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The impact of prenatal diagnosis on neural tube defect (NTD) pregnancy versus birth incidence in British Columbia

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Abstract. The birth incidence of neural tube defect (NTD) cases in British Columbia (B.C.), and elsewhere in North America, is reported to be declining. This decline is being attributed to folic acid (FA) supplementation and food fortification, but 2nd trimester prenatal screening of pregnancies for NTDs and other congenital anomalies has increased during this timeframe, as well. This descriptive, population-based study evaluates the impact of prenatal screening of NTD-affected pregnancies on (1) pregnancy outcome and (2) reporting of NTD births to the provincial Health Status Registry (B.C.H.S.R.); and it assesses (3) the use of periconceptional FA supplementation. NTD cases were ascertained from medical records of health centres providing care to families with NTD-affected pregnancies and newborns; and from NTD cases reported to the B.C.H.S.R. In 1997–1999, the B.C.H.S.R. published a NTD incidence of 0.77/1000. In this study, 151 NTD-affected pregnancies were identified, with an incidence of 1.16/1000. Partial Reporting of induced abortions in a NTD incidence 45.5% low than the actual incidence. Medical records were available for review on 144/151 pregnancies. Prenatal screening identified 86.1% (124/144) of NTD-affected pregnancies, with 72.6% (90/124) resulting in pregnancy termination, and 27.4% (34/124) continuing to term. Use of FA supplementation in the periconceptional period was recorded in 36.4% of pregnancies (39/107). Thus in B.C. the decline in the NTD incidence is due predominantly to pregnancy terminations following prenatal diagnosis, which reduces the NTD incidence by 60%, from 1.16/1000 to 0.47/1000. Continued efforts for primary and the option of secondary prevention of NTDs are recommended in order to improve newborn health in B.C. and elsewhere. These interventions need to be monitored, however, for optimal health care planning.

Key words: anencephaly, B.C. Health Status Registry, birth defects registry, folic acid, incidence of NTDs, neural tube defects, NTD pregnancy outcome, prenatal diagnosis of NTDs,prevention of NTDs, spina bifida.

Introduction

An apparent decline in the newborn incidence of neural tube defects has recently been reported in British Columbia (Hall et al. 1988; Chambers et al. 1994; Health Status Registry 1999), elsewhere in Canada (Lowry 2001; Health Canada 2002; Gucciardi et al. 2002; Persad et al. 2002; De Wals et al. 2003), in the United States (Stevenson et al. 2000; Honein et al. 2001; CDC 2005; Feldkemp et al. 2002; Williams et al. 2002) and other countries (Castilla et al. 2003). The Province of British Columbia (B.C.) has reported a significant decline in NTD incidence from 1.25/1000 in 1958–1984 to 0.77/1000 in 1997–1999 (Hall et al. 1988; Health Canada 2002). After a decade of public health initiatives recommending daily folic acid (FA) supplementation and food fortifica-

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tion (CDC 1992; Oakley 1993; Van Allen et al. 1993; Wilson and Van Allen 1993), the declining NTD incidence has stimulated optimism that efforts for primary prevention are having an effect (Oakley 2002; Brent et al. 2000; Gucciardi et al. 2002; Health Canada 2002; Stevenson et al. 2000; Feldkemp et al. 2002; Persad et al. 2002; De Wals 2003; Oakley et al. 2004).

Concurrent with FA public health initiatives, however, there is increasing utilization in B.C. of prenatal screening for detection of NTDs and other congenital anomalies by using 2nd trimester fetal ultrasounds (US) and maternal triple marker screening (TMS) (Cochrane et al. 1996). The limitation of many of the recent publications evaluating the impact of FA initiatives on the NTD incidence is incomplete ascertainment of aborted NTD-affected fetuses diagnosed with prenatal screening. Several recent studies have evaluated these issues, and found significantly higher NTD incidences when there is more complete ascertainment of NTD-affected fetuses (Feldkamp et al. 2002; Health Canada 2002; Lowry 2001; Ethen and Canfield 2002; Persad et al. 2002).

