

# Trend in Prevalence of Neural Tube Defects in Quebec

Philippe De Wals,<sup>1,2\*</sup> Ira David Rusen,<sup>3</sup> Nora S. Lee,<sup>4</sup> Pascale Morin,<sup>5</sup> and Théophile Niyonsenga<sup>6</sup>

<sup>1</sup>Département de Médecine Sociale et Préventive, Université Laval, Québec, Canada

<sup>2</sup>Institut National de Santé Publique du Québec, Québec, Canada

<sup>3</sup>Division of Health Surveillance and Epidemiology, Health Canada, Ottawa, Canada

<sup>4</sup>Bureau of Nutritional Sciences, Health Canada, Ottawa, Canada

<sup>5</sup>CLSC de la Région-Sherbrookoise, Sherbrooke, Québec, Canada

<sup>6</sup>Centre de Recherche Clinique du Centre Hospitalier Universitaire de Sherbrooke, Québec, Canada

Received 5 June 2003; Accepted 6 August 2003

**BACKGROUND:** In Canada, the first recommendations on the use of folic acid (FA) supplements by women planning a pregnancy or capable of becoming pregnant were issued in 1993. In 1998, fortification of flour with FA became mandatory. The objective of this study was to assess the impact of these measures on the prevalence of neural tube defects (NTDs) in the province of Quebec. **METHODS:** The study population included stillbirths, live births, and elective terminations for fetal malformations that were reported in 1992–2000 for women residing in the province of Quebec. NTD cases were identified from stillbirth certificates and hospital discharge summaries. **RESULTS:** There was a marked decrease in the total NTD rate after 1997. The average NTD rate was 1.89 per 1000 total births during the period of 1992–1997, and 1.28 per 1000 in 1998–2000, a 32% reduction ( $p < 0.001$ ). **CONCLUSIONS:** Fortification of flour, which began in early 1997 and gradually became widespread, is a very plausible explanation for the timing, shape, and magnitude of the decrease in NTD prevalence observed in Quebec and other Canadian provinces. An increase in FA supplement use may have played only a minor role. *Birth Defects Research (Part A) 67:919–923, 2003.* © 2003 Wiley-Liss, Inc.

**Key words:** neural tube defects; folic acid; vitamin supplementation; food fortification

## INTRODUCTION

Neural tube defects (NTDs) are among the most common and severe congenital malformations in humans (Elwood et al., 1992). Despite modern medical and surgical treatment, case-fatality rates remain high. Many survivors have severe disabilities and are at risk of psychosocial maladjustment (Date et al., 1993; Zurmohle et al., 1998; Wong and Paulozzi, 2001). Common problems include learning disabilities, deformation and paralysis of lower limbs, and bladder, bowel, and sexual dysfunction. Clinical trials and observational studies have shown the protective effect of folic acid (FA) supplements taken during the periconception period (Botto et al., 1999). Recommendations on the use of a daily supplement of 0.4 mg FA by all women planning a pregnancy or capable of becoming pregnant were issued by Health Canada (1993), the Canadian Society of Obstetricians and Gynaecologists (SOGC Genetics Committee, 1993), and the Canadian Task Force on the Periodic Health Examination (1994). To be effective, FA supplements should be taken before the neural tube is completely closed at the end of the 6th week of gestation (Jones, 1997) (a time when pregnancy usually has not been confirmed) and before the first antenatal visit. Since behavioral changes are difficult to achieve, a prevention program based on food fortification with FA was implemented in North America. In the United States, the standards of identity for several enriched grain products were amended on March 5, 1996, to require that these products be fortified

with FA at the level of 0.14 mg/100 g of the cereal grain product, effective January 1, 1998 (Food and Drug Administration, 1996a, b). In Canada, the Food and Drug Regulations were amended on December 6, 1996, to raise the upper level of FA permitted in Canadian flour and pasta to the same levels as in the United States (Canada Gazette Part II, 1996). On November 11, 1998, fortification became mandatory for white flour, and for cornmeal and pasta labeled “enriched” (Canada Gazette Part II, 1998). The level of enrichment is 0.15 mg/100 g for white flour and cornmeal, and 0.20–0.27 mg/100 g for pasta (which is higher to allow for expected losses resulting from boiling). In contrast to the United States rice enrichment is not permitted in Canada at this time. In addition, breakfast cereals may be enriched at much higher levels in the United States than in Canada. In a previous study using a simulation model, the additional average daily FA intake among women of childbearing age resulting from food fortification was predicted to be between 0.1 mg and 0.2 mg (Boushey et al., 2001). The goal of the current study was to assess the trend in NTD prevalence in the province of

Grant sponsor: Health Canada.

