

Periodic health examination, 1994 update: 3. Primary and secondary prevention of neural tube defects

Canadian Task Force on the Periodic Health Examination

Objective: To make recommendations on nutritional interventions and screening manoeuvres to prevent the birth of infants with neural tube defects (NTDs).

Options: Folic acid consumption through diet or supplementation in women at low risk and at high risk of having a fetus with an NTD, and maternal serum α -fetoprotein (MSAFP) screening in low-risk pregnancies.

Outcomes: A reduction in the incidence rate of NTDs and potentially harmful effects of false-positive results of screening tests (i.e., abortion of a normal fetus).

Evidence: A MEDLINE search with the use of medical subject headings "neural tube defects," "prenatal diagnosis" and "prevention and control" identified 103 original articles published between January 1979 and March 1993. Two reviewers extracted the data by applying the rules of evidence developed by the Canadian Task Force on the Periodic Health Examination.

Values: The task force's evidence-based methods and values were used; high value was placed on prevention of NTDs and on limitation of the harmful effects of a pregnancy involving a fetus with an NTD.

Benefits, harms and costs: Evidence suggests that folic acid supplementation can decrease the incidence rate of NTDs in low-risk pregnancies by 40% to 60% with no adverse effects. MSAFP screening between the 16th and 18th weeks of gestation can reach a sensitivity of 83% and a specificity of 98% when it is used as part of an organized program. The effect of screening on the incidence rate of NTDs depends on whether affected fetuses are aborted.

Recommendations: All women of childbearing age should be advised to increase their consumption of folic acid through diet or supplementation to 0.4 mg/d beginning 1 month before

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pregnancy and ending at the start of the second trimester. MSAFP screening is recommended in low-risk pregnancies only when it is part of a screening program that includes access to all necessary diagnostic services. High-risk women should be referred to genetic counselling before they plan a pregnancy.

Validation: These recommendations are comparable to the current recommendations of the US Centers for Disease Control and Prevention, the Society of Obstetricians and Gynaecologists of Canada, the Canadian Laboratory Centre for Disease Control and the Canadian College of Medical Geneticists, and they were validated through external review.

Sponsor: These guidelines were developed and endorsed by the Canadian task force, which is funded by Health Canada.

Objectif : Présenter des recommandations sur les interventions nutritives et les moyens de dépistage afin de prévenir la naissance de nouveau-nés atteints de malformations du tube neural (MTN).

Options : Consommation d'acide folique alimentaire ou administration de suppléments aux femmes à faible risque et à risque élevé de porter un fœtus atteint de MTN, et dépistage d' α -foetoprotéine dans le sérum de la mère (AFPSM) dans le cas des grossesses à faible risque.

Résultats : Réduction de l'incidence de MTN et des effets nocifs possibles de résultats faussement positifs de tests de dépistage (c'est-à-dire avortement d'un fœtus normal).

Preuves : Une recherche effectuée dans MEDLINE à l'aide des titres médicaux «neural tube defects», «prenatal diagnosis» et «prevention and control» a permis de repérer 103 articles originaux publiés entre janvier 1979 et mars 1993. Deux examinateurs ont extrait les données en appliquant les règles de la preuve établies par le Groupe d'étude canadien sur l'examen médical périodique.

Valeurs : On a utilisé les méthodes fondées sur des données cliniques et les valeurs du groupe d'étude; on a accordé une valeur élevée à la prévention des MTN et à la limitation des effets nocifs d'une grossesse au cours de laquelle le fœtus est atteint d'une MTN.

Avantages, préjudices et coûts : Les preuves indiquent qu'un supplément d'acide folique peut réduire de 40 % à 60 %, sans effet défavorable, le taux de MTN dans les cas de grossesse à faible risque. Le dépistage de l'AFPSM entre les 16^e et 18^e semaines de la gestation peut atteindre une sensibilité de 83 % et une spécificité de 98 % lorsqu'on l'utilise dans le cadre d'un programme structuré. L'effet du dépistage sur le taux d'incidence de MTN dépend de la décision d'avorter ou non les fœtus affectés.

