Prevention of Folate Deficiency by Food Fortification

PART V. A PILOT FIELD TRIAL OF FOLIC ACID-FORTIFIED MAIZE MEAL

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SUMMARY

Red cell folate levels were measured for 6 weeks in an index member and the oldest member of each of 6 families who had been given folic acid-fortified maize meal for use in the home. Five of the index subjects were pregnant and one was lactating. The amount of folic acid added to the maize was calculated so that each adult would receive 500 μg folic acid daily. In the index subjects of 5 of the 6 families studied, red cell folate levels rose significantly. The changes in red cell folate levels suggest that pregnant women consume more maize meal than elderly subjects. This possibility would tend to increase the margin of safety when folic acid-fortified foods are consumed by populations in which vitamin B_{12}-deficient megaloblastic anaemia is found.

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There is evidence that folate-deficient megaloblastic anaemia occurs commonly in South African Black females in association with pregnancy and lactation.[1-5] In order to prevent folate deficiency during these periods of increased physiological requirement, routine administration of folic acid tablets to pregnant Black females has been advocated,[6] and is practised in many antenatal clinics. However, large numbers of females, particularly in rural areas, do not attend antenatal clinics, and for these subjects fortification of staple foods with folic acid may provide a possible practical alternative to the conventional method of supplementation. To investigate the feasibility of this approach we fed folic acid-fortified maize meal (FAMM) to pregnant women attending the Charles Johnson Memorial Hospital, Nqutu, KwaZulu, and have shown significant improvement in the folate nutrition of these subjects.[7] In this hospital-based trial the folic acid-fortified meal was cooked at the hospital, and administered under supervision. However, in order to prove conclusively the value of a food fortification programme, it is necessary to demonstrate an improvement in nutritional status in populations who store, cook and eat the fortified food in the home environment in accordance with their custom. It was considered that this investigation would reveal whether any aspect of local custom which had been unaccounted for in the hospital-based trial might interfere with the efficacy of such a food fortification programme.

In the present investigation, the effect of the maize meal in the home environment was examined by giving folic acid-fortified meal to selected families for home use. A pregnant (or lactating) member, as well as the oldest member of each family, was studied. The oldest member of each family was included to assess the effect of the folic acid-fortified food on members of the age group in which the incidence of pernicious anaemia is highest.

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PATIENTS AND METHODS

Subjects Studied

Six index patients were selected for the trial from the Charles Johnson Memorial Hospital at Nqutu, KwaZulu. Five were healthy women in the 28th week of pregnancy who had come to the antenatal clinic for the first time, and 1 was a healthy lactating woman who was studied from the 8th week after delivery. None of the patients had received folic acid supplements before the study. The pregnant women were all given iron supplements from the start of the study, and the lactating subject had received iron during pregnancy. These patients were selected for study because they lived in relatively close proximity to the hospital. The oldest member of each index subject's family was also studied. All of these older subjects were women.

Calculation of Dietary Intake

Individual dietary intake was assessed by relating family size to the amount of maize meal purchased monthly. In order to correct for age variations in food consumption the following approximations were made: children above the age of 16 years were regarded as adults, those between 2 and 16 years were assumed to be consuming half as much as adults, and children less than 2 years of age were disregarded. This method was used because it has been found that the amount of maize meal bought each month, corrected for varying consumption on the basis of age, is a reliable index for estimating maize meal intake, whereas weighing the amount of maize meal cooked for a single meal is less satisfactory.[8]

Provision of Fortified Maize Meal

Separate batches of FAMM were prepared for each family according to this calculated maize meal intake. The amount of folic acid added to a batch was such that the average daily helping consumed by each adult in the particular family was intended to contain 500 μg of added folic acid. An appropriate amount of crystalline pteroylglutamic acid was mixed with the maize meal for 12 hours, using a Y-blender to achieve homogeneity. On the basis of previous observations it could be expected that approximately one half of this dose would be absorbed from FAMM.[9]

Based on the calculated dietary intake, families were given enough meal to supply their needs for 6 weeks, and were instructed to use this meal exclusively until it had all been consumed. Families were not told how long the meal was expected to last, and were asked to report when it had all been used. The folic acid in FAMM is stable on storage for at least one year.[7]

Procedure

Blood was taken from the index subject and the oldest member of each family on two consecutive days before the start of the trial and weekly thereafter for folate and vitamin B_{12} assay and haemoglobin estimation. In order to prevent loss of folate activity during transport and storage, specimens were handled as described previously.[7]

Laboratory Methods

Red cell folate was assayed with *Lactobacillus casei* by the method of Hoffbrand *et al.*[10] Serum vitamin B_{12} was measured by radio-isotope dilution using chicken serum as binder.[11]

Normal ranges are as follows: red cell folate 160 - 640 ng/ml red cells; serum vitamin B_{12} 400 - 1 020 pg/ml. All samples from a particular subject were assayed for folate and vitamin B_{12} within the same batch. Haemoglobin concentration was measured by the cyanmethaemoglobin method.

