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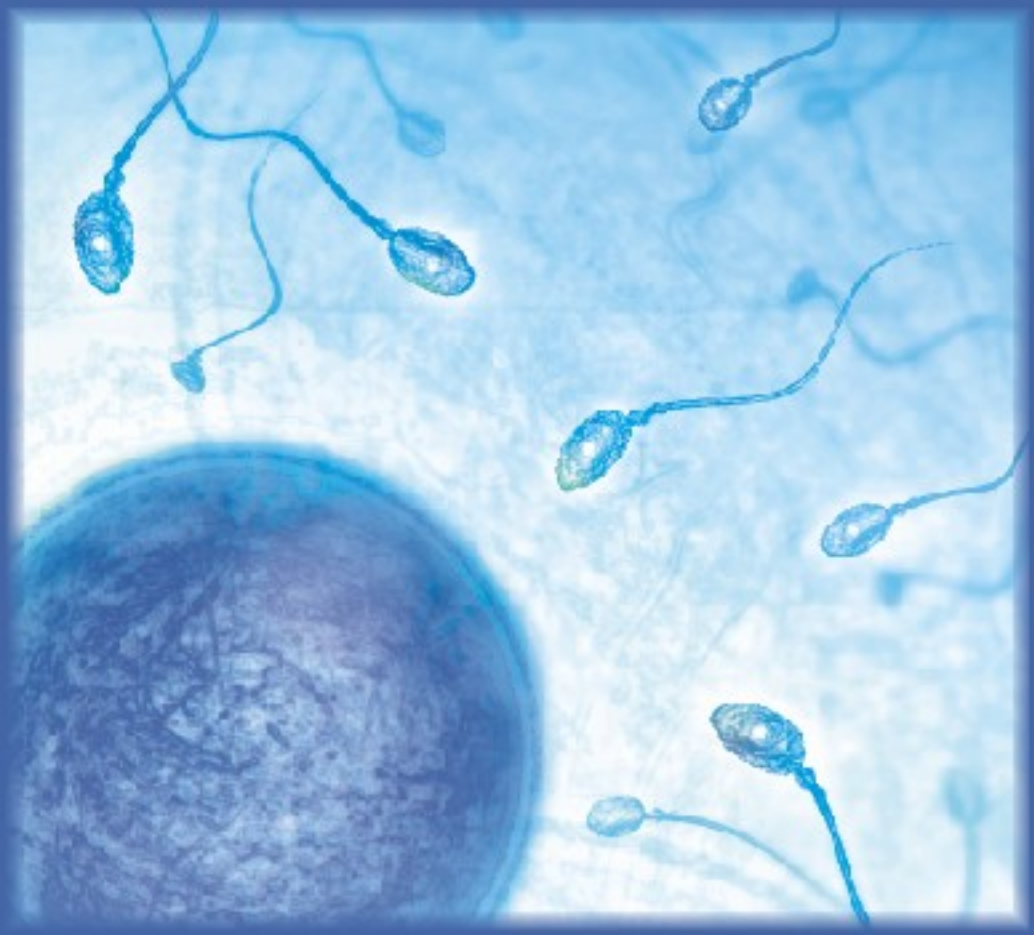
Preconception Health

Folic Acid for the Primary Prevention of Neural Tube Defects



A Resource Document for Health Professionals, 2002

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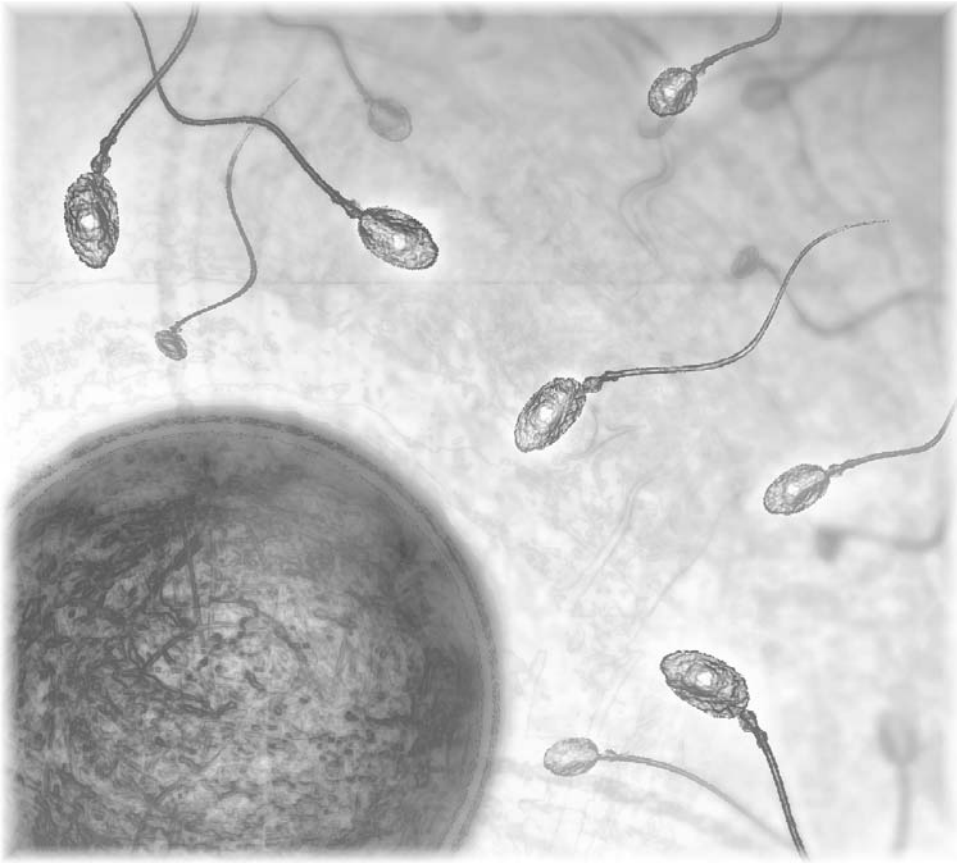