Recommandations : Il faudrait conseiller à toutes les femmes en âge de procréer de consommer davantage d'acide folique alimentaire ou sous forme de supplément, jusqu'à concurrence de 0,4 mg/j à compter d'un mois avant la grossesse, jusqu'au début du deuxième trimestre. Le dépistage de l'AFPSM est recommandé dans le cas des grossesses à faible risque seulement dans le cadre d'un programme de dépistage qui comprend l'accès à tous les services de diagnostic nécessaires. Les femmes à risque élevé devraient consulter un généticien-conseil avant de planifier une grossesse.

Validation : Ces recommandations sont compatibles avec les recommandations actuelles des Centers for Disease Control and Prevention des États-Unis, de la Société des obstétriciens et gynécologues du Canada, du Laboratoire de lutte contre la maladie du Canada et du Collège canadien de généticiens médicaux. Elles ont été validées au moyen d'une revue externe.

Commanditaire : Ces lignes directrices ont été élaborées et approuvées par le Groupe d'étude canadien sur l'examen médical périodique qui est financé par Santé Canada.

In 1979 the Canadian Task Force on the Periodic Health Examination concluded that there was fair evidence to include screening for neural tube defects (NTDs) with the use of the maternal serum α -fetoprotein (MSAFP) screening test in periodic health examinations of pregnant women.^{1,2} Since 1979 several large studies have evaluated the effects of screening programs.³⁻⁸ Many studies have also shown that folic acid supplementation can prevent the development of an NTD in a fetus.⁹⁻¹¹ Since 95% of NTDs occur in low-risk pregnancies, all primary care providers who see women of child-

bearing age should know about this primary prevention manoeuvre.

Our purpose in this article is to offer guidelines for family physicians on primary and secondary prevention interventions aimed at reducing the incidence rate of NTDs. The clinical options considered were counselling women of childbearing age to increase their consumption of folic acid through diet or supplementation before conception and during the first trimester and MSAFP screening between the 16th and 18th weeks of gestation. The reduction of the incidence rate of NTDs was the

main health outcome considered; others were potential harm from increased folic acid consumption and abortion of a normal fetus because of a false-positive result of screening. The methods and values established by the task force were used; high value was placed on the prevention of NTDs and on the limitation of the harmful effects of a pregnancy involving a fetus with an NTD. It was assumed that some women would rather have a therapeutic abortion than deliver an anencephalic infant. The timeliness of information was also valued; most women would prefer to anticipate the birth of a child with an NTD than to have such a birth come as a surprise.

A MEDLINE search of articles published between January 1979 and March 1993 was conducted with the use of the medical subject headings "neural tube defects," "prenatal diagnosis" and "prevention and control," as well as all subheadings. Animal studies were excluded. Reviews, editorials, opinion articles and letters were excluded but were used for background information and insight into controversial issues. Priority was given to the articles with the highest levels of evidence according to the task force's criteria.

The task force's rules for the evaluation and grading of evidence were applied to the 103 articles found through the search.¹² Priority was given to trials with the strongest design that led to valid statistical results. Studies giving results that were not statistically significant ($p > 0.05$), that is, with less than 80% statistical power to detect the effect of a manoeuvre on the incidence rate of NTDs, were rejected.

Two authors (M.D.B and B.B.) reviewed the literature and provided a written report to all members. Consensus was then reached on the thoroughness of the review and on the grading of the evidence. The report was then reviewed by external experts.

Burden of suffering

NTDs are congenital defects of the central nervous system that arise from improper development during embryogenesis. The most severe NTD is anencephaly.

