Recurrent neural tube defects, risk factors and vitamins

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SUMMARY Data from our trial of periconceptional vitamin supplementation for the prevention of
neural tube defects have been analysed to assess the influence of various factors on recurrence rates of
neural tube defect. Our data suggest that the risk of recurrence of neural tube defect is
influenced by the number of previous neural tube defects, area of residence, immediately prior
miscarriage, and interpregnancy interval. None of these factors, however, contributed any
significant differential risk between supplemented and unsupplemented mothers. Hence we
conclude that the highly significant difference in recurrence rates of neural tube defect between
supplemented and unsupplemented mothers was due to vitamin supplementation.

We have reported a highly significant reduction in the recurrence rate of neural tube defect in mothers
given a periconceptional multivitamin supplement (Pregnavite Forte F) when compared with unsupplemented
mothers recorded by the same centres over the same period.1 As our study was not randomised several workers2–5 have suggested that
supplemented and unsupplemented mothers had different prior risks of recurrence of neural tube
defect and that this, rather than any effect of the vitamins, could be responsible for the observed
difference in recurrence rates. In this report supplemented mothers are those referred to as fully
supplemented in previous reports—that is, they have taken Pregnavite Forte F from not less than 28
days before conception until the time of the second
missed menstrual period.

We report here the distribution in our supple-
mented and unsupplemented mothers of factors
that are known or suspected to modify the risk of
occurrence of neural tube defect. Factors affecting
the occurrence risk would be expected also to
modify the recurrence risk, although there are few
direct data to confirm this. We have considered the
following factors:

(1) Number of previous neural tube defects. All
mothers, whether supplemented or unsup-
plemented, had had at least one previous
neural tube defect, but it is known that the
rate of recurrence increases in relation to the
number of previous neural tube defects. Two
or more previous neural tube defects are
therefore regarded as indicative of ‘high risk’.
(2) Social class. A social class gradient has been
recognised for many years, the birth preva-
ance of neural tube defect being lowest in
social class I and highest in social class V. One
study has reported a similar gradient in
recurrence rates.6 For purposes of analysis,
classes I, II, and III non-manual are regarded
as ‘low risk’ and classes III manual, IV, and
V, as ‘high risk’.
(3) Place of residence. Of the centres collaborat-
ing in our studies, the highest birth prevalence
of neural tube defect is in Northern Ireland,
and residence here is indicative of ‘high risk’.
(4) An excess of spontaneous abortions has been
noted in the pregnancies immediately prece-
ding births with neural tube defect.7,8 A
spontaneous abortion immediately before a
study pregnancy is therefore regarded as
carrying a ‘high risk’.
(5) The possibility that an immediately prior
therapeutic abortion conveys increased risk is
also considered.

Recurrence analyses of individual risk factors and their interactions using a linear logistic model were performed with GENSTATS. The results led to the identification of four factors associated with an increased risk of recurrence: two previous neural tube defects, residence in Ireland, immediately prior spontaneous abortion, and 12 months between abortion and study pregnancy. The interaction of these factors was also considered, but no significant effects were found.

The differential risk between supplemented and unsupplemented pregnancies due to that factor is then:

\[
\frac{\% \text{ Unsupplemented with factor} \times \text{relative risk}}{\% \text{ unsupplemented without factor}} + \frac{\% \text{ supplemented with factor} \times \text{relative risk}}{\% \text{ supplemented without factor}}
\]

Secondly, the contribution of factors individually or in combination was studied by multivariate analysis using a linear logistic model on the computer package GENSTATS. No distinction was made between spontaneous and therapeutic abortions in the immediately prior pregnancy, and fallow period was not considered. This analysis was performed on 795 outcomes where there were no missing data; these included all three recurrences in the supplemented group and 22 of 24 in the unsupplemented group.

