

THE USE OF FOLIC ACID FOR THE PREVENTION OF NEURAL TUBE DEFECTS AND OTHER CONGENITAL ANOMALIES

This guideline has been prepared by the Genetics Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR

R. Douglas Wilson, MD, FRCSC, Philadelphia PA

GENETICS COMMITTEE

R. Douglas Wilson (Chair), MD, FRCSC, Philadelphia PA

Gregory Davies, MD, FRCSC, Kingston ON

Valérie Désilets, MD, FRCSC, Montreal QC

Gregory J. Reid, MD, FRCSC, Winnipeg MB

Anne Summers, MD, FRCPC, Toronto ON

Philip Wyatt, MD, PhD, Toronto ON

David Young, MD, FRCSC, Halifax NS

Abstract

Objective: To provide information regarding the use of folic acid for the prevention of neural tube defects (NTDs) and other congenital anomalies, in order that physicians, midwives, nurses, and other health-care workers can assist in the education of women in the preconception phase of their health care.

Option: Folic acid supplementation is problematic, since 50% of pregnancies are unplanned and the health status of women may not be optimal.

Outcomes: Folic acid supplementation has been proven to decrease or minimize specific birth defects.

Evidence: A systematic review of the literature, including review and peer-reviewed articles, government publications, the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement of March 1993, and statements from the American College of Obstetrics and Gynecology, was used to develop a new clinical practice guideline for the SOGC.

Values: Peer-review process within the committee structure.

Benefits, harms, and costs: The benefit is reduced lethal and severe morbidity birth defects and the harm is minimal. The personal cost is of vitamin supplementation on a daily basis and eating a healthy diet.

Recommendations:

1. Women in the reproductive age group should be advised about the benefits of folic acid supplementation during wellness visits (birth control renewal, Pap testing, yearly examination), especially if pregnancy is contemplated. (III-A)

2. Women should be advised to maintain a healthy nutritional diet, as recommended in *Canada's Food Guide to Healthy Eating* (good or excellent sources of folic acid: broccoli, spinach, peas, Brussels sprouts, corn, beans, lentils, oranges). (III-A)
3. Women who could become pregnant should be advised to take a multivitamin containing 0.4 mg to 1.0 mg of folic acid daily. (II-1A)
4. Women taking a multivitamin with folic acid supplement should be advised *not* to take more than 1 daily dose of vitamin supplement, as indicated on the product label. (II-2A)
5. Women in intermediate- to high-risk categories for NTDs (NTD-affected previous pregnancy, family history, insulin-dependent diabetes, epilepsy treatment with valproic acid or carbamazepine) should be advised that high-dose folic acid (4.0 mg–5.0 mg daily) supplementation is recommended. This should be taken as folic acid *alone*, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A. (I-A)
6. The choice of a 5 mg folic acid daily dose for women considering a pregnancy should be made under medical supervision after minimizing the risk of undiagnosed vitamin B₁₂ deficiency (hypersegmentation of polymorphonuclear cells, macrocytic indices, large ovalocytes, leukopenia, thrombocytopenia, markedly elevated lactate dehydrogenase level, confirmed red blood cell folate level). (II-2A)
7. Signs or symptoms of vitamin B₁₂ deficiency should be considered before initiating folic acid supplementation of doses greater than 1.0 mg. (III-A)
8. A three-generation pedigree on the families of both the pregnant woman and the biological father should be obtained to

Key Words

Folic acid, neural tube defect, prevention, myelomeningocele, anencephaly, spina bifida, risk reduction

These guidelines reflect emerging clinical and scientific advances as of the date issued and are subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of the contents may be reproduced in any form without prior written permission of SOGC.

identify increased risk for congenital birth defects (i.e., NTD, cardiac, chromosomal, genetic). (III-A)

9. Women who become pregnant should be advised of the availability of noninvasive screening tests and invasive diagnostic tests for congenital birth defects (including NTDs): maternal serum "triple marker screen" at 15 to 20 weeks, ultrasound at 16 to 20 weeks, and amniocentesis after 15 weeks of pregnancy if a positive screening test is present. (I-A)

Validation: This is a revision of a previous guideline and information from other consensus reviews from medical and government publications has been used.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

J Obstet Gynaecol Can 2003;25(11):959-65.

