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POSSIBLE PREVENTION OF NEURAL-TUBE DEFECTS BY PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

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SUMMARY

Women who had previously given birth to one or more infants with a neural-tube defect (NTD) were recruited into a trial of periconceptional multivitamin supplementation. 1 of 178 infants/fetuses of fully supplemented mothers (0.6%) had an NTD, compared with 13 of 260 infants/fetuses of unsupplemented mothers (5.0%).

INTRODUCTION

The well-known social-class gradient in the incidence of neural-tube defects (NTD) suggests that nutritional factors might be involved in NTD aetiology. A possible link between folate deficiency and NTDs in man was first reported in 1965.[1] More recently, significant social-class differences in dietary intakes in the first trimeter,[2] and in first-trimester values for red cell folate, leucocyte ascorbic acid, red-blood-cell riboflavin, and serum vitamin A have been reported,[3] dietary and biochemical values being higher in classes I and II than in classes III, IV, and V. Furthermore, 7 mothers, of whom 6 subsequently gave birth to NTD infants and 1 to an infant with unexplained microcephaly, had first-trimester mean values for red cell folate and leucocyte ascorbic acid that were significantly lower than those of controls.[3]

These observations are compatible with the hypothesis that subclinical deficiencies of one or more vitamins contribute to the causation of NTDs. We report preliminary results of an intervention study in which mothers at increased risk of having NTD infants were offered periconceptional multivitamin supplements.

PATIENTS AND METHODS

Women who had had one or more NTD infants, were planning a further pregnancy, but were not yet pregnant were admitted to the study. All women referred to the departments involved in the study and who met these criteria were invited to take part. Most patients were recruited from genetic counselling clinics, although some were referred by obstetricians and general practitioners informed of the study. Patients came from Northern Ireland, South East England, Yorkshire, Lancashire and Cheshire. 185 women who received full vitamin supplementation (see below) became pregnant.

The control group comprised women who had had one or more previous NTD infants but were either pregnant when referred to the study centres or declined to take part in the study. Some centres were able to select a control for each supplemented mother, matched for the number of previous NTD births, the estimated date of conception, and, where possible, age. There were 264 control mothers. The numbers of fully supplemented (S) and control (C) mothers in each centre were as follows: N. Ireland S 37, C 122; S.E. England S 70, C 70; Yorkshire S 38, C 35; Lancashire S 31, C 27; Cheshire S 9, C 10.

All mothers in supplemented and control groups were offered amniocentesis. 6 mothers in N. Ireland (3 supplemented, 3 controls) declined amniocentesis and their pregnancies continue. They are not included in the figures above or in the accompanying table. All mothers with raised amniotic-fluid alpha-fetoprotein (AFP) values (1 supplemented, 11 controls) accepted termination of pregnancy.

Study mothers were given a multivitamin and iron preparation ('Pregnavite Forte F' Bencard), 1 tablet three times a day for not less than 28 days before conception and continuing at least until the date of the second missed period - i.e. until well after the time of neural-tube closure. Pregnavite forte F provides daily vitamin A 4000 I.U., vitamin D 400 I.U., thiamine 1.5 mg, riboflavin 1.5 mg, pyridoxine 1 mg, nicotinamide 15 mg, ascorbic acid 40 mg, folic acid 0.36 mg, ferrous sulphate equivalent to 75.6 mg Fe, and calcium phosphate 480 mg. Women conceiving less than 28 days after starting supplementation, or starting supplementation shortly after conception, or known to have missed tablets for more than 1 day, are regarded as partly supplemented. They were excluded from the main study and their results will be considered elsewhere.

