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**Folate levels and neural tube defects: implications for prevention.** *Leslie E. Daly; Peadar N. Kirke; Anne Molloy; Donald G. Weir; John M. Scott.*

**Abstract:** The incidence of neural tube defects could be reduced significantly by fortifying food with folic acid through a population approach. Researchers found that a large sample of Irish women who gave birth to babies with neural tube defects had much lower levels of plasma and red cell folate at 15 weeks' gestation. Among pregnant women whose red cell folate levels were less than 340 nmol/L, the risk of having a baby with neural tube defects was eight times greater than among women who with levels of 906 nmol/L or higher. A strategy that would increase red cell folate levels for women before pregnancy appears to be the optimum approach. With a population intake of 0.4 mg per day of folic acid, a reduction of 48% in the rate of neural tube defects is estimated to be possible.

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Using data from a recent case-control study, a woman's risk of having a child with a neural tube defect (NTD) was found to be Associated with early pregnancy red cell folate levels in a continuous dose-response relationship. These findings were used to calculate the reduction in NTD cases that would be expected under two different strategies to raise folate levels. Targeting high-risk individuals has a small effect on the population prevalence but can substantially change an individual's risk. Targeting the population produces a small change in individual risk but has a large effect on the population prevalence. Supplementation of high-risk women would be the most efficient method to implement the high-risk strategy, while food fortification would be preferable for the population approach. The current guidelines for the prevention of NTD are for an increased folic acid intake of 0.4 mg per day. This would result in a 48% reduction in NTDs, which may be near optimal. The two intervention strategies should be considered complementary in prevention of NTDs.

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THE Medical Research Council trial on the prevention of the recurrence of neural tube defects (NTDs)[1] and the Budapest trial on the prevention of the first occurrence of the same condition[2] have shown conclusively that

a woman's risk of an affected pregnancy can be reduced substantially by taking folic acid periconceptionally. Previous and subsequent investigations[3-6] are confirmatory of this result. The major question now is how to respond to this new knowledge. National expert committees have advised that women who have already had an NTD birth should take a supplement of 4 or 5 mg of folic acid daily before conception and during the early months of pregnancy to prevent recurrence.[7,8] For primary prevention all women at risk of pregnancy are advised to take an extra 0.4 mg of folic acid daily.[7,8] This increased intake of folic acid would be difficult to achieve with dietary changes alone, and a medicinal or food supplement may be required.

In this article we expand on the results of a recent study[9] and report on the relationship between NTD risk and early pregnancy maternal red cell and plasma folate levels. In particular, we quantify the effect of various intervention strategies on NTD risk and discuss the implications for public health policy and clinical practice.

#### CASE-CONTROL STUDY

Blood samples were collected, specifically for a case-control, study of NTDs, from all women attending their first antenatal clinic in one of the three main Dublin, Ireland, maternity hospitals from March 1986 to March 1990. This collection resulted in 56 049 samples, which numerically corresponds to about 70% of births in these hospitals during the study period and 25% of all births in the Republic of Ireland. Births in these hospitals affected by NTDs (cases) were subsequently ascertained from multiple sources. Using hospital records, a systematic sample of three controls per case was taken from births without NTDs of gestations of 23 weeks and more in the same hospital and during the same period as the cases. Controls were not matched to cases. From the stored bank of samples (taken at a median gestational age of 15 weeks, similar in cases and controls), blood was retrieved for 84 cases and 266 controls, and red cell folate, plasma folate, and other biochemical parameters were measured. (The subjects include three cases and 19 controls omitted in the previous report because levels of plasma folate and vitamin [B.sub.12] were not available.) Cases and controls were similar with regard to maternal age. In addition, controls were representative of normal births. The initial report, which concentrated on biochemical aspects of the study, found that cases had significantly lower levels of plasma and red cell folate.[9] Case-control differences in blood vitamin levels were not due to confounding by any factors measured in the study. Details of the variables measured, case-control differences, case ascertainment methods, prior sample size estimates, representativeness of the final sample, and blood storage and analysis are described in the original publication.

