Long term effects of periconceptional multivitamin supplements for prevention of neural tube defects: a seven to 10 year follow up

Monica Holmes-Siedle, Jennifer Dennis, R H Lindenbaum, Anonna Galliard

Abstract
Periconceptional supplementation with Pregnavite Forte F was offered to women who presented consecutively to the Oxford genetic counselling service in the early 1980s who had previously had one or more pregnancies complicated by a neural tube defect. The first 100 children born alive to these women are the subject of this study. Birth weight, gestation, and congenital abnormalities were recorded. At age 2–5 years all 96 children remaining in the United Kingdom were assessed clinically and developmentally and behavioural information was obtained by questionnaire. At age 7–10 years, follow up of 91 children by telephone and postal questionnaire yielded further information about growth, general health, vision, hearing, and educational and behavioural status. Entry criteria excluded single mothers but the social class distribution of the sample was otherwise representative of the Oxfordshire population. There were no recurrences of neural tube defects. One child had radiological evidence of spina bifida occulta affecting only the fifth lumbar vertebra. One had an autosomal recessive disorder. Eight had random minor congenital anomalies. Birth weight for gestational age was significantly greater than for the local population and at age 7–10 years the girls were considerably taller than expected. Health, auditory, visual, and developmental status were no different from the general population. None of the children had special educational needs. None showed a major behaviour disorder but worries, fussiness, and fearfulness were highly significantly over represented.

Periconceptional supplementation with Pregnavite Forte F (Bencard) as a primary prevention of neural tube defects has been carried out in various centres in the United Kingdom for more than a decade.1–3 The publication of the results of the Medical Research Council trial showed similarly successful results for high doses of folic acid alone.4 This will give added impetus to periconceptional treatment.5–6 The administration of any drug to women during the critical period of organogenesis in the embryo is best avoided. In the original studies care was taken to monitor any birth defects present. This confirmed that no overt harm had been caused to the children by the multivitamin treatment.5–6 The possibility must be examined, however, that the vitamin treatment may have more subtle or indirect effects only seen later in life. This paper describes a long term study which addresses this question.

Subjects and methods
SUBJECTS
The subjects were women who had previously had one or more pregnancies complicated by a neural tube defect and presented consecutively to the Oxford genetic counselling service. They were with the same partners as for the previous pregnancy but were not yet pregnant again. These women were offered periconceptional supplementation according to the Smithells's protocol.7 The supplement used was Pregnavite Forte F, a multivitamin preparation which includes folic acid (0·36 mg daily) and minerals. Those who accepted and took this for a minimum of 28 days before conception and continued at least until the second missed menstrual period were regarded as fully supplemented. The complete lack of recurrence of neural tube defects in the offspring of these Oxford women has been reported in the multicentre study of Sellier et al.6 The children in the present study were the first 100 children born alive to this group of women. This unselected group represents the offspring of 93 women who delivered between April 1981 and June 1984. Six of these women had had two previous pregnancies complicated by neural tube defects and 87 one such previous pregnancy. Seven had two pregnancies during the study period and there was one twin pair. The mean length of preconceptional supplementation was 128 days; the maximum was 437 days. After conception the mean supplementation period was 107 days and the maximum 252 days.

METHODS
Birth information
Information about birth weight and gestation was obtained from contemporaneous records at the time of delivery. Information about congenital abnormalities was obtained from contemporaneous records supplemented by information from the women at the time of first follow up.

First follow up (age 2–5 years)
Children were seen in their own homes by the
principal investigator (MH-S). They were examined clinically and information about their general health and specific problems was obtained in standard format. Head circumference and height were measured. If a child had recently passed a health visitor's hearing test no further hearing check was made but if not, children were tested using a Manchester rattle and the seven toy speech discrimination test. Vision was checked by the Stycar vision test; gross and fine motor, language, and social skills were assessed using the Denver developmental screening test (DDST) and the Richman behaviour screening questionnaire (BSQ) was completed by the parents.

Second follow up (age 7–10 years)
The mothers were not seen personally. All the mothers were interviewed by telephone by MH-S following a standard format. Information was sought about general health together with their agreement to complete a postal questionnaire. This produced information on height, weight, vision, hearing, and educational status. The parents were asked to comment on their child’s development in relation to other children of the same age and to complete the Rutter behavioural scale (A2, for parents).