\*Correspondence to: Philippe De Wals, M.D., Ph.D., Département de Médecine Sociale et Préventive, Université Laval, 2180 Chemin Sainte-Foy, Québec (QC) G1K 7P4. E-mail: Philippe.De.Wals@sss.gouv.qc.ca

DOI: 10.1002/bdra.10124

Table 1  
Prevalence of Neural Tube Defects in the Province of Quebec,  
According to Type of Pregnancy Outcome 1992–2000

Year	1992	1993	1994	1995	1996	1997	1998	1999	2000	Total
Livebirths (LB)	96,417	92,322	90,417	87,258	85,130	79,724	75,674	73,579	72,000	752,521
Anencephaly cases in LB	6	8	8	1	4	3	4	1	4	39
Spina bifida cases in LB	41	48	55	46	36	30	30	21	31	338
Encephalocele cases in LB	9	7	14	4	7	11	4	5	5	66
NTD cases in LB	56	63	77	51	47	44	38	27	40	443
NTD LB rate per 1000 LB	0.58	0.68	0.85	0.58	0.55	0.55	0.50	0.37	0.56	0.59
Stillbirths (SB)	413	380	359	366	334	331	320	312	305	3,120
Anencephaly cases in SB	1	1	0	0	5	1	2	2	1	13
Spina bifida cases in SB	3	3	4	2	1	7	0	0	0	20
Encephalocele cases in SB	0	0	0	0	0	1	0	0	0	1
NTD cases in SB	4	4	4	2	6	9	2	2	1	34
NTD rate per 1000 (SB)	9.69	10.53	11.14	5.46	17.96	27.19	6.25	6.41	3.28	10.90
Induced abortions (IA)										
CNS anomaly cases in IA	99	126	99	114	116	89	59	63	53	818
Total births (LB + SB)	96,830	92,702	90,776	87,624	85,464	80,055	75,994	73,891	72,305	755,641
Total NTD (LB + SB + IA)	159	193	180	167	169	142	99	92	94	1,295
NTD rate per 1000 births	1.64	2.08	1.98	1.91	1.98	1.77	1.30	1.25	1.30	1.71
Ratio CNS cases in IA/ NTD cases in LB and SB	1.65	1.88	1.22	2.15	2.19	1.68	1.48	2.17	1.29	1.71

NTD, neural tube defects; CNS, central nervous system.

Quebec, from 1992 to 2000, in relation to vitamin supplement use and FA food fortification.

## MATERIALS AND METHODS

The study population included stillbirths, live births, and elective terminations for fetal malformations that were reported in 1992–2000 for women residing in the province of Quebec. In Quebec, terminations of pregnancies for medical reasons are performed in public hospitals only. The province-wide hospital administrative database, Med-Echo, was the main source for ascertaining NTD cases. For each admission-discharge from an acute-care hospital, a summary of the causes of hospitalization, diagnoses, medical and surgical interventions, and outcome is written by the physician in charge of the case. Medical archivists code the main diagnosis and up to 15 secondary diagnoses, using the 9th Revision of the International Classification of Disease (ICD-9). The entire database was searched for infants less than one year of age with any diagnostic code indicating anencephaly (ICD-9: 740), spina bifida (ICD-9: 741), or encephalocele (ICD-9: 742.0). Multiple records from a single infant were identified using the Quebec Health Insurance Number. This unique identifier is usually not available for newborns, and thus additional record linkage was performed manually using a set of variables, including the date of birth, sex, place of residence (three-digit postal code), date of admission and discharge, and transfer to another hospital. Records of women admitted for medically-induced abortion (ICD-9: 635), and of fetuses with malformation of the central nervous system (CNS) (ICD-9: 655.0) were also retrieved from the Med-Echo database.