INTRODUCTION

It is estimated that at least 5% of babies are born with some serious congenital anomaly.¹ Of these 5 babies in 100, 2 or 3 will have anomalies that can be recognized prenatally by a non-invasive screening test, through invasive diagnostic testing, or at birth, while the other 2 babies will have developmental or functional anomalies recognized during the first year of their life.¹ The ingestion of folic acid by a woman prior to conception and during the early stages of pregnancy plays a role in preventing neural tube defects (NTDs) and has been associated with preventing other congenital anomalies.² Public health initiatives to increase the awareness and prevention of birth defects have

focused on folic acid intake for the prevention of NTDs, but there are several studies that have indicated that taking multiple vitamins containing folic acid during the periconception period can reduce the risk of other neonatal conditions such as congenital heart defects,²⁻⁵ urinary tract anomalies,^{5,6} oral facial clefts,^{2,7-9} limb defects,² and pyloric stenosis.³ It has been estimated that as many as half of all birth defects can be prevented if women of childbearing age consume an adequate amount of folic acid, either by eating sufficient quantities of foods that are fortified with folic acid or by taking vitamin supplements.¹⁰

The objective of this clinical practice guideline update is to inform women's health-care providers of new information regarding the use of folic acid for the prevention of neural tube defects and other congenital anomalies. The quality of evidence reported in this guideline has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination (Table 1).¹¹

METHODS

A systematic review of the literature, including review and peer-reviewed articles, government publications, the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement *The Use of Folic Acid for Prevention of Neural Tube Defects* published in March 1993,¹² and statements from the American College of Obstetrics and Gynecology,¹³ was used to develop a new clinical practice guideline for the SOGC.

TABLE 1 QUALITY OF EVIDENCE ASSESSMENT ¹¹	CLASSIFICATION OF RECOMMENDATIONS ¹¹
<p>The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination.</p> <p>I: Evidence obtained from at least one properly randomized controlled trial.</p> <p>II-1: Evidence from well-designed controlled trials without randomization.</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</p> <p>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Canadian Task Force on the Periodic Health Examination.</p> <p>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</p> <p>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</p> <p>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</p>

RESULTS

NEURAL TUBE DEFECTS

INCIDENCES AND INHERITANCE

Neural tube defects are severe birth anomalies, due to the lack of neural tube closure at either the upper or lower end in the third to fourth week after conception (day 26 to day 28 post-conception).¹⁴ The incidence and the empiric recurrence risk for NTDs vary across North American regions (Table 2).^{10,14-22}

In Canada, the birth prevalence of NTDs has declined from a rate of 11.6 per 10 000 live births in 1989 to 7.5 per 10 000 total births (live births and stillbirths) in 1997.²³ Reasons given for this decrease in the rate of NTDs include an increased usage of prenatal diagnoses (ultrasound, maternal serum screening) with subsequent pregnancy termination and, possibly, increased vitamin supplementation.²³ The rate of NTDs tends to be higher in Eastern Canada than in Western Canada.^{24,25} Women of certain ethnic groups including Celtic²⁶ and Sikh,²⁷ as well as women from Northern China,²⁸ are at higher risks of having children with NTDs.²⁴⁻²⁸ It remains unclear whether these risks vary due to genetic predisposition, culture dietary preferences, or a combination of these factors.

Multifactorial inheritance^{24,29,30} is the most common cause of NTDs, but monogenic, chromosomal, and teratogenic causes have specific risks and have not been studied in association with folic acid deprivation or supplementation (Table 3).¹⁴ The prevalence of aneuploidy and additional anatomical abnormalities in fetuses with open spina bifida was reviewed using Utah birth defect network data.³¹ Chromosome results were known in 45 of 51 cases of open spina bifida, with 6 cases (13%) having aneuploidy.