A Resource Document for Health Professionals, 2002

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Introduction

Not since the introduction of mass immunization against rubella have Canadian health professionals had an opportunity to prevent congenital anomalies through public health policy.[1] Nearly a decade ago, accumulated evidence on the effectiveness of folic acid, a B vitamin, in preventing neural tube defects (NTDs) resulted in North American recommendations for daily folic acid supplementation by women. Despite efforts by a number of organizations and governments to develop guidelines and recommendations on folic acid supplementation and disseminate this information, awareness among health professionals and members of the public about the benefits of folic acid in preventing NTDs remains low. Even fewer are effecting these changes in their daily lives and recommending similar action among their families and patients.[2-7]

In 1995, Health Canada sponsored a national workshop on the primary prevention of NTDs, bringing together various groups that were responding to the evidence on the health benefits of folic acid.[8] After this workshop, Health Canada prepared an *Update on Reducing the Risk of Neural Tube Defects*, which was published in *Nutrition for a Healthy Pregnancy: National Guidelines for the Childbearing Years*.[9] The Department also undertook to develop this resource document for health professionals in order to inform them about folic acid and NTDs. In turn, the informed health professional would be better able to educate his or her co- workers, patients and community, helping to effect change.

This document can be used in conjunction with other Health Canada publications, specifically *Nutrition for a Healthy Pregnancy*[9] and *Canada's Food Guide to Healthy Eating*,[10] as well as medical guidelines published by various Canadian medical organizations.[11-14]

Background Information

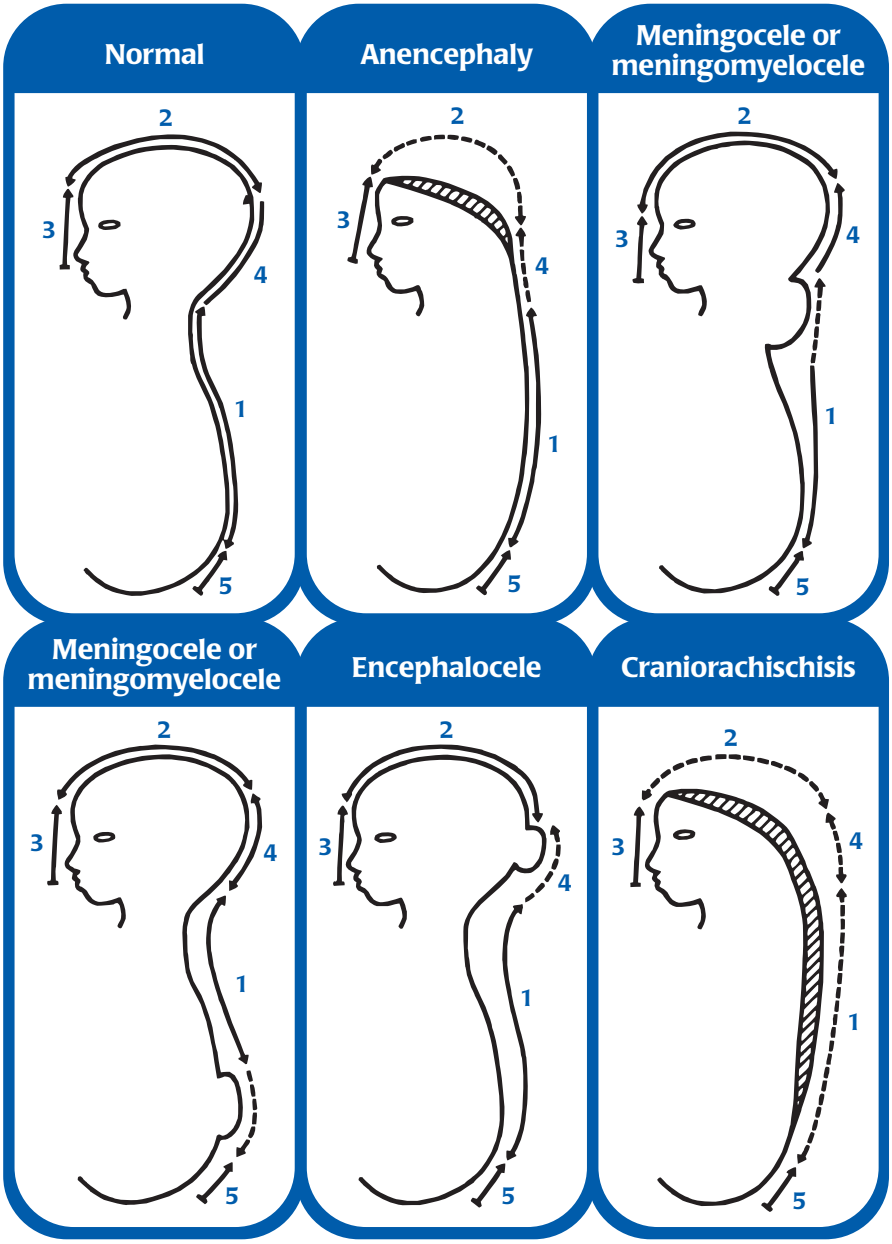
Congenital anomalies. What are we talking about?