Stillbirth certificate data were used for this category of births. Although stillbirth certificates can contain information on several contributing causes of death, only a main cause is entered on the computer file at the Quebec National Statistics Institute. A main cause of death is selected from among all contributing causes according to standard

criteria, and congenital malformations are high in the hierarchy. The 10th revision of the ICD was introduced for the year 2000 data. Records with a code for anencephaly and similar anomalies (ICD-9: 740 or ICD-10: Q00), spina bifida (ICD-9: 741 or ICD-10: Q05), or encephalocele (ICD-9: 742.0 or ICD-10: Q01) were retrieved.

In tabulation, the anencephaly category includes cranio-rachischisis. The spina bifida category includes iniencephaly but excludes cases associated with anencephaly. The encephalocele category excludes cases associated with spina bifida. Total prevalence refers to the number of NTD cases in live births, stillbirths, and fetuses from pregnancies terminated after a prenatal diagnosis of a malformation, divided by the total number of births. Excluding the small proportion of medically-induced abortions from the denominator does not affect rates significantly. The annual numbers of live births and stillbirths were provided by the Quebec National Statistics Institute. Confidence intervals (CIs) of rates and probability values in comparisons were computed using exact methods (Statxact 3 for Windows; Cytel Software Corp., Cambridge, MA).

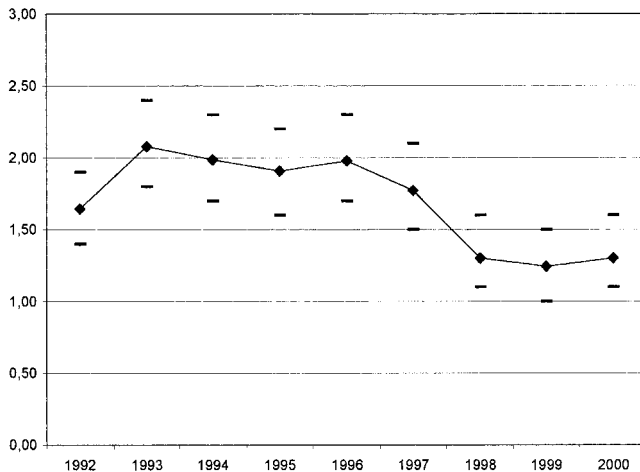
## RESULTS

During the study period we identified 443 NTD cases in live births, 34 NTD cases in stillbirths, and 818 CNS anomaly cases in induced abortions (Table 1). On average, the ratio of CNS cases in induced abortions to NTD cases in live and stillbirths was 1.71, and there was no trend in this ratio over the study years.

As seen in Figure 1, there was a marked decrease in the NTD rate after 1997. The average NTD rate was 1.89 per 1000 total births in 1992–1997 and 1.28 per 1000 in 1998–2000, a 32% reduction ( $p < 0.001$ ).

## DISCUSSION

The downward trend in NTD prevalence observed in Quebec should be interpreted with caution, as this study



**Figure 1.** Prevalence of NTDs (including anencephaly, spina bifida, and encephalocele in live and stillbirths, and CNS anomalies in induced abortions) in the Province of Quebec, 1992–2000 (rate per 1000 total births and 95% CIs).

had certain limitations. In a pilot survey in the Montérégie and Eastern Townships area, multiple sources were used to identify NTD cases, including a review of hospital and outpatient clinic records (De Wals et al., 1999). From this survey, the Med-Echo file was found to be 100% sensitive for the ascertainment of NTD cases in live births; however, a few false-positive records were present. For example, an NTD code can be recorded for an infant admitted for suspicion of NTD, even though the diagnosis was not confirmed during hospitalization. Ascertainment of NTD in stillbirth certificates may also be incomplete, because another code may have been listed as the main cause of death for a fetus with multiple malformations. There is also a low rate of accidental errors in the computerization of diagnostic codes in provincial databases. However, there is no reason to believe that the quality of these databases deteriorated during the study period and thus affected the NTD rate.

In the ICD-9, there is no specific code for a mother having a fetus with NTD, and all congenital anomalies of the CNS are included in the 655.0 category. Indeed, abortions are performed for cases of severe anomaly of the CNS other than NTD. In Quebec, antenatal screening of fetal malformation is mainly based on second-trimester ultrasonography (SOGC, 1994). The use of prenatal diagnostic services has always been high, and there was no major technological breakthrough in the 1990s. In the present study, the ratio of CNS anomaly cases in medically-induced abortions to NTD cases in live and stillbirths was stable from 1992 to 2000, suggesting that no substantial change occurred in the use or performance of prenatal diagnostic services, or in acceptance of termination of pregnancies with fetal malformation. In this study, the total NTD prevalence was 1.64 per 1000 in 1992, which is very close to the 1.41 per 1000 rate found after extensive analysis (Statxact 3 for Windows) in the Montérégie and Eastern Townships area. Any improvement over time in the sensitivity of prenatal detection of CNS anomalies other than NTD, if present, could only obscure a real downward trend in NTD prevalence.