TABLE 2

INCIDENCE AND RECURRENCE RISK FOR NTD IN DIFFERENT REGIONS OF CANADA AND THE UNITED STATES^{1,10,19-22}

Region	Incidence (per 1000 total births)	Recurrence Risks (%)
British Columbia	1.6	2.1
Ontario	1.2 (1986) 1.6 (1995) 0.9 (1999)	2.4
Quebec	4.0	4.5
Nova Scotia	2.6 (1991-1997) 1.2 (1998-2000)	
Newfoundland	4.0	5.0
United States	1.4-1.6	1.5-3.0
Canada	0.75 (1997)	

Additional major anatomic abnormalities were present in 4 of the 6 cases and included cardiac, renal, omphalocele, brain, and bilateral oral clefting. There was a 4% risk of aneuploidy in sonographically isolated spina bifida cases within this population.³¹

PRENATAL DIAGNOSIS

Prenatal diagnosis should be specifically and appropriately timed to women with an increased risk of having a child with an NTD.³²⁻³⁸ Folic acid supplementation will not eliminate but

TABLE 3

RECOGNIZED CONDITIONS ASSOCIATED WITH NEURAL TUBE DEFECTS^{14*}

- 1. Multifactorial:** Homocysteine metabolism variants (MTHFR)
- 2. Monogenic:**
 - AR Acrocallosal syndrome
 - Cerebro-costo-mandibular syndrome
 - Fanconi's pancytopenia syndrome
 - Fraser's syndrome
 - Hydrolethalus syndrome
 - Jarcho-Levin syndrome
 - Meckel-Gruber syndrome
 - AD Waardenburg's syndrome
- 3. Chromosomal:** Miller-Dieker syndrome (deletion 17p13.3)
 Triploidy
 Trisomy 9 (mosaic)
 Trisomy 13
 Trisomy 18
- 4. Teratogen:**
 - Fetal hyperthermia spectrum
 - Fetal alcohol syndrome
 - Fetal amniopterin/methotrexate syndrome
 - Fetal rubella
 - Fetal valproate/carbamazepine/maternal epilepsy syndrome
 - Maternal insulin-dependent diabetes (preconception)
- 5. Unknown:**
 - Caudal dysplasia sequence
 - Child syndrome
 - Extrophy of cloacae sequence
 - Laterality sequences
 - Limb-body Wall complex
 - Monozygotic twinning

*NTD: neural tube defect; MTHFR: 5,10-methylenetetrahydrofolate reductase; AR: autosomal recessive inheritance; AD: autosomal dominant inheritance.

only reduce the risk of NTDs.³⁹ Women at increased risk for a pregnancy complicated by NTDs often have a history of:

- a previous fetus or child with an NTD^{12,13,37,40}
- a first-, second-, or third-degree relation with an NTD^{12,37,40}
- insulin-dependent (type 1) diabetes^{12,37,40}
- epilepsy and the ingestion of valproic acid or carbamazepine for seizure control^{12,37,40}
- use of folic acid antagonists (amniopterin, methotrexate)^{12,37,40}

Noninvasive prenatal diagnoses by ultrasound and maternal serum screening³⁸ should be offered at 16 to 20 weeks' and 15 to 20 weeks' gestation, respectively, and will identify 95% to 100% of NTDs (anencephaly, 100%; spina bifida, 95%). Ultrasound imaging^{41,42} of the cranium and the identification of cranial scalloping (lemon sign) and cerebellar crowding (banana sign) in association with mild ventriculomegaly is diagnostic of an open myelomeningocele, even if a defect is not easily identifiable in the spine due to the level of the spinal defect, fetal position, or maternal habitus. After 15 weeks of pregnancy, invasive prenatal diagnosis with ultrasound-guided amniocentesis, with confirmation by increased levels of amniotic fluid alpha-fetoprotein and acetylcholinesterase, can be diagnostic of open or closed lesions, and used to evaluate fetal karyotype.³⁸