Three percent of all newborns in Canada are born with some type of congenital anomaly, also called "birth defects". This rate increases in the first 2 years of life to 7%, as other congenital anomalies not apparent in the newborn are diagnosed. Congenital anomalies are the leading cause of infant death in Canada.[15] The birth of a child with a severe congenital anomaly represents a personal tragedy for the child and its family. Many congenital anomalies are treatable; others are not. Residual health concerns can affect the quality of life, impose chronic disabilities, and carry with them social, financial and psychological burdens.[16]

Among the most common congenital anomalies are congenital heart anomalies, urinary tract anomalies, cleft lip and palate, limb abnormalities including clubbed feet, and NTDs. Included among the NTDs are the more commonly recognized abnormalities of anencephaly and spina bifida cystica (commonly referred to as spina bifida), including meningocele, meningomyelocele and lipomeningocele.[12] Other NTDs less commonly encountered are encephalocele, craniorachischisis, double neural tube defects, acranium, exencephaly, faciocranioschisis and faciocraniorachischisis. Figure 1 illustrates some of these NTDs. The most severe of the NTDs are invariably lethal, often resulting in spontaneous miscarriage and stillbirth. Less severe NTDs, including lipomeningocele, encephalocele and spina bifida, are usually not lethal and have a survival rate in infancy of over 90% of those born in North America.[17]

Until recently, congenital anomalies were viewed by health professionals, and as a consequence by lay people, as a fact of life about which nothing could be done. We now have solid evidence that the congenital anomaly risk can be reduced substantially by increasing the intake of the B vitamin folic acid and its naturally occurring folate forms.

Figure 1. Selected NTDs from errors in multi-site closure of the neural tube. Modified from Van Allen, Kalousek et al., 1993.[49]



Could I see people affected by congenital anomalies and NTDs in my practice? In my community?

Yes, most certainly. Improved health care and prolonged survival mean that everyone, every day, will interact with, work with, work for and encounter individuals born with congenital anomalies, including spina bifida and other milder NTDs. Spina bifida is the most common cause of ambulatory disability due to a congenital anomaly.[17,18]

In Canada, the birth prevalence of NTDs has been declining gradually. The 1997 national rate was 7.5 per 10,000 total births (live births and stillbirths), or about 260 affected births per year, down from a rate of 11.6 per 10,000 total births in 1989.[19] Possible reasons for this decrease in the rate of NTD births include increased vitamin supplementation and increased use of prenatal diagnosis with subsequent pregnancy termination. There are only limited national data to estimate rates of termination of affected pregnancies following prenatal diagnosis.

The rates of NTDs tend to be higher in the eastern provinces than in western Canada. Certain ethnic groups, including people of Celtic, Northern Chinese and Sikh heritage, are at higher risk of having children with NTDs.[18,20-23] It remains unclear to what extent these risks are due to genetic predisposition, cultural dietary preferences or a combination of factors (see later section on Etiology of NTDs).

What are the implications of being born with an NTD?

Newborns with severe NTDs, such as anencephaly and craniorachischisis, die in the first days of life. No treatment is available to alter their clinical course, and supportive care is provided. The majority of infants born with spina bifida survive, requiring extensive medical and surgical care. In the United States, the estimated fatality rate in infancy is 10%.[17] Long term outcome studies have documented survival into the third decade of life in 52%[17] and in 68%[24] of NTD-affected people who had surgical treatment as newborns.

The lifetime implications for those with multiple impairments and for their families can be challenging.[16] For spina bifida and other anomalies, management of the health care concerns is best done by a multispecialty team. The level of the meningomyelocele influences the overall range of predicted outcome.[25] Those with sacral and lumbosacral lesions fare best, as compared with those with thoracolumbar NTDs. Ability to ambulate independently, urinary and bowel continence, degree of developmental delay and school performance vary according to the level of spinal lesion and the neurological deficit. Over 90% of affected people have an associated Arnold-Chiari malformation of the brain and hydrocephalus requiring shunting. Shunt revisions are frequently necessary. Secondary disabilities in the adult meningomyelocele population include obesity, hydronephrosis and renal failure, pressure ulcers, loss of ambulation, osteoporosis, contractures, social isolation and depression.[26-28]

The estimated monetary costs of spina bifida are substantial. In Canada a decade ago, hospital and rehabilitation services alone were estimated to cost $42,507 during the first 10 years of life for a child with spina bifida.[29] These costs have, without a doubt, increased substantially, although accurate figures are not available. In the United States it is estimated that $200 million annually are spent in direct medical costs for individuals with spina bifida.[30] The lifetime economic cost to society per person with spina bifida is about $258,000 USD.[31]

Primary Prevention of Neural Tube Defects with Folic Acid

What is the evidence that NTDs are preventable?

Without a doubt, good nutrition through a diet containing abundant fresh fruits and vegetables along with a well-balanced intake of other representative food groups goes a long way towards preventing NTDs. In all geographic regions during periods of drought, famine and war, the rate of NTDs strikingly increases, and during periods of prosperity it declines.[18,32]

Intervention studies evaluating the impact of micronutrients, in particular folic acid, have been done using folic acid with or without other vitamins and minerals. The evidence is clear that periconceptional use of supplements containing folic acid substantially reduces the risk of occurrence (first affected pregnancy) and recurrence (additional affected pregnancies) of NTDs. Table 1 (see pages 16-18) summarizes the results of cohort and case control studies, randomized and nonrandomized trials and a community-based public health campaign. From these studies it is estimated that at least half the cases of NTDs may be prevented if women consume sufficient amounts of folic acid before conception and during early pregnancy. There is some evidence to suggest that periconceptional use of supplements containing folic acid is also effective in reducing the risk of other common congenital anomalies of multifactorial etiology. These anomalies result from incomplete development and/or failure of fusion of migrating cell masses. Folic acid may reduce the risk of congenital heart anomalies, in particular conotruncal heart defects,[33-35] some types of limb anomalies,[33,34] obstructive urinary tract anomalies,[33,36] pyloric stenosis[33] and orofacial clefts.[33,34,37,38]

How does folic acid work?