Results
Maternal age at delivery ranged from 22 to 39 years (mean 29.2 years). Social class distribution, as determined by paternal occupation, differed from 1981 census figures for Oxfordshire in that only 3% were ascribed to the category ‘other’ in contrast with 24% in the county. This is because a criterion for inclusion in this study was that the women should be with the same partner as when their previous child with neural tube defects had been conceived. This made it unlikely that single mothers would be included. When this difference was allowed for the distribution within social classes I–V did not differ from the county population.

FIRST FOLLOW UP
Follow up was achieved for all 96 children still resident in the United Kingdom. There were 52 boys and 44 girls. Age ranged from 22 months to 5 years (mean 3 years 6 months). Most were 2, 3, or 4 years old.

Birth information
Information about birth weight and gestation was reliably available for 97 of the original sample of 100, including one twin pair. Ninety of the singleton pregnancies (95%) had continued beyond 38 weeks. Four babies (4%) had been born at 37 weeks and one (1%) at 36 weeks. The distribution of birth weight for gestational age for singleton births was slightly skewed to the right (fig 1) compared with Oxford standard birth charts. The excess of birth weights above the 50th centile was significant at the 1% level.

Congenital abnormalities
After reporting backache at the age of 5 years, one child showed radiological evidence of a small spina bifida occulta affecting only the fifth lumbar vertebra. She was one of a same sexed twin pair whose mother had previously given birth to one anencephalic and one normal girl. There were nine other children with abnormalities. One had an autosomal recessive disorder (oculocutaneous albinism). The other abnormalities were one child each with pyloric stenosis, terminal hypospadias, thyroglossal cyst, left congenital corectopia (displaced pupil), positional talipes, and three boys with unilateral cryptorchidism.

Clinical findings
Inspection of the spine showed a skin covered sacral dimple in three children, one of whom had a father who was said to show a similar feature. The child with congenital corectopia had astigmatism, one child had a right convergent squint, and two were myopic. One child had brief absences. Three children had mild hearing loss due in one child to mumps meningitis and in the others to glue ear.

Growth
Data for height and head circumference (OFC) were analysed separately by sex and expressed as centiles for age according to Tanner-Whitehouse standards. The distribution of height for both sexes was slightly but not significantly skewed to the right. Head circumference showed a similar trend. As the OFC distribution among the general Oxford population was known to differ from Tanner-Whitehouse standards centiles were reassigned according to the data of Ounsted et al and a close match was

Figure 1  Supplemented group. Distribution of birth weight for gestational age for singleton births according to Oxford standards.
achieved. This suggests that the height discrepancy may also have arisen because the Tanner-Whitehouse norms are not relevant to our local population.

Development
No child either 'failed' or was ascribed 'questionable' developmental status according to the set criteria for scoring the DDST. Four children (4%) showed delay in the language sector of the test. This sector of the screening test shows poor sensitivity and identifies only 53% of children who have expressive language delay on formal speech and language evaluation. Richman et al, on formal evaluation, identified language delay in 20 of 105 (19%) 3 year olds in an outer London borough and Silva identified expressive language delay in 13% of unselected Dunedin 5 year olds. Thus language delay in the study group, even allowing for the poor specificity of the test used, is unlikely to have been greater than in the general population.

Behaviour
Only one girl and one boy achieved scores of 11 or more on the BSQ, which is the cut off point suggesting behavioural disturbance. This represents only 2% of the study group (two of 96). Stevenson and Richman found 14% (101 of 705) of 3 year olds in an outer London borough scoring above this cut off, and in the original standardisation test sample five of 57 'controls' (9%) were in this range. It thus seems that overall our study sample showed a low level of behavioural disturbance compared with the general population. Item by item analysis showed fewer high scorers on all items except 'worries' where 4% scored 2 as opposed to 2–3% of the Stevenson sample. This difference does not reach statistical significance but is of interest in relation to findings in the second follow up.

SECOND FOLLOW UP
One further child had left the United Kingdom since the first follow up, two families were untraceable, and two families, though completing the telephone interview, did not return the questionnaires. This left 91 children in the second phase of the study, 51 boys and 40 girls. Ages ranged from 7-1 to 10-2 years (mean 8-8 years).