FOLIC ACID AND PREVENTION

A recent Health Canada document⁴⁰ entitled *Preconception Health: Folic Acid for Primary Prevention of Neural Tube Defects – a Resource Document for Health Professionals 2002*, states that, from the human data, it is clear that periconceptional use of supplements containing folic acid substantially reduces the risks of occurrence (first affected pregnancy) and recurrence (additional affected pregnancies) of neural tube defects.

Women should be advised to maintain a healthy nutritional diet as recommended in *Canada's Food Guide to Healthy Eating*.⁴³ Good or excellent sources of folic acid are found in broccoli, spinach, peas, Brussels sprouts, corn, lentils, and oranges.

A randomized trial⁴⁴ for the prevention of primary occurrence found periconceptional vitamin supplementation (12 vitamins including 0.8 mg of folic acid, 4 minerals, 3 trace elements) decreased the incidence of a first occurrence of an NTD. Previous case control studies had provided supportive and equivocal evidence that pregnant women using multivitamins containing folic acid or dietary folic acid had a lower risk of occurrence of NTDs than women not taking supplements.⁴⁵⁻⁴⁹

For prevention of recurrence of NTDs, a randomized double-blind clinical trial,³⁹ involving 1195 completed pregnancies in high-risk women from 33 centres, reported 72% fewer cases of NTDs among the children of the folic acid

supplementation group than among the offspring of controls who did not take folic acid supplementation.³⁹ The recurrence rate decreased from 3.5% to 1% for women randomized to receive 4 mg folic acid supplementation prior to pregnancy and throughout the first 6 weeks of pregnancy. The results in the group taking vitamins without folic acid were similar to the results in the group not taking vitamin supplementation, with recurrence risks of 3.5%.

Wald *et al.*⁵⁰ looked at the dose of folic acid to maximize the already known benefit of folic acid in preventing NTDs. The study analyzed published data from 13 other studies of folic acid supplementation on serum folate concentrations, as well as results from a large cohort study of the risk of NTDs according to serum folate. The results of the analysis indicated that the folic acid preventive effect is greater in women with an initial low serum folate concentration than in women with higher serum folate concentrations. The results of serum folate levels have also been used to predict direct observations from large randomized trials on the effect of food fortification in preventing NTDs. For Caucasian women, a serum folate of 5 ng/mL, about 0.2 mg per day (the United States' level of folic acid fortification) would be expected to reduce NTDs by about 20%.⁵⁰ A similar effect can be expected from the current British fortification recommendation of 0.24 mg per day. An increase of 0.4 mg/day would reduce the risk by about 36%, 1 mg per day by 57%, and the use of a 5 mg tablet daily would reduce risk by about 85%. Wald *et al.*⁵⁰ concluded that folic acid fortification levels should be increased accordingly, and that women planning a pregnancy should take 5 mg folic acid tablets daily instead of the 0.4 mg dose presently recommended. Subsequent letters to the editor showed support^{51,52} for the concept while others recommended caution.⁵³ The choice of a 5 mg folic acid daily dose for Canadian women considering a pregnancy should be made under medical supervision after minimizing the risk of undiagnosed vitamin B₁₂ deficiency.

FOLIC ACID SUPPLEMENTATION AND BIRTH DEFECTS OTHER THAN NEURAL TUBE DEFECTS

Folic acid supplementation has been shown to benefit other congenital anomalies, such as congenital heart defects,²⁻⁵ urinary tract anomalies,^{5,6} oral facial clefts,^{2,7-9} limb defects,² and pyloric stenosis.³ A recent review⁵⁴ summarizes the recent literature regarding prevention of congenital anomalies with periconceptional folic acid supplementation.

