid supplementation and voluntary food fortification†

Carol Bower [1 2 *], Heather D'Antoine [2], Fiona J. Stanley [2]

[1]Western Australian Birth Defects Registry, Women and Newborn Health Service, King Edward Memorial Hospital, Subiaco, Western Australia

[2]Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth

email: Carol Bower (caroline.bower@health.wa.gov.au)

[*]Correspondence to Carol Bower, WA Birth Defects Registry, King Edward Memorial Hospital, 374 Bagot Rd, Subiaco, Western Australia 6008, Western Australia 6872

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KEYWORDS

neural tube defects • encephalocele • folic acid • fortification • spina bifida • anencephaly

ABSTRACT

BACKGROUND:

Use of periconceptional folic acid supplementation has been promoted in Western Australia since late 1992, and voluntary fortification of some foods with folic acid has been permitted in Australia since 1996. Reduced rates of neural tube defects (NTDs) have been observed since 1995. Aboriginal infants have a higher rate of NTDs, but no fall in rates has been documented. Encephaloceles have not been examined separately.

METHODS:

Data on anencephaly, spina bifida, and encephalocele were obtained from the Western Australian Birth Defects Registry. The prevalence ratio for each type of NTD was calculated, comparing 1993 to 1995 (promotion of supplements, no fortification) and 1996 to 2006 (promotion of supplements and voluntary fortification) with 1980 to 1992 (no promotion or fortification).

RESULTS:

From 1996 to 2006, there was a 32% reduction in anencephaly, 23% in spina bifida, and 34% in encephalocele compared with 1980 to 1992. There were no differences seen from 1993 to 1995 compared with 1980 to 1992. For Aboriginal infants, the rates were higher than for non-Aboriginal infants, for each type of NTD. The prevalence ratios, comparing 1996 to 2006 with 1980 to 1995, were 0.70 (CI, 0.61-0.79) for non-Aboriginal infants and 0.90 (CI, 0.61-1.32) for Aboriginal infants.

CONCLUSIONS:

Overall, the rates of encephalocele, anencephaly, and spina bifida have fallen to a similar extent in association with promotion of folic acid supplements and voluntary fortification. No such falls were seen for Aboriginal infants. These data will provide a useful baseline against which to monitor the effects of mandatory fortification on NTDs when it is introduced in Australia in September 2009. Birth Defects Research (Part A), 2009.

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ARTICLE TEXT

The Western Australian Birth Defects Registry had been operating for less than one year when Dick Smithell's seminal paper was published in 1980 (Smithells et al., [1980]), showing that periconceptional multivitamins offered protection from recurrence of NTDs. Excited by the findings, the need for further research, and the enormous potential for prevention, we decided that we could contribute by conducting a case-control study specifically examining dietary folate for the prevention of occurrence of NTDs. Our study began in 1982, the first major research project of our fledging registry. The results of that study, showing a protective effect of dietary folate, were published in 1989 (Bower and Stanley, [1989]), and neural tube defects have continued to be the focus of our research.

INTRODUCTION

Following randomized controlled trial evidence of the prevention of neural tube defects (NTDs) with folic acid (Czeizel and Dudas, [1992]; MRC Vitamin Study Research Group, [1991]), the National Health and Medical Research Council (NHMRC) in Australia issued guidelines recommending that women planning a pregnancy take periconceptional folic acid supplements and all women of childbearing age increase their intake of dietary folate (NHMRC, [1994]).

Between mid-1992 and March 1995, we undertook health promotion activities in the state of Western Australia to promote the use of folic acid supplements for the prevention of NTDs. Information sheets for health professionals and posters and brochures for women were distributed to all general practitioners, obstetricians, pediatricians, child health nurses, and pharmacists in the state on three occasions over the period. Promotional materials were also distributed to schools, child care centers, family planning facilities, and public libraries, and 150 presentations were made to community, student, and workplace groups. There was an average of 2.5 unpaid media items on folate and NTD per month over the period, as well as several paid media activities (three newspaper advertisements, two radio commercials, and advertisements on 40 taxis for 3 months in 1994) (Bower et al., [1997]). Evaluation of the program showed that women of child-bearing age had increased their knowledge that folate can prevent spina bifida from 8% before the program began to 67.5% 2.5 years later, 70% of general practitioners were recommending periconceptional folic acid supplementation, and 87.5% of pharmacists had noticed an increase in sales of 0.5-mg supplements of folic acid (the recommended dose). Wholesale sales by the major provider of 0.5-mg folic acid tablets had increased markedly compared to other Australian states, where little or no health promotion had been undertaken. Reported use of periconceptional folic acid supplements increased from <13% in 1993 (Marsack et al., [1995]) to 30% in 1995 (Bower et al., [1997]) and has remained at approximately 30% since 1995 (Bower et al., [2005]). At the conclusion of the Western Australian program, the state Department of Health continued further health promotion at lower intensity. Other states have conducted campaigns (Chan et al., [2001]; Watson et al., [2001]; Watson et al., [1999]), and there has been limited national health promotion.