General medical problems
Respiratory problems, either current or previous, were reported for 13 children (14%). These children were described as having 'asthma' or as being 'chesty'. Seventeen (19%) had had accidents, 13 (14%) having sustained fractures. Eleven (12%) were reported to have congenital/genetic disorders; 10 of these had been identified at the first follow up and the additional case was a previously unreported hydrocele. Sixteen (19%) children had had ear, nose, and throat problems, mainly glue ear. Eight children wore spectacles and a further five had ocular problems, giving a total of 14% with visual problems. Two (2%) had had meningitis (one mumps, one meningococcal). There were 13 other miscellaneous problems. No problem group was over represented when compared with the general population of 7–10 year olds. Eighty four per cent were right handed, 13% left handed, and 3% ambidextrous.

Growth
Height measurements taken by mothers were analysed separately by sex and expressed as SD scores according to Tanner-Whitehouse standards (fig 2). The means for both sexes (boys ±0.21 SD; girls ±0.52 SD) were greater than the Tanner-Whitehouse norms, that for girls being significantly more so (p<0.02). These findings show that the heights of the children in the study at 7–10 years of age show the same upward shift compared with Tanner-Whitehouse norms as is found in all children in Oxfordshire at ages 3 and 4-5 years (D Dunger and J A Macfarlane, personal communication).

Behaviour
Children who score 13 or more on the Rutter A2 scale are likely, on clinical evaluation, to be diagnosed as having psychiatric disorders. In this study five of 51 boys (10%) and one of 40 girls (3%) scored at or above this cutoff point. Taking both sexes together six scored above the cutoff against an expected figure of 5·4 derived from Isle of Wight control subjects aged 9–12 years. Thus the level of psychiatric disorders among the study group appears to be similar to that found in the general population.

The 18 items scored on the Rutter scale can be grouped into four behavioural domains reflecting motor activity, relationships, antisocial behaviour, and neurotic traits. The scale has been adapted for 5 year olds by excluding two of the 18 items which are predominantly developmentally determined and Yule has obtained general population data for 396 Isle
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Rutter behavioural scale: item by item comparison with general population figures

<table>
<thead>
<tr>
<th></th>
<th>Siblings of those with neural tube defect (vitamin supplement sample) (n=91)</th>
<th>Isle of Wight general population (n=396)</th>
<th>Isle of Wight general population (n=2189)</th>
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</thead>
<tbody>
<tr>
<td>Boys</td>
<td>51</td>
<td>192</td>
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<tr>
<td>Girls</td>
<td>40</td>
<td>204</td>
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<tr>
<td>Age (years)</td>
<td>7-10</td>
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<td>9-12</td>
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<tr>
<td>Motor items</td>
<td></td>
<td></td>
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<tr>
<td>Restlessness</td>
<td>23 (25)**</td>
<td>206 (52)**</td>
<td>31</td>
</tr>
<tr>
<td>Fidgety/squirmyness</td>
<td>16 (18)</td>
<td>93 (25)</td>
<td>12</td>
</tr>
<tr>
<td>Twitchiness/tics</td>
<td>2 (2)</td>
<td>11 (3)</td>
<td>4</td>
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<tr>
<td>Unable to settle</td>
<td>10 (11)**</td>
<td>86 (22)**</td>
<td>22*</td>
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<tr>
<td>Relationships</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Irritability</td>
<td>30 (33)</td>
<td>138 (35)</td>
<td>30</td>
</tr>
<tr>
<td>Not much liked</td>
<td>4 (4)</td>
<td>7 (2)</td>
<td>5</td>
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<tr>
<td>Solitary</td>
<td>16 (18)</td>
<td>104 (26)</td>
<td>23</td>
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<tr>
<td>Antisocial</td>
<td></td>
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<tr>
<td>Destructive</td>
<td>4 (4)</td>
<td>50 (12)</td>
<td>4</td>
</tr>
<tr>
<td>Disobedient</td>
<td>35 (39)**</td>
<td>195 (49)</td>
<td>26*</td>
</tr>
<tr>
<td>Lies</td>
<td>26 (29)**</td>
<td>71 (18)**</td>
<td>11***</td>
</tr>
<tr>
<td>Bullies</td>
<td>3 (3)</td>
<td>25 (6)</td>
<td>5</td>
</tr>
<tr>
<td>Fights</td>
<td>16 (18)</td>
<td>68 (17)</td>
<td>10*</td>
</tr>
<tr>
<td>Neurotic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Worried</td>
<td>48 (53)**</td>
<td>108 (27)**</td>
<td>39*</td>
</tr>
<tr>
<td>Miserable</td>
<td>19 (21)**</td>
<td>76 (19)</td>
<td>11*</td>
</tr>
<tr>
<td>Fearful</td>
<td>39 (43)**</td>
<td>81 (20)</td>
<td>27*</td>
</tr>
<tr>
<td>Fussy</td>
<td>25 (27)**</td>
<td>69 (17)**</td>
<td>16*</td>
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*p<0.05; **p<0.01; ***p<0.005; comparison with 9-12 year old general population group.
*p<0.05; **p<0.01; ***p<0.005; comparison with 5 year old general population group.
*Corrected for continuity
§Personal communication, W Yule.