POTENTIAL HARM OF EXCESS FOLIC ACID INTAKE

Folic acid, in the recommended dosage of 0.4 to 1.0 mg,^{12,13,40} is not known to cause demonstrable harm to the developing fetus or the pregnant woman.¹⁶⁻²¹ Folic acid is water soluble and its excess is excreted through the urinary tract. The effects of higher intake of folic acid (i.e., >1 mg) are not well known, but they include masking the diagnosis of vitamin B₁₂ deficiency. This concern has led to a recommendation that, for healthy women,

1 mg of folic acid daily (from either folic acid supplements or fortified foods) be considered the maximum dose.^{12,13}

Folic acid can mask vitamin B₁₂ deficiency by correcting the mesoblastic anemia changes normally identifiable, but it does not prevent the neurological complications of vitamin B₁₂ deficiency. In fact, there has been some concern that high doses of folic acid may precipitate or exacerbate neurological symptoms of vitamin B₁₂ deficiency.⁵⁰⁻⁵³ Clinical symptoms of vitamin B₁₂ deficiency include tiredness, fatigability, chronic malaise, sore tongue, ataxic gait, and numbness of the fingers.⁵⁵ Women with signs of red cracked tongue, peripheral neuropathy, ataxia, pallor, and other signs of anemia, and those given a dose of folic acid greater than 1 mg per day, should be investigated for possible vitamin B₁₂ deficiency.⁵⁵ Other hematological characteristics⁵⁵ of vitamin B₁₂ deficiency include hypersegmentation of polymorphonuclear cells, macrocytic indices, large ovalocytes, leukopenia, and thrombocytopenia. A markedly elevated lactate dehydrogenase level and red blood cell folate level are also usually observed.⁵⁵

Folic acid rarely has allergic responses but these may include erythema, rash, itching, general malaise, and bronchospasm.⁵⁶

INTERACTION OF DRUGS WITH FOLIC ACID

Serum folic acid levels may be affected by the metabolism of other medications, including antineoplastic agents, epileptic medications, oral contraceptives, and other medications (Table 4).^{12,13,40} Folic acid has recognized drug interactions⁵⁷ with other commonly used medications such as hypertensive/thiazide combinations, digoxin, thyroid hormones, tetracycline, and thiazide diuretics.

VITAMINS AND MINERALS

There is strong evidence that the use of a multivitamin–multimineral supplement containing folic acid at 0.4 mg per daily dose reduces the risk of a first-occurrence NTD.⁴⁰ The combination of ingredients varies greatly in over-the-counter preparations. It is suggested that multivitamin–multimineral preparations with 0.4 mg–1.0 mg of folic acid per daily dose be taken,⁴⁰ but that mineral supplementation may *not* be

necessary, due to the low risk of deficiency in Canada.⁴⁰ Supplements containing herbs and other “nonmedicinal ingredients” should be avoided, as they have neither been proven to have any benefit nor been studied regarding harm.

Multivitamins should have vitamin A as beta-carotene rather than as retinol. Excess retinol (10 000 IU; 3300 RE) on a daily basis may cause birth defects.⁵⁸ For this reason, women should *not* take more than 1 daily dose, as indicated on the product label.

FOLIC ACID FOOD FORTIFICATION

In Canada since 1998, in an effort to reduce the rate of NTDs, there has been mandatory fortification of white flour, enriched pasta, and cornmeal with folic acid. The overall benefit of fortification in reducing NTDs is yet to be determined.^{40,59} The minimal effective dose is also unknown.^{40,59}

CONCLUSION

Folic acid (through diet and supplementation) has been proven to decrease or minimize specific birth defects including neural tube defects, congenital heart disease, urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis.²⁻⁹ Preconceptional folic acid supplementation should be recommended to women who may become pregnant. The dose of folic acid supplementation should be adjusted according to the patient’s history and needs.