The specific action of folic acid in affecting the pathogenesis of NTDs is largely unknown.[35] Folic acid is essential for the synthesis of nucleic acids and amino acids and for cell division. In this capacity, it would be anticipated that not only NTDs but also other isolated structural anomalies due to incomplete development would be influenced by the availability of folic acid during embryogenesis.

Folic acid may have other health benefits as well. Folic acid supplementation is effective in reducing high blood homocysteine levels, which are associated with increased risk of coronary heart disease.[39] Also, poor folate status has been associated with an increased risk of cancer, particularly colorectal cancer.[40]

To be effective in preventing NTDs, when should folic acid be taken?

Abundant folic acid needs to be available in early gestation while the neural tube is closing — i.e., from 21 to 28 days after conception, or the 6th week after the beginning of the last menstrual period. It is recommended that daily folic acid supplementation be started at least 2 to 3 months before conception and continued throughout the first trimester of pregnancy. However, many pregnancies are unplanned. For women who are not intending to get pregnant but nevertheless could become pregnant, daily folic acid supplementation on an ongoing basis would be advisable.

For maternal nutritional needs, folic acid needs to be continued throughout the remaining months of pregnancy, as well as during lactation.

What type of supplement can I recommend to women who could become pregnant?

The available evidence best supports a recommendation for a multivitamin-multimineral supplement containing folic acid at 0.4 mg per daily dose to reduce the risk of first occurrence of an NTD.

Over-the-counter vitamin and mineral supplements, however, are available in a great variety of combinations of nutrients at a wide range of levels. None of these supplements is designed specifically for use in the periconceptional period. At this time, there are no guidelines that define the appropriate composition of multivitamin-multimineral supplements for this use. While recommended daily intakes and tolerable upper levels (ULs) of daily intake have been determined for some nutrients and, in some cases, for nutrient intakes by pregnant women, ULs have not been established specifically for the periconceptional period.

A few guidelines can be offered to help in the choice and use of a supplement:

- Choose a multivitamin-multimineral supplement that contains 0.4 mg folic acid in a daily dose.
- There is no need to choose a product labelled "For therapeutic use only". These supplements usually provide nutrients at a higher dose than is necessary and may be more expensive. They may contain trace minerals such as molybdenum, selenium and chromium, but there is very little likelihood that a woman will be deficient in these nutrients and require a supplement.

- To be prudent, avoid supplements containing herbs and various other extraneous "non-medicinal ingredients".
- Try to select a product containing vitamin A as beta-carotene rather than as retinol. High doses of vitamin A as retinol cause several types of birth defects in animals, including neural tube defects, and have caused birth defects in humans.[41] Although the exact dose above which vitamin A can cause harm to the fetus is unknown, supplements sold without a prescription may not contain more than 10,000 IU (3,330 RE) of vitamin A per tablet,[9] which is also the upper limit of supplementation with retinol recommended by the Teratology Society.[41] Many supplements include at least a portion of the vitamin A in the form of beta-carotene, which is not believed to have teratogenic effects.[41]
- Women should *not* take more than one daily dose as indicated on the product label. If a woman misses taking a tablet on 1 or more days, she should not try to "catch up" by taking the missed pills all at one time. Excessive amounts of some nutrients, including vitamin A as retinol, may be harmful, particularly to an embryo in the very early stages of development.

What about food fortification? Why should women still take supplements containing folic acid?

In Canada since 1998, white flour and enriched pasta and cornmeal have been fortified with folic acid on a mandatory basis as a public health strategy to improve dietary folate intakes, with the expectation that the rate of NTDs might be reduced. White flour is fortified with folic acid to a level of 0.15 mg per 100 g of flour. This is a little more than twice the level of naturally occurring folate* found in the whole grain. Enriched pasta is fortified with folic acid to 0.20 mg per 100 g. A serving of cooked, enriched pasta contains about 0.125 mg of folic acid (some of the added folic acid is lost in the cooking water) and two slices of white bread contain 0.06 mg.

The amount of folic acid added to flour and the other cereal products was kept low because of concerns that higher amounts would create a risk for individuals with undiagnosed vitamin B12 deficiency. The prevalence of low vitamin B12 status has been found to be relatively high, especially among people over 50 years of age.[42]

Overall, fortification is estimated to increase the daily intake of folic acid among women 18-34 years of age by approximately 0.1 mg. Since the average daily diet of women of reproductive age contains approximately 0.2 mg of folate, fortification increases the average intake of this nutrient by approximately 50%. Although this is a substantial increase, it does not result in the intakes achieved in the studies cited above. Nevertheless, the ultimate benefit of fortification in reducing the risk of NTDs is yet to be determined, since the minimum effective dose of folic acid is not known.

Many of my patients have healthy diets. Do they need to take supplements?

Even allowing for food fortification with folic acid, it would be difficult for most women to consume enough folic acid from diet alone to achieve a daily intake equivalent to a 0.4 mg supplement on top of diet. All women should be encouraged to eat a healthy diet, according to *Canada's Food Guide to Healthy Eating*,[10] and those who could become pregnant should also take a daily supplement containing folic acid.

Appendix I, which lists dietary sources of folate, will help women choose the foods from the various food groups that are higher in folate. Folate is found in nearly all foods, but levels vary considerably. Folate is susceptible to destruction by excessive or prolonged heating, so overcooked foods may be low in folate.

Some of my patients may not be able to afford supplements. What can I do?