of Wight 5 year olds using this adaptation (W Yule, personal communication). Item by item analysis (see table) was carried out comparing the study group with the two Isle of Wight samples. This shows that compared with these general groups those items which reflect motor restlessness and attention deficit were scored less often for the study group while those reflecting neurotic traits (worries, misery, fearfulness, and fussiness) were notably, and often significantly, over represented. With respect to antisocial items, a tendency to disobedience and fighting appeared to be developmentally graded but significantly more of the study group children told lies than in either the 5 or 9-12 year old population groups.

Schooling All children were in mainstream schools. None had attended special needs provision either at nursery or school age. One 9 year old was receiving help from a speech therapist and three other children had had speech therapy in their preschool years. Eight of the children (8%) were receiving extra help in school with reading, writing, or other learning skills. All these children were above the age of 8-5 years (mean age of sample 8-8 years).

Discussion In our group of 100 children at relatively high risk of a neural tube defect because of a previously affected sibling, three or four lesions of the neural tube would have been expected. No open lesions were present but in this detailed examination one child with spina bifida occulta was identified; this affected the fifth lumbar vertebra only. Fawcett's review suggests that the incidence of spina bifida occulta may be as high as 94% in the 0-5 year old group, with isolated L5 defects occurring in 15% of this group. If radiographed after a few years, it is likely that these children would be considered to be normal. Thus we believe that the spina bifida occulta found in one child in this study should not be regarded as a recurrence of a neural tube defect. Similarly the finding of three children with a skin covered sacral dimple is within the expected range as stated by Méhes. There was no increase above expected numbers for other congenital malformations. This adds further support to evidence that Pregnanate Forte F is not teratogenic.

A higher proportion of pregnancies progressed to term than is usual, the birth weights for gestational age of the children were greater than expected for the local population, and there is some suggestion that growth has been enhanced among the girls. This latter finding cannot be confirmed until contemporary growth standards for the United Kingdom population become available. The children have all had good health and there is no evidence that major learning difficulties or sensory impairment are over represented. The possibility that subtle cognitive deficits could nevertheless be present could only be tested by individual neuropsychological assessment.

The behavioural findings are of interest in that worries, fearfulness, and fussiness are notably over represented among the 7-10 year olds and a trend towards being overworried was already emerging in the same group at an age of 2-5 years. The simple explanation of this is that these neurotic traits have arisen secondarily to...
maternal anxiety about the child. All the women had had a previous pregnancy with a neural tube defect. For many this had resulted in the birth of a liveborn child and all that entailed in terms of handicap, suffering, and death. For most of the women the children in this study were the first to be born after the affected child. It would not be surprising if maternal anxiety about these children extended far beyond the early months of pregnancy and if their previously distressing experiences of childrearing determined a style of parenting likely to produce anxiety in the child. There was indeed anecdotal evidence from the women that this was so. For instance, one mother of a 9 year old child recounted that she still remained outside the school gates for 10 minutes after the children had gone in, feeling unable to leave in case her child needed her.

This interpretation of the findings must, however, be set alongside the fact that worries, fearfulness, and fussiness can be organically determined. The most compelling information derives from two studies. Udwin and coworkers have evaluated the psychiatric aspects of children and adults with Williams' syndrome (idiopathic infantile hypercalcaemia).23 24 The Rutter parent scale was used and as in the study reported here the findings were compared with the Isle of Wight control data. A second comparison group was a group of children with mental handicap from causes other than idiopathic infantile hypercalcaemia. A distinct behavioural phenotype including a high incidence of worries, fearfulness, and fussiness was found for the children with idiopathic infantile hypercalcaemia and these features were enhanced and often disabling in adult life. The conclusion was that these features were likely to be biologically determined. The second study which supports this idea is that of Shaffer et al who examined the relation between neurological 'soft signs' and behaviour in a subsample of 7 year old children who had been enrolled in the US collaborative perinatal project in 1962 and 1963.25 Those with 'soft' signs scored significantly higher on the dependency/withdrawal scale (which included ratings for fearfulness, self confidence, and need for attention/help), but not on the hyperactivity or aggression scales. This pattern of psychiatric functioning is similar to some of the siblings of children with neural tube defects in this study.