Although one could speculate that the decline in the B.C. NTD birth incidence is due to FA initiatives, incomplete ascertainment of prenatally diagnosed NTD cases must be also considered as a contributing factor. Like many other registries, the B.C.H.S.R. excludes fetuses <500 g and/or < 20 weeks gestation in order to avoid overestimating the birth incidence of anomalies by inclusion of spontaneous losses. As a result, many otherwise viable NTD-affected fetuses may not be reported to the B.C.H.S.R. because detection and therapeutic abortions (TAB) often occurs before 20 weeks gestation. Other factors contributing to underreporting of cases to the B.C.H.S.R. are privacy issues surrounding selective pregnancy termination of a fetus with structural anomalies; fetal anomalies identified by ultrasound may not be confirmed post-delivery due to the method of pregnancy termination; and/or limited access to fetal autopsy services in community hospitals may result in incorrect or no diagnosis.

In this study, the impact of prenatal screening for NTD-affected fetuses on the outcome of pregnancies and on the B.C. birth incidence is evaluated. The availability of autopsy and newborn medical records on almost all cases provides additional information on the changing incidence of specific types of NTDs, site of involvement, the presence or absence of associated structural anomalies, maternal use of periconceptional folic acid supplementation, and parental prenatal decision-making.

Material and methods

This is a descriptive, population-based study of NTD-affected births in British Columbia. Included NTD cases are anencephaly, exencephaly, encephalocele, craniorachischisis, iniencephaly with open cranial and/or spine defects, spina bifida, meningomyelocele, meningocele, and lipomeningoceles. Excluded NTD cases are spina bifida occulta, sacral teratomas with connections to the spinal canal, and iniencephaly without an open neural tube defect.

The B.C. Health Status Registry (B.C.H.S.R.) cases are ascertained at birth, with additional information on the cases obtained from multiple sources, including medical records during infancy. Inclusion criteria are congenital anomalies diagnosed in liveborns, neonatal deaths and stillbirths 20 weeks 0 days gestation and/or 500 g. Cases were ascertained for the years 1997–1999 by using the following ICD-9 codes: 740 (anencephalus and similar anomalies), 740.0 (anencephalus), 740.1 (craniorachischisis), 740.2 (iniencephaly) if there was a neural tube defect associated with it; 741 (spina bifida, excluding spina bifida occulta); 741.0 (spina bifida with hydrocephalus) or if there was an Arnold Chiari malformation identified on fetal ultrasound; 741.9 (spina bifida without hydrocephalus); and 742.0 (encephalocele). Other malformations included in the 742 category were excluded because they were not considered to have a pathogenesis resulting from failure of embryonic closure of the neural tube. Cases of lipomeningocele were included.

Medical records case ascertainment

Provincial medical, obstetrical and surgical specialty services are centralized in B.C., which allows ascertainment of NTD cases from a limited number of hospital and outpatient programs by using data bases and/or patient logs. Hospital and program records reviewed included those at B.C. Children's and Women's Health Centre in Vancouver, including the Provincial Medical Genetics Programme; the Spina Bifida clinic; the Centre for Prenatal Diagnosis and Treatment; the Fetal Diagnostic Services Clinic; the Fetal Pathology Ser-

vice; and the division of Paediatric Neurosurgery. In Victoria, the reviewed records were from the Medical Genetics, Perinatology, and Spina Bifida Clinic programmes at Victoria General Hospital.

Case selection

Cases included are all NTD-affected fetuses born following TABs, stillbirths, and newborns born to mothers residing in B.C. Cases excluded were spontaneous abortions (SABs) < 20 weeks gestation and offspring of women from out of province delivering in B.C.

Results

Cases ascertained: A total of 151 NTD-affected pregnancies were identified during the study period and their outcome is summarized in Table 1.

The difference in cases ascertained by the B.C.H.S.R. and Health Centre medical records review is summarized in Table 2. Duplicate entries were determined by cross-referencing mother's name, date of birth and personal health numbers. A total of 47% of identified NTD cases were not reported to the B.C.H.S.R. The B.C.H.S.R. NTD incidence determined by this study is lower than published incidence because non-NTD cases were excluded (e.g. hydranencephaly, cranial teratoma, iniencephaly without an open neural tube defect). All missed cases not entered in the registry were fetuses < 20 weeks gestation. Review of medical records identified 95% of the total B.C. NTD cases. Cases identified by the B.C.H.S.R. but not by the medical records were stillbirth fetuses 20 weeks gestation and/or 500 g delivered in rural B.C. communities.