### Results

Table 1 shows the analysis of individual risk factors. Four factors (two previous neural tube defects, residence in Ireland, immediately prior spontaneous abortion, and 12 months between abortion and study pregnancy) apparently lead to an increased risk. Only for two or more previous neural tube defects, however, is the increase significant, and when the distribution of the factors between the supplemented and unsupplemented groups is taken into account none of the factors leads to a predicted increase of more than 4% in the recurrence rate in the unsupplemented compared with the supplemented group (Table 1, right hand column). In the multivariate analysis in Table 2 the effect of n factors is measured by the reduction in the deviance when they are introduced into the analysis. This reduction has a χ² distribution with n degrees of freedom, and its significance can be found in χ² tables. One factor (two previous neural tube defects) is significant (p < 0.01), and the remaining factors are not significant.
defects) produces a significant reduction in the deviance (compare regression 2 with regression 1), but none of the other factors except vitamin supplementation has a significant effect. Immediately prior abortion, residence in Ireland, and social class jointly have no significant effect once the effect of having two or more previous neural tube defects is taken into account (compare regression 6 and 2). Vitamins have a highly significant effect either allowing just for two or more previous neural tube defects (regressions 7 and 2) or all other factors (regressions 8 and 6).

### Discussion

After the publication of our trial of vitamin supplementation for the prevention of neural tube defect,^1^ several workers^2-5^ suggested that supplemented and unsupplemented mothers were at ‘differential risk’ for recurrence of neural tube defect. We have already responded to some of these criticisms.^6^  ^12^  ^13^  

Certainly, the difference between the recurrence rates for the supplemented and unsupplemented groups is too large and consistent between cohorts to be a chance effect; either vitamin supplementation reduces the risk of neural tube defect or the supplemented and unsupplemented groups differ about sevenfold in prior risk. Our results show that none of the factors considered here contributes any significant differential risk.

### 1  Number of previous neural tube defects

The well known increased risk of recurrence for mothers with two or more previous neural tube defects is seen in our data. Reports of our studies have always separated mothers with one previous neural tube defect from those with two or more, but Table 1 shows that the proportions are similar in the supplemented and unsupplemented groups, partly because of deliberate matching in some centres.

### 2  Social class

There is a well established relation between social class and occurrence of neural tube defect, but only one study (in Northern Ireland) has reported a similar relation between social class and recurrence of neural tube defect. In the present study the recurrence rate of neural tube defect is similar when comparison is made between classes I, II, and III non-manual (3-0%) and classes III manual, IV, and V (2-8%). Consequently, although there were proportionally more unsupplemented than supplemented women in the lower social class group, the unsupplemented:supplemented risk ratio in relation to social class is close to unity.

### 3  Area of residence

The higher occurrence of neural tube defect in Northern Ireland than in the rest of the United Kingdom is probably associated with a higher risk of recurrence;^6^ our data suggest a 35% higher risk if vitamins have no effect. The unsupplemented group contains rather more mothers from Northern Ireland than the supplemented, which leads to a predicted 4% increase in the recurrence rate in the unsupplemented group.

### 4  Immediately prior pregnancy ending in spontaneous abortion

Smithells et al noted that fetal death (spontaneous abortion plus stillbirth) was particularly common in pregnancies immediately before the birth of an anencephalic child.^7^ A similar excess of fetal deaths was found in pregnancies immediately before spina bifida. Clarke examined data from his own^9^ and other^14^ surveys of children affected by anencephaly or spina bifida. Considering only siblings in which at least one pregnancy had occurred both before and after the affected child, he found that there were always more spontaneous abortions plus stillbirths immediately before the affected child than immediately after. More recently, Cuckle has shown the increased frequency of a second neural tube defect in the pregnancy immediately after a spontaneous abortion in women with previous neural tube defect pregnancies.^10^  

In our data the recurrence rate after a spontaneous abortion was 5·4% compared with 2·5% after all other outcomes, but this difference was not quite significant (p=0·06). In our unsupplemented women with one previous neural tube defect the association of neural tube defect with an immediately prior spontaneous abortion is similar to that found by Cuckle. The recurrence rate was 8·8% after a spontaneous abortion compared with 3·4% after all other outcomes (p=0·05). The frequency of spontaneous abortion in the immediately prior
pregnancy is similar, however, in the supplemented and unsupplemented groups, and the differential risk introduced is only 3%.