In the context of this study it is possible that these features represent a behavioural phenotype associated with the genetic determinants of neural tube defects. Vitamin supplementation could prevent expression of the major physical manifestation but not all other genetic effects. The possibility also has to be considered that the behavioural attributes could be actually determined by periconceptional vitamin supplementation. The relative importance of all three possible determinants (parenting style, genetic influences, and periconceptional vitamin supplementation) could be tested by a relatively simple multicentre behavioural study of children including those born before and after an index child with a neural tube defect and those born after an index child with a neural tube defect who have or have not had periconceptional supplementation with Pregnanate Forte F. Databases exist in sufficient centres to make this possible and the findings would be of great importance for families at risk of neural tube defects.

It must be noted here that it is not possible to speculate on the applicability of our results to the children reported in the recent Medical Research Council randomised multicentre study.4 In that study mothers received folic acid alone (4 mg/day) during the periconceptional period. Pregnanate Forte F provides only 0.36 mg folic acid daily together with a cocktail of vitamins and minerals.

CONCLUSIONS
Periconceptional vitamin supplementation had a protective effect on 100 children assessed in that there was no recurrence of neural tube defects. No harmful effect was detected. A possible beneficial effect was noted on growth. Over representation of worries and anxiety among the children at age 7–10 years merits further inquiry.

We are grateful to Professor Martin Bobrow who suggested the original study and to our colleagues for their advice and encouragement, in particular Dr Mary Seller, Professor RW Smithells, and Professor John Edwards. We also thank family members of MH-S and JD for help in collating the data. Secretarial assistance was provided by the department of medical genetics, University of Edinburgh. We are grateful to the patient who gave us a financial contribution; to the referring doctors; and for the supply of vitamins from the John Radcliffe Hospital pharmacist and Bencard. Finally our warm thanks go to the study families for their patient cooperation over the past few years.

17 Richman N, Stevenson JE, Graham PJ. Prevalence of behaviour problems in 3 year old children: an epidemi-

Not by vitamin A alone
A good deal of excitement has been generated by trials showing considerable reductions in mortality in children in Asia given supplements of vitamin A (see Archivist 1992, p288). Now a trial done in northern Sudan points to possible limitations of this approach (M Guillermo Herrera and colleagues, Lancet 1992;340: 267–71).

In a double blind placebo controlled trial 28 753 children aged between 9 and 72 months were given either 200 000 IU vitamin A plus 40 IU vitamin E or 40 IU vitamin E alone every six months for three doses. Those with clinical evidence of xerophthalmia were treated with vitamin A and excluded from the trial. No effect on mortality was demonstrated. Of 14 455 children given vitamin A 123 died and in the placebo group there were 14 298 children and 117 deaths. No subgroup was identifiable in whom vitamin A significantly reduced mortality. Signs of xerophthalmia were reduced but not abolished in the treated group.

There are a lot of unanswered questions. Other studies in which the vitamin has been given more frequently (200 000 IU every four months) or in a lower dose much more frequently (8333 IU weekly) have shown reductions in mortality of between 30 and 54%. It may simply be, therefore, that a dose of 200 000 IU every six months is not enough. There is evidence that supplementation is more effective where existing rates of mortality are higher. It is possible too, that vitamin A supplementation is more effective in areas where natural vitamin A intakes are lowest but the evidence from the trials done so far would not suggest that. Other factors which may alter the effect of giving vitamin A include diet, intestinal parasites, and prevalent bacterial or other pathogens. In this study a low baseline dietary intake of vitamin A was associated with increased mortality suggesting that dietary fortification might be more effective than giving large doses infrequently.

The study is a reminder, if one is needed, that vitamin A supplementation, important as it may be, cannot be the whole answer. Reducing poverty, improving nutrition, and reducing the burden of microbiological assault must remain the goals.

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