In N. Ireland, Yorkshire, and Cheshire women taking oral contraceptives (OCs) were asked to adopt alternative means of contraception from the date of starting vitamins because OCs may lower blood levels of certain vitamins.[4]

RESULTS

187 control mothers have delivered 192 infants (including 5 twin pairs) without NTDs, and a further 38 have normal amniotic-fluid AFP values (table). 13 mothers have been delivered of NTD infants/fetuses,

OUTCOME OF PREGNANCY IN FULLY SUPPLEMENTED AND CONTROL MOTHERS

	Fully supplemented	Controls
Infant fetus with NTD	1	12
Infant without NTD	140(3)	192(5)
Subtotal (1)	141(3)	204(5)
Normal amniotic AFP	26	38
Subtotal (2)	167(3)	242(5)
Spontaneous abortions		
Examined, NTD	0	1
Examined, no NTD	11	17
Subtotal (3)	178(3)	260(5)
Not examined	10	9
Total	188(3)	269(5)

All numbers relate to infants/fetuses.
Figures in parentheses indicate numbers of twin pairs included.

1 by spontaneous abortion, 11 by termination after amniocentesis, and 1 by spontaneous delivery (skin-covered lesion, normal AFP). 17 fetuses of a further 26 control mothers who aborted spontaneously were examined and had no NTD. The provisional recurrence-rate of NTDs is

5.0% (13 in 260). 26 control mothers were at increased risk by virtue of having had 2 previous NTD infants. 3 of them had a further affected child, a recurrence-rate of 11.5%. Both these recurrence-rates are consistent with those previously reported and widely adopted in genetic counselling.

137 fully supplemented mothers have given birth to 140 babies (including 3 twin pairs) without NTD, 26 have normal amniotic-fluid AFP values and their pregnancies continue, and 1 has had a further affected infant. 11 fetuses of 21 mothers who aborted spontaneously were examined; none had an NTD. The provisional recurrence-rate in the supplemented group is therefore 0.6% (1 in 178). 15 supplemented mothers were at increased risk by virtue of having had 2 previous affected NTD infants. None had a further affected child.

Comparison of NTD frequencies in the supplemented and control groups by Fisher's exact test showed significant differences ($p < 0.01$) for subtotals (1), (2), and (3) (table).

DISCUSSION

Despite problems with choosing controls, the control women in this study have shown recurrence-rates for NTDs entirely consistent with published data. By contrast the supplemented mothers had a significantly lower recurrence-rate. Possible interpretations of this observation include the following:

(1) A group of women with a naturally low recurrence risk has unwittingly selected itself for supplementation. - Apart from geographic and secular variations there is no evidence to suggest that any particular sub-group within populations, whether by social class or any other division, has a higher or lower recurrence risk. In genetic counselling clinics it is customary to quote the same risk for all mothers after one affected child. We cannot exclude the possibility that women who volunteered and cooperated in the trial might have had a reduced risk of recurrence of NTD. However, one might have expected such an effect to be found in mothers who cooperated in potato-avoidance trials, but this was not seen.[5]

(2) Supplemented mothers aborted more NTD fetuses than did controls. - The proportion of pregnancies ending in spontaneous abortion is similar in the two groups (supplemented 11.4%, control 9.6%). If the supplemented mothers have aborted more NTD fetuses, they must have aborted fewer other fetuses or had a lower initial risk of abortion. 11 of 21 abortuses of supplemented mothers have been examined and none had an NTD. 18 of 27 abortuses of control mothers were examined and 1 had an NTD. An explanation based on selective abortion of fetuses with NTD seems improbable, especially since more abortions are likely to have been ascertained in the supplemented group since controls were enrolled later in pregnancy.

(3) Something other than vitamin supplementation has reduced the incidence of NTDs in the treated group. - This is an almost untestable hypothesis, but if anything has reduced the incidence of NTDs it needs to be identified urgently. The only measure introduced by the study other than vitamin supplementation (and that only in some centres) was discontinuation of OCs at least 28 days before conception. Although the possibility of sex hormones having teratogenic action is not yet entirely resolved, evidence[6] strongly suggests that the phenomenon we report is not attributable to stopping OCs.

(4) Vitamin supplementation has prevented some NTD. - This is the most straightforward interpretation and is consistent with the circumstantial evidence linking nutrition with NTDs. If the vitamin tablets are directly responsible, we cannot tell from this study whether they operate via a nutritional or a placebo effect.

We hope that the data presented will encourage others to initiate similar and related studies. We intend to publish a more detailed report when the last of the present cohort of women receiving vitamin supplements has had her baby (due April 1980).

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