The number of FA-containing supplements reported each year to Health Canada as newly-marketed therapeutic products increased markedly from 13 in 1992 to 103 in 1997 (Health Canada, personal communication). The mean FA dose of 240 newly-marketed products was 0.310 mg, with no increase over the years 1992–1997. In Quebec, data on vitamin/mineral supplement use were collected by standard health surveys conducted in 1987, 1992–1993, and 1998 (Quebec National Statistics Institute, personal communication). Among nonpregnant women 18–40 years old, no marked trend was seen in the proportion of users of vitamin/mineral supplements during the two days preceding the interview (18.4% in 1987, 21.6% in 1992–1993, and 21.3% in 1998). In another provincial survey focusing on nutrition, in 1990, 30.9% of women 18–34 years old reported taking some kind of supplement at least once, during the month preceding the interview, and 14.6% mentioned a product containing FA, for a mean dose of 0.192 mg (Bertrand, 1995). Results from two surveys among pregnant women (many of whom planned their pregnancy) attending routine ultrasound examinations showed no substantial change in vitamin supplement use before conception (27.5% in 1997–1998, and 31.6% in 1999–2000) or initiated before the 12th week of pregnancy (36.0% in 1997–1998, and 30.6% in 1999–2000) (Morin et al., 2002a, b). However, the actual proportion of FA-supplement users may be lower because socially disadvantaged women are underrepresented in such surveys, and desirable behaviors are overreported. In a study among pregnant women in the United Kingdom, overreporting of FA-supplement use was apparent for 7% of participants who completed a self-administered questionnaire and agreed to provide a blood sample to test their folate status (Burton et al., 2001). A slight increase in 1992–2000 in the proportion of pregnant women who took an FA supplement, or in the average supplementation dose during the critical period of organogenesis, cannot be dismissed; however, such behavioral changes at the population level are usually gradual and would not explain an abrupt decrease in NTD frequency from 1998 onward.

At the industry level, premixed vitamins (including FA) are incorporated into different varieties of flour, which are then sold to food manufacturers. According to the main premix supplier in Canada, virtually no flour was fortified in 1996. Sales of FA-enriched premix really started in January 1997 and increased gradually for the next six months, at which time only FA-enriched products were supplied (American Ingredients Corporation, personal communication). According to the Canadian National Miller Association, a significant quantity of flour produced in Canada and destined for the U.S. market has been enriched with FA since the early months of 1997, but fortification for the Canadian market occurred mostly in November and December 1997 (Canadian National Miller Association, personal communication; Robin Hood Multifoods Inc., personal communication). At least one company started fortification as early as January 1997 (Hayhoe Mills Ltd., personal communication). Food products imported from the United States may have been fortified earlier than those produced in Canada.

In a study of results from laboratory tests performed each month in Ontario, mean red cell folate levels rose steadily from 550 nmol/L in April 1997 to 900 nmol/L in June 1999, and did not increase thereafter, while average

serum B12 levels remained unchanged during the entire study period (1997–2000). This is a clear indication that increased FA intake in the population resulted mainly from food fortification and not from increased consumption of multivitamin supplements (Ray et al., 2002b). The increase in red cell folate levels that began in April 1997 is compatible with the gradual fortification of flour that was initiated in January 1997.

Based on the expected increase in FA intake resulting from food fortification at the prescribed levels, and the relationships between FA intake and serum folate, and between serum folate and NTD risk, the predicted reduction in total NTD prevalence was 20% (Daly et al., 1997; McNulty, 2001; Wald et al., 2001). In some instances, fortification levels have been higher than prescribed. In previous studies of food products and serum folate concentrations in the United States, it was found that actual folate concentrations in FA-enriched products were frequently 1.5–2 times higher than required by regulations (Rader et al., 2000), and FA intake from FA-fortified foods was more than twice the level originally predicted (Quinlivan and Gregory, 2003). In Canada, quality-control analyses (conducted March 1999 to August 2000) of 1245 food products indicated that, on average, the added-FA levels were about 33% higher than required, and that only 30 samples (2.4%) had concentrations that were double the standard or more (American Ingredients Corporation, personal communication). Increased consumption of breakfast cereals and other enriched products could also translate into higher FA intake.