Serum folate levels in the subjects studied showed wide variations from week to week. This could have been due to the variable times at which blood samples were taken after the patients had eaten the fortified meal. This factor could not be controlled in a field study of this nature, and the serum folate results are therefore not presented.

RESULTS

Table I shows the ages of the subjects studied, the calculated number of 'adults' in each family, and the time each family took to consume the maize meal intended to last for 6 weeks. All the families, except No. 3, consumed the meal within 5 - 7 weeks. In family 3, the meal lasted 71 days, so that approximately 60% of the predicted amount of folic acid was consumed during the 6-week test period. This corresponds to about 300 μg folic acid/subject/day.

TABLE I. DETAILS OF SUBJECTS GIVEN FOLIC ACID-FORTIFIED MAIZE MEAL IN THE HOME (ALL THE INDEX SUBJECTS WERE PREGNANT, EXCEPT THAT OF FAMILY 1, WHO WAS LACTATING)

Family	Age of index subject	Oldest subject	'Adults' in family*	Days taken to consume fortified maize meal†
1	26	58	3	43
2	16	60	4,5	40
3	28	56	4,5	71
4	30	63	4,5	39
5	33	76	5	41
6	24	58	5	46

* The method of calculating the number of adults in each family is described in the text.

† The meal was fortified on the assumption that it would last for 42 days.

The results of laboratory investigations are summarised in Table II. The haemoglobin level and serum vitamin B_{12} concentration remained essentially unchanged in all subjects.

At the end of the study, the red cell folate concentrations were greater than at the start in all except the older subject of family 4. Weekly red cell folate concentrations

TABLE II. LABORATORY FINDINGS BEFORE AND AFTER RECEIVING FOLIC ACID-FORTIFIED MAIZE MEAL FOR 6 WEEKS

Family	Subject	Haemoglobin (g/100 ml)		Vitamin B_{12} (pg/ml)		Red cell folate (ng/ml)	
		Before*	After	Before*	After	Before*	After
1	a	13,0	12,7	584	551	116	383
	b	13,6	13,6	966	971	310	396
2	a	13,7	13,5	766	796	166	355
	b	13,8	13,9	1 114	1 115	127	187
3	a	11,0	12,0	696	686	381	405
	b	14,7	15,0	1 484	1 156	228	275
4	a	11,7	11,8	903	876	159	493
	b	15,0	16,0	1 670	1 889	248	242
5	a	12,2	12,2	891	789	208	369
	b	13,2	13,1	659	707	533	603
6	a	12,0	12,2	608	640	170	257
	b	12,4	12,7	739	853	216	294

a = index subject.

b = oldest member of family.

* Mean of 2 observations.

in each subject are shown in Fig. 1. The rate of rise was minimal in both members of family 3 who consumed less than the predicted amount of FAMM. In the index subjects of all the other families there was a marked rise in red cell folate concentration. In each subject, the weekly rise in red cell folate was calculated as the change from the initial value, and the rate of this rise was obtained by linear regression. The formula for the composite regression line in the 4 pregnant subjects whose families consumed the amount of maize meal predicted (families 2, 4, 5 and 6) was $y = 39,3\,x - 47$ ($r = 0,7861$), where y is change in red cell folate concentration in ng/ml, and x is the time in weeks. The rate of rise in the lactating subject was greater than that of the group of pregnant subjects ($y = 46,4\,x - 12,7$; $r = 0,9973$).

The regression line for the older subjects in the 6 families was $y = 12,7\,x - 19,8$ ($r = 0,7540$). When this line was compared with the regression line for the 6 index subjects, it was found that the rate of rise in the index subjects was significantly greater ($t = 3,34$; $P<0,01$). This is mainly attributable to the much greater rise in the index subjects of families 1, 2 and 4 than in the corresponding older subjects.

It was considered possible that the rise in red cell folate concentration in each subject over the 6-week period might be related to the initial value, but no correlation was found between these two values ($r = 0,4679$; $P>0,1$).