Accepting the controls to be representative of the nonaffected births and taking the overall NTD rate to be 1.9 per 1000 births in the study hospital (based on independent data), we were able to estimate NTD risks in different groupings of plasma or red cell folate levels. Each control was assigned a weighting factor, and the odds of disease in any subgroup were estimated by dividing the number of cases by the weighted number of controls. Risks were derived from these odds, and confidence intervals (CIs) were calculated assuming no sampling variability in the population figures and a Poisson distribution for the number of cases.[10] Further details are available from the authors on request.) Table 1 shows the distribution of plasma folate levels in cases and controls and the estimated risk of an NTD in each plasma folate category. A clear dose-response effect is seen.

[TABULAR DATA OMITTED]

While it is clear that the fetus accesses folate through maternal plasma folate, in this article we concentrate on the relationship of risk to red cell folate levels. Since blood samples were taken at a median of 15 weeks' gestation, plasma and red cell folate levels were both determined subsequent to neural tube closure. Red cell folate, however, is likely to be the better proxy for folate status at that time, since it reflects the folate turnover during the previous 120 days.[9]

Table 2 shows the distribution of red cell folate in cases and controls and NTD risk in each category. There is a more than eightfold difference in risk between those with red cell folate levels less than 340 nmol/L (150 ng/mL) compared with those with levels of 906 nmol/L (400 ng/mL or higher ( $P < .001$ )) (to convert values from nmol/L to ng/mL, divide by 2.266). A logistic regression based on nongrouped red cell folate values was used to examine the relationship of NTD risk to red cell folate as a continuous factor. The Figure shows the risk relationship and the degree of fit with the observed data of Table 2.

[TABULAR DATA OMITTED]

Although red cell folate levels have been shown to be significantly lower in early pregnancy in women who had affected infants than in those who did not,[9,11] this article is to our knowledge the first to show that NTD risk is associated with red cell folate levels in a continuous dose-response relationship. Risk is reduced as red cell folate levels increase well past the point when levels would have been considered normal. The lower limit of the normal range for red cell folate is 317 nmol/L (140 ng/mL),[12] and our views on what may constitute a desirable level of red cell folate may have to change radically on the basis of these results.

Although our logistic model suggests that risk would continue to decrease as red cell folate levels increase to higher than 1292 nmol/L (570 ng/mL) (which is the mean level of all controls in the [greater than or equal to]906 nmol/L [400 ng/mL] grouping of Table 2), there are too few cases for a stratified analysis to confirm this. We have thus been unable to determine an optimum level of red cell folate for NTD prevention. We decided, however, to take a conservative approach in modeling the effects of red cell folate changes on NTDs and assumed no additional protective effect beyond 1292 nmol/L (570 ng/mL). The Figure shows the risk relationship with red cell folate levels under this assumption also. Red cell folate levels higher than 1292 nmol/L (570 ng/mL) may confer additional protection against NTDs, but further research is needed on this important question.

The recent trials[1,2] have shown conclusively that folic acid intake directly affects NTD risk, and it now appears that red cell folate levels in early pregnancy are a marker of that risk. It follows that changes in red cell folate levels will be related to changes in risk. The precise mechanism of this remains unclear, though the involvement of the enzyme methionine synthase has been proposed.[9,13]

## IMPLICATIONS FOR PREVENTION

### Generalizability of Results

The implications of our findings for a preventive strategy depend on the degree to which our results are generalizable to other populations and on the completeness of our case finding. Our study design ensured that the cases and controls were representative of the NTD and normal births in Ireland, and our case ascertainment is likely to be considerably higher than in any country where termination of affected pregnancies can result in underreporting.

Termination of pregnancy was not available in Ireland during the study period, and although about 4000 terminations of pregnancies in women with Irish addresses were performed annually in the United Kingdom (a figure corresponding to approximately 8% of live births in Ireland), the evidence suggests that few of these were due to a prenatal diagnosis of NTD. First, prenatal ultrasound screening was not practiced widely in Ireland during the 1980s, and serum [alpha]-fetoprotein screening was not available at all. Second, a recent survey of 58 Irish women seeking terminations of pregnancies in the United Kingdom showed that none was doing so because of a fetal abnormality and that none had seen a specialist and thus could not have had a prior ultrasound examination.[14] Consequently, we are confident that our case ascertainment is not biased because of terminations of affected pregnancies.