We observed a 32% reduction in NTD prevalence in Quebec. In Newfoundland and Labrador, total NTD prevalence was around 4.6 per 1000 births in the 1992–1996 period. It fell to 2.2 per 1000 in 1997, and then to 1.2 per 1000 in 1998—a 74% reduction (Crane et al., 2001). In Nova Scotia, total NTD prevalence did not change significantly from 1991 to 1997, with an average rate of 2.6 per 1000 births. This decreased gradually thereafter, reaching 0.9 per 1000 in 2000—a 64% reduction (Persad et al., 2002). In Ontario, the prevalence of anencephaly and open spina bifida among women who underwent antenatal maternal serum screening declined from 1.13 per 1000 before fortification to 0.58 thereafter—a 48% difference (Ray et al., 2002a). Since the relationship between FA intake and NTD risk tends to follow a negative exponential curve (Daly et al., 1997; McNulty, 2001; Wald et al., 2001), it is plausible that the effect of FA fortification was higher in regions with higher baseline NTD prevalence rates. It would be interesting to examine data from the western provinces of Canada, where NTD rates are traditionally low (Elwood et al., 1992). In the United States a decrease in the NTD rate was temporally associated with FA fortification (Honein et al., 2001; Williams et al., 2003), but the real impact of this intervention is difficult to measure because of difficulties in ascertaining NTD cases in induced abortions. In China, periconceptional use of pills containing 400 µg FA was associated with a decrease in the NTD rate from 6.5 to 0.7 per 1000 pregnancies in the northern region, and from 0.8 to 0.6 per 1000 in the southern region (Berry et al., 1999). An increase in the level of FA fortification in Canada could result in a further decrease in the NTD rate.

## CONCLUSIONS

Fortification of flour with FA, which was initiated in early 1997 and gradually became more widespread, is a very plausible explanation for the timing, shape, and magnitude of the recent decrease in NTD prevalence observed in Quebec and other Canadian provinces. Deterioration in the quality of databases, and a sudden increase in multivitamin consumption by women at the time of conception are not likely explanations. The increased availability of multivitamin supplements containing 0.4 mg of FA may have played a minor role. Because of the limitations of the present study, more valid analyses are needed to assess the impact of FA fortification on the epidemiology of NTD. A retrospective epidemiological study of approximately 2 million births in seven provinces in Canada from 1993 to 2002 was recently approved by the Canadian Institutes for Health Research. In this study, multiple sources will be used for ascertainment of NTD cases in live births, stillbirths, and medically induced abortions, and medical records will be reviewed to validate diagnoses. In addition, more studies are needed to assess consumption of FA-containing vitamin supplements and dietary FA intake in the Canadian population.

## ACKNOWLEDGMENTS

Line Beauchesne from the Ministère de la Santé et des Services Sociaux du Québec, Jean Drapeau from the Centre Hospitalier Universitaire de Sherbrooke, and Martine Six from the Centre de Recherche du Centre Hospitalier Universitaire de Québec contributed to this study.

