Infant feeding and allergy

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SUMMARY The effect of withholding cows’ milk was examined in 487 infants at high risk of allergic disease. Before birth they were randomly allocated either to a control group, most of whom received cows’ milk preparations, or to an intervention group, who were offered a soya based substitute. Eczema and wheezing occurred to a similar extent in the two groups during the first year of life, although napkin rash, diarrhoea, and oral thrush were commoner in the intervention group, especially during the first three months. Breast feeding for any length of time was associated with a reduced incidence of wheezing and diarrhoea.

In 1936 it was first suggested that bottle fed infants are more liable to eczema than those who are breast fed.1 During the past 50 years numerous studies have been published on the relation between infant feeding and allergy. In several (but not all) of these studies the findings have suggested that the mode of feeding during the first few months of life affects the risk of allergic disease in subsequent years.2 It has not been clear as to whether the association—if it is causal—arises from a protective effect of breast feeding or from an adverse effect of cows’ milk and perhaps other foods. In some studies allergic disease occurred less often in children who had been given a soya preparation than in those given cows’ milk. At the time the present study was set up only three randomised controlled trials investigating this subject had been published; one was very small,3 one was invalided by non-compliance,4 and the third was apparently open to bias in that clinical assessment of the children was not ‘blind’.5 A randomised controlled trial was therefore set up in infants at high risk of allergic disease to determine whether withholding cows’ milk reduced their risk of allergic disease. The hypothesis that breast feeding confers positive protection could not be tested by means of a controlled trial as it did not seem reasonable to allocate mothers to breast and bottle feeding randomly. The study did, however, provide observational data on the relation between allergic disease and breast feeding, other foods, and certain environmental factors. This paper presents the findings during these infants’ first year of life.

Subjects and methods

Pregnant women were recruited at two antenatal clinics in South Wales. At the booking clinic all women were asked whether they, their husbands, or any of their children had ever suffered from eczema, hay fever, or asthma. Those who answered affirmatively were told about the study and asked if they were willing to participate. The women who agreed to take part were randomly allocated to an intervention or a control group by means of sealed envelopes containing cards that were coded according to a computer generated randomisation procedure. Those in the intervention group were asked not to give their babies cows’ milk, or any food made from it, for at least four months. A soya preparation was supplied for those mothers not wishing to breast feed and for those breast feeding who wished to supplement their feeds. Mothers in the intervention group were advised to restrict their daily milk intake to a half pint (284 ml) during the pregnancy and while they were breast feeding.

A list of foods containing cows’ milk (and therefore to be avoided for the baby) was given to mothers in the intervention group. Both groups of babies were followed up at home at regular intervals by a dietician, who supplied soya milk to the intervention group as required for six months. All the mothers were given diaries in which they were asked to record the type of milk they gave their babies and also the first time any new food was given.

The babies were examined at the ages of 3, 6, and 12 months by a physician (FGM) who was unaware of their allocation in the trial. The skin was examined for the presence of a rash; a diagnosis of eczema was made always by the same physician. The presence of any nasal discharge was noted, and the
mothers asked whether the babies had had any 
thrush, napkin rash, diarrhoea, or wheezing (defined 
as a whistling noise coming from the chest) since the 
previous examination. Skin tests (using Bencard 
extracts) were performed at 6 and 12 months against 
certain common allergens; the foods tested were 
milk, cod, whole egg, wheat flour, and soya. Blood 
was taken at birth and at 3 and 12 months for 
immunological assay, the results of which will be 
published separately.

The significance of differences in symptomatology 
between the study groups was assessed by means of 
a 2x2 χ² test statistic, using Yates's correction, the 
sample sizes being adequate in all cases for the 
application of this test.