Medical records were available for review on 144/151 (95%) of the cases, allowing for a more detailed analysis. All of these cases had results of autopsy and/or medical evaluations in the neonatal period allowing for further analysis. Table 3 summarizes the incidence of different types of NTDs involving different NT closure regions. Table 4 summarizes the types of NTDs and associated non-CNS structural anomalies, Table 5

Table 1. Outcome of the 151 NTD-affected pregnancies identified in British Columbia

Pregnancy outcome	1997	1998	1999	Total
Stillbirths	5	4	4	13 (8.6%)
Therapeutic abortions	34	22	34	90 (59.6%)
Livebirths	11	13	24	48 (31.7%)
Total	50	39	62	151

Table 2. Case ascertainment of NTD births from the B.C.H.S.R. and from medical records from B.C. Health Centres, B.C. births, and NTD incidences

Source	Number of NTDs				Incidence of NTDs per 1000[a]			
	1997	1998	1999	Total	1997	1998	1999	Mean
B.C.H.S.R.[b]	25	22	33	80	0.56	0.51	0.78	0.61[d]
Health Centres[c]	48	33	58	139	1.07	0.76	1.38	1.07
Total NTDs	50	39	62	151	1.11	0.90	1.47	1.16

[a]Calculated basing on total numbers of B.C. births: 44 734 in 1997, 43 141 in 1998, and 42 040 in 1999; [b] B.C.H.S.R. registers livebirths, stillbirths, and TABs 20 weeks gestation and/or 500 g birth weight; [c] Health Centre medical records identifies livebirths, stillbirths, and all TABs referred for medical services; [d] This incidence is lower than the published incidence of 0.77/1000 (Health Canada 2002) because in this study incidence excludes all TABs under 20 wk/500 g and excludes malformations that do not fit the study criteria

Table 3. Numbers of NTD by site of involvement (all identified cases)

Site of involvement	Number of NTDs				Incidence of NTDs per 1000[a]			
	1997	1998	1999	Total	1997	1998	1999	Mean
Anencephaly	17	12	28	57	0.80	0.28	0.66	0.44
Encephalocele	6	4	6	16	0.13	0.09	0.14	0.12
Spina bifida	27	23	28	78	0.60	0.53	0.66	0.60
Total NTDs	50	39	62	151	1.11	0.90	1.47	1.16

[a]Calculated basing on total numbers of B.C. births: 44 734 in 1997, 43 141 in 1998, and 42 040 in 1999

Table 4. The types of NTDs and associated non-CNS structural anomalies documented in health records of 144 cases with autopsy and/or newborn examinations

NTD	No other non-CNS anomalies (-)	Other non-CNS anomalies (+)	% with other non-CNS anomalies
Open cranial:	33/54	21/54	(38.8%)
Anencephaly	32/43	11/43	(25.6%)
Craniorachischisis	1/5	4/5	(80%)
Iniencephaly	0/6	6/6	(100%)
Encephalocele	3/14	11/14	(78.6%)
Spinal:	53/76	23/76	(30.3%)
Cervical	0/2	2/2	(100%)
Thoraco-lumbar-sacral	8/14	6/14	(42.8%)
Lumbo-sacral	37/48	11/48	(22.9%)
Sacral	3/5	2/5	(40%)
Lipomeningocele	5/7	2/7	(28.6%)
Total NTDs	89/144	55/144	(38.2%)

Table 5. Types of anomalies in 34 pregnancies continued after prenatal NTD diagnosis

NTD site involved	Continued		Remaining cohort	
Open cranial	7	(20.6%)	47	(42.7%)
Encephalocele	1	(2.9%)	13	(11.8%)
Spinal:	26	(76.5%)	50	(45.5%)
Cervical	1	(2.9%)	1	(0.9%)
Thoraco-lumbo-sacral	5	(14.7%)	9	(8.2%)
Lumbo-sacral	15	(44.1%)	33	(10.0%)
Sacral	4	(11.8%)	1	(0.9%)
Lipomeningocele	1	(2.9%)	6	(5.4%)
Total NTDs	34	(100%)	110	(100%)

summarizes the type of NTD anomalies in the continuing pregnancies following prenatal diagnosis.