Based on the recommendations of an expert panel convened by the NHMRC in 1995 (NHMRC, [1995]), voluntary fortification of certain foods with folic acid was permitted for the first time in Australia in 1996. Only 13 fortified products were available by the end of 1996. The number increased slowly until, by June 1999, 104 products were fortified with up to 200 μg of folic acid - mainly breakfast cereals (almost 50% of the market share) and breads (18% of market share) (Abraham and Webb, [2001]).

These interventions have been evaluated using data from the Western Australian Birth Defects Registry and have shown a fall of 30% in the total rate of NTDs (and anencephaly and spina bifida individually) from 1996 to 2000, compared with 1980 to 1995 (Bower et al., [2002]). We also found that NTDs occurred at a higher rate in Aboriginal infants, but there had been no reduction in total NTDs in Aboriginal infants since the introduction of health promotion and voluntary fortification. (Bower et al., [2004]) Trends in encephaloceles were not examined separately in either of these analyses.

Encephaloceles, although usually considered an NTD, also have some characteristics that distinguish them from anencephaly and spina bifida. They are more likely to be associated with other birth defects and occur more frequently as part of a syndrome (Rowland et al., [2006]). In Western Australia, encephaloceles occur almost twice as often in Aboriginal versus non-Aboriginal infants (Bower et al., [2004]).

We undertook an analysis of data from the Western Australian Birth Defects Registry to examine trends in encephaloceles occurring from 1980 to 2006, to compare them with trends in anencephaly and spina bifida over the same period, and to include an analysis by Aboriginality.

METHODS

Western Australia is the largest Australian state, with a population of 2.1 million, 3% of whom are Aboriginal (or Torres Strait Islander). There are 25,000 births per year, 6% of them to Aboriginal women.

Data on cases of NTD (anencephaly, spina bifida, and encephalocele) were obtained from the Western Australian Birth Defects Registry, which is a population-based registry that uses multiple sources of case ascertainment, including prenatal diagnostic services, hospital inpatient and outpatient records, post mortem records, and notifications from obstetricians, pediatricians, and geneticists. Live births, stillbirths and terminations of pregnancy for fetal anomaly are included; birth defects diagnosed prenatally and up to 6 years of age are registered. The collection has high ascertainment (Bower et al., [2001]). Data are coded using the five-digit British Pediatric Association (BPA) extension of ICD-9.

To avoid double-counting of the few cases of multiple NTDs, a case was counted as *anencephaly* if it had a code of anencephaly (BPA code 74000-74009), regardless of whether there was also a spina bifida code present. Spina bifida (BPA code 74100-74109) was counted as *spina bifida* even in the presence of a code for encephalocele, but only if there was no anencephaly present. Encephalocele (BPA code 74200-74209) was counted as *encephalocele* only if there was no spina bifida present.

Cases of NTD were categorized as *isolated* if the NTD was the only abnormality or if the only other birth defects were related to or a consequence of the NTD (such as talipes equinovarus and hydrocephalus). All other cases with nonneural birth defects were categorized as *multiple*.

Years of birth were grouped as follows: 1980 to 1992, before promotion of folic acid; 1993 to 1995, folic acid promotion but no voluntary fortification; and 1996 to 2006, folic acid promotion and voluntary fortification.

The prevalence of each type of NTD was calculated per 1000 births by grouped year, using all births with NTDs (live births, stillbirths, and terminations of pregnancy) in the numerator and all live and still births in Western Australia as the denominator.

