

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 foodstuffs. 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 invalidated 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 2×2 χ^2 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 infants 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 information 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 infants 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 breast feed 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

Table 1 *Infants admitted and excluded*

No of women recruited	527
No of twin births	6
No of total possible infants	533
Exclusions (% of possible subjects)	
Abortion, stillbirth	14 (3)
Birth weight <2000 g	5 (1)
Non-cooperation	9 (2)
Uncertainty regarding randomisation	10 (2)
Outside area	8 (2)
Total No excluded (%)	46 (9)
No (%) of infants admitted to trial	487 (91)

Table 2 *Certain characteristics of intervention and control groups*

	Intervention group (n=238)	Control group (n=249)
Mean maternal age (years) (last birthday)	25.2	24.7
No (%) with smoker in house	118 (51)	129 (54)
No (%) from non-manual social class	66 (28)	53 (22)
No (%) from manual social class	131 (56)	139 (57)
No (%) of students/unemployed	37 (16)	51 (21)
No (%) of firstborn	91 (38)	104 (42)
No (%) of boys	119 (50)	137 (55)
Mean birth weight (g)	3320	3350
No (%) ever breast fed	78 (33)	107 (43)

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

Food	Group	No infants	Cumulative percentage of infants having received food				
			Week 1-4	Week 5-13	Week 14-19	Week 20-26	Week 26+
Cows' milk	Intervention	238	11	26	44	61	100
	Control	249	91	96	98	99	100
Egg	Intervention	236	0	9	33	61	100
	Control	244	0	26	65	84	100
Wheat/rye	Intervention	236	1	56	85	95	100
	Control	244	8	64	90	97	100

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 4 Incidence of certain conditions during first year according to allocation in trial

Condition	Intervention group		Control group		Significance level
	Total No	No (%) affected	Total No	No (%) affected	
Eczema	228	94 (41)	233	80 (34)	NS
Wheeze	232	84 (36)	242	80 (33)	NS
Nasal discharge	228	96 (42)	232	104 (45)	NS
Thrush	232	118 (51)	242	97 (40)	$p < 0.05$
Diarrhoea	232	167 (72)	242	161 (67)	NS

Table 5 Duration of breast feeding and incidence of wheeze, nasal discharge and diarrhoea in first year of life

Symptom	Duration of breast feeding (weeks)				Any breast feeding	All infants
	0	<1-4	5-25	26+		
Wheeze						
Total No	293	85	64	40	189	482
No (%) affected	125 (43)	20 (24)	10 (16)	11 (28)	41 (22)	166 (34)
Nasal discharge						
Total No	282	85	63	38	186	468
No (%) affected	132 (47)	38 (45)	21 (33)	13 (34)	72 (39)	204 (44)
Diarrhoea						
Total No	293	85	64	40	189	482
No (%) affected	224 (76)	54 (64)	42 (66)	15 (38)	111 (59)	335 (70)

group to breast feed in comparison with the intervention group, the incidence of eczema, wheeze, nasal discharge, and diarrhoea in the two randomised groups was compared after adjusting for breast feeding.⁶ No differences approaching significance were found for any of these conditions. When social class and the presence of smokers in the house were taken into account, breast feeding was still negatively associated with wheezing and diarrhoea. Details of these and of other related factors will be published separately.

The feeding diaries were examined to see whether various foods had been introduced at an earlier age for infants who developed eczema compared with those who did not. No difference was found in the ages at which milk, wheat and rye, egg, beef, other meat, or fruit had been introduced. For the whole cohort of infants, the median week at which each foodstuff was introduced was as follows: cows' milk protein, week 2; wheat or rye, week 12; egg protein, week 20; beef, week 16; other meat, week 16; fruit (usually as juice), week 7; most had not received fish by 26 weeks. Infants who wheezed tended to have received wheat or rye protein significantly earlier, and beef significantly later, than infants without a history of wheezing ($p < 0.05$ using the