5 Immediately prior pregnancy ending in a therapeutic abortion. This happened in 12.4% of supplemented but only 5.2% of unsupplemented women. We have discussed before how our method of recruiting mothers for supplementation through genetic counselling clinics leads to an excess of women who have just had a neural tube defect pregnancy. Termination of the immediately prior pregnancy has not been considered before as a possible risk factor, and because of the imbalance between the supplemented and unsupplemented groups it could be important. Table 1 shows, however, that there is no increased risk of neural tube defect when the preceding pregnancy was terminated.

6 Length of fallow period. The excess of spontaneous abortions in the immediately prior pregnancy seems well established. Whether there is a causal connection is less clear. Knox first postulated that residual trophoblast was important in the aetiology of neural tube defect. Clarke suggested that the retention of trophoblast material is much more likely after a spontaneous abortion than after a normal delivery. There is little information about the survival of trophoblast in vivo. In vitro human trophoblast material taken from caesarian section at term has been successfully cultured for up to eight months, but a similar technique was not successful with early trophoblast. It seems likely that the longer the interval between the spontaneous abortion and the next conception the less likely is trophoblastic material to remain.

Table 1 shows that there is a threefold increase in the risk of recurrence in pregnancies started within 12 months of an abortion (spontaneous or therapeutic) compared with those with a prior abortion but a fallow period of a year or more. If confirmed, this would be the most powerful risk factor we have found, but the difference does not reach significance (p=0.2). Table 1 shows that this effect does not account for any of the difference in recurrence rate between our supplemented and unsupplemented groups. We have already reported that for all supplemented pregnancies the average time interval between conception and the end of the previous pregnancy was slightly shorter than for unsupplemented pregnancies.

Most spontaneously aborted fetuses are not examined, and it is therefore possible that some of them have neural tube defects. In the obstetric histories studied by Clarke there is no indication whether aborted fetuses were examined. Bell and Gosden examined over 500 unsupplemented spontaneously aborted fetuses and found neural tube defect in 4.1% of them. In our study pregnancies roughly half the spontaneously aborted fetuses were examined; neural tube defect was found in 0/19 examined fetuses of supplemented women and 1/25 of unsupplemented women. Although this small sample cannot be assumed to be representative, it suggests that the recurrence rate of neural tube defect among aborted fetuses may be similar to that in full term pregnancies. A small part of the increased recurrence of neural tube defect observed after a spontaneous abortion may therefore be attributable to previous but undetected neural tube defect. The effect of prior spontaneous abortion per se can only be determined by investigating recurrence rates of neural tube defect after spontaneous abortions that were examined and found to be unaffected.

Many questions will remain unanswered until more complete data on a very large number of women are available. It is clear, however, that the difference in recurrence rates of neural tube defect between vitamin supplemented and unsupplemented mothers cannot be attributed to any of the factors considered here, either alone or in combination. Indeed they cannot account for even a twofold difference in prior risk. On the differential risk hypothesis this is surprising: even if none of the factors considered here were the direct cause of the difference, all the likely nutritional, social, and obstetric variables should show some correlation. We cannot totally exclude the possibility that some ‘invisible’ factor influencing the risk of recurrence has segregated differentially as between supplemented and unsupplemented mothers. If, however, such a factor were causing a sevenfold difference the visible partially correlated factors might be expected to show some difference.

The method used here to look at individual factors may show some small apparent differential risk even if vitamins directly cause the whole of the difference observed. This is because any irrelevant factor that is randomly increased in the supplemented group may be scored as a positive risk factor (because most of the recurrences of neural tube defect are in the unsupplemented group), and this positive risk factor will by definition be increased in that group. Hence the small positive contributions by some factors to the risk ratio are not evidence that if a sufficient number of such factors were considered then the whole differential risk could be explained. Further statistical analysis of our vitamin supplementation trial therefore
suggests that the highly significant difference in recurrence rates of neural tube defect between supplemented and unsupplemented mothers was not attributable to differential risks between the two groups but to some aspect of vitamin supplementation. It is possible, however, that factors associated with the taking of vitamin tablets—for example, subtle preconceptional changes of life style—may have contributed to the reduced recurrence rate of neural tube defect. It remains true that periconceptional vitamin supplementation is associated with a significantly reduced rate.

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References


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