Although the population of Ireland has a relatively high NTD rate and perhaps different dietary patterns than those of other populations, our quantification of the relationship of red cell folate levels to NTD risk should be generalizable. Our estimates of the population effect of intervention strategies depend on the distribution of red cell folate levels in the population and may have to be adjusted when applying our results to a population with a different distribution. Interlaboratory variation may also need consideration. The population of Ireland has a low rate of folic acid supplement use (5% in our study population), and a population with a high rate would have a different red cell folate distribution. However, in the context of a typical Western diet and low to moderate supplementation, our findings should be of general applicability.

### Preventive Strategies

Our finding of a continuous gradation of risk with red cell folate levels has major implications for preventive strategies. One strategy is the high-risk approach. This approach involves identifying individual women at high risk because of low red cell folate levels and raising their levels to reduce their risk. Though this approach has been suggested from the theoretical point of view,[15] it is only with our quantification of the relationship of risk to red cell folate levels that a target intervention level can be determined and the implications of such a policy examined.

The second strategy for prevention is a population approach.[16,17] This approach involves increasing red cell folate levels of all women before pregnancy, irrespective of initial level, and shifting the entire distribution of red cell folate upward. This approach implicitly accepts that most of the NTDs occur in women with relatively normal levels of red cell folate.

We examined the effect of the different intervention strategies by determining the change in red cell folate distribution that would be seen in the population represented by our cases and controls. For the high-risk strategy, an individual's red cell folate level was increased to the mean value observed in the category above the target level. For the population strategy, a given red cell folate level was increased by the appropriate percentage. We also modeled lack of compliance with a given strategy. The total number of NTD cases that would arise under the new scenario was then estimated by applying the logistic regression equation predicting NTD risk from red cell folate) to the new distribution but allowing no decrease in risk beyond 1292 nmol/L (570 ng/mL). The number of NTDs prevented was then expressed as a percentage of the 84 cases expected without intervention with an approximate 95% CI. (A detailed description of the approach is available from the authors on request.)

It is possible, however, that some NTDs have an etiology that is not related

to red cell folate levels or, equivalently, are not responsive to changes in folic acid intake.[18] In the Medical Research Council trial,[1] folic acid failed to prevent 28% of the expected NTDs. Accepting this percentage as an estimate of the proportion of NTDs that are not related to folate levels, the reduction in NTDs is also given as a percentage of the expected 60.5 folate-responsive cases (72% of 84).

### High-risk Strategy

Table 3 shows the percentage reduction in NTD cases for various scenarios under a high-risk intervention strategy. If a policy of intervention in women with red cell folate levels less than 453 nmol/L (200 ng/mL) and a target of increasing levels above this figure were adopted, the maximum reduction in the total number of NTDs would be 12% (95% CI, 4% to 30%), equivalent to 17% of folateresponsive NTDs. The relatively small reduction in total NTDs is due to the finding that only 13% of women are actually in this high-risk category and 71% of the NTDs are born to women with red cell folate levels higher than 453 nmol/L (200 ng/mL) (Table 2). The reduction figure assumes that all women with levels lower than the target would be identified and all would increase their red cell folate sufficiently. Many, however, would not be screened, and compliance with therapy may be low. Table 3 shows a 9% (95% CI, 3% to 22%) decrease in total NTDs (13% of folate-responsive NTDs) if three quarters of the women achieved the 453 nmol/L (200 ng/mL) target and a 6% (95% CI, 2% to 15%) reduction (9% of folate-responsive NTDs) for the possibly more realistic assumption of the target being reached by half of the women. Setting the red cell folate intervention level higher would obviously have a greater impact, but the cost in terms of the screening effort and treatment would also be high.

[TABULAR DATA OMITTED]

Though a high-risk strategy may have a relatively small effect on the population prevalence of NTDs, the change of risk for the individual can be substantial. If women with red cell folate levels less than 340 nmol/L (150 ng/mL) were to increase their levels to higher than 906 nmol/L (400 ng/mL), their risk would reduce by 88%, from 6.6 to 0.8 per 1000 births (Table 2).