RECOMMENDATIONS

1. Women in the reproductive age group should be advised about the benefits of folic acid supplementation during wellness visits (birth control renewal, Pap testing, yearly examination), especially if pregnancy is contemplated. (III-A)
2. Women should be advised to maintain a healthy nutritional diet, as recommended in *Canada’s Food Guide to Healthy Eating* (good or excellent sources of folic acid: broccoli, spinach, peas, Brussels sprouts, corn, beans, lentils, oranges). (III-A)

Drugs	Effect	Mechanism	Importance
Chloramphenicol	Reduced folic acid effect	Interference with erythrocyte maturation	Caution
Phenobarbital, phenytoin, primidone	Reduced folic acid levels	Increased folic acid metabolism	Caution
Phenytoin	Loss of seizure control; decreased phenytoin levels	Increased phenytoin metabolism	Monitor phenytoin levels
Sulfasalazine	Decreased folic acid levels	Impaired absorption	Caution

3. Women who could become pregnant should be advised to take a multivitamin containing 0.4 mg to 1.0 mg of folic acid daily. (II-1A)
4. Women taking a multivitamin with folic acid supplement should be advised *not* to take more than 1 daily dose of vitamin supplement, as indicated on the product label. (II-2A)
5. Women in intermediate- to high-risk categories for NTDs (NTD-affected previous pregnancy, family history, insulin-dependent diabetes, epilepsy treatment with valproic acid or carbamazepine) should be advised that high-dose folic acid (4.0 mg–5.0 mg daily) supplementation is recommended. This should be taken as folic acid *alone*, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A. (I-A)
6. The choice of a 5 mg folic acid daily dose for women considering a pregnancy should be made under medical supervision after minimizing the risk of undiagnosed vitamin B₁₂ deficiency (hypersegmentation of polymorphonuclear cells, macrocytic indices, large ovalocytes, leukopenia, thrombocytopenia, markedly elevated lactate dehydrogenase level, confirmed red blood cell folate level). (II-2A)
7. Signs or symptoms of vitamin B₁₂ deficiency should be considered before initiating folic acid supplementation of doses greater than 1.0 mg. (III-A)
8. A three-generation pedigree on the families of both the pregnant woman and the biological father should be obtained to identify increased risk for congenital birth defects (i.e., NTD, cardiac, chromosomal, genetic). (III-A)
9. Women who become pregnant should be advised of the availability of noninvasive screening tests and invasive diagnostic tests for congenital birth defects (including NTDs): maternal serum “triple marker screen” at 15 to 20 weeks, ultrasound at 16 to 20 weeks, and amniocentesis after 15 weeks of pregnancy if a positive screening test is present. (I-A)