The prevalence ratio for each type of NTD was calculated as the ratio of the prevalence from 1993 to 1995 and 1996 to 2006, divided by the prevalence in the baseline years (1980-1992). Ninety-five percent confidence intervals (CIs) around these ratios were calculated.

RESULTS

During the study period, there were 667,825 births in Western Australia and 1160 cases of NTD: 507 with anencephaly, 549 with spina bifida, and 104 with encephalocele.

Table 1 shows the characteristics of each type of NTD. Similar proportions of cases of each type of NTD occurred in females and had mothers who resided in the metropolitan area. A lower proportion of encephaloceles occurred in multiple births, and only 52.9% were isolated defects, compared with more than 80% for anencephaly and spina bifida. Most cases of anencephaly occurred in terminations of pregnancy and stillbirths, similar proportions of cases of spina bifida and encephalocele were pregnancy terminations, and most cases of spina bifida were liveborn.

Table 1. Characteristics of Cases of Anencephaly, Spina Bifida, and Encephalocoele: Western Australia, 1980 to 2006

	Anencephaly	Spina bifida	Encephalocoele
	N (%)	N (%)	N (%)
Number of cases	507 (100%)	549 (100%)	104 (100%)
Female	269 (53.1%)	283 (51.5%)	53 (51.0%)
Isolated	436 (86.0%)	443 (80.7%)	55 (52.9%)
Multiple birth	27 (5.4%)	18 (3.3%)	1 (1.0%)
Metropolitan residence	368 (72.9%)	379 (69.3%)	71 (68.3%)

Outcome of pregnancy			
Live birth	45 (8.9%)	308 (56.1%)	49 (47.1%)
Stillbirth	64 (12.6%)	21 (3.8%)	10 (9.6%)
Termination	398 (78.5%)	220 (40.1%)	45 (43.3%)
Prevalence per 1000 births			
Aboriginal	0.85	1.54	0.29
Non-Aboriginal	0.75	0.78	0.15

N (%), number of cases and percentage of all cases of that NTD type.

The prevalence per 1000 births was greater for each type of NTD in Aboriginal compared with non-Aboriginal births (Table 1). The total prevalence for Aboriginal infants was 2.69 per 1000 births, and 1.68 per 1000 births for non-Aboriginal infants. Figure 1 shows a decline in each type of NTD and total NTDs per 1000 births over time from 1980 to 2006 in Western Australia.

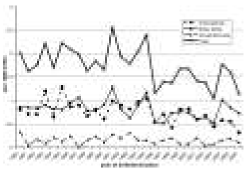

Figure 1. Trends in neural tube defects, Western Australia 1980-2006. [Normal View 17K | Magnified View 40K]

Compared to the prepromotion and prefortification period (1980-1992), there were no differences in NTD rates in the early period (1993-1995) of promotion of supplements (but no fortification). A reduction in anencephaly, spina bifida, and encephalocele were seen during 1996 to 2006 (the period of supplement promotion and voluntary fortification) compared with 1980 to 1992. The reductions were similar for all three types of NTD - 32% for anencephaly, 23% for spina bifida, and 34% for encephalocele; for the former two, the confidence intervals excluded unity (Table 2).

Table 2. Prevalence and Prevalence Ratios for Anencephaly, Spina Bifida, and Encephalocoele before and after the Introduction of Promotional of Folic Acid Supplements and Voluntary Fortification of Foods with Folic Acid: Western Australia, 1980 to 2006

	Anencephaly		Spina bifida		Encephalocoele	
All NTD	**N (Prev)**	**PR (CI)[a]**	**N (Prev)**	**PR (CI)[a]**	**N (Prev)**	**PR (CI)[a]**
1980-1992	267 (0.86)	1	281 (0.91)	1	53 (0.17)	1
1993-1995	73 (0.96)	1.11 (0.85-1.43)	69 (0.91)	0.99 (0.76-1.29)	16 (0.21)	1.22 (0.69-2.14)
1996-2006	167 (0.59)	0.68 (0.56-0.83)	199 (0.70)	0.77 (0.64-0.92)	32 (0.12)	0.66 (0.42-1.02)

[a] Confidence interval, 95%.
NTD, neural tube defect; N (Prev), number of cases (prevalence per 1000 births); PR, prevalence ratio; CI confidence interval.