Results

The numbers of babies available for the trial and 
those actually admitted to it are shown in table 1. 
The nine babies omitted because of non-cooperation 
were never effectively admitted to the trial as their 
mothers changed their minds about participating at 
or soon after their birth; six of these mothers had 
been allocated to the intervention group and three 
to the control group. Ten babies were omitted 
because it was uncertain, owing to clerical error, 
whether they were allocated to the intervention or 
the control group. These infants were followed up 
in the same way as the rest, and the data used for 
observational purposes only. A further eight were 
excluded because they were born, or were about to 
move, outside the study area. The 487 infants 
admitted to the trial were all seen by the assessing 
physician on at least one occasion, except for one 
baby who died before the age of 3 months. Most 
ininfants were seen at 3, 6, and 12 months, but a few 
failed to attend for one or two assessments. The 
information about various symptoms was collected 
both from the mother’s history and from the 
doctor's examination; occasionally one or other of 
these sources was incomplete, producing slight 
variations in the total numbers available for informa-
tion about different symptoms. Feeding diaries 
were completed for the babies, dietary information 
being supplemented by notes made by the dietician 
as to the type of milk that had been given when the 
babies were 3 months old. Information on the 
second three months was slightly less complete than 
for the first three months in that some mothers 
ceased to maintain these diaries. The numbers of 
inphants for whom the various items of information 
were available are shown in tables 2–5.

Table 2 compares the intervention and the control 
groups in various respects. The two groups were 
broadly comparable with regard to the mothers’ age 
and parity, the families’ social class and smoking 
habits, and the babies’ sex and birth weight. The 
mothers in the intervention group were less likely to 
bray their babies than were those in the control group, possibly because they were offered 
a free supply of soya milk.

Table 3 shows the time at which cows’ milk 
protein was first given to the babies in the two 
groups. The time of introduction refers to cows’ 
milk in any form, whether as a powder or liquid 
preparation for bottle feeding or as an ingredient of 
some other food. Nearly all the control group 
received cows’ milk protein within the first few 
weeks of life, whereas it was given to only about a 
tenth of the intervention group in the first month 
and to about a quarter in the first three months.

It was recognised that the withholding of foods 
containing cows’ milk would tend to prevent other 
foodstuffs from being given to babies where those 
foodstuffs are combined with milk protein in 
prepared foods. Table 3 therefore shows the timing 
of introduction of egg and wheat or rye protein in the 
two groups. Seven babies are omitted from this part 
of the table as their mothers did not complete any
dietary diary; information about cows’ milk and breast feeding was available from the dietician’s notes in these cases. There is some uncertainty about the numbers who had not received the food by 6 months; where a food had not been shown in the diary by this time it was assumed that it had not been given, although in some cases the mother may have simply forgotten to record it. There is, however, no reason to suppose that the two groups behaved differently in this regard. Both egg and wheat protein tended to be given later in the intervention than in the control group, the difference being particularly great in the case of egg.

Table 4 shows the incidence of certain conditions during the first year of life in the two randomised groups. The total numbers vary slightly because of incomplete information in some cases. The incidence of eczema was higher in the intervention group than in the controls, but the difference was not significant, nor were the differences for wheeze or nasal discharge. There was, however, a significantly higher incidence of oral thrush in the intervention group. No differences between the two groups emerged in regard to severity of eczema, nor as to whether it had been treated by a doctor.

With regard specifically to the first three months, napkin rash occurred in 132 out of 235 (56%) of the intervention group, and in 113 out of 246 (46%) of the controls (p<0.05). During this period, diarrhoea was reported in 83 (35%) of the intervention group and in 60 (24%) of the controls (p<0.05), although taken over the full year the difference was not significant. Within the first three months, diarrhoea and napkin rash were significantly associated with each other (p<0.05), and so were napkin rash and thrush (p<0.001), although the association between diarrhoea and thrush just failed to reach significance at the 5% level.

Table 5 shows the incidence of certain conditions during the first year of life according to whether the infants were breast fed and for how long, irrespective of their randomised allocation in the trial. The numbers of infants in this table are greater than those in table 4 owing to the inclusion of some who were excluded from the trial because their randomised allocation was uncertain. Wheeze occurred about twice as frequently in those never breast fed (125/293) as in those ever breast fed (41/189), the difference being highly significant (p<0.001). The breast fed infants had less diarrhoea (111/189) than the non-breast fed infants (224/293) (p<0.001); nasal discharge was also less frequent in those breast fed than in those never breast fed (72/186 and 132/282, respectively), but the difference was not significant. Duration of breast feeding was examined in relation to these symptoms by means of the Wilcoxon rank sum test in the breast fed infants; duration was significantly and negatively related to risk of diarrhoea (p<0.05) but not to risk of wheeze or nasal discharge. The incidence of eczema was similar in those ever and never breast fed (35% and 40%, respectively), so the effect of duration on eczema was not examined. Although 8% of the babies were breast fed for six months, exclusive breast feeding was rare, only eight babies (2%) receiving no other food in their first eight weeks of life. The effects of exclusive breast feeding were therefore not examined.

