THE USE OF FOLIC ACID FOR THE PREVENTION OF NEURAL TUBE DEFECTS

This Statement has been prepared by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada and approved by its Council in January 1993.

BACKGROUND

Neural tube defects (NTD) are severe birth anomalies due to the lack of neural tube closure at the upper or lower end in the third and fourth week after conception (day 26-28). Isolated NTD’s (anencephaly, meningomyelocele, encephalocele) are most commonly due to multifactorial inheritance. The incidence and empiric recurrence risks for NTD’s varies across Canadian regions (Table 1). Certain ethnic populations in Canada have been shown to have an increased incidence of NTD.

Table 1: Incidence and Empiric Recurrence Risks for NTD’s in Different Regions in Canada.

<table>
<thead>
<tr>
<th>Province</th>
<th>Incidence (per 1000 births)</th>
<th>Empiric Recurrence Risks (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Ontario</td>
<td>1.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Quebec</td>
<td>4.0</td>
<td>4.5</td>
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<tr>
<td>Newfoundland</td>
<td>4.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

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Multifactorial inheritance is the most common cause of NTD's but monogenic, chromosomal and teratogenic causes have different specific recurrence risks and have not been studied in association with folic acid.

**Prevention of Recurrence for NTD**

Recent studies have provided strong scientific support for maternal periconceptional use of folic acid significantly reducing the recurrence risk for couples with a previous child with a NTD. In a randomized double-blind clinical trial involving 1195 completed pregnancies in high-risk women from 33 centres, 72% fewer cases of NTDs occurred among the offspring of the folic acid supplementation group than among the offspring of controls without folic acid. 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 result in the group with vitamins without folate was similar to the result in the group with no vitamin supplementation with a recurrence risk of 3.5%

**Prevention of Primary Occurrence of NTD**

A recent randomized Hungarian trial published results that periconceptional vitamin supplement (12 vitamins including 0.8 mg folic acid, 4 minerals, 3 trace elements) decreases the incidence of a first occurrence of neural tube defects. Previous case control studies have provided supportive and equivocal evidence that pregnant women using multivitamins containing folic acid or dietary folic acid have a lower risk of occurrence NTDs than women not taking supplements.

Folic acid appears to be a vitamin responsible for decreasing recurrence of neural tube defects and may prevent first occurrence of NTDs. Folic acid, in the recommended dosages, is not known to cause demonstrable harm to the developing fetus or pregnant women. The optimal dosage of folic acid is optimal for reducing the recurrence risk for NTDs is not known. The dosage of folic acid used in the MRC study was 4.0 mg/day. Other studies showing a reduction in NTD recurrence or incidence have used folic acid in doses ranging from 0.36-5.0mg/day.

**RECOMMENDATIONS**

**Low Risk Women**

All women of child bearing potential should consider a minimum of 0.4 mg folic acid supplementation or adequate dietary equivalent according to Canada’s Food Guide to Healthy Eating on a daily basis. Pregnancy vitamin supplements contain 0.8-l.O mg folic acid per tablet.
**Alternate approach** is that women with a low risk for NTD planning a pregnancy should consider folic acid supplementation (0.4 mg) or dietary equivalent after discontinuation of reliable birth control until 10-12 weeks after LMP.

**High Risk Women**

All women with a previous pregnancy affected with NTD should consider 4 mg folic acid daily after discontinuation of reliable birth control (or at least 2-4 weeks prior to conception) until 10-12 weeks after LMP.

**Intermediate Risk Women**

All women with no previous history of NTD but having an increased risk due to medical or family conditions (insulin dependent diabetes, epilepsy treatment with valproic acid or carbamazepine, first degree relative with NTD) should consider 1.0-4.0 mg folic acid supplementation after discontinuation of reliable birth control until 10-12 weeks after LMP.

**Prenatal diagnosis** should be offered to women at an increased risk of having a child with a NTD\(^{22-27}\). Folic acid supplementation will **not** eliminate but will only reduce the risk of NTD. Individuals at increased risk for a pregnancy complicated with NTD include:

a) previous child with NTD
b) first, second, or third degree relative (living or dead) with NTD.
c) women with insulin dependent diabetes (type 1)
d) women with epilepsy on valproic acid or carbamazepine for seizure control
e) women on folic acid antagonists (amniopterin, methotrexate).

**Noninvasive** prenatal diagnosis by ultrasound and maternal serum alpha fetoprotein can be used between 15-20 weeks gestation to identify 85-90% of NTDs. **Invasive** prenatal diagnosis by ultrasound and amniocentesis can be used starting at 15 weeks to identify 95% of NTDs with a 0.5% risk of pregnancy loss due to the amniocentesis.

Prenatal or other multivitamin preparations should not be used in multiple dosage in order to increase the amount of folic acid due to the increased risk of excessive vitamin A.

The effects of higher intake of folic acid are not well known but include complicating the diagnosis of vitamin \(B_{12}\) deficiency. Should not be used alone in pernicious anemia or other severe vitamin \(B_{12}\) deficiency. Care should be taken to keep folic acid consumption at less than 1 mg per day, except under the supervision of a **physician**\(^{28}\).
CONTRAINDICATIONS AND PRECAUTIONS:

Caused in undiagnosed anemia. Pernicious anemia must be ruled out as hematological effects may be corrected but neurologic damage will progress due to persisting vitamin $B_{12}$ deficiency. Should not be used alone in pernicious anemia or other severe vitamin $B_{12}$ deficiency; anemia may be corrected but neurologic damage will progress unless vitamin $B_{12}$ is also used.

Caution in seizure disorders; convulsions may occur in previously controlled patients.

SIDE EFFECTS:

Relatively non-toxic.

Hypersensitivity: Rarely allergic response including erythema, rash, itching, general malaise, bronchospasm.

INTERACTIONS:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Reduced folic acid effect</td>
<td>Interference with erythrocyte maturation</td>
<td>Caution</td>
</tr>
<tr>
<td>Phenobarbital, phenytoin, primidone</td>
<td>Reduced folic acid levels</td>
<td>Increased folic acid metabolism</td>
<td>Caution</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Loss of seizure control; decreased phenytoin levels</td>
<td>Increased phenytoin metabolism</td>
<td>Monitor phenytoin levels</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Decreased folic acid levels</td>
<td>Impaired absorption</td>
<td>Caution</td>
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REFERENCES


Reprints and copies can be ordered by writing to Dr. André Lalonde, SOGC’s Executive Vice President, at the following address: 774 Echo Drive, Ottawa, Ontario, K1 S 5N8.