### Population Strategy

Table 4 shows the percentage reduction in NTD cases if, using a population strategy of prevention, each woman was to increase her red cell folate level before pregnancy by a given percentage (equivalent to a corresponding change in the population geometric mean level of red cell folate). Table 4 also shows the NTD reduction for different proportions of the population actually achieving this change. Overall, the change of risk for any

individual is small, but the population effect is large.

[TABULAR DATA OMITTED]

Increasing red cell folate levels by 25% in all women would result in a 22% (95% CI, 10% to 37%) decrease in total NTD prevalence; this 22% decrease becomes a 17% (95% CI, 7% to 28%) decrease if the red cell folate increase was achieved by three quarters of the population. The corresponding reductions as percentages of folate-responsive NTDs are 31% and 23%. If all women achieved a 50% increase in red cell folate, a 35% (95% CI, 18% to 56%) total NTD reduction (49% of folate-responsive NTDs) would occur, while a doubling of red cell folate (100% increase) is required for a 48% (95% CI, 22% to 72%) total NTD reduction. If three quarters of the women achieved a doubling of red cell folate, the total burden of NTDs would be reduced by 36% (95% CI, 17% to 54%), corresponding to 50% of folate-responsive disease.

Our assumption of no risk reduction beyond a red cell folate level of 1292 nmol/L (570 ng/mL) means that we may have underestimated the effect of the population intervention strategies. If the assumption were not made, a doubling of red cell folate in all women of childbearing age would result in a 57% reduction in NTDs compared with the 48% figure given in Table 4.

#### Implementation of Strategies

Apart from a change in the pattern of dietary intake, which is difficult to implement and has variable and perhaps insufficient effects, there are two basic approaches to increasing folic acid intake. Supplementation may be used, which means that an individual increases intake by regularly taking a tablet containing folic acid. The second option is through fortification of the diet, whereby folic acid is added to a universal staple food, such as flour, so that its consumption is increased passively, without a change in dietary intake patterns.[19]

#### Supplementation

##### and a High-risk Strategy

Increasing folic acid intake through supplementation is likely to be the most efficient method for a high-risk approach to NTD prevention. If red cell folate was to be adopted as a marker of increased risk, high-risk women could be identified through opportunistic biochemical screening and advised to take a folic acid-containing vitamin preparation. With such individual advice, allied to the knowledge of risk status, compliance may be high. Many women would not be screened, however, since more than half of all pregnancies are unplanned and the neural tube closes before

most women even realize that they are pregnant.

Notwithstanding that such a high-risk strategy may fail to identify many high-risk women and may have a limited effect on the population burden of NTD, the prevention paradox remains. In individual women identified as high risk who comply with advice, the risk reduction can be substantial.

It should also be noted that those with a previously affected pregnancy are also at high risk. Such women can be identified without screening and can be counseled appropriately or, as is the case at the moment with the public health guidelines, can be advised as a group to take a vitamin supplement.

### Food Fortification

#### and a Population Strategy

The UK Expert Advisory Group[7] and the US Public Health Service[8] each propose a population strategy for the primary prevention of NTDs through an increased intake of 0.4 mg of folic acid daily. Supplementation, however, may not be the most effective method of increasing folic acid intake before pregnancy in the population of all women who could become pregnant. In the United Kingdom, 67% of those attending an antenatal clinic for the first time were unaware of the recommendations regarding folic acid, and of those who were aware, only 37% received the information before conception.[20] Only 3% took folic acid tablets before becoming pregnant. In addition, supplementation requires not only knowledge of the recommendations, but also motivation to act on them. Motivation is difficult to engender since the benefit to any individual is small.

Food fortification with folic acid is likely to be a preferable solution for a population approach. There is much debate at present in the United States as to the optimum level of fortification,[21] and this in turn relates to the optimum level of folic acid intake necessary to reduce the prevalence of NTDs. On the basis of the NTD reductions seen in both controlled trials and observational studies, the Public Health Service report concluded that with 0.4 mg of folic acid daily "a reasonable estimate of the expected reduction in the United States is 50%"[8] The Expert Advisory Group in the United Kingdom, stressing that "there was less evidence than they would have wished on which to base their recommendations,"[7] did not quantify the expected population benefit from this folic acid intake.

