Periconceptional Folic Acid and Neural Tube Defects: Public Health Issues

RAFAEL PÉREZ-ESCAMILLA

This review examines evidence linking periconceptional folic acid intake to neural tube defects (NTDs) and related public health issues in the United States and developing countries. Sources of information were identified through on-line searches (Medline, UCAT—University of Connecticut) and by contacting researchers in the field.

The distribution of NTDs varies across regions. Recurrent NTDs can be prevented with high-dosage folic acid supplementation during periconception, but it is not clear if such a protective effect can be achieved with lower dosages or in low-NTD-risk populations. Overall, it appears that women with a previous NTD pregnancy should receive folic acid supplementation during periconception under medical guidance. Dietary counseling regarding foods rich in folate should be given to all women of childbearing age. However, primary prevention of NTDs through widespread food fortification with folic acid seems unwarranted in both the United States and developing countries due to the low prevalence of NTDs relative to other problems and a potentially unfavorable benefit/risk ratio.

BIRTH DEFECTS OCCUR IN 2.9% OF ALL LIVE-BORN INFANTS AND ARE THE LEADING CAUSE OF DEATH AMONG CHILDREN IN THE UNITED STATES. THE CAUSES OF APPROXIMATELY 70% OF THESE MALFORMATIONS ARE STILL UNKNOWN (1).

Neural tube defects (NTDs) such as anencephaly and spina bifida are among the most common birth defects. An NTD exists when the brain or spinal cord is malformed or protrudes out through its normal skeletal covering as a result of disturbances in the process of midline fusion of the skull and spine (2). NTDs occur during the periconceptional period surrounding fertilization of the female egg because the neural tube closes between days 17 and 30 of gestation (3). Whereas anencephaly is incompatible with survival, spina bifida can be anything from a minor defect to a severe one (4). Medical costs associated with treating spina bifida in the United States are estimated at US$200 million annually (5).

Compelling scientific evidence has linked increased intake of folic acid during the periconceptional period with prevention of NTD recurrence. As a result, the U.S. Centers for Disease Control (CDC) recommended in 1991 that all women with a previous NTD-affected pregnancy should take high-dose folic acid supplements (4 mg daily) when they plan to become pregnant again (6). In 1992 the U.S. Public Health Service recommended that all women of childbearing age should consume 0.4 mg of folic acid daily (7). In 1994 the U.S. Food and Drug Administration (FDA) approved a folic acid/NTD health claim for inclusion in labels of dietary supplements containing this vitamin (8, 9). Similar recommendations have been issued by health authorities in other industrialized nations (10–12).
Proposals for implementing some of these recent recommendations have generated public health debate in the U.S. (8, 9, 13–16). The implications of these recommendations for developing countries are unclear.

NTD EPIDEMIOLOGY

This subject has recently been reviewed by Little and Elwood (4). The worldwide distribution of NTDs is summarized in Table 1. In Europe, the British Isles are a relatively high-risk area, with Northern Ireland, the Irish Republic, and Scotland experiencing the highest rates. The current rates in the U.K. range from 1 to 4 cases per 1 000 births (all rates in this section are per 1 000 births), which are significantly lower than the 2–9 reported about 20 years ago.

Reports from continental Europe suggest a current range of 0.4–1.6, while the comparable U.S. range (0.7–1.0) is similar but narrower. Improvement over time is found in both Europe and the U.S., the U.S. rates declining from a peak of about 6 in 1930 to less than 2 in 1970 (17). Canada shows an east-west gradient, with rates ranging from 3.1 in the east to 1.3 in the west. Australia and New Zealand have rates similar to those in Western Canada.