REFERENCES

1. Kohut R, Rusen ID. Congenital anomalies in Canada. Health Canada: a perinatal health report 2002. Ottawa: Ministry of Public Works and Government Services Canada; 2002.
2. Czeizel AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. *BMJ* 1993;306:1645–8.
3. Shaw GM, O'Malley CD, Wasserman CR, Tolarova MM, Lammer EJ. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. *Am J Med Genet* 1995;59:536–45.
4. Botto LD, Khoury MJ, Mulinara J, Erickson JD. Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. *Pediatrics* 1996;98:911–7.
5. Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996;62:179–83.
6. Li DK, Daling JR, Mueller BA, Hickok DE, Fantel AG, Weiss NS. Periconceptional multivitamin use in relation to the risk of congenital urinary tract anomalies. *Epidemiology* 1995;6:212–8.
7. Hayes C, Werler MM, Willett WC, Mitchell AA. Case-control study of periconceptional folic acid supplementation and oral clefts. *Am J Epidemiol* 1996;143:1229–34.
8. Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet* 1995;345:393–6.
9. Tolarova M, Harris J. Reduced recurrence of orofacial clefts after periconceptional supplementation with high-dose folic acid and multivitamins. *Teratology* 1995;51:71–8.
10. Hall JG. Folic acid: the opportunity that still exists. *Can Med Assoc J* 2000;162:1571–2.
11. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Examination. Ottawa: Canada Communication Group; 1994. p. xxxvii.
12. SOGC Genetics Committee. Recommendations on the use of folic acid for the prevention of neural tube defects. SOGC Policy Statement. *J Soc Obstet Gynaecol Can* 1993;15(Suppl March 1993):41–6.
13. Maternal serum screening. American College of Obstetrics and Gynecology Educational Bulletin 1996;228:603–11.
14. Jones KL. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: W.B. Saunders; 1997. p. 608.
15. Trimble BK, Baird PA. Congenital anomalies of the central nervous system. Incidence in British Columbia 1952–1972. *Teratology* 1978;17:43–9.
16. Hunter AGW. Neural tube defects in eastern Ontario and western Quebec: demography and family data. *Am J Med Genet* 1984;19:45–63.
17. Frecker M, Fraser FC. Epidemiological studies of neural tube defects in Newfoundland. *Teratology* 1987;36:355–61.
18. Dallaire L, Melancon SB, Potier M, Mathieu M-P, Ducharme G. Date of conception and prevention of neural tube defects. *Clinical Genetics* 1984;26:304–7.
19. McBride ML. Sib risks of anencephaly and spina bifida in British Columbia. *Am J Med Genet* 1979;3:377–87.
20. Dallaire L, Michaud J, Melancon SB, Potier M, Lambert M, Mitchell G, et al. Prenatal diagnosis of fetal anomalies during the second trimester of pregnancy: their characterization and delineation of defects in pregnancies at risk. *Prenat Diagn* 1991;11:629–35.
21. Gucciardi E, Pietrusiak MA, Reynolds DL, Rouleau J. Incidence of neural tube defects in Ontario, 1986–1999. *Can Med Assoc J* 2002;167(3):237–40.
22. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *Can Med Assoc J* 2002;167(3):241–5.
23. Health Canada. Canadian perinatal health report 2000. Ottawa: Minister of Public Works and Government Services Canada; 2000.
24. Hall JG, Friedman JM, Kenna BA, Popkin J, Jawanda M, Arnold W, et al. Clinical, genetic, and epidemiological factors in neural tube defects. *Am J Hum Genet* 1988;43:827–37.
25. Chambers K, Popkin J, Arnold W, Irwin B, Hall JG. Neural tube defects in British Columbia. *Lancet* 1994;343:489–90.
26. Little J, Elwood JM, editors. Epidemiology and control of neural tube defects. Vol 20. In: Monograph in epidemiology and biostatistics. Oxford: Oxford University Press; 1992.
27. Baird PA. Neural tube defects in the Sikhs. *Am J Med Genet* 1983;16:49–56.
28. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Mulinara J, et al. Prevention of neural-tube defects with folic acid in China. *N Engl J Med* 1999;341:1485–90.
29. Holmes LB, Driscoll SG, Atkins LA. Etiologic heterogeneity of neural tube defects. *N Engl J Med* 1976;294:365–9.