In view of the greater tendency of the control

<table>
<thead>
<tr>
<th>Food</th>
<th>Group</th>
<th>No infants</th>
<th>Cumulative percentage of infants having received food</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 1–4</td>
<td>Week 5–13</td>
</tr>
<tr>
<td>Cows' milk</td>
<td>Intervention</td>
<td>238</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>249</td>
<td>91</td>
</tr>
<tr>
<td>Egg</td>
<td>Intervention</td>
<td>236</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>244</td>
<td>0</td>
</tr>
<tr>
<td>Wheat/rye</td>
<td>Intervention</td>
<td>236</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>244</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3  Time of introduction of cows' milk, egg, wheat and rye proteins

Table 4  Incidence of certain conditions during first year according to allocation in trial
Table 5  Duration of breast feeding and incidence of wheeze, nasal discharge and diarrhoea in first year of life

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duration of breast feeding (weeks)</th>
<th>Any breast feeding</th>
<th>All infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt;1-4</td>
<td>5-25</td>
</tr>
<tr>
<td>Wheeze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No</td>
<td>293</td>
<td>85</td>
<td>64</td>
</tr>
<tr>
<td>No (%) affected</td>
<td>125 (43)</td>
<td>20 (24)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No</td>
<td>282</td>
<td>85</td>
<td>63</td>
</tr>
<tr>
<td>No (%) affected</td>
<td>132 (47)</td>
<td>38 (45)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No</td>
<td>293</td>
<td>85</td>
<td>64</td>
</tr>
<tr>
<td>No (%) affected</td>
<td>224 (76)</td>
<td>54 (64)</td>
<td>42 (66)</td>
</tr>
</tbody>
</table>

Discussion

The possibility that infant feeding affects the risk of subsequent allergy can be expressed as three alternative hypotheses. Firstly, cows’ milk (and perhaps certain other foods) in early life may be specifically allergenic; secondly, any food other than breast milk may promote allergic disease; and thirdly, breast milk may be specifically protective. The present study tests the first hypothesis by means of a randomised controlled trial, and provides observational evidence on the third hypothesis; it cannot address the second hypothesis because of the rarity of exclusive breast feeding in this population. A recent attempt was made to test the second hypothesis in a controlled trial, but without success in that exclusive breast feeding occurred to the same extent in the intervention and control groups. There was, however, less eczema in breast fed infants, supporting the third hypothesis. An earlier controlled trial tested the first hypothesis: cows’ milk was replaced by soya milk, and egg, wheat, and beef were excluded until the children were 7 months old. Ten years later the intervention group had significantly less asthma and allergic rhinitis than the controls, although the lack of blind assessment leaves open the possibility of bias.

Numerous observational and non-random part intervention studies have been published on the subject. In four recent studies breast feeding, or the avoidance of cows’ milk and early solids, was associated with a lower incidence of allergy, especially in high risk infants. Others have shown little or no relation, however, while one paper reported a positive association between breast feeding and eczema. Earlier studies showed a similar lack of agreement. It is difficult to assess the strength of this evidence as it was seldom clear whether detailed information was collected con-
continuously in a manner which would have shown an occasional milk supplement. Still fewer studies seem to have incorporated blind assessment into the study design, so that some bias may (however unintentionally) have intruded. The present study was designed to avoid these weaknesses as far as was practicable. The feeding diaries provided dietary information from day to day, and compliance appeared to be reasonably good. Admittedly some babies in the intervention group were given cows’ milk protein, a quarter of them having received it on at least one occasion by the age of 13 weeks. But the difference between the two groups in this regard (96% receiving cows’ milk in the control group compared with 26% in the intervention group) was such that an important protective effect of cows’ milk avoidance seems very unlikely, particularly in view of the fact that eczema and wheezing occurred more frequently in the intervention group. Some mothers may of course have forgotten to record certain foods, but most of them seemed to take the study seriously. Although the mothers in the intervention group were advised to restrict their own milk intake, the study was not designed to test the effect of maternal antigen avoidance, which may be important in the prevention15 and treatment16 of infantile eczema.