### Modeling the Effect

#### of Fortification Policies

The Centers for Disease Control and Prevention position paper on food fortification has two models on which to gauge the effect of a food fortification policy with fortification at different levels.[21] Both models relate intake directly to NTD risk, but neither allows for a continuous gradation of risk with intake. Because a minimum effective dose of folic acid supplementation is unknown, both models also assume that there is a threshold level of folic acid intake below which no protective effect is conferred.

Our results allow a modeling of NTD risk reduction based on alteration of maternal red cell folate levels, rather than of folic acid intake, and on a continuous gradation of risk (up to a red cell folate level of 1292 nmol/L [570 ng/mL]). Still missing, however, are firm data on the effect of folic acid intake on red cell folate levels, especially in women of childbearing age. However, if even small changes in folic acid intake can increase red cell folate levels, our results suggest that any increase in folic acid intake should have a beneficial effect.

Based on the available literature,[15,22-24] we estimated that an approximate doubling of the red cell folate level might be achievable with an increased folic acid intake of approximately 0.4 mg per day. From Table 4, this corresponds to a maximum reduction of 48% (95% CI, 22% to 72%) of all NTDs and 66% of folate-responsive NTDs. We estimated that red cell folate might increase by up to 150%, with an increased daily intake of 1.0 mg of folic acid. This would lead to a maximum 53% (95% CI, 25% to 78%) total NTD reduction (73% of folate-responsive cases). (Details of the derivation of the relationship between folic acid intake and red cell folate levels are available from the authors.)

Further dose-response studies relating folic acid and dietary folate intake to red cell folate levels in women of childbearing age are needed to confirm these findings. For the United States, results from the third National Health and Nutrition Examination Survey[25] should allow determination of the red cell or plasma folate distributions in such women and additionally should allow precise modeling of the effect of food fortification on folate levels. These results, combined with the risk relationships presented in this article, would allow much more realistic modeling of the effect of food fortification on NTDs.

## CONCLUSION

Current views on the prevention of NTDs emphasize a population approach with food fortification as a preferred alternative to direct folic acid supplementation. We have proposed a model that can relate folic acid intake to NTD risk through a continuous relationship with maternal red cell folate levels. We estimate that a 48% (95% CI, 22% to 72%) reduction in

the total NTD rate (66% of folate-responsive NTDs) is theoretically achievable with an increased population intake of 0.4 mg per day of folic acid. Reduced compliance, however, will reduce the magnitude of this effect. Thus, our results broadly confirm the Public Health Service advisory group figure of a 50% reduction in NTDs with this dosage, which was admitted not to be a firm estimate.<sup>8</sup> An increase of intake to 1.0 mg of folic acid per day would give just a 5% additional reduction in the total NTD rate. The current guidelines of 0.4 mg per day of folic acid may therefore be near optimal, particularly given the concern that too high an intake of folic acid may result in a masking of vitamin [B.sub.12] deficiency." It is also worthwhile noting that a population increase in folic acid intake may also have a protective effect on heart disease, cervical cancer, and colorectal cancer.[26]

In terms of reducing the population prevalence of NTD, we have shown that a high-risk strategy, requiring screening for low folate status, is on its own likely to be less effective than the population approach. The two strategies can be considered complementary, however, and we propose that, in addition to population measures, serious consideration be given to implementing opportunistic screening by the primary care physician of women planning pregnancies. If women with red cell folate levels less than 340 nmol/L (150 ng/mL) were identified and supplemented, their NTD risk could be reduced by more than 85%. Counseling every woman known to be planning a pregnancy to take 0.4 mg of folic acid daily, without screening for red cell folate, is unlikely to have the same effect. First, a higher dose may be needed in those with very low folate levels, and the response to therapy can be monitored under the screening scenario. Second, compliance is likely to be better when a woman knows she has a low folate level and how that relates to risk. In attempting to reduce the overall burden of NTD, it would be invidious to concentrate solely on a population approach and to ignore the great potential we have to prevent the condition in high-risk women who can now be easily identified with a simple blood test.

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