Demographics: The study mothers had a mean age of 30.45 years (range 1842) and a mean of 2.42 pregnancies (range 16).

Prenatal diagnosis (PND) with ultrasound confirmation of anomalies was reported in the records of 86.1% (124/144) of pregnancies, or 82% (124/151) of the entire cohort. Eighteen percent (27/151) of pregnancies had no reported prenatal testing and continued to term presumably unaware of the fetal concerns. Through medical records it was identified that 2 cases (2/124; 1.6%) had prenatal screening with ultrasound in the communities and the anomalies were not identified. One of these newborns had a skin-covered lipomeningocele in the lumbosacral area. The other had a small meningocele in the sacral area.

Pregnancy planning following prenatal diagnosis: All NTD-affected pregnancies identified prenatally were referred to specialty services in Vancouver and/or Victoria for further evaluation, diagnostic testing, counselling, and pregnancy management. Services consulted included the Fetal Diagnosis and Treatment Service clinic, perinatology, medical genetics, neurosurgery, spina bifida clinics, and neonatology, as indicated.

Of the 124 pregnancies with NTD-affected fetuses identified by prenatal diagnosis, 78.2% (97/124) were < 24 weeks gestation, 12% (15/124) were 24 weeks gestation, and for 9.7% (12/124) the gestation at diagnosis was not recorded in the medical records. A gestational age of 23 weeks 6 days was the working cut-off for availability of pregnancy termination for non-lethal anomalies in B.C. during the study period. In 2 cases over that gestational age, the couples decided to deliver at facilities in the U.S.A. offering ‘late’ TABs.

Pregnancy choices: Following comprehensive prenatal evaluation and counselling, 72.6% (90/124) of women chose not to continue their

pregnancy, 25.8% (32/124) chose to continue to term, and 1.6% (2/124) continued to term unaware that there were fetal anomalies.

Continuing pregnancies: Of those 27.4% (34/124) pregnancies that continued following prenatal diagnosis, 5.9% (2/34) resulted in stillbirths and 94% (32/34) resulted in liveborn infants. Of those born alive, 31.25% (10/32) were neonatal deaths. All deaths were attributable to medical problems related to the central nervous system (CNS) and/or associated structural anomalies (see Table 5).

The overall survival rate was 64.7% (22/34) for continuing pregnancies and 15.2% (22/144) for the total cohort of identified NTD cases.

nificant difference in the number of NTD cases reported to the B.C. Health Status Registry, compared to cases identified through medical records and cross-matched to the B.C.H.S.R. cases (see Table 2). All unreported cases were fetuses < 20 weeks gestation and < 500 g. Partial reporting to the registry of induced abortions resulted in a NTD incidence that was 45.5% lower than the actual incidence. Review of medical records from health centres providing prenatal diagnosis and genetic services did not identify 8% of NTD cases. All of the unidentified cases were stillborns delivered in community hospitals.

The B.C. experience of under-reporting of NTD-affected fetuses born following induced

Table 6. Documented use of folic acid supplementation during the periconceptional period recorded in medical records

FA supplements	1997	1998	1999	Total
(-)	25/50	21/36	22/58	68/144
(+)	13/50	8/36	18/58	39/144
No information	12/50	7/36	18/58	37/144
Total taking FA supplements	13/38 (34.2%)	8/29 (27.6%)	18/40 (45%)	39/107 (36.4%)

Periconceptional folic acid (pcFA) and post-pregnancy diagnosis FA (ppdFA) supplement use is summarized in Table 6. PcFA supplement use was documented in the medical records of 36.4% (39/107) pregnancies. PpdFA supplement use was reported by 83.1% of women for whom information was available.

Information on FA supplement use was not recorded in 25.7% (37/144) medical records. To estimate pcFA use in the entire cohort, one approach is to assume that FA intake of women with this information recorded in their charts is no different than that of women without documentation. In this case, FA use is estimated to be 36.4%. Alternatively, if one assumes that women without chart documentation of pcFA use were not taking supplements, then pcFA intake for the entire cohort would be 27% (39/144).