Another type of NTD, spina bifida, can range from mild (spina bifida occulta) to severe (myelomeningocele). Associated conditions include paraplegia, bladder and bowel incontinence, and other physical disabilities as well as mental impairment (which occurs in approximately 25% of cases).¹² Hospital stays for rehabilitation often exceed 4 months for defects of the thoracic spine and 3 months for those of the lumbar spine.¹³

The worldwide incidence rates of fetal NTDs range from 1 to 8 per 1000 births and vary considerably from one region to another.¹² The highest incidence rate is in Britain, particularly in Ireland, where it is about 8 to 9 per 1000 births.¹² In Canada, the rate is 1 to 2 per 1000 births but varies regionally, increasing from west to east. The rate in British Columbia and Ontario is 1.6 per 1000 births, yet it is as high as 4 per 1000 births in Quebec

and Newfoundland.^{14,15} Approximately 400 to 800 Canadian infants delivered annually have an NTD (based on the 1991 birth rate and the prevalence of NTDs). Although 90% to 95% of NTDs occur in families with no history, a family or obstetric history of an NTD places a pregnant woman at much higher risk of having a fetus with an NTD. The risk of recurrence in a woman who has had one fetus with an NTD is estimated at about 2% to 3%, more than 10 times the risk in the general population.^{12,16}

Effectiveness of prevention and treatment

Prevention of the birth of an infant affected by an NTD generally implies early prenatal screening followed by abortion of the affected fetus. However, in recent years increasing attention has been paid to the role of nutrition in the development of NTDs and, hence, to primary prevention.

Primary prevention with folic acid supplementation

Studies of dietary adequacy and of serum or red-cell concentrations of folic acid and other vitamins have almost uniformly shown an association between nutrition and the occurrence of NTDs.¹⁷⁻¹⁹ Case-control studies have found a protective effect of high maternal red-cell folate concentrations,²⁰ of high maternal dietary folate intake^{9,21} and of periconceptional folic acid supplementation of 0.4 mg/d.⁹ The results of two recent randomized controlled trials (RCTs) have confirmed the causal association between maternal folic acid consumption and prevention of NTDs.^{10,11}

Folic acid acts as a coenzyme in the synthesis and metabolism of nucleic acid. Folate deficiency leads to impaired cell division and to alteration in protein synthesis, the effects of which are more pronounced in rapidly growing tissues. Foliates are unstable molecules that are rendered inactive by heat, oxidation, extremely high or low pH levels and ultraviolet light. Hence, folates in food are likely to be lost during storage and cooking.²²

The daily allowance recommended for nonpregnant women is 170 µg.²² The mean daily intake of Canadian women is estimated to be around 150 µg.²² As a result, 10% of women have below-normal levels of red-cell folate.²² Similar prevalence rates of low folate levels have been found in US and British populations.²²

Folate requirement is increased during pregnancy. Clinical and subclinical folate deficiency during pregnancy has been frequently reported.²² The prevalence of this deficiency is estimated to be about 25% in North America and Britain.²² This is not surprising since the daily requirement during pregnancy is at least 400 µg, well above the 150 µg consumed by the average Canadian woman. Also, the use of oral contraceptives can lower levels of folate, probably through impaired ab-

sorption and metabolism.²³ However, the study showing this did not control for dietary intake.

Liver, kidneys, asparagus, wheat and dry beans are rich in folates, providing from 100 to 300 µg per gram (a regular portion of meat is 200 to 300 g). Green leafy vegetables are also good sources, providing about 50 µg per serving. However, other vegetables, fruits and meat have a low folic-acid content, 30 µg per 100 g on average.²⁴ The folate content of all foods is considerably decreased by prolonged cooking.

Dietary interventions in high-risk populations: In 1989 a large cohort study involving women with first-degree relatives affected by an NTD or a previous pregnancy with an affected fetus showed a significant protective effect of multivitamins containing between 0.1 and 1.0 mg of folic acid.²⁵ The odds ratio of a fetus with an NTD in women who took periconceptional vitamin supplements compared with women who took none was 0.36 (95% confidence interval [CI] 0.15 to 0.83).

Conclusive evidence of the protective effect of folic acid in high-risk pregnancies was provided by the results of a multicentre double-blind RCT conducted through the British Medical Research Council.¹⁰

The trial involved 33 centres in seven countries including Canada. Women who had had a previous fetus with an NTD were randomly assigned to one of four treatment groups: the first group took 4 mg/d of folic acid, the second took 4 mg/d of folic acid as part of a multivitamin supplement, the third took neither folic acid nor other vitamins, and the fourth took multivitamins without folic acid. Compliance was good: only 7% of the women stopped taking their supplements, and of the remainder 95.4% took 80% or more of their supplements.