The diagnosis of eczema is inevitably subjective, and it is possible that another physician might have diagnosed some of the rashes differently. But the infants were all seen by the same physician, whose criteria of diagnosis were at least consistent. Furthermore, it is remarkable that the one year incidence of eczema (38%) was precisely the same as that reported in the recent study of very similar design conducted in Bristol.7 The clinical assessment was indeed blind and the physician remained unaware of the infants’ allocation within the trial and of their actual feeding history, so that diagnostic bias was excluded.

It was not possible to conduct the trial in a double blind manner, nor to control everything that the mothers gave their babies. Inevitably they knew which group they were in, and their behaviour may have been influenced in unforeseen ways by the offer and delivery of free formula. One such effect was the lower incidence of breast feeding in the intervention group. When this tendency was allowed for there was still no difference between the two randomisation groups in respect of eczema, wheezing, or nasal discharge. But the possibility must be recognised that other unsuspected biases may have operated.

The findings so far give no support to the belief that withholding cows’ milk reduces the risk of allergic disease. It is of course possible that cows’ milk and soya milk are equally allergenic. Soya allergy is known to occur,17 18 and it may be that if some other milk substitute had been used the incidence of allergy would have been reduced. In view of the evidence from some of the earlier studies, it seemed reasonable to assume that soya milk was likely to be less allergenic than cows’ milk. But perhaps the allergenicity of cows’ milk formulae has been sufficiently reduced in the last 30 years for all advantage of soya to disappear. These results relate only to the first year of life; the infants are being followed up to see whether an effect appears in the future, as might be expected from the trial of Johnstone and Dutton.5 The soya milk did appear to cause more diarrhoea, napkin rash, and thrush, and while these conditions were not usually serious they have to be considered as disadvantages to be weighed against any potential (and uncertain) reduction in allergic disease. The associations between these three symptoms suggest that the effects of soya milk upon them may be interrelated; apart from the fact that diarrhoea aggravates napkin rash, the mechanisms of these effects can only be conjectured.

A randomised controlled trial provides more reliable evidence on aetiology than does an observational study. Some caution is therefore called for in interpreting the observed associations in this study that were not part of the randomisation design. Mothers who choose to breast feed or delay the introduction of various foods to their infants’ diets may differ from other mothers in various ways relevant to the risk of allergic disease. With this proviso the infants can be regarded as constituting a cohort in which the determinants of allergy can be studied prospectively.

Breast feeding was clearly associated with a halving of the incidence of wheeze, and a significant reduction in diarrhoea. The possible immunological basis of these effects will be discussed in a further communication, but obviously the mechanism may not just involve allergic disease. There is some evidence that breast feeding reduces the risk of respiratory syncytial virus infection.19 The duration of breast feeding did not seem so important in relation to wheezing as whether or not the infants had been breast fed at all. Relatively few babies were breast fed for six months, and even fewer were exclusively breast fed for as long as eight weeks, other foodstuffs (particularly fruit juice) being introduced early in most cases. It therefore seems likely that even small quantities of breast milk have a positively protective effect irrespective of other foods being given. If the skin tests are taken to represent allergy to foods, egg may well be involved in infantile eczema, as other workers have sug-
gested, although the age at which it was introduced seemed to be unimportant. The observation that wheezy children tended to have received wheat or rye protein earlier than others may be relevant; wheat protein has been suspected as potentially allergenic, and it is antigenically very similar to grass pollen, a major culprit in allergic disease. The fact that beef was introduced later on average to the diet of wheezy infants was presumably fortuitous, as it is difficult to see how beef could be protective.

It seems reasonable to conclude that breast feeding appears to be highly advantageous, and that no evidence has so far emerged to suggest that soya milk is better than cows' milk in regard to the risk of allergic disease. We shall continue to follow up these babies to see whether there is any evidence of long term benefit of early avoidance of cows' milk.

We are very grateful to Miss DM Gratton and Mr HR Elliott for permission to study their patients; to Dr M Cohen and Dr MJ Maguire for their support and encouragement; to the staff of Merthyr General and Aberdare General Hospitals for ascertaining that the babies received the correct milk; to Wyeth Laboratories for financial support and supplies of Wysoy milk; and to the Welsh Scheme for the Development of Health and Social Research for a financial grant.

References


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Accepted 17 November 1987
Infant feeding and allergy.

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Arch Dis Child 1988 63: 388-393
doi: 10.1136/adc.63.4.388

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