Women who indicate that they cannot afford vitamin supplements may also have poor diets and possibly other risk factors for adverse pregnancy outcomes. Health professionals can help women who may not be able to afford supplements by referring them to local programs and services that support economically disadvantaged women and their families. An example is the Canada Prenatal Nutrition Program (see http://www.hc-sc.gc.ca/hppb/childhood-youth/cbp/cpnp/). These issues are discussed in more depth in *Nutrition for a Healthy Pregnancy: National Guidelines for the Childbearing Years*,[9] and *Family-Centred Maternity and Newborn Care: National Guidelines*.[43]

* The forms of folate that are present naturally in foods are polyglutamate forms. They have a lower bioavailability (rate of absorption from the intestine) than synthetic folic acid.

Etiology of NTDs and Pregnancies at Increased Risk for NTDs

What causes NTDs and who is at increased risk?

The majority of NTDs are the result of multifactorial inheritance, meaning the combined effect of genetic and environmental factors. Poverty, famine, wars, seasonal variations and dietary preferences have contributed to our recognition that poor quality diets are an important environmental contributor.

One type of genetic factor that has been implicated in multifactorial NTDs is the genetic variants in enzymes used in the homocysteine metabolism cycle, e.g. 5,10-methylene tetrahydrofolate reductase (MTHFR). There are considerable population variations in the frequency of the enzyme variants, so their importance as a contributor differs among ethnic groups. In this situation, folic acid supplementation helps improve enzyme function.

Most babies born with an NTD are born to couples with no specific pregnancy, health or genetic concerns.

Family members with close relatives with an NTD are at increased risk for an NTD-affected pregnancy, and this risk is influenced by the population rate of NTDs. Couples with a previous child with an NTD have a 2% to 5% risk for another affected pregnancy, depending on the baseline population risk. Siblings and second degree relatives of an NTD- affected child have a 1% to 2% risk, and third degree relatives have a 0.5% to 1% risk for an affected pregnancy. Among individuals with an NTD, the risk for an NTD-affected pregnancy is 4%, independent of the underlying population risk.

A minority of NTDs result from underlying teratogenic exposures, maternal health problems, genetic disorders, syndromes and chromosomal abnormalities. The proportion due to these causes appears to be increasing as NTDs due to nutritional causes decline, and it is now 20% to 30% of all NTDs. Unfortunately, most of the NTDs due to underlying disorders are not preventable with folic acid.

Teratogenic exposures associated with an increased risk for NTDs include excessive maternal alcohol consumption, antineoplastic agents, maternal hyperthermia and maternal use of valproic acid, carbamazepine and other anticonvulsants.

Poorly controlled maternal diabetes mellitus is associated with a two to three fold increased risk of all congenital anomalies, including a 1% risk for NTDs.[44] Maintaining preconceptional and first trimester diabetic control can substantially reduce but not eliminate this increased risk.

Maternal epilepsy is associated with a 1% to 2% risk for offspring with NTDs and an overall two to three fold increased risk for congenital anomalies in the offspring. This risk is considered to be due to anticonvulsant use, in particular valproic acid and carbamazepine. Genetic factors leading to epilepsy may also predispose offspring to having NTDs.

Independent of quality of diet, women with obesity have an increased risk over the background risk for NTD-affected pregnancy.[45-47]

Low maternal vitamin B12 status has been identified as an independent risk factor for NTDs.[48] Maternal disorders leading to B12 deficiency, including pernicious anemia, malabsorption disorders such as celiac sprue, and inflammatory bowel disease, create an increased risk for NTDs. Women who have cultural and dietary preferences that exclude red meat and other sources of vitamin B12 have an increased risk for NTDs not correctable with high dose folic acid.

A number of single gene disorders and syndromes are associated with NTDs.[49] Many of these disorders and the anomalies they cause are not preventable with folic acid. All chromosome disorders, such as Down syndrome and trisomy 13 and 18, are associated with an increased risk of NTDs. Folic acid neither prevents the NTDs nor prevents the chromosome abnormalities.

It is important to determine the underlying etiology of the NTD. The overall prognosis and medical management of an affected individual is altered according to the underlying diagnosis. Additionally, the risk for the parents and other family members of having further children affected with NTDs is dependent on the etiology. In some cases, treatment of maternal health concerns can substantially reduce the risk of another affected pregnancy.

How much folic acid is recommended for women whose pregnancy is at increased risk for NTDs?

Research has demonstrated that among women with a previous NTD-affected pregnancy 4.0 mg per day of folic acid taken in

the periconceptional period reduces the recurrence risk by 72%.[50]

Studies of women with epilepsy who are using carbamazepine and valproic acid suggest that they may benefit from periconceptional use of 4.0 mg folic acid per day. However, the concern remains that these medications are teratogens acting directly on the developing neural tube. The physician may wish to reduce the dosages of anticonvulsants, change to other anticonvulsants or reduce the number of anticonvulsants taken for seizure control, in addition to prescribing high dose folic acid supplements.

Women with diabetes reduce their risk for NTDs by ensuring optimal glycemic control in the periconceptional period. High dose folic acid supplementation may or may not provide added benefit compared with the usual dosage of 0.4 mg folic acid daily.

It is not known whether women with obesity can decrease their risk of NTDs by taking folic acid.

My patient took folic acid as recommended and still had a child with an NTD. What advice should she be given? What about her next pregnancy?