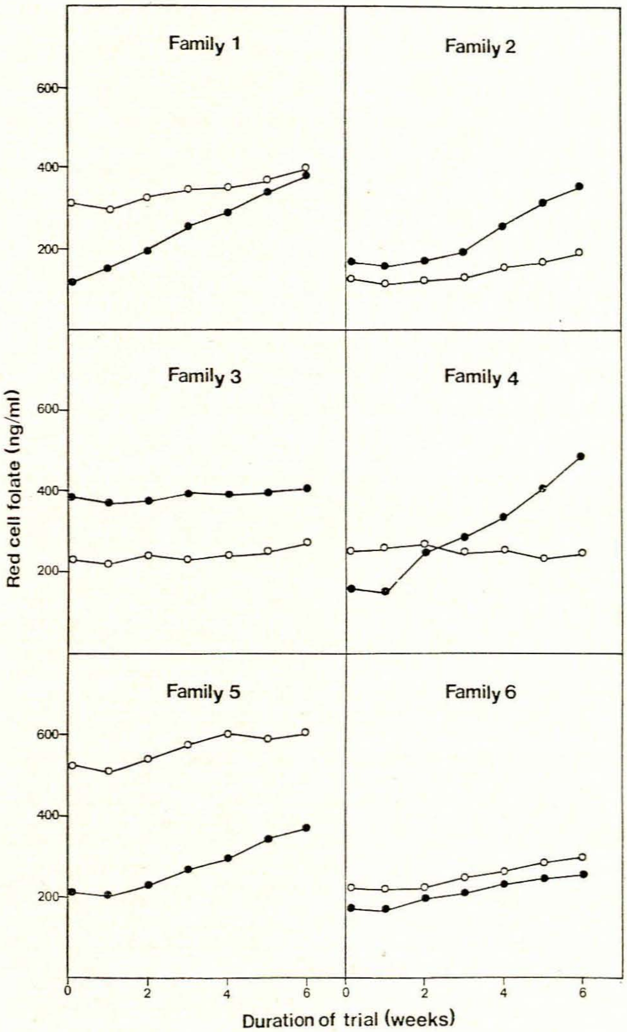

Fig. 1. Weekly red cell folate concentrations in families supplied with folic acid-fortified maize meal (closed circles—index subjects; open circles—oldest members of family).

DISCUSSION

Previous work has shown that maize meal, the staple food of the vast majority of South African Black subjects, can be used as a vehicle for the administration of essential nutrients to this population.[8] Du Plessis *et al.*[8] conducted a trial in which maize was fortified with riboflavin and nicotinic acid at a mill which was the only source of the food in a certain area. A group of schoolchildren in this area was compared with a control group living in an adjacent village. On the basis of clinical and biochemical observations, it was concluded that fortified maize meal caused a significant reduction in the incidence of deficiency of the two vitamins.

The present study, which was a more limited pilot field trial with folic acid-fortified maize meal, showed a significant rise in the red cell folate concentration in 9 of the 12 subjects receiving the fortified food. In one family, whose members consumed only 60% of the amount predicted (equivalent to 300 μg folic acid per day), the pregnant index subject showed a slower rate of rise in red cell folate concentration. The results of the present study indicate that FAMM can be used effectively to supply folic acid supplements to pregnant women who store, cook and eat the meal according to local custom.

It is of interest that the red cell folate level in the index subjects of 3 of the 6 families rose more rapidly than in the corresponding older women. This observation suggests that the consumption of maize meal, or absorption of folic acid, was not uniform in the adults in each family. The younger pregnant or lactating females are likely to have consumed more than the average intake in the family, and there is evidence that, in general, elderly people have reduced food consumption.[12] Alternatively, it is possible that defective absorption in the older subjects may have contributed to this difference.

If this pilot trial reflects the general pattern of food consumption in the population, these findings have considerable significance in planning for food fortification with folic acid. The main hazard of fortifying food with folic acid for consumption by the general population is that haematological response could occur in an occasional patient with undiagnosed megaloblastic anaemia due to vitamin B_{12} deficiency. The smallest daily dose of folic acid that has been shown to cause such a response is 400 μg[13] but not all patients with pernicious anaemia will respond to this dose.[14,15] We have shown that the daily supplement of folic acid which is required to prevent folate deficiency in pregnant subjects at Nqutu is 200 μg.[16] Therefore the margin of safety between the requirements of pregnant women and the dose capable of causing response in vitamin B_{12} deficiency is 200 μg folic acid daily.

Based on the above considerations, the amount of folic acid which need be added to maize meal to prevent deficiency in pregnancy could be reduced below that used in the present study. To provide a 200 μg/day effective supplement, an amount of 400 μg of folic acid must be added to the average daily intake of maize meal, i.e. 100 μg less than the amount used in the present study. A further diminution of this dose could be made if one takes into account the differential intakes of pregnant and elderly subjects. On the one hand, the higher maize intake of pregnant women would ensure an adequate folic acid intake. On the other hand, the decreased food consumption of older patients, who are more susceptible to pernicious anaemia, would result in an intake of folic acid safely below the levels associated with haematological response to folic acid in vitamin B_{12} deficiency.

The results of the present study, in conjunction with the more extensive trials of FAMM carried out in hospital patients,[7] suggest that serious consideration be given to the fortification of maize meal with folic acid in South Africa.

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