NTDs recurred in 6 (1.0%) of the 593 fetuses of women who received folic acid and in 21 (3.5%) of the 602 fetuses of women who did not, for a relative risk (RR) of 0.28 (95% CI 0.12 to 0.71). The only folic acid dosage tested in this trial was 4 mg/d. Although it is unknown whether a lower dosage would have an equivalent preventive effect, other evidence suggests that a lower dosage is effective.²⁵

Dietary interventions in low-risk populations: A double-blind RCT of periconceptional multivitamin supplementation with 0.8 mg/d of folic acid for the prevention of first occurrences of NTDs has recently been completed in Hungary.¹¹

The study, conducted by Czeizel and Dudas,¹¹ involved 4753 women who visited family planning clinics. They were randomly assigned to take either a mineral and multivitamin capsule or a mineral and placebo capsule daily for at least 1 month before conception and for the first trimester. The nutritional status of all the study participants was considered good. The total daily consumption of folic acid of women in both groups was 180 µg on average, which is less than the daily requirement for pregnant women but is within the range of the

average diet of women in North America and Europe. Compliance with the vitamin regimen was adequate.

The study group had a decreased prevalence of congenital malformations as a whole (13.3 per 1000 births in the study group v. 22.9 per 1000 births in the control group, $p = 0.02$) and of first occurrences of NTDs (no cases v. 6 cases, $p = 0.029$). No adverse effects were reported.

A few months after the results of this RCT were published, Werler, Shapiro and Mitchel⁹ published the results of a well-conducted case-control study in the United States that showed the same association between folate supplementation and a lower incidence rate of NTDs, taking into account the potential effect of diet in women who did not use supplements. For all women who took daily multivitamin supplements containing folic acid in the periconceptional period the RR was 0.4 (95% CI 0.2 to 0.6). The most commonly used dosage was 0.4 mg/d (RR 0.3, 95% CI 0.1 to 0.6). For dietary folate, there was a dose-related decline in risk. The relative risk in women who consumed more than 0.3 mg/d was 0.6 (95% CI 0.4 to 1.1).

Adverse effects of folic acid: Research on the safety and adverse effects of folic acid supplementation is scanty. Some have claimed that folic acid causes a reduction in the intestinal absorption of zinc, which could lead to pregnancy complications. Mukherjee and associates²⁶ found a strong correlation between pregnancy complications and high levels of folate ($p < 0.008$) associated with low plasma concentrations of zinc ($p < 0.02$) in 450 pregnant women.

Simmer and collaborators²⁷ tested zinc absorption before and after a 2-week course of folic acid supplementation and found a significant reduction in such absorption after the supplementation ($p < 0.02$). One randomized double-blind clinical trial in which 50 women were assigned to receive either 10 mg/d of folic acid or a placebo showed no difference in plasma zinc concentrations between the groups after 2 and 4 months.²⁸

The discrepancies in results from one study to another are difficult to interpret, because there were important differences in the ways that zinc absorption was measured. However, studies that have examined long-term metabolic balance have not shown negative effects of folic acid on zinc absorption.²⁹

Nevertheless, physicians should be aware that a dosage of folic acid of 4 mg/d may mask the hematologic manifestations of vitamin B₁₂ deficiency without preventing its neurologic consequences. Also, large doses of folic acid may precipitate convulsions in epileptic women whose seizures are well controlled with phenytoin.³⁰

Prenatal screening manoeuvres

The manoeuvre for prenatal detection of an NTD is measurement of the MSAFP level. Detailed ultrasound examination and measurement of the levels of amniotic

fluid α -fetoprotein (AFAFP) and amniotic fluid acetylcholinesterase (AFACHe) are confirmatory and should not be regarded as part of routine screening.

