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Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies

This Clinical Practice Guideline was prepared by the Genetics Committee, reviewed by the Family Physician Advisory Committee, and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide updated information on the pre- and post-conception use of oral folic acid with or without a multivitamin/micronutrient supplement for the prevention of neural tube defects and other congenital anomalies. This will help physicians, midwives, nurses, and other health care workers to assist in the education of women about the proper use and dosage of folic acid/multivitamin supplementation before and during pregnancy.

Evidence: Published literature was retrieved through searches of PubMed, Medline, CINAHL, and the Cochrane Library in January 2011 using appropriate controlled vocabulary and key words (e.g., folic acid, prenatal multivitamins, folate sensitive birth defects, congenital anomaly risk reduction, pre-conception counselling). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English from 1985 and June 2014. Searches were updated on a regular basis and incorporated in the guideline to June 2014 Grey (unpublished) literature was identified through searching the

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Key Words: Folic acid, folate, prenatal multivitamins, micronutrients, neural tube defect, spina bifida, myelomeningocele, congenital anomalies, fetal anomalies, folate sensitive birth defects, congenital anomaly risk reduction, preconception counseling, birth defects, pregnancy, prevention

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
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	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in here has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[193]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[193]

websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Costs, risks, and benefits: The financial costs are those of daily vitamin supplementation and eating a healthy folate-enriched diet. The risks are of a reported association of dietary folic acid supplementation with fetal epigenetic modifications and with an increased likelihood of a twin pregnancy. These associations may require consideration before initiating folic acid supplementation. The benefit of folic acid oral supplementation or dietary folate intake combined with a multivitamin/micronutrient supplement is an associated decrease in neural tube defects and perhaps in other specific birth defects and obstetrical complications.

Values: The quality of evidence in the document was rated using the criteria described in the Report of the Canadian Task Force on Preventative Health Care (Table 1).

Summary Statement

In Canada multivitamin tablets with folic acid are usually available in 3 formats: regular over-the-counter multivitamins with 0.4 to 0.6 mg folic acid, prenatal over-the-counter multivitamins with 1.0 mg folic acid, and prescription multivitamins with 5.0 mg folic acid. (III)

Recommendations

1. Women should be advised to maintain a healthy folate-rich diet; however, folic acid/multivitamin supplementation is needed to achieve the red blood cell folate levels associated with maximal protection against neural tube defect. (III-A)
2. All women in the reproductive age group (12–45 years of age) who have preserved fertility (a pregnancy is possible) should be advised about the benefits of folic acid in a multivitamin supplementation during medical wellness visits (birth control renewal, Pap testing, yearly gynaecological examination) whether or not a pregnancy is contemplated. Because so many pregnancies are unplanned, this applies to all women who may become pregnant. (III-A)
3. Folic acid supplementation is unlikely to mask vitamin B12 deficiency (pernicious anemia). Investigations (examination or laboratory) are not required prior to initiating folic acid supplementation for women with a risk for primary or recurrent neural tube or other folic acid-sensitive congenital anomalies who are considering a pregnancy. It is recommended that folic acid be taken in a multivitamin including 2.6 ug/day of vitamin B12 to mitigate even theoretical concerns. (II-2A)
4. Women at HIGH RISK, for whom a folic acid dose greater than 1 mg is indicated, taking a multivitamin tablet containing folic acid, should be advised to follow the product label and not to take more than 1 daily dose of the multivitamin supplement. Additional tablets containing only folic acid should be taken to achieve the desired dose. (II-2A)
5. Women with a LOW RISK for a neural tube defect or other folic acid-sensitive congenital anomaly and a male partner with low risk require a diet of folate-rich foods and a daily oral multivitamin supplement containing 0.4 mg folic acid for at least 2 to 3 months before conception, throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues. (II-2A)
6. Women with a MODERATE RISK for a neural tube defect or other folic acid-sensitive congenital anomaly or a male partner with moderate risk require a diet of folate-rich foods and daily oral supplementation with a multivitamin containing 1.0 mg folic acid, beginning at least 3 months before conception. Women should continue this regime until 12 weeks' gestational age. (1-A) From 12 weeks' gestational age, continuing through the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid. (II-2A)
7. Women with an increased or HIGH RISK for a neural tube defect, a male partner with a personal history of neural tube defect, or history of a previous neural tube defect pregnancy in either partner require a diet of folate-rich foods and a daily oral supplement with 4.0 mg folic acid for at least 3 months before conception and until 12 weeks' gestational age. From 12 weeks' gestational age, continuing throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid. (I-A). The same dietary and supplementation regime should be followed if either partner has had a previous pregnancy with a neural tube defect. (II-2A)