Discussion

This study evaluates the impact of prenatal screening and selective pregnancy termination on the birth incidence of NTDs in British Columbia. A total of 151 NTD cases were identified, with a 3-year incidence of 1.16/1000. There was a sig-

abortions has been a problem observed elsewhere in North America and Europe (Stevenson et al. 2000; Cuckle and Wald 1987; Lowry 2001; Roberts et al. 1994; Allen et al. 1996; Velie and Shaw 1996; Rosano et al. 1999; State Birth Defects Surveillance Program Directory 2002). The U.S. Center for Disease Control (CDC) reports that an estimated 9–42% of NTD-affected pregnancies are ascertained prenatally (CDC 2005). Re-evaluation of the Metropolitan Atlanta Congenital Defects Program (MACDP) found that 30% of the NTD- affected babies born during 1990–1991 were not reported due to prenatal diagnosis and pregnancy termination (Roberts et al. 1994). Allen et al. (1996) reported that during a 24-month period from 1992 to 1994, 83% of the NTD-affected pregnancies were diagnosed prenatally. Forty- nine percent of these pregnancies were electively or spontaneously aborted prior to 26 weeks gestation. Vital statistics ascertained only 6% of the terminated cases identified in their study. Ethan and Canfield (2002) reported that the birth incidence increased by 29% for anencephaly and by 13% for spina bifida when elective terminations before 20 weeks gestation were included in their NTD incidence calculations.

In this study, prenatal screening with 2nd-trimester fetal ultrasound was done on 82% (124/151) of NTD-affected pregnancies. Following comprehensive assessment and counselling, 72.5% (90/124) of women chose not to continue their pregnancies. Secondary prevention using pregnancy termination resulted in a 60% reduction, from 1.16/1000 to 0.47/1000, in the incidence of vital births with NTDs.

Public health initiatives for primary prevention of NTDs with FA supplementation and food fortification continue to gain momentum. However, primary prevention with FA has limitations: (1) over half to 2/3 of women who become pregnant are not taking preconception FA; (2) food fortification with FA is estimated to provide, on average, only half of the recommended dosage; (3) even when there is adequate FA intake the occurrence of NTDs is reduced, not eliminated. As such, secondary prevention using pregnancy screening and pregnancy termination of identified pregnancies will continue to be needed.

Following prenatal diagnosis, 27.4% (34/124) of couples chose to continue with the pregnancy. Couples were more likely to continue with pregnancies when there were less severe NT anomalies, no associated anomalies in other organ systems, if there was a normal co-twin (see Table 5), and/or they would have to go out of province for a pregnancy termination. Among continuing pregnancies there was a 5.9% rate of stillbirths. Of those born alive, 31% were neonatal deaths. All deaths were attributable to medical problems related to the underlying CNS and/or associated structural anomalies.

In this study, 36.4% of women for whom there was information were taking FA with or without multivitamins during the preconception period (Table 6). Of the total cohort of women with a NTD-affected pregnancy, an estimated 27–36.4% took preconception FA. Previous studies evaluating the effectiveness of FA supplementation have demonstrated that this intervention reduces, but does not eliminate, the occurrence of NTDs (MRC Vitamin Study Research Group 1991; Czeizel and Dudas 1992; CDC 1992). Population studies of FA supplement use and awareness that are similar to the U.S. studies done by the Gallop Organization for the March of Dimes are not available for the B.C. population (Gallop Organization-March of Dimes 1997). In 1992, when FA recommendations were issued, an estimated 10% of B.C. women were taking daily vitamins containing FA 0.4 mg. In 1998, French and Levy-Milne (2000) found that 25.7% of a random sample of Greater Vancouver non-pregnant women were taking daily vitamins and 85.7% were meeting the estimated requirement of 320 g/day of dietary folate equivalents. Morin et al. (2001) reported that in 1999, 48.6% of pregnant women attending the B.C. Women's Hospital clinic responded by questionnaire that they were taking periconceptional FA. These surveys are of selected populations and may not be representative of pcFA supplement use in the entire province.