Different screening strategies can be considered depending, first, on the presence of risk factors and, second, on the availability of biochemical and ultrasonographic services, which vary across Canada. Generally, it is recommended that a second MSAFP test be ordered if the result of the first one is abnormal. If the second result is abnormal, a high-resolution ultrasonographic examination is needed to rule out other causes of a high MSAFP level. Amniocentesis is offered to women if the result of the ultrasonographic examination does not conclusively rule out or confirm an NTD.

The MSAFP level is measured between 16 and 18 weeks of gestation. Values greater than 2.0 to 2.5 multiples of the median for the gestational age are considered suspect. Care should be taken when interpreting MSAFP results in women with diabetes mellitus, since they have both increased levels of MSAFP and an increased incidence rate of fetuses with NTDs.

Other causes of high MSAFP levels include multiple fetuses, fetal malformations other than NTDs and fetal death. In low-risk populations, the detection rate (sensitivity) of MSAFP testing for open NTDs varies from 72% to 91% and the specificity from 96.2% to 98.7%.³⁻⁷ In all of the screening programs the predictive value of a negative test result has been greater than 98.96%. The proportion of the screened population with an abnormal result of a first MSAFP test varied between 1.2 and 3.9%.³⁻⁷ Generally, only half of these women had to undergo confirmatory amniocentesis; results of an ultrasonographic examination had explained the abnormal result in the others.³⁻⁷

Measurement of the levels of AFAFP and AFACHe obtained by amniocentesis is considered the diagnostic test for a fetal NTD.⁸ However, recent improvements in diagnosis based on ultrasonographic examination, with specificity and sensitivity of almost 100%, have led some experts to question the need for amniocentesis when the level of MSAFP is high but the result of the ultrasonographic examination is normal.^{31,32} The controversy over the best diagnostic strategy to rule out an NTD is not completely resolved.³³⁻³⁵ Clearly, the answer depends on the quality of the ultrasonographic evaluation. Thus, the controversy cannot be settled on a general basis. The final decision depends on the test characteristics in the conditions at each genetic counselling service.

Effectiveness of screening programs

In Canada, except for Manitoba, none of the provincial genetic screening networks includes systematic MSAFP screening in its program. Some centres in Ontario operate their own screening programs.³⁶ In Quebec, most tertiary care centres rely on screening with ultrasonography for low-risk women. In high-risk women the

practice is to determine the MSAFP level and to perform a high-resolution ultrasonographic examination between the 16th and the 18th week of gestation in a centre with expertise in genetic counselling.³⁷

Benefits of screening: There have been no RCTs of the effectiveness of screening programs for the early detection of NTDs. Of the two screening strategies for low-risk women, measurement of the MSAFP level has been more intensively studied. However, only one study that investigated the effectiveness of a program of MSAFP screening took into account the practicalities of implementation.⁷ In this study MSAFP screening was offered to all 15 687 pregnant women who attended prenatal clinics in a town in Wales during the study period.⁷ Only 70% (10 949) were screened; of the 66 NTDs that occurred, 12 were in the unscreened population (2 per 1000 births) and 54 in the screened group (5 per 1000 births).

The higher incidence rate in the screened group suggests that women in this group were at higher risk. Eleven (20%) of the NTDs in the screened group were not detected, and another six were detected, but the affected fetuses were not aborted. If the effectiveness of such a program is defined as the proportion of fetuses in which NTDs were detected and abortion was performed, then the effectiveness of the program in this study was 56.1% (37/66) for all open NTDs, although the detection rate was 80%.

However, abortion of affected fetuses is not necessarily the only positive outcome of a screening program. The opportunity to counsel women who choose to continue their pregnancies may also be beneficial. There is also some evidence that the management of the delivery affects the neonatal outcome.³⁸ Thus, prenatal detection of an NTD may facilitate optimal management of the delivery, thereby reducing the subsequent disability in the infant.

Several economic analyses of prenatal programs to screen for NTDs have concluded that screening is cost-effective, even in low-incidence areas.^{13,39} In Ontario Tosi and colleagues¹³ estimated that such screening has a cost benefit as long as the incidence rate is greater than 0.7 per 1000 births and the sensitivity of the MSAFP test is greater than 61%.