Similar reductions were seen for isolated and multiple NTDs. Comparing 1993 to 1995 with 1980 to 1992, the prevalence ratio for isolated NTDs was 1.08 (CI, 0.89-1.31) and for multiple NTDs was 1.03 (CI, 0.69-1.53). Comparing 1996 to 2006, with 1980-1992, the prevalence ratio for isolated NTDs was 0.74 (CI, 0.64-0.85) and for multiple NTDs was 0.71 (CI, 0.53-0.94). When we examined anencephaly, spina bifida, and encephalocele separately, similar decreases were also seen for isolated and multiple cases (data not shown).

The reduction in each type of NTD (and the total) is shown for non-Aboriginal infants in Figure 2A. Given the absence of any difference between 1980 to 1992 and 1993 to 1995, these years have been combined (1980-1995). Figure 2B shows that for Aboriginal infants, the rates are higher for NTD overall and for each type (particularly spina bifida and encephalocele), and there has been only a small reduction over time. The prevalence ratios, comparing 1996 to 2006 with 1980 to 1995, were 0.70 (CI, 0.61-0.79) for non-Aboriginal infants and 0.90 (CI, 0.61-1.32) for Aboriginal infants.

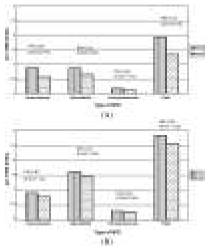

Figure 2. (A) Neural tube defects per 1000 births for non-Aboriginal infants. (B) Neural tube defects per 1000 births for Aboriginal infants. [Normal View 11K | Magnified View 28K]

DISCUSSION

We have shown that the prevalence of all types of NTD (anencephaly, spina bifida, and encephalocele) has fallen over the period when the use of periconceptional folic acid supplementation has been promoted and voluntary fortification of some foods was allowed. There has been a similar reduction for anencephaly (32%), for spina bifida (23%) and for encephaloceles (34%). Similar reductions have been reported in the United States and Canada, following mandatory fortification of flour with folic acid. In Canada, there was a 38% reduction in anencephaly, 52% in spina bifida, and 31% in encephalocele (De Wals et al., [2007]). In the United States, data from birth defects monitoring programs with prenatal ascertainment of cases showed a reduction of approximately 17% for anencephaly and 36% for spina bifida (Centers for Disease Control and Prevention, [2004]). No data for encephaloceles were presented in this analysis, but in a study based on data from the Metropolitan Atlanta Congenital Defects Program, a 40% reduction in encephaloceles and spina bifida and a 20% reduction in anencephaly were seen following fortification (Rowland et al., [2006]).

Our findings of a reduction in both isolated and multiple NTDs with health promotion and voluntary fortification are in keeping with the findings of Rowland et al. ([2006]), who reported similar reductions for isolated and multiple encephaloceles following fortification, and Khoury et al. ([1996]), who reported reductions in isolated and multiple cases of anencephaly and spina bifida with periconceptional folic acid supplement use from two case-control studies.

During 1993 to 1995, when there was no fortification permitted and the use of supplements was increasing, we saw no reduction in NTD. Supplement use peaked at 30% and has stayed at that level since 1996, the year voluntary fortification first started, but even by late 1998, voluntary fortification had shown little effect on folate intakes among the target population (Abraham and Webb, [2001]). The rate of NTDs fell in 1996 and there have been no further reductions over time, suggesting that the major effector has been folic acid supplement use.

Aboriginal Australians have a higher rate of NTD, especially spina bifida and encephalocele (Bower et al., [2004]), and there has been only a small (10%) reduction in relation to health promotion and voluntary fortification. This difference in effect was an important factor when Food Standards Australia New Zealand was considering mandatory fortification to protect against NTDs. Mandatory fortification in Australia was approved in 2007, and wheat flour for breadmaking will be fortified with 230 to 280 μg of folic acid per 100 gm of flour by September 2009. Flour designated as *organic* will be exempt. Approval for voluntary fortification of foods, with the exception of bread, will continue (Food Standards Australia New Zealand, [2008]).

Overall, we have shown that the rates of encephalocele, anencephaly, and spina bifida have fallen to a similar extent in association with promotion of folic acid supplements and voluntary fortification. No such falls were seen for Aboriginal infants. These data will provide a useful baseline against which to monitor the effects of mandatory fortification on NTD, when it is introduced in Australia in September 2009.

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