The transition period for the introduction of FA fortified flour and selected prepared foods into B.C. occurred during the evaluated study period. In March, 1996 the U.S. FDA approved FA fortification of enriched grain products (0.14 mg/100 g grain) to be implemented by January 1, 1998, with voluntary fortification allowed prior to this date. Health Canada approved a similar fortification plan (0.15 mg/100 g grain) to be initiated by November 1, 1998. Because of the importation from the U.S. of fortified food products prior to this date, countered by the long shelf/cupboard life of unfortified flour and cereals, it is difficult to create an accurate time-line for when all B.C. women began consuming FA-fortified foods. Certainly, during the studied years, 1997–1999, there appeared to be no significant decline in the NTD incidence that could be attributed to the preventative effect of FA supplements or food fortification.

Previous studies suggest that FA interventions may have a greater impact on high versus low NTD incidence regions (Mills et al. 1989; Berry et al. 1999). The CDC population FA-intervention study in China reported that the lower incidence region of Southern China had a 40% reduction (0.8/1000 to 0.6/1000) in NTD incidence compared to an 85% decrease (6.5/1000 to 0.7/1000) in the higher incidence region of Northern China (Berry et al. 1999). B.C. historically has a low NTD birth incidence as compared to other regions in Canada, so the impact of FA public health interventions may not be as significant as in higher incidence provinces. Complete ascertainment of NTD cases is essential in order to accurately evaluate FA public health interventions.

The strengths of this study are that it is population-based, with cooperation between the B.C. Vital Statistics Agency and provincial medical programs providing health care for NTD-affected pregnancies and births. Case ascertainment is from multiple sources and is comprehensive. Limitations of this study are that it did not identify

NTD cases delivered in the community that were unreported to the B.C.H.S.R. or families were not referred for specialty medical consultation at regionalized centres. It is unusual for induced abortions in the 2nd trimester to be done in community hospitals so that the number of unidentified TABs is most likely very small. Similarly, failure to register stillbirths is unusual even in the most remote communities. The impact of FA public health interventions on the NTD incidence in 1997–1999 cannot be determined because lack of information on use of FA supplements and availability of FA fortified foods.

REFERENCES

Allen WP, Stevenson RE, Thompson SJ, Dean JH, 1996. The impact of prenatal diagnosis on NTD surveillance. Prenatal Diagnosis 16: 531–535.

Berry RJ, Li Z, Erickson JD, et al. 1999. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med 341: 1485–1490. (Erratum in: N Engl J Med, 1999. 341: 1864).

Brent RL, Oakley GP, Mattison Dr. 2000. The unnecessary epidemic of folic acid-preventable spina bifida and anencephaly. Pediatrics 106: 825–827.

Castilla EE, Orioli IM, Lopez-Camelo JS, et al. 2003. Preliminary data on changes in neural tube defect prevalence rates after folic acid fortification in South America. Am J Med Gen 123A: 123–128.

Centers for Disease Control and Prevention, 1992. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 38: 264–267.

Centers for Disease Control and Prevention, 2005. Spina bifida and anencephaly before and after folic acid mandate – United States, 1995–1996 and 1999-2000. MMWR 53: 362–365.

Chambers K, Popkin J, Arnold W, Irwin B, Hall JG, 1994. Neural tube defects in British Columbia. Lancet 343: 489–490.

Cochrane DD, Wilson RD, Steinbok P, et al. 1996. Prenatal spinal evaluation and functional outcome of patients born with myelomeningocele: Information for improved prenatal counselling and outcome prediction. Fetal Diagn Ther 11: 159–186.

Cuckle H, Wald N, 1987. The impact of screening for open neural tube defects in England and Wales. Prenatal Diagnosis 7: 91–99.

Czeizel AE, Dudas I, 1992. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. N Eng J Med 327: 1832–1835.

De Wals P, Rusen ID, Lee NS, et al. 2003. Trend in prevalence of neural tube defects in Quebec. Birth Defects Research (Part A) 67: 919–923.

Ethen MK, Canfield MA, 2002. Impact of including elective pregnancy terminations before 20 weeks gestation on the birth defect rates. Teratology 66 (supplement 1): 32–35.

Feldkamp M, Friedrichs M, Carey JC, 2002. Decreasing prevalence of neural tube defects in Utah, 1985-2000. Teratology 66(supplement 1): 23–28.

