Folic Acid and the Prevention of Neural-Tube Defects

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In 1991, a randomized trial funded by the Medical Research Council demonstrated that folic acid supplementation before pregnancy and during its early stages markedly reduced the risk of neural-tube defects in newborns.[1] This finding — which indicated that neural-tube defects may be considered to represent a vitamin-deficiency disorder — led to the recommendation that all women who are planning to become pregnant should take folic acid supplements beginning before pregnancy is recognized and continuing through its early stages. Once a pregnancy has been confirmed, it is probably too late for supplemental folic acid to be protective.

In this issue of the Journal, Rothenberg and colleagues (pages 134–142) show that women who have had a pregnancy complicated by a neural-tube defect have autoantibodies to folate receptors. This observation suggests a mechanism through which a folate deficiency may cause neural-tube defects and how folic acid supplementation may prevent them.

What is needed to guide public health policy is specification of the dose–response relation between extra folic acid and the reduction in the risk of neural-tube defects. What is the effect of different doses of folic acid on risk, and is there a dose that will prevent nearly all neural-tube defects?

A two-stage dose–response model predicts the effects of a given amount of supplemental folic acid.[2] The first part of the model specifies the relation between dietary folic acid and plasma folate, and the second part specifies the relation between the plasma folate level and the risk of a neural-tube defect. The first relation is additive: a given dose of folic acid adds a constant increment to a person's plasma folate level, irrespective of dietary folate intake. The second relation is proportional: a given percentage

increase in the plasma folate level results in a constant percentage reduction in the risk of a neural-tube defect. The risk of such a defect thus decreases with increasing folic acid intake, but it decreases to a diminishing extent as the dose and the background plasma folate level increase. The model predicts both the moderate preventive effect seen in case–control and cohort studies (in which the usual dose of folic acid supplementation has been 0.4 mg daily) and the larger preventive effect observed in the Medical Research Council study, in which supplementation with 4 mg of folic acid per day prevented 83 percent of neural-tube defects (according to the analysis restricted to women who took the folic acid before they became pregnant).

According to the model, folic acid at a dose of about 5 mg per day is expected to decrease the risk of a neural-tube defect by an estimated 85 percent in women with a background serum folate level of 5 ng per milliliter, which is typical in many Western countries (see Table). Little is gained with higher doses. A dose of 0.4 mg per day (the amount contained in a standard multivitamin) reduces the risk by an estimated 36 percent.

Educational campaigns encouraging women to take folic acid before becoming pregnant are useful, but many women remain unaware of the need, and about half of pregnancies are unplanned. Achieving sufficient folate levels through dietary change is impractical. Folic acid fortification is thus essential.

In the United States, it was mandated that by January 1, 1998, flour and other grain products be fortified at a minimal level of 0.14 mg of folic acid per 100 g of cereal grain. The average level of fortification was necessarily higher, leading to an increase in folic acid intake of about 0.2 mg per day; correspondingly, the rate of neural-tube defects decreased by approximately 20 percent (as predicted by the model). The fortification level is unnecessarily low, constrained by the arbitrary setting of a "tolerable upper limit" of 1 mg per day of folic acid. Chile has set a higher fortification target designed to deliver an extra 0.4 mg per day, on average. There are grounds for setting an even higher level of fortification of 0.6 to 0.8 mg per day. This is the minimal fully effective dose of folic acid that can lower the serum homocysteine level by about 3 mmol per liter, an effect that is associated with a decrease of about 15 percent in the risk of ischemic cardiac events and a decrease of about 25 percent in the risk of stroke, deep venous thrombosis, and pulmonary embolism.[3] There is no evidence that folic acid fortification at these levels poses a risk to health, and there is compelling evidence that the failure to fortify a staple food at an adequate level causes considerable harm.

Concern about possible risk associated with folic acid supplementation arose because of a misplaced worry that it might mask vitamin B_{12} deficiency by partially correcting the associated anemia while allowing associated neurologic dysfunction to progress. However, the detection of a vitamin B_{12} deficiency does not depend on anemia, and anemia is not a universal finding in patients with such a deficiency. Furthermore, there is evidence that folic acid fortification in the United States has not caused such a masking effect.[4]

The cost of fortification is very small. In the United States, it costs about 1 cent per person per year, or about $1,000 per neural-tube defect prevented. In countries such as Mexico, where the prevalence of neural-tube defects is much higher, the cost effectiveness of fortification is more favorable. As of September 2003, 38 countries had introduced or agreed to introduce folic acid fortification of flour, but no countries in the European Union are among them.

Medical authorities are unlikely to recommend fortification at a level higher than about 0.4 to 0.8 mg of folic acid per day, so a public health policy should include both the mandatory fortification of flour and a recommendation that all women planning a pregnancy take 5 mg of folic acid per day (available by prescription in most countries and over the counter in some). Such a policy would have a sizable effect. Each year, about a quarter of a million pregnancies worldwide result in the birth of an infant with a neural-tube defect or an abortion performed because of such a defect. Half these cases could be prevented simply and safely through adequate fortification, and 85 percent of them could

Table. Dose–Response Relation between Folic Acid and Neural-Tube Defects.

Increase in Daily Folic Acid Intake*	Percentage of Neural-Tube Defects That Would Be Prevented	Effect of an Extra 0.2 mg	Effect of an Extra 1 mg
mg		%	
0	0	23	57
0.2	23		
0.4	36		
0.8	52	5	
1.0	57		
4.0	82		3
5.0	85		

* The analysis assumes a base-line serum folate level of 5 ng per milliliter.

be prevented if all women took 5-mg folic acid supplements before pregnancy and during the first trimester.

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3. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002; 325:1202.

4. Mills JL, Von Kohorn I, Conley MR, et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. Am J Clin Nutr 2003;77:1474-7.