30. Khoury MJ, Erickson JD, James LM. Etiologic heterogeneity of neural tube defects: clues from epidemiology. *Am J Epidemiol* 1982;115:538–48.
31. Babcook CJ, Ball RH, Feldkamp ML. Prevalence of aneuploidy and additional anatomic abnormalities in fetuses with open spina bifida: population based study in Utah. *J Ultrasound Med* 2000;19:619–23.
32. Mills JL, Knopp RH, Simpson JL, Jovanovic-Peterson L, Metzger BE, Holmes CB. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *N Engl J Med* 1988;318:671–6.
33. Martin RH, Nimrod C. Crohn's disease, folic acid, and neural tube defects (NTD). *Br Med J* 1984;289:228.
34. Lammer EJ, Sever LE, Oakley GP Jr. Teratogen updates: valproic acid. *Teratology* 1987;35:465–73.
35. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991;324:674–7.
36. Warkany J. Amniopterin and methotrexate: folic acid deficiency. *Teratology* 1978;17:353–8.
37. Chodirker BN, Cadrin C, Davies GAL, Summers AM, Wilson RD, Winsor EJT, et al. SOGC Genetics Committee Members, CCMG Prenatal Diagnosis Committee Members. Canadian guidelines for prenatal diagnosis. Genetic indications for prenatal diagnosis. SOGC Clinical Practice Guidelines, No. 105, June 2001. *J Soc Obstet Gynaecol Can* 2001;23(6):525–31.
38. Chodirker BN, Cadrin C, Davies GAL, Summers AM, Wilson RD, Winsor EJT, et al. SOGC Genetics Committee Members, CCMG Prenatal Diagnosis Committee Members. Canadian guidelines for prenatal diagnosis. Techniques of prenatal diagnosis. SOGC Clinical Practice Guidelines, No. 105, July 2001. *J Obstet Gynaecol Can* 2001;23(7):616–24.
39. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;338:131–7.
40. Van Allen MI, McCourt C, Lee NS. Preconception health: folic acid for the primary prevention of neural tube defects. A resource document for health professionals, 2002. Ottawa: Ontario Minister of Public Works and Government Services Canada; 2000.
41. Monteagudo A, Timor-Tritsch IE. Fetal face and central nervous system. In: Jaffe R, Bue TH, editors. *Textbook of fetal ultrasound*. New York: Parthenon; 1999. p. 109–11.
42. Pilu G, Hobbins JC. Sonography of fetal cerebrospinal anomalies. *Prenat Diagn* 2002;22:321–30.
43. Health Canada. Canada's Food Guide to Healthy Eating. Available on-line at <www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/food_guide_rainbow_e.html>. Accessed August 27, 2003.
44. Czeizel AE, Dudas L. Prevention of the first occurrence of neural tube defects by periconceptual vitamin supplementation. *N Engl J Med* 1992;327:1832–5.
45. Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptual use of multivitamins and the occurrence of neural tube defects. *J Am Med Assoc* 1988;260:3141–5.
46. Mills JL, Rhoads GG, Simpson JL, Cunningham GC, Conley MR, Lassman MR, et al. The absence of a relation between the periconceptual use of vitamins and neural-tube defects. *N Engl J Med* 1989;321:430.
47. Milunsky A, Jick H, Jick SS, Bruell CL, MacLaughlin DS, Rothman KJ, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *J Am Med Assoc* 1989;262:2847–52.
48. Morbidity and Mortality Weekly Report. Use of folic acid for prevention of spina bifida and other neural tube defects – 1983–1991. *MMWR* 1991;40:513–6.
49. Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. *Med J Aust* 1989;150:613–8.
50. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. *Lancet* 2001;358:2069–73.
51. Davis RE. Effects of folic acid [letter]. *Lancet* 2002;359:2038–9.
52. Abramsky L, Noble J. Effects of folic acid [letter]. *Lancet* 2002;359:2039.
53. Reynolds E. Effects of folic acid [letter]. *Lancet* 2002;359:2039–40.
54. McDonald SD, Ferguson S, Tam L, Loughheed J, Walker MC. The prevention of congenital anomalies with periconceptual folic acid supplementation. *J Obstet Gynaecol Can* 2003;25(2):115–21.
55. Duffy TP. Hematologic aspects of pregnancy. In: Barrow GN, Duffy TP, editors. *Medical complications during pregnancy*. 5th ed. Philadelphia: WB Saunders; 1999. p. 82–3.
56. Leathem AM, editor. *Drug information reference*, second edition. British Columbia Drug and Poison Information Centre; 1984.
57. ePocrates Rx Pro [software program]. Version 6. San Mateo (CA): ePocrates, Inc.; 2003.
58. Teratology Society. Teratology Society position paper: recommendations for vitamin use during pregnancy. *Teratology* 1987;35:269–75.
59. Kadir RA, Economides DL. Neural tube defects and periconceptual folic acid. *Can Med Assoc J* 2002;167(3):255–6.