French, Levy-Milne, 2000. Folate intakes and knowledge of women of childbearing age. The status in British Columbia. MSc thesis, Vancouver, UBC, August 2000.

Gallop Organization-March of Dimes, 1997. Preparing for pregnancy II. March of Dimes, Birth Defects Foundation. White Plains, NY.

Gucciardi E, Pietrusiak M-A, Reynolds DL, Rouleau J, 2002. Incidence of neural tube defects in Ontario. 1986-1999. CMAJ 167: 237–240.

Hall JG, Friedman JM, Keena BA, et al. 1988. Clinical genetics and epidemiologic factors in neural tube defects. Am J Hum Genet 43: 827–837.

Health Canada, 2002. Congenital anomalies in Canada – a perinatal health report, 2002. Ottawa: Minister of Public Works and Government Services Canada, Ottawa.

Health Status Registry, 1999. Selected vital statistics and health status indicators. Annual report 1999. Victoria, B.C.: Division of Vital Statistics.

Honein MA, Paulozzi LJ, Mathews TJ, et al. 2001. Impact of folic acid fortification on the US food supply on the occurrence of neural tube defects. JAMA 285: 2981–2986.

Lowry B, 2001. Alberta Congenital Anomaly Surveillance System. Fifth Report, 1980–1998. Division of Vital Statistics, Alberta Registries, Edmonton, Alberta.

Mills JL, Rhoads GG, Simpson JL, et al. 1989. The absence of a relation between the periconceptional use of vitamins and neural-tube defects. N Engl J Med 321: 430–435.

Mills JL, Signore C, 2004. Neural tube defect rates before and after food fortification with folic acid. Birth Defects Research (Part A) 70: 844–845.

Morin VI, Mondor M, Wilson RD, 2001. Knowledge on periconceptional use of folic acid in women of British Columbia. Fetal Diagn Ther 16: 111–115.

MRC Vitamin Study Research Group, 1991. Prevention of neural tube defects: results of the Medical Research Vitamin Study. Lancet 338: 131–137.

Oakly GP Jr, 1993. Folic acid preventable spina bifida and anencephaly. JAMA 269: 1292–1293.

Oakley GP Jr, 2002. Inertia on folic acid fortification: public health malpractice. Teratology 66: 44–54.

Oakley GP Jr, Bell KN, Weber MB, 2004. Recommendations for accelerating global action to prevent folic acid-preventable birth defects and other folate-deficiency diseases: Meeting of experts on preventing folic acid-preventable neural tube defects. Birth Defects Research (Part A) 70: 835–837.

Persad VL, Van den Hoff MC, Dube JM, Zimmer P, 2002. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. CMAJ 167: 241–245.

Roberts HE, Moore CA, Fernhoff PM, Cragan JD, Khoury MJ, 1994. The impact of prenatal diagnosis on the birth prevalence of neural tube defects, Metropolitan Atlanta, 1990–1991. Teratology 49: 386.

Rosano A, Smithells D, Cacciani L, et al. 1999. Time trends in neural tube defects prevalence in relation to preventive strategies: An international study. J Epidemiol Community Health 53: 630–635.

State Birth Defects Surveillance Programs Directory, 2002. Neural tube defects (NTDs) rates, 1995–1999. Teratology 66: 59–128.

Stevenson RE, Allen WP, Pai GS, et al. 2000. Decline in prevalence of neural tube defects in a high-risk region of the United States. Pediatrics 106: 677–682.

Van Allen MI, Fraser FC, Dallaire L, et al. 1993. Recommendations on the use of folic acid supplementation to prevent the recurrence of neural tube defects. Can Med Assoc J 149: 1239–1243.

Velie EM, Shaw GM, 1996. Impact of prenatal diagnosis and elective termination on prevalence and risk estimates of neural tube defects in California, 1989-1991. Am J Epidemiol 144: 473–479.

Wilson RD, Van Allen MI, 1993. The use of folic acid for prevention of neural tube defects. J Soc Obstet Gynaecol Can 15 (March suppl): 41–46.

Williams LJ, Mai CT, Edmonds LD, et al. 2002. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. Teratology 66: 33–39.