In Asia, the rates found in three industrialized areas (Hong Kong, 0.9; Tokyo, 0.9; and Singapore, 1.2) are similar to those in Continental Europe and the U.S. But rates reported from China (0.7–

Table 1. Available data on the epidemiology of neural tube defects (NTD).*

<table>
<thead>
<tr>
<th>Region</th>
<th>NTD prevalence (per 1 000 births)†</th>
<th>Period</th>
<th>No. of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Industrialized areas:</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>United Kingdom</td>
<td>2.5–8.7</td>
<td>1950–79</td>
<td>17</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.0–4.1</td>
<td>1980–86</td>
<td>5</td>
</tr>
<tr>
<td>Continental Europe</td>
<td>0.9–4.0</td>
<td>1911–79</td>
<td>13</td>
</tr>
<tr>
<td>Continental Europe</td>
<td>0.4–1.6</td>
<td>1970–85</td>
<td>17</td>
</tr>
<tr>
<td>United States</td>
<td>0.7–3.3</td>
<td>1930–79</td>
<td>11</td>
</tr>
<tr>
<td>United States</td>
<td>0.7–1.0</td>
<td>1980–85</td>
<td>3</td>
</tr>
<tr>
<td>Canada</td>
<td>1.4–4.0</td>
<td>1952–79</td>
<td>7</td>
</tr>
<tr>
<td>Canada</td>
<td>1.3–3.1</td>
<td>1970–84</td>
<td>9</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>1.3–2.0</td>
<td>1942–79</td>
<td>4</td>
</tr>
<tr>
<td>Australia</td>
<td>1.4–2.1</td>
<td>1980–85</td>
<td>4</td>
</tr>
<tr>
<td>Israel</td>
<td>0.9–1.5</td>
<td>1958–85</td>
<td>3</td>
</tr>
<tr>
<td>Hong Kong, Japan, &amp; Singapore</td>
<td>0.9–1.2</td>
<td>1961–87</td>
<td>3</td>
</tr>
<tr>
<td><strong>Developing areas:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>0.9–8.0</td>
<td>1946–76</td>
<td>10</td>
</tr>
<tr>
<td>China</td>
<td>0.7–10.6</td>
<td>1986–87</td>
<td>1</td>
</tr>
<tr>
<td>Middle East†</td>
<td>2.9–5.2†</td>
<td>1953–88</td>
<td>5</td>
</tr>
<tr>
<td>Latin America &amp; the Caribbean</td>
<td>0.1–1.3</td>
<td>1970–89</td>
<td>5</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>0.5–2.6†</td>
<td>1961–84</td>
<td>13</td>
</tr>
</tbody>
</table>

* Adapted from Little and Elwood (4).
† Only studies with less than 30% statistical variability are included for the industrialized nations (except Israel) and for India, China, and Latin America and the Caribbean.
‡ Includes Egypt, Beirut, Iran, and Turkey.
§ One study in Bursa, Turkey, reported an unusually high NTD rate of 12.5 per 1 000 births.
∥ One study in Transkei, South Africa, reported an NTD rate of 6.1 per 1 000.
10.6), India (0.9–8.0), and some Middle Eastern countries (Turkey, 2.9–12.5; Beirut, Lebanon, 3.6; Shiraz, Iran, 4.0; and Alexandria, Egypt, 5.2) suggest these countries have high-risk NTD areas.

In contrast, recent studies of 7–10 South American nations (indicating rates of 1.1–1.3) and 2 Caribbean countries (Jamaica, 0.1–0.5; Guadeloupe, 1.3) have found NTD rates similar to those in low-NTD-risk areas of industrialized nations. Similarly, data from Mexico City and Panama City in the 1960s showed rates of 0.9 and 1.3, respectively. In sub-Saharan Africa the reported rates range from 0.5 to 2.6.

Regarding within-country variations, the U.K. has wide variations with a geographic distribution similar to those of infant mortality and low birthweight. Large variations have also been reported in Belfast, Northern Ireland, and (as already noted) in Canada, India, and Turkey (4). The rate in China in 1986–1987 was 2.4 with wide variations (18) ranging from 0.7 in Hubei to 10.6 in Shanxi. A recent study conducted in California (29) indicated NTDs were more common among Hispanics than other ethnic groups.

Regarding socioeconomic variations, studies have identified an inverse association between NTD rates in industrialized countries and socioeconomic status (20). Similar data from the developing world are not available, but NTD rates in China have been found higher in rural than in urban areas (21).

In sum, there does not seem to be an NTD rate differential based on countries’ socioeconomic development—in contrast to certain health indicators such as low birthweight and infant mortality. However, methodologic limitations urge caution in interpreting these data. Often the source of NTD ascertainment is unknown or unreliable; studies have been based on hospital samples, which could result in overreporting due to selective admission or underreporting due to exclusion of high-risk groups in countries where a substantial proportion of deliveries are not attended by the health care system (22). In addition, anencephaly might be underestimated by failure to report stillbirths and spina bifida by failure to report less severe cases (4).

STUDIES ON FOLIC ACID AND NTDs

Observations in the U.K. during the 1950s–1970s suggested that intake of micronutrients, notably folic acid, was lower in women with NTD pregnancies than in matched controls (17). The observational (23–26) and intervention (27–32) trials that followed in the 1980s (Table 2) strongly support the hypothesis that folic acid can prevent recurrent and perhaps first-occurrence NTDs.

Folic Acid and NTD Recurrences

In the British Isles, Smithells et al. (28, 29) found the rate of NTD recurrences 86% lower in women (n = 429) supplemented with a multivitamin/mineral supplement (0.36 mg folic acid daily) for at least 28 days prior to conception and until the date of the second missed menstruation than among unsupplemented controls (n = 510). In Cuba (see Table 3), Vergé et al. (30) found periconceptional folic acid supplementation (5 mg daily) protected completely against NTD recurrence. The supplemented group included 101 women; the unsupplemented control group (n = 114) consisted of women who were already pregnant at recruitment. Both of these studies were nonrandomized trials.

Laurence et al. (27) conducted a double-blind study in South Wales, U.K., that randomly assigned 218 women with prior NTD pregnancies to receive a high-dose folic acid supplement (4 mg daily) or a placebo from the time they stopped contraception until the 12th week of pregnancy. The results of 111 pregnancies...
Table 2. Effects of periconceptional folic acid supplementation on neural tube defects: experimental studies in industrialized countries. (RR = relative risk, FS = fully supplemented, PS = partially supplemented, SUP = supplemented, US = unsupplemented, FM = folate plus minerals, FVM = folate plus vitamins and minerals, VM = vitamins and minerals without folate, M = minerals.)

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Control group</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of NTDs, unrandomized: Smithells et al. (28, 29), Northern Ireland and England</td>
<td>(FS): multivitamin supplement containing 0.36 mg folic acid daily over 28 days before conception (n = 429)</td>
<td>(US): women already pregnant at recruitment (n = 510)</td>
</tr>
<tr>
<td></td>
<td>(PS): multivitamin supplement containing 0.36 mg folic acid daily less than 28 days before conception (n = 113)</td>
<td></td>
</tr>
<tr>
<td>Recurrence of NTDs, randomized: Laurence et al. (27), Wales</td>
<td>(SUP): 4 mg folic acid daily at least 1 month before conception until first trimester (n = 60)</td>
<td>(US): placebo (n = 51)</td>
</tr>
<tr>
<td>UK MRC (32), UK, Hungary, France, Israel, former USSR</td>
<td>(FVM): 4 mg folic acid daily + multivitamins + minerals at least 1 month before conception until first trimester</td>
<td>(VM): multivitamins + minerals without folic acid for same period of time as exposed group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(FM): 4 mg folic acid daily + minerals at least 1 month before conception until first trimester (n of FVM + FM = 593)</td>
</tr>
<tr>
<td>First-occurrence NTDs, randomized: Czeizel and Dudás (31), Hungary</td>
<td>(FVM): multivitamin/mineral supplement containing 0.8 mg folic acid daily for at least one month before conception and until the first trimester (n = 2 104)</td>
<td>(M): mineral supplement for same period of time as exposed group (n = 2 052)</td>
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Suggested the supplement produced a 58% reduction in the NTD risk (P > 0.05).

The above studies were inconclusive due to lack of randomization procedures or small sample sizes. This uncertainty prompted design of the MRC double-blind randomized trial (32) conducted in 33 centers in Europe, Canada, Australia, and Israel (see Table 2). A total of 1 817 women who had at least one prior NTD pregnancy and were planning to become pregnant were randomly assigned to one of four groups receiving the following supplements: (a) minerals/folic acid (4 mg daily); (b) minerals/folic acid (4 mg daily)/multivitamins; (c) minerals/multivitamins (without folic acid); and (d) minerals/placebo. The women were asked to take a daily capsule from the date of randomization through the 12th week of preg-
Table 3. Periconceptional folate and neural tube defects: studies in developing countries and during the Dutch famine of 1944–1945. (RR = relative risk, FS = fully supplemented, PS = partially supplemented, US = unsupplemented, CA = cases, CO = controls, FAM = famine survivors, EXP = expected.)

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Control group</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vergel et al. (30), Cuba (recurrent NTDs, nonrandomized intervention)</td>
<td>(US): women already pregnant at recruitment without supplementation (n = 114)</td>
<td>FS + PS: 0/101 NTDs US: 4/114 NTDs</td>
</tr>
<tr>
<td>for less than 1 menstrual period before conception through week 10 of pregnancy (n = 81)</td>
<td>(P &gt; 0.05)</td>
<td></td>
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<td>(PS): received folic acid for less than FS group (n = 20)</td>
<td>Duff &amp; Cooper (63), Jamaica (case-control)</td>
<td>(CA): women with mothers who had an NTD (n = 17)</td>
</tr>
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<td></td>
<td>(CO): matched controls without NTD pregnancy after Hurricane Gilbert (n = 51)</td>
<td>Periconception folate intake: CA: 0.154 mg daily CO: 0.254 mg daily (P &lt; 0.0001)</td>
</tr>
<tr>
<td></td>
<td>Susser &amp; Stein (66), Stein &amp; Susser (67), The Netherlands (Dutch famine of 1944–45, observational, retrospective)</td>
<td>(FAM): offspring survivors of pregnant women exposed to famine during first trimester of pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR: (FAM/EXP) = 2.0</td>
</tr>
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</table>

nancy; compliance was high. Results based on 1 195 well-documented pregnancies indicated an NTD risk reduction of 71% (P < 0.001). The whole effect was attributed to folic acid, since women who took minerals/multivitamins without folic acid had an NTD recurrence rate similar to that of the minerals/placebo group.

Summing up, intervention studies done before the MRC trial strongly suggested that high-dose (27, 30) and low-dose (28, 29) folic acid supplementation could prevent the recurrence of NTDs. The MRC double-blind randomized trial has left no doubt that high-dose folic acid supplementation during the periconceptional period can indeed prevent the recurrence of NTDs.

Folic Acid and First-Occurrence NTDs

About 95% of all NTDs occur among primiparas or women who have not previously had an NTD pregnancy. For this reason it is important to review the evidence regarding folic acid intake and the prevention of first-occurrence NTDs.

Several observational studies on folic acid and first-occurrence NTDs have been conducted in the United States (23, 25, 26, 33, 34), Canada (34), and Australia (24). Four (23, 24, 33, 34) out of five (23–25, 33, 34) case-control studies and one prospective cohort study (26) have indicated that women who had a first-occurrence NTD pregnancy had lower dietary folic acid intake (24, 34) or were less likely to consume multivitamins (containing 0.1–1 mg folic acid daily) during the periconceptional period (23, 33, 34). One case-control study (25) did not find significant differences between mothers of NTD cases and controls in their use of multivitamins (up to 0.8 mg folic acid) during periconception.

Most of the observational studies support the hypothesis that increased folic acid intake during periconception might prevent first-occurrence NTDs (RR: 0.14–
However, it is difficult to infer causality from these studies, because women who have better diets or choose to use multivitamins during the periconceptional period might have different lifestyles and background characteristics than women who do not follow these practices (35).

In Hungary, Czeizel and Dudás (31) conducted a double-blind randomized trial where women planning their first pregnancy were randomly assigned to receive a single tablet of a multivitamins/minerals supplement (including 0.8 mg folic acid daily) or a minerals supplement. Supplements were taken from at least one month before conception until the date of the second missed menstrual period and were associated with full protection against NTDs. In this study the multivitamins/minerals supplement (containing low-dose folic acid) was causally linked to the prevention of first-occurrence NTDs. However, it was not possible to attribute the impact to folic acid alone, since other nutrients present in the multivitamins/minerals supplement but not in the minerals supplement could have contributed to the outcome.

PUBLIC HEALTH ISSUES IN THE UNITED STATES

Folate RDA

The recommended daily allowance (RDA) of folate for nonpregnant women of childbearing age in the U.S. was decreased from 0.40 mg daily in the NRC’s 9th edition of Recommended Daily Allowances published in 1980 to 0.18 mg daily in the 10th edition published in 1989 (36). The U.S. Public Health Service’s current recommendation of a higher folic acid intake for prevention of NTDs, plus the health claim recently approved by the FDA, suggests that the present RDA for folate should revert to the 1980 edition’s RDA level of 0.40 mg daily (16). Furthermore, it has been argued that failure to increase the current RDAs promptly would result in inadequate provision of folic acid to many low-income women, since the nutritional standards of U.S. food assistance programs are based on the RDAs (16).

Recommendations for Recurrent NTDs

An implicit assumption of the aforementioned CDC recommendation—that all women with a prior NTD-affected pregnancy should take daily 4 mg supplements of folic acid when they plan to become pregnant again—is that the benefits observed in a population with relatively high NTD rates will apply to a low-risk population such as that in the United States. This assumption is unproven, and there is concern that NTDs might not be prevented through folic acid supplementation in areas with NTD rates that are ≤1 per 1,000 births (3, 37).

The CDC recommendation also faces serious logistic difficulties. More than half the pregnancies in the U.S. are unplanned, and few women see their physicians before becoming pregnant (3). Therefore, many women become aware of their pregnancy at a time when the NTD might have already developed. There is also concern that high-level folic acid intakes might have negative side-effects on women or that it could damage neural tissues of the embryo (38–42).

Extra folic acid can confound the diagnosis of pernicious anemia, thereby leading to irreversible neurologic disorders characteristic of vitamin B-12 deficiency. This issue is particularly relevant for the elderly, since in industrialized nations the prevalence of pernicious anemia is approximately 1 per 1,000 persons and increases with age (to 1 per 100 among people over 65 years old) (42). It is estimated that a million people in the U.S. have this disorder (14). Also, special pre-
cautions might be required in providing folic acid supplementation to African-American women of childbearing age, since they seem particularly susceptible to vitamin B-12 deficiency (41) and less likely to develop NTDs (19, 41).

Furthermore, more studies are needed to document the incidence of neurologic manifestations of vitamin B-12 deficiency, particularly in the absence of hematologic changes, and to find the minimum levels of folic acid that could potentially mask the hematologic manifestations of vitamin B-12 deficiency (37). It has been suggested that folic acid intakes below 1–1.5 mg daily are unlikely to be associated with neurologic disorders (37, 43) but that intakes above these levels should require medical supervision (6, 37).

Folic acid supplementation is also of concern to some epileptic patients, because it antagonizes the effects of anticonvulsant drugs. Conversely, anticonvulsant drugs antagonize folic acid and increase the risk of NTDs (44). For this reason, epileptic patients should receive additional folic acid only under medical supervision (43). Folic acid supplementation might also interfere with the action of other medications, including some used to treat malaria (45). In addition, it has been suggested that folic acid supplementation might induce zinc deficiency. However, in the MRC trial (32) high-dose folic acid supplementation did not have an impact on serum zinc levels (46). There is also concern that high-dose folic acid might damage neural tissue during early embryonic development (39), though this hypothesis was not supported by the outcomes of the MRC trial (32).

For the reasons mentioned above, it is important to consider using lower doses of folic acid (i.e., 0.4–0.8 mg daily), as suggested by some studies, for prevention of recurrent NTDs (29, 43). This approach could avoid exposing the population to unnecessary risks.

Recommendations for First-Occurrence NTDs

Developing recommendations for first-occurrence NTDs has been much more challenging than doing so for recurrent NTDs. Although folic acid supplementation's protective impact on NTD recurrence has been proven, its impact on first-occurrence NTDs has not. This is a relevant public health issue, since about 95% of all NTD cases are first-occurrence. Also, if it is decided to increase folic acid intake by women of childbearing age, it is unclear whether the best strategy would be supplementation, food fortification, or dietary counseling (8, 9).

At first glance, the best answer would seem to be distribution of low-dose folic acid tablets to women planning to get pregnant. But many pregnancies are unplanned, and supplements are less likely to reach the population at highest risk (e.g., low-income people) (37, 47). Also, supplementing all women of childbearing age with folic acid would be logistically difficult and would substantially decrease the cost-effectiveness of the intervention (38).

Another approach, additional fortification of the food supply with folic acid, would provide the target population (i.e., women of childbearing age) with additional amounts of this vitamin on a routine basis. This approach, however, is not without risks. It is reasonable to assume that fortification with low levels of folic acid should pose fewer potential health risks than an intervention involving high intakes of this vitamin. Breakfast cereals in the U.S. have been fortified for many years with folic acid, typically at a level of 0.1 mg per serving, and multivitamin supplements containing low levels of folic acid (0.4 mg per unit) have also been on the market a long time. To date, there is no evidence that consumption of these products represents a health risk for the population. In fact, some have proposed
that the secular trend involving re-
duction of NTDs in the U.S. has been
due partly to consumption of these prod-
ucts and general dietary improvements.
There is concern, however, that addi-
tional fortification of the food supply could
expose segments of the population to
health risks.

The FDA has proposed fortification of
enriched cereal-grain products at a level
of 0.14 mg folic acid per 100 g. This dose
would deliver 0.035 mg folic acid per slice
of bread (8, 48) or 0.060 mg folic acid per
serving of pasta (49). Given such fortifi-
cation, it has been estimated that people
over age 50 (a group at a higher risk of
masking vitamin B-12 deficiency symp-
toms with folic acid administration) would
have a maximum consumption of folic
acid from food of about 0.84 mg daily
(50), which is within the currently ac-
cepted safe range if there is no significant
folic acid consumption from vitamin sup-
plements. Unfortunately, this fortifica-
tion level might only be enough to pro-
hibit 25% of the women at risk of NTDs
(48). For this reason, a cereal-grain prod-
uct fortification level of 0.35 mg per 100
g has been proposed (48). This level of
fortification would require careful moni-
toring, since it could increase the maxi-
imum estimated intake of folic acid among
the elderly to levels near or beyond the
upper safety limit (1 mg of folic acid daily)
(50).

The FDA has recently estimated that
13 000 people could face the risk of mask-
ning B-12 deficiency symptoms if wide-
spread folic acid fortification were imple-
mented (15). Since estimates (37) indicate
this policy would prevent only about
1 000 cases of NTD per year in the U.S.,
opposition to this public health option is
not surprising (13–15).

Where feasible, it is always desirable
to seek prevention of nutrition-related
disorders through dietary improvements
(9). In the case of folic acid, it is likely
that increasing the consumption of fo-
late-rich foods (e.g., citrus fruits and
juices, dark green leafy vegetables, beans
and other legumes, and whole grains)
will provide other health benefits besides
prevention of NTDs (51). The observa-
tional studies previously discussed also
suggest that NTDs might be prevented
through dietary improvements. Promoting
a daily absorption of 0.6 mg per day would
translate into an intake of about 1.2 mg
per day, since the bioavailability of dietary
folate (i.e., conjugated folic acid) is about
50%, vs. about 100% in supplements that
use unconjugated folic acid (43).

In 1990, adult British women had a me-
dian folate intake of 0.2 mg per day, in-
dicating that a six-fold increase in dietary
folate would be required to meet the stated
target. In the U.S., 65% of low-income
women and 45% of higher-income women
of childbearing age consume <0.18 mg
folate daily (52), and deficiency of this
vitamin could be common (53). In 1976–
1980 only 5% of the white women and
4% of the black women 19-29 years old
(52) consumed the recommended five or
more servings of fruits and vegetables
daily (54).

Folate dietary deficits could be partly
made up by multivitamin supplements.
However, U.S. data for 1987 (57) indicate
that among women 17–24 years old, only
15% of the whites and 12% of the blacks
took vitamin/mineral supplements, most
of which were one-a-day vitamins.

A substantial portion of the female
population of childbearing age in the U.S.
and U.K. is likely to be consuming folic
in amounts well below the target level of
0.6 mg of absorbed folic acid daily. Major
dietary changes involving higher con-
sumption of fruits and vegetables would
be required to meet this goal. It has re-
cently been estimated (55) that a sample
menu meeting the current USDA food
pyramid recommendations would pro-
vide 0.19 mg of folic acid daily. This would
meet the 1989 RDA for nonpregnant
women but would be substantially less

Pérez-Escamilla  Prevention of Neural Tube Defects  257
than the current recommendation for primary prevention of NTDs among women of childbearing age.

Prevention of NTDs in the United States

Public health interventions for preventing NTDs seem feasible, since highly bioavailable and stable folic acid is commercially available in large quantities and at a low price (about US$0.13 per gram—56), and the technology needed to fortify foods or produce supplements is well-developed. There are still important questions regarding dosage, side-effects, and the likelihood of response in low- vs. high-risk NTD areas that might be answered in the future. Public health decisions, however, should be based not only on the efficacy and feasibility of an intervention but also on relative costs, benefits, and risks. The CDC estimates that about 2,500 NTD cases occur per year in the U.S., and that less than half would be prevented through folic acid supplementation (37).

Widespread food fortification or supplementation with folic acid to prevent NTDs might not be justified in the U.S., because the number of cases prevented would be small, and even a rare occurrence of side-effects would diminish the potential benefits. The counter-argument has been that folic acid supplementation could provide many additional health benefits to the nontarget population (57)---e.g., by decreasing precancerous lesions in the female cervix (58) and smokers' lungs (59) and by cutting heart disease risk by lowering homocysteine levels (60, 61). This argument has two major weaknesses. First, the research on which the non-NTD-related health claims are made is not as conclusive as that supporting the causal relationship between folic acid supplementation and decreased NTDs. Second, the same claim could be made on similar grounds for advocating supplementation with almost any other nutrient.

Another argument is that public health policy should be designed to protect the many, even though few are affected (57). As an example, folic acid supplementation advocates have stated that we advise people not to smoke, even though only 10% of smokers will get lung cancer (57). This rate, however, represents an incidence of 100/1,000, being at least 100 times higher than the NTD rate in the U.S. Furthermore, there is compelling evidence, not merely suggestive as in the case of folic acid, that not smoking has substantial noncancer-related health benefits. In 1985 smoking was responsible for US$22 billion in direct health costs and US$43 billion in indirect costs (lost productivity) in the United States (62). By contrast, the annual economic benefit from preventing NTDs through a low-level folic acid fortification policy has been estimated at only US$122 million (63). Furthermore, this policy could potentially increase the incidence of neurologic disease among subjects with pernicious anemia, further reducing this economic benefit. Nevertheless, it is important to underscore that increasing folic acid consumption to appropriate levels through dietary modifications should be encouraged whenever possible (9).

Based on the MRC study (32) and the fact that the risk of recurrent NTDs (2%–10%) is much greater than the risk of first-occurrence NTDs (<0.04%) (3), it would be unethical to withhold preventive treatment (i.e., folic acid supplementation) from women at risk of recurrent NTDs. In fact, it is not hard to imagine the possibility of malpractice suits against physicians who fail to follow this recommendation (37). However, this intervention should be carefully targeted and carried out under medical supervision.
PUBLIC HEALTH ISSUES IN DEVELOPING COUNTRIES

NTD/Folic Acid Studies

The studies discussed in this section are summarized in Table 3. The prospective cohort study by Vergel et al. (30) in Cuba, the only intervention trial reported in a developing country, found high-dose periconceptional folic acid supplementation to have a protective effect against NTDs. A recent report from Jamaica (64) indicated that consumption of dietary folate during periconception was significantly lower among mothers of NTD cases than among matched controls. The same researchers had previously reported increased NTD rates among mothers with sickle cell anemia that was presumably associated with a decreased periconceptional folate intake in the aftermath of a hurricane that devastated the island (65). This is consistent with the finding that women exposed to the Dutch famine of 1944–1945 during their first trimester of pregnancy delivered children with an excessive rate of various birth defects including NTDs. It is now believed that the latter were due to deficient folate intake during the periconceptional period (66, 67).

NTD Prevention in the Developing World

As Table 4 shows, even if the reported NTD rates from developing countries are reliable (a strong assumption), the NTD problem is dwarfed by other nutrition-related health conditions. It is estimated that 300 000 to 400 000 NTD births occur every year worldwide. But it is also estimated that over 1 billion people in the developing world are affected by deficiencies of specific micronutrients such as iron or iodine that could easily be prevented (68).

Table 4. The magnitude of the NTD problem, as compared to various other health problems.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of neural tube defects worldwide (No. of births per year)</td>
<td>300 000–400 000 (3)</td>
</tr>
<tr>
<td>People living with spina bifida in the U.S. (No. of cases)</td>
<td>30 000 (3)</td>
</tr>
<tr>
<td>NTD-affected pregnancies in the U.S. (No. of cases per year)</td>
<td>2 500 (37)</td>
</tr>
<tr>
<td>Estimated NTD cases that would be prevented through widespread fortification in the U.S. (No. of cases per year)</td>
<td>1 000 (37)</td>
</tr>
<tr>
<td>Overt cretinism in developing countries (No. of cases)</td>
<td>6 million (67)</td>
</tr>
<tr>
<td>Goiter in developing countries (No. of cases)</td>
<td>211 million (67)</td>
</tr>
<tr>
<td>Anemia among 15–49 year old women in developing countries (No. of cases)</td>
<td>258 million (67)</td>
</tr>
<tr>
<td>Premature deaths attributed to smoking worldwide (No. per year)</td>
<td>3 million (62)</td>
</tr>
<tr>
<td>Deaths attributed to smoking in the U.S. (No. per year)</td>
<td>434 000 (62)</td>
</tr>
</tbody>
</table>

Supplementing women in the developing world at risk of recurrent NTDs is justified by the scientific evidence available. However, as in the developed nations, this measure should be closely monitored by physicians. Special care should be taken in regions where vitamin B-12 deficiency and malaria are prevalent. (A primate study suggests people with folic acid deficiency might be put at a greater risk of developing malaria if their folic acid intake were increased—69.) Moreover, carrying out a health-care-based intervention might not be simple in areas where most pregnancies, deliveries, and postpartum care are not handled by the health sector (22).

Pérez-Escamilla Prevention of Neural Tube Defects 259
Developing countries that decide to adopt the CDC recommendations should monitor the outcomes of at-risk pregnancies to provide feedback on the safety of the dosage(s) used and the efficacy of this intervention under Third World conditions. These countries should also try to find out whether low-dose folic acid could prevent recurrent NTDs.

The industrial technology for folic acid fortification of food products such as breakfast cereals is available in many developing countries, and community-based folic acid fortification programs have been tested successfully (70). However, relatively low NTD prevalences, unknown risks, and serious logistic constraints suggest that massive folic acid interventions for the prevention of NTDs are currently unwarranted in these countries.

CONCLUSIONS

The finding that folic acid has a protective effect against development of NTDs is a landmark in the history of birth defect prevention. Mothers at risk of NTD recurrence require folic acid supplementation under a physician’s guidance. All women of childbearing age should be advised to increase their consumption of foods rich in folate. Massive folic acid interventions for NTD prevention may not be warranted, because of the relatively small numbers of cases to be prevented and the potential health risks involved. Ultimately, this decision should be based on comparing the costs, benefits, and risks of different public health measures.

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Volunteer Opportunity in Suriname

The Albert Schweitzer Institute for the Humanities invites physicians to join a team of clinical specialists in a humanitarian effort to bring essential medical services to the people of Nickerie, Suriname. As part of its Program for Health Care Development, the Albert Schweitzer Institute has been providing medical supplies, equipment, and educational programs to Suriname for several years. Recently, it has worked with the Inter-American Development Bank and the country’s Ministry of Health to renovate and staff a 75-bed hospital in Nickerie district, a relatively remote area with approximately 40,000 inhabitants.

With completion of the construction phase of the project scheduled for the end of 1995, the Institute is seeking to recruit specialists in internal medicine, surgery, anesthesiology, obstetrics and gynecology, and pediatrics who are willing to spend a minimum of three months in Nickerie Hospital. The goal is to introduce and maintain an acceptable level of medical services over the next 3–5 years, while facilitating the training of indigenous physicians, nurses, and administrators who will ultimately assume permanent responsibility. A well-trained hospital administrator and medical director are already on-site.

The official language of Suriname is Dutch, but most people can communicate fluently in English. Severe economic problems in recent decades have led to serious declines in the level of available medical services. The district of Nickerie has been especially hard hit, and the inhabitants are strongly supportive of this project and willing to open their homes to visiting physicians and their families.

Physicians who would like to receive more information about this project, or who wish to find out about short-term volunteering opportunities in Eastern Europe and other regions, should contact:

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