Referral to a medical genetics clinic is recommended for further evaluation prior to a subsequent pregnancy and for counselling regarding prenatal testing. It is recommended that women not use high dose folic acid continuously for a prolonged period of time, because it may contribute to zinc deficiency. Rather, when not planning a pregnancy, a patient who has had a child with an NTD should be advised to take 1.0 mg folic acid daily in a multivitamin-multimineral supplement. When pregnancy planning begins, 4.0 mg folic acid daily should be prescribed, in conjunction with a daily multivitamin. Vitamin B12 status should be evaluated before initiation of this treatment. At the end of the first trimester of pregnancy, the patient should return to the usual dosage of folic acid in pregnancy.

Recurrence of NTDs resulting from genetic, syndromic and chromosomal causes does not appear to be influenced by high dose folic acid supplementation. The evidence for this is anecdotal, coming from case series of NTDs and not from rigorous, controlled intervention trials.

My patient had one child with an NTD, was taking high dose folic acid, and had another child with an NTD – what next?

Unfortunately, some recurrent NTDs are not preventable with high dose folic acid supplementation. In these situations, it is far more likely that there is an underlying disorder causing the NTD. Further investigations are warranted, and the patient should be referred to a medical genetics clinic for evaluation. The baby should be evaluated for underlying disorders and the mother reassessed for possible underlying medical conditions. Mutation testing for MTHFR and enzymes of the homocysteine-methionine metabolism pathway as well as assessment of micronutrients, including vitamin B12 and red cell and serum folate, need to be considered.

Prenatal Screening, Diagnosis and Intervention

What are the possibilities for prenatal diagnosis of NTDs?

Prenatal diagnosis of NTDs and other severe congenital anomalies is possible using available pregnancy screening tests. Maternal serum alpha-feto protein (MSAFP) screening detects approximately 85% to 90% of NTDs. When it is combined with second trimester fetal ultrasound screening, the detection rates for anencephaly and spina bifida are virtually 100% and 95% respectively. The most difficult NTDs to detect are small sacral meningoceles and lipomeningoceles, with the reliability of ultrasound and MSAFP screening decreasing significantly when the lesions are skin-covered.

Although prenatal screening for congenital anomalies is available in many jurisdictions, most provinces/territories do not have organized prenatal screening programs. Screening for congenital anomalies should be available to all women wanting these services, irrespective of location or income. The advantages of identifying NTDs prenatally include the ability to prepare emotionally and logistically for the delivery of an affected infant, the option to terminate an affected pregnancy and, in the future, the increasing potential for in utero treatment (see below).

The choice of whether or not a couple will continue with an NTD-affected pregnancy is a very difficult one. Clearly, many factors influence this decision. It is imperative that all pregnancies identified as having fetal abnormalities be evaluated by specialists in perinatology and genetics, and that couples receive appropriate counselling before making their decision about the pregnancy.

What about management of a pregnancy and delivery of a fetus diagnosed prenatally with an NTD or other congenital anomaly?

Referral is recommended to a high-risk fetal diagnosis centre with combined perinatology, medical genetics and other specialties. It is imperative that the nature of the structural anomalies be delineated by sophisticated ultrasound and other prenatal testing to confirm preliminary ultrasound findings.

Most pregnancies with an NTD-affected fetus are evaluated and delivered by an obstetrician or perinatalogist at a medical centre that can provide neonatology and surgical consultation and treatment of the newborn. One of the delivery concerns is ventriculomegaly due to underlying Arnold-Chiari malformation, which may pose practical difficulties. It remains controversial whether a Cesarian birth is indicated in order to reduce the likelihood of rupturing a meningocele or encephalocele sac, causing further neurological damage.

In utero treatment may be available for some types of congenital anomalies as part of a clinical investigative trial. Currently, in utero surgery is being done on fetuses with spina bifida and fetuses with diaphragmatic hernias on an experimental basis at several centres in the United States. It is not yet clear whether there will be any long term benefits to in utero treatment, both with respect to maternal complications and acceptable newborn outcomes.

What is being done to monitor outcomes of prenatal screening and diagnosis programs?

All prenatal diagnosis programs in Canada have built-in quality control activities. Embryofetal pathology assessment is done on all aborted fetuses with parental consent. Morbidity and mortality reviews assess the performance of prenatal screening programs. The limitation of these programs is that they rely on the delivering physicians and specialists to report back to the prenatal programs regarding the outcome of term infants. No mechanism is currently in place for verifying the outcome of pregnancies with normal prenatal screening tests. Collaboration among prenatal genetics, prenatal obstetrics and other related services would allow for better monitoring of the effects of prenatal screening and diagnosis programs.

At the national level, the Canadian Congenital Anomalies Surveillance System (CCASS) monitors the birth prevalence of congenital anomalies in live births and stillbirths, using hospitalization data and data from the Alberta Congenital Anomalies Surveillance System (ACASS).[19] CCASS cannot ascertain fetal anomalies from pregnancies less than 20 weeks' gestation. At the provincial/territorial level, only Alberta routinely or regularly reports on these anomalies.[51] As a result, special efforts are required to determine the national impact of secondary prevention of NTDs through the detection by MSAFP screening and fetal ultrasound resulting in selective termination of pregnancies.

Safety Issues

How safe is folic acid?

Folic acid has few safety concerns associated with it. Like vitamin C, it is water soluble and excess is excreted in the urine, which helps to limit its toxicity. Nevertheless, recommended doses should not be exceeded unnecessarily.

The primary concern for the general population is that folic acid may affect undiagnosed vitamin B12 deficiency. As a result, a tolerable upper intake level (UL) of 1 mg daily has been set for folic acid obtained from either supplements or fortified foods.[52] A prescription is necessary for folic acid supplements in excess of 1 mg per daily dose to ensure physician assessment of the vitamin B12 status of the individual.

Folic acid may interfere with the metabolism of medications, including anticonvulsants, antineoplastic agents that interfere with folic acid metabolism, oral contraceptives and others.