Adverse effects of screening: An obvious potential adverse effect of prenatal screening for NTDs is the risk of fetal death or spontaneous abortion due to amniocentesis. The rate of such death is difficult to ascertain, since women undergoing amniocentesis are already at increased risk of fetal loss. The risk of fetal loss of 0.5% to 1.0% previously reported would be considered by many as unacceptably high. However, the safety of the test has greatly improved with time. A recent case series suggests that the risk is as low as 0.04% if the test is performed by an experienced clinician.⁴⁰ Despite concern that screening programs may increase the number of women having amniocentesis, studies have shown that

the amniocentesis rates remained quite low, ranging from 0.3% to 2.1% of the entire population screened.³⁻⁷

Abortion of normal fetuses as a result of false-positive results of screening and diagnostic tests is also a major consideration. The rate of abortion of normal fetuses is very low (0.006%).³⁴ None the less, it is important to bear in mind that these "unintended" fetal losses are added to fetal losses caused by amniocentesis and other procedures.

Concern has been raised that routine prenatal screening for women at low risk of having a fetus with an NTD may cause undue maternal anxiety and psychologic stress. Four studies have confirmed that women with an abnormal result of a screening test experience increased anxiety until confirmatory investigation shows that the fetus is normal.^{39,41-43} The anxiety level of these women at delivery was the same as that of women who had a normal result of a screening test.

Assuming that 600 Canadian infants with NTDs are born each year on average, the MSAFP test has a sensitivity of 83% and all affected fetuses would be aborted, mass screening could prevent 498 of the 600 possible

NTDs. Screening would prevent 336 of the affected births if the 56% effectiveness rate reported by Roberts,³¹ which takes into account noncompliance with screening and refusal to abort an affected fetus, were applied. If amniocentesis were performed because of an abnormal result of a screening test in 2% of the screened population and fetal loss due to amniocentesis were 0.04%, a total of 3 normal fetuses would be lost and 336 NTDs prevented each year in a population with a total of 402 528 live births.

Conclusions and recommendations (Table 1)

Nutritional intervention

For women at low risk of having a fetus with an NTD, there is fair to good evidence that supplementation with folic acid at a dosage of 0.4 mg/d (fair evidence from analytic studies) to 0.8 mg/d (good evidence from an RCT) reduces the risk of an NTD. To be effective, supplementation should begin at least 1 month before conception and continue during the first trimester. We do

Table 1: Summary of manoeuvres, effectiveness, levels of evidence and recommendations for the prevention and early detection of neural tube defects (NTDs)

Manoeuvre	Effectiveness	Level of evidence*	Recommendation*
Periconceptional folic acid supplementation			
In high-risk women	Supplementation with 4 mg/d during the 3 mo before and 3 mo after conception prevents the development of a fetus with an NTD	Randomized controlled trial (RCT) ¹⁰ (level I)	Good evidence to prescribe supplementation with 4 mg/d for women with a personal or family history of a fetus with an NTD† (A)
In low-risk women	Supplementation with 0.4 to 0.8 mg/d from at least 1 mo before until 3 mo after conception decreases the risk of an NTD by 60%	RCT of 0.8 mg/d ¹¹ (level I), case-control study of 0.4 mg/d ⁹ (level II-2)	Good evidence to advise all women capable of becoming pregnant† to increase their consumption of folic acid to 0.4 mg/d. Supplementation appears to be the most effective practical way to achieve this goal (A)
Measurement of maternal serum α -fetoprotein (MSAFP) level at 16 to 18 weeks of gestation; an abnormal result is followed by ultrasonographic examination and amniocentesis if needed	Screening programs that include the necessary diagnostic services, with abortion of affected fetuses, can significantly reduce the number of infants born with NTDs. Up to 90% of open NTDs can be detected. However, there is some risk of abortion of normal fetuses	Cohort studies ^{3-8,13} (level II-2)	Fair evidence to include in the periodic health examination of all pregnant women as long as it is part of a quality-controlled program. Screening with high-resolution ultrasonography may be adequate for low-risk women, but MSAFP screening should be made available to high-risk women (B)

*For descriptions of levels of evidence and classification of recommendations see Appendix 1 in part 1 of the 1992 update (*Can Med Assoc J* 1992; 147: 443).