## REFERENCES

- Berry RJ, Li Z, Erickson JD, et al. 1999. Prevention of neural-tube defects with folic acid in China. *N Engl J Med* 431:1485–1490.
- Bertrand L. 1995. Les Québécoises et Québécois mangent-ils mieux? Rapport de l'enquête québécoise sur la nutrition, 1990. Montréal: Ministère de la Santé et des Services Sociaux.
- Botto LD, Moore CA, Khoury MJ, Erickson JD. 1999. Neural tube defects. *N Engl J Med* 341:1509–1519.
- Boushey CJ, Edmonds JW, Welshimer KJ. 2001. Estimates of the effects of folic-acid bioavailability for women. *Nutrition* 17:873–879.
- Burton A, Wilson S, Gillies AJ. 2001. Folic acid: is self reported use of supplements accurate? *J Epidemiol Community Health* 55:841–842.
- Canada Gazette Part II. 1996. Food and drugs regulations—amendment, SOR/96–527, vol. 130(26): 3318–3320.
- Canada Gazette Part II. 1998. Regulatory impact analysis statement, SOR/98–550, vol. 132 (24): 3029–3033.
- Canadian Task Force on the Periodic Health Examination. 1994. Periodic health examination, 1994 update: 3. Primary and secondary prevention of neural tube defects. *Can Med Assoc J* 151:159–166.
- Crane JMG, Sun C, Hutchens D, Crowley M. 2001. The epidemiology of neural tube defects in Newfoundland and Labrador. *J Soc Obstet Gynaecol Can* 23:510–514.
- Daly S, Mills JL, Molloy AM, et al. 1997. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet* 350: 1666–1669.
- Date I, Yagyu Y, Asari S, Ohmoto T. 1993. Long-term outcome in surgically treated spina bifida cystica. *Surg Neurol* 40:471–475.
- De Wals P, Trochet C, Pinsonneault L. 1999. Prevalence of neural tube defects in the province of Quebec, 1992. *Can J Public Health* 90:237–239.
- Elwood JM, Little J, Elwood JH. 1992. Epidemiology and control of neural tube defects. New York: Oxford University Press pp 1–926.
- Food and Drug Administration. 1996a. Food additives permitted for direct addition to food for human consumption; folic acid (Folacin); final rule. *Fed Reg* 61:8797–8807.
- Food and Drug Administration. 1996b. Food standards: amendment of the standards of identity for enriched grains products to require addition of folic acid; final rule. *Fed Reg* 61:8781–8797.
- Health Canada. 1993. Folic acid: the vitamin that helps protect against neural tube (birth) defects. *Issues* April 9.
- Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. 2001. Impact

- of folic acid fortification of the US food supply on the occurrence of neural tube defects. *JAMA* 285:2981–2986.
- Jones KL. 1997. *Smith's recognizable patterns of human malformation*. 5th ed. Philadelphia: W.B. Saunders Company.
- McNulty H. 2001. Increasing evidence in favour of mandatory fortification with folic acid. *Br J Nutr* 86:425–426 pp 1–857.
- Morin P, De Wals P, Noiseux M, et al. 2002a. Pregnancy and folic acid supplement use: results from a survey in Quebec. *Prev Med* 35:143–149.
- Morin P, De Wals P, St-Cyr-Tribble D, et al. 2002b. Pregnancy planning: a determinant of folic acid supplements use for the primary prevention of neural tube defects. *Can J Public Health* 93:259–263.
- Persad VL, Van den Hof MC, Dubé JM, Zimmer P. 2002. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ* 167:241–245.
- Quinlivan EP, Gregory III JF. 2003. Effect of food fortification on folic acid intake in the United States. *Am J Clin Nutr* 77:221–225.
- Rader JJ, Weaver CM, Angyal G. 2000. Total folate in enriched cereal-grain products in the United States following fortification. *Food Chem* 70:275–289.
- Ray JG, Meier C, Vermeulen MJ, et al. 2002a. Association of neural tube defects and folic acid food fortification in Canada. *Lancet* 360:2047–2048.
- Ray JG, Vermeulen MJ, Boss SC, Cole DEC. 2002b. Declining rate of folate insufficiency among adults following increased folic acid fortification in Canada. *Can J Public Health* 93:249–253.
- SOGC Genetics Committee. 1993. Recommendations on the use of folic acid for the prevention of neural tube defects. *J Soc Obstet Gynaecol Can Supp* 15:41–46.
- SOGC. 1994. Lignes directrices concernant l'exploration par ultrasons en obstétrique et en gynécologie. *Direct Clin Obstét* 8:1–7.
- Wald NJ, Law MR, Morris JK, Wald DS. 2001. Quantifying the effect of folic acid. *Lancet* 358:2069–2073.
- Williams LJ, Mai CT, Edmonds LD, et al. 2003. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. *Teratology* 66:33–39.
- Wong LYC, Paulozzi LJ. 2001. Survival of infants with spina bifida: a population study, 1979–94. *Paediatr Perinat Epidemiol* 15:374–378.
- Zurmohle UM, Homman T, Schroeter C, et al. 1998. Psychosocial adjustment of children with spina bifida. *J Child Neurol* 13:64–70.