How do I identify patients who may have vitamin B12 deficiency?

Clinical symptoms of vitamin B12 deficiency include tiredness, easy fatiguability, chronic malaise, sore tongue, ataxic gait, particularly in the dark, and numbness of the fingers. Patients with signs of red crack tongue, peripheral neuropathy, ataxia, pallor and other signs of anemia should be investigated for B12 deficiency.

One of the concerns of recommending daily folic acid supplementation, in particular dosages exceeding 1.0 mg/day, is the potential for an undetected vitamin B12 deficiency. Folic acid can mask B12 deficiency by correcting the megaloblastic anemia changes normally identifiable on routine hematologic panels, but it does not prevent the neurological complications of B12 deficiency. There is the added concern that high doses of folic acid may precipitate or exacerbate B12 deficiency neurological symptoms.

A prudent physician needs to keep in mind the possibility of a vitamin B12 deficiency. Routine dietary interviews can help detect vegetarians and those excluding fresh fruits and vegetables and liver from their diets. A greater level of suspicion is needed to identify individuals with occult pernicious anemia, celiac sprue and related disorders. Inflammatory bowel disease, diabetes mellitus and gastrocolonic bypass treatment for obesity are examples of disorders for which patients are at risk of B12 deficiency.

All women given high dose folic acid (i.e. > 1.0 mg/day) need to be evaluated for possible vitamin B12 deficiency. Women taking folic acid supplements at < 1.0 mg/day without multivitamins that include B12 who are vegetarians, have underlying health concerns limiting absorption of micronutrients, or have related concerns should be assessed for B12 deficiency.

Anything Else I Should Know?

Yes. As with all of science, our knowledge of congenital anomalies, including the prevention of NTDs, is continually evolving. New research findings may emerge that will require this resource document to be updated. For example, several initiatives are under way in Canada to assess the effect of food fortification with folic acid. In the United States, a recent study found that the birth prevalence of NTDs in that country dropped by 19% following the introduction of a fortification program similar to that in Canada.[53]

Researchers have looked at the relationship between use of folic acid supplements in the periconceptional period and the rate of multiple births.[54,55] At this time, the evidence for an association between increased periconceptional folic acid consumption and increased rate of twins is inconclusive. However, because of population differences in the frequency of twins, there remains the possibility that the twin rates in populations with higher existing rates of twinning, such as Afro-Americans, may be affected by folic acid consumption, as compared with populations such as the Chinese that have much lower rates of twinning. Keep in mind that NTDs occur more frequently in twin pregnancies, particularly monozygotic twins, than in singleton pregnancies, independent of folic acid use.[12]

A recent initiative to improve population-based surveillance of congenital anomalies, including fetal anomalies, is the Canadian Congenital Anomalies Surveillance Network (CCASN). The network, led by an advisory group of experts in genetics, epidemiology and related fields, will lead the development of standards and guidelines for the collection of data on congenital anomalies in Canada.

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Table 1. Epidemiologic Studies of Folate/Folic Acid and Risk of Neural Tube Defect

Study	Design	Subjects	Exposure	Results	Comments
Laurence et al., 1981 (56)	Randomized controlled trial in Wales	Pregnant women with prior NTD[a] affected pregnancy; supplemented mothers took 4 mg of folic acid daily Unsupplemented mothers took a placebo	4 mg of folic acid or placebo daily at least 1 mo before conception through the 1st trimester	2 NTD pregnancies in 60 supplemented women 4 NTD pregnancies in 51 placebo-treated women Relative risk = 0.40, not statistically significant	60% reduction in risk
Smithells et al., 1983 (57)	Non-randomized controlled multi-centre trial in UK	Pregnant women with prior NTD-affect pregnancy Supplemented mothers took 0.36 mg of folic acid plus multivitamins daily Unsupplemented mothers took nothing	0.36 mg of folic acid plus multivitamins or no use from 1 mo before conception through the 1st trimester	3 NTD pregnancies in 454 supplemented women 24 NTD pregnancies in 519 unsupplemented women Relative risk = 0.14, $p < 0.05$	86% reduction in risk
Mulinare et al., 1988 (58)	Case/control in metropolitan Atlanta	NTD case infants and normal control infants Pregnant women without a prior NTD-affected pregnancy	Multivitamin supplement containing 0-0.8 mg of folic acid at least 1 mo before conception through the 1st trimester	24 NTD cases in infants from women supplemented and 157 cases in infants from women unsupplemented 405 normal cases in infants from supplemented mothers and 1,075 normal cases in infants from unsupplemented women controls Odds ratio = 0.40, $p < 0.05$	60 % reduction in risk
Bower and Stanley, 1989 (59)	Case/control in Western Australia	Spina bifida case infants and normal control infants Pregnant women without a prior NTD-affected pregnancy	Dietary folate and multivitamin supplement at least 1 mo before conception through the 1st trimester	77 NTD cases and 154 control mothers in study. The highest folate quartile was compared with the lowest. An increasing protective effect was observed from the lowest to the highest quartile. Odds ratio = 0.25, $p < 0.05$	75% reduction in risk
Mills et al., 1989 (60)	Case/control in California and Illinois	NTD case infants and normal control infants Pregnant women without a prior NTD-affected pregnancy	Multivitamin plus folate supplement containing up to 0.8 mg of folic acid plus diet at least 1 mo before conception through the 1st trimester	89 NTD cases in infants from supplemented women and 214 cases in infants from unsupplemented women 90 normal infants from supplemented women and 196 normal infants from unsupplemented women controls Odds ratio = 0.91, not statistically significant	No protective effect
Milunsky et al., 1989 (61)	Prospective cohort in New England	NTD case infants and normal control infants Pregnant women without a prior NTD-affected pregnancy	Multivitamin plus folate supplement containing 0.1-1.0 mg of folic acid plus diet at least 1 mo before conception through the 1st trimester	10 NTD pregnancies among 10,713 women who took multivitamin plus folate 39 NTD pregnancies among 11, 944 women who took multivitamins without folate Relative risk = 0.28, $p < 0.05$	72% reduction in risk