†Folic acid supplementation may cause convulsions in women with epilepsy controlled by anticonvulsant drugs. It may be prudent to counsel these women to include folate in their diet rather than advise supplementation.

not know whether women whose diet meets the current recommended standards for folic acid consumption during pregnancy must also take vitamin supplements. Whether nutritional interventions to increase the level of folates in the diet of the population at risk would be as effective as supplementation is also unknown.

Given the lack of harmful effects of such supplementation and other benefits of a good diet, all women of childbearing age capable of becoming pregnant, including those taking oral contraceptives, should be advised to increase their daily intake of folic acid to meet the recommended periconceptional and pregnancy requirement of 0.4 mg. Supplementation appears to be the most practical way to achieve this goal (grade A recommendation). Preparations containing folic acid alone are preferred to avoid the risk of teratogenic effects of vitamin A.

If all Canadian women could increase their folate consumption 1 month before conception and throughout the first trimester, half of all NTDs in Canada would be prevented without abortion of any fetuses. However, given the large population to be reached, the fact that half of pregnancies are unplanned and the difficulty low-income women may have in buying food that enables them to meet the standards, some authorities have advocated fortification of food with folic acid, as was done with vitamin D, because it is the only public health intervention that can reach the population at risk.^{44,45} Meanwhile, primary care physicians are in a good position to inform and counsel women of childbearing age.

For high-risk women (women with a personal or family history of a fetus affected by an NTD), there is good evidence from an RCT to recommend folic acid supplementation of 4.0 mg/d 3 months before conception and during the first trimester (grade A recommendation). This intervention does not replace genetic counselling and follow-up.

Prenatal screening

For primary caregivers who practise in an area where an organized screening program and laboratory quality controls, genetic counselling and amniocentesis and ultrasonography expertise are available, there is fair evidence to include MSAFP screening for NTDs at 16 to 18 weeks of gestation in the periodic health examination of low-risk pregnant women (grade B recommendation). If the result shows a high level of MSAFP, a second, confirmatory test should be performed and then a high-resolution ultrasonographic examination or amniocentesis or both, in a centre with expertise in genetic counselling.

Practitioners with access to high-resolution ultrasonography performed by trained radiologists could rely on this screening manoeuvre as long as it is performed between the 16th and the 18th weeks of gestation.

Women at high risk of having a fetus with an NTD should be referred directly to specialized services.

Validation

These recommendations are in agreement with other guidelines from various associations and agencies. The US Centers for Disease Control and Prevention recommend that high-risk women should be advised to start taking 4 mg/d of folic acid as soon as they plan to become pregnant. They also recommend that all women of childbearing age who are capable of becoming pregnant should "be advised of the options available to them to obtain daily intakes of 0.4 mg of folic acid and be encouraged to meet this goal."⁴⁶ The Society of Obstetricians and Gynaecologists of Canada (SOGC)⁴⁷ and the Canadian Laboratory Centre for Disease Control⁴⁸ have issued the same recommendations.

The Canadian College of Medical Geneticists and the SOGC consider screening with the MSAFP test of value in low-risk pregnancies when provided in conjunction with access to high-quality laboratory, ultrasonography, amniocentesis and counselling services. High-risk women should be offered MSAFP screening in conjunction with high-resolution ultrasonographic examination and genetic counselling.³⁷

These recommendations were reviewed by two experts from the Canadian College of Medical Geneticists and an expert with the Health Protection Branch, Health Canada.

Research priorities

Given the large number of women to be reached, the fact that half of pregnancies are unplanned and the need for intervention before most pregnant women visit a physician, the feasibility and effectiveness of a public health program to enrich commercial food with folic acid should be evaluated. This could be the most effective strategy to reach the population at risk.

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