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Potential Prevention of Neural Tube Defects by Assessment of Women of Childbearing Age Through Monitoring of Folate

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Summary

Background—Three quarters of neural tube defects (NTD) can be prevented by sufficient dietary folate supplementation. Despite this knowledge, most women do not supplement their diet effectively. Red cell folate concentrations correlate with the risk of NTD, and levels of less than 900 nM are associated with an increased risk of these serious congenital anomalies.

Objective—Laboratory tests to assess anemia include testing for folate. This study was conducted to estimate the potential benefits of informing women of reproductive age who are unaware of their low folate levels, uncovered in their anemia tests.

Methods—The number of Ontario women of reproductive age who undergo folate tests and are at an increased risk of NTD was calculated. In addition, the authors calculated the number of NTD cases that could have been prevented if these women were informed of the possible consequences of their low folate levels should they become pregnant.

Results—In 1998, red cell folate concentrations were measured in 23,109 women of childbearing age (15–45 y). Approximately half of the women [$n = 11,392$ (49.3%)] had folate levels below 900 nM and thus were at an increased risk of giving birth to a child with NTD should they have become pregnant. Their overall mean relative risk (RR) of NTD was 1.95, or 1:512 births. If they would have been informed of this risk and subsequently increased their consumption of folate before becoming pregnant, 22.3 cases of NTD per year could have possibly been prevented at no extra cost, since the folic acid results were a part of investigational blood tests performed for another reason (anemia).

Conclusions—Women of reproductive age who are being evaluated for the cause of anemia and have low red cell folate results constitute a high-risk group for NTD in their children. These women should be informed of the increased risk and of methods of dietary folate supplementation.

Keywords

Folic acid; Pregnancy; Pregnancy outcome; Dietary supplements; Neural tube defects; Preventative health services; Primary prevention

Neural tube defects (NTD) such as spina bifida and anencephaly occur very early, usually in the first month of pregnancy, at a time when most women may not be aware they are pregnant. Seventy-five percent of NTD-affected pregnancies end in miscarriage or still-birth, and the remainder result in live births. Both genetic (inherited) and environmental

factors are believed to cause neural tube defects. The role of folic acid (folate), a B vitamin, in preventing neural tube defects was established a decade ago by two randomized, placebo-control studies (1,2). Tremendous efforts have been invested in informing women on such risk and in counseling them to supplement with at least 400 µg/d of this vitamin to prevent occurrences, or 4 mg/d to prevent recurrences of NTD. However, these attempts have largely failed: recent studies have shown that most physicians do not counsel their patients to supplement their diet with folic acid, and indeed most women are not supplementing while planning pregnancy or during the first month of gestation (3,4).

In 1998, the US and Canadian governments implemented a flour fortification program, leading to an almost doubling of red cell folate levels (5,6); however, large numbers of women are still at an increased risk of NTD because the implemented program is not sufficient to fully supplement to 400 µg/d folate (6,7).

Presently, folic acid levels are monitored in a large number of Canadian women who suffer from anemia as part of the investigation of the causes of their anemia. These low folate levels are acted upon only if they are under those associated with megaloblastic anemia (i.e., 400 nM) (8).

The objectives of the present investigation were: 1) To calculate the relative risk of NTD among women whose folate levels have been ordered as part of the evaluation for the causes of anemia.

2) To propose a system to inform the women with low levels of folate of their risk for NTD and how to supplement appropriately.

MATERIALS AND METHODS

We reviewed all red cell folate concentrations requested on women of reproductive ages (15–45 y) by a large clinical laboratory in Ontario, Canada (in Toronto). Increased risk for NTD was defined as red cell folate levels below 900 nM, using the dose–response curve developed by Daly et al (9). Similarly, the relative risks of NTD for a given folate level were adapted from the same source (9) (Table 1). The total number of folate measures per year among Ontario women 15 to 45 years of age was calculated. Their mean relative risk for NTD was calculated from the distribution of their measured levels as compared with Daly's data (Table 1).

RESULTS

The reference laboratory conducted a total of 25,317 folate tests in 8 months (1998), 4,975 of which were among women of reproductive age (19.6%) who were normocytic. During the same year, a total of 117,904 tests for red cell folate were conducted in Ontario (10). Hence, the calculated number of women of reproductive years undergoing this test was 23,109.

In the reference laboratory, 49.3% (n = 11,392) of women of reproductive age had red cell folate levels below 900 nM, rendering at least 11,392 women in the population at a high risk for giving birth to children with NTD. When reviewing the subgroup of women with normal values of hemoglobin and MCV, the same figure emerged. The overall relative risk, calculated from the data shown in Table 1 was RR = 1.95. Assuming the general risk of NTD in Ontario is 1:1000 births (10), the risk among the Ontario women found to have folate levels below 900 nM was 1: 512 births.

If these 11,392 women were informed about their increased risk for NTD, and if all of them supplemented appropriately with at least 400 µg/d folate before or during their first month

of pregnancy, this could have potentially prevented 22.3 cases of NTD per year in Ontario, assuming that their levels were not corrected by other means between the time of testing and conception.

DISCUSSION

The economic burden of children born with NTD is very high. Although no single study has captured all the direct and indirect costs associated with this serious disability, the burden is believed to be in the millions of dollars throughout the life of the individual (11–14). Our study has identified a previously unrecognized group of women who are at high risk for NTD should they become pregnant, namely women of childbearing age who have low red cell folate and may only become aware of it while a test for folate is conducted in the process of exploring the causes for their anemia. Although we do not have access to the exact indication for these folate tests, presently the test is indicated in the context of investigating the cause of folate deficiency anemia. Although most of these women did not have folate deficiency anemia, half of them had red cell folate levels conferring higher-than-baseline-risk for NTD.

Presently, requested red cell folate concentrations are compared with reference levels to prevent pernicious anemia (i.e., 400 nmol/L). However, more than two-fold higher levels are needed to prevent NTDs (8,9).

We have recently shown that only 20% of these women are likely to supplement with folate prior to pregnancy (3). The rest are likely to sustain their lower levels, resulting in higher risk for NTD. While counseling on supplementation with folate has largely failed (3,4), it is fair to assume that physicians and their female patients are likely to take the cue of pathologic laboratory test results much more seriously and increase their folate intake due to these results. In the United States, a survey commissioned by the March of Dimes in 2001 showed that only 29% of US women of childbearing age take a daily multivitamin containing folic acid, and that three in four women said their doctors did not discuss the importance of taking the supplement.

If the laboratory test result indicates the red cell folate level is <900 nM, we would suggest that the following text accompany the laboratory report to be given to the patient: “Beware, your folic acid level is low. This may put you at an increased risk of giving birth to a baby with spina bifida and other neural tube defects. This could be corrected by taking a tablet containing folic acid or by consuming enough folate in your food daily. Consult your physician immediately”. Further research and focus groups may be needed to optimize such a message.

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Biography

GK is a Senior Scientist of The Canadian Institutes for Health Research and holder of the Research Leadership in Better Pharmacotherapy During Pregnancy and Lactation.

TABLE 1

Distribution of red cell folate levels among Ontario women whose physicians ordered the test in 1998

Red cell folate (nmol/L)	Relative risk of NTD (9)	Toronto—1998 % of cases
0–339	6.6	0
340–452	3.2	1.6
453–679	2.3	25
680–905	1.6	29.9
>905	0.8	43.5
Total		100