Table 1. Epidemiologic Studies of Folate/Folic Acid and Risk of Neural Tube Defect

Study	Design	Subjects	Exposure	Results	Comments
Vergel et al., 1990 (62)	Non-randomized controlled trial in Cuba	Pregnant women with prior NTD-affected pregnancy Supplemented mothers took 5 mg of folic acid daily Unsupplemented mothers took nothing	5 mg of folic acid or no use from 1 mo before conception through the 1st trimester	0 NTD pregnancies in 81 supplemented women 4 NTD pregnancies in 114 untreated women Indeterminant protective effect, not statistically significant	Complete protective effect.
MRC Vitamin Study, 1991 (50)	Randomized controlled multicentre trial in United Kingdom and Hungary	Pregnant women with prior NTD-affected pregnancy Supplemented mothers took 4 mg of folic acid daily Unsupplemented mothers took a placebo	4 mg of folic acid or placebo daily at least 1 mo before conception through the 1st trimester	6 NTD pregnancies in 593 supplemented women 21 NTD pregnancies in 602 unsupplemented women Relative risk = 0.28, $p < 0.05$	72% reduction in risk
Czeizel and Dudas, 1992 (63)	Randomized controlled trial in Hungary	Women planning a pregnancy Supplemented women took 0.8 mg of folic acid plus multivitamins daily Unsupplemented women took a trace-element supplement	Supplements taken for at least 1 mo before conception and until the date of the second missed period	0 NTD pregnancies in 2,104 supplemented women 6 NTD pregnancies in 2, 052 unsupplemented women Relative risk = 0.0, $p = 0.029$	Complete protective effect
Kirke et al., 1992 (64)	Randomized controlled multicentre trial in Ireland	Pregnant women with prior NTD-affected pregnancy Supplemented women took 0.36 mg of folic acid with or without multivitamins daily Unsupplemented women took multivitamins daily excluding folic acid	Supplements taken for at least 2 mo before conception and until the date of the third missed menstrual period	0 NTD in 172 infants/fetuses of supplemented women 1 NTD in 89 infants/fetuses of unsupplemented women Indeterminate protective effect, not statistically significant	Trial was prematurely terminated
Werler et al., 1993 (65)	Case/control in Boston, Philadelphia, and Toronto	NTD cases and controls with other major malformations Mothers of cases and controls	Daily use of multivitamins, mostly 0.4 mg of folic acid, from 28 d before through 28 d after last menstrual period	34 supplemented and 250 unsupplemented NTD case women 339 supplemented and 1,253 unsupplemented women controls Adjusted odds ratio = 0.6 (95% CI = 0.4-0.8)	40% reduction in risk
Shaw et al., 1995 (66)	Case/control in California	NTD cases and normal control infants	Any use of folate-containing vitamins in the 3 mo before conception	88 supplemented and 207 unsupplemented NTD case women 98 supplemented and 149 unsupplemented women controls Odds ratio = 0.65 (95% confidence interval = 0.45-0.94)	35% reduction in risk

Table 1. Epidemiologic Studies of Folate/Folic Acid and Risk of Neural Tube Defect

Study	Design	Subjects	Exposure	Results	Comments
Berry et al., 1999 (23)	Public health campaign in two regions in China	Women at the time of their premarital examination	Supplement containing 0.4 mg folic acid alone, purchased by the women and taken before last menstrual period and through first trimester	**Northern Region** 13 NTD cases among 13,012 women with periconceptional folic acid use 16 NTD cases among 3,318 women who had not taken folic acid Relative risk = 0.21 (95% confidence interval = 0.10-0.43)	79% reduction in risk
				Southern Region 34 NTD cases among 58,638 women with periconceptional folic acid use 28 NTD cases among 28,265 women who had not taken folic acid Relative risk = 0.59 (95% confidence interval = 0.36-0.97)	41% reduction in risk

[a] NTD = neural tube defect

Source: Adapted from *Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects*. MMWR. 1992;41(No. RR-14):2-3.

Appendix I

Dietary Sources of Folate (based on usual serving size)

Excellent source of folate (55 mcg or more)	Good source of folate (33 mcg or more)	Source of folate (11 mcg or more)
Cooked fava, kidney, pinto	cooked lima beans	cooked carrots, beet greens, sweet potato
roman, soy and white beans	corn, bean sprouts, cooked	snow peas, summer or winter squash
chickpeas, lentils	broccoli, green peas, brussels	rutabaga, cabbage, cooked green beans
cooked spinach, asparagus	sprouts, beets	cashews, walnuts
romaine lettuce	orange	egg
orange juice, canned pineapple juice	honeydew	strawberries, banana
sunflower seeds	raspberries, blackberries	grapefruit, cantaloupe
	avocado	whole wheat or white bread
	dry roasted peanuts	pork kidney
	wheat germ	breakfast cereals
		milk, all types

Source: Health Canada, Canadian Nutrient File, 1997.

Table taken from: Health Canada. *Nutrition for a healthy pregnancy: national guidelines for the childbearing years*. Ottawa: Minister of Public Works and Government Services Canada, 1999.

Note: Although pork, beef and chicken liver is high in folate, it is also very high in vitamin A, which precludes recommending it as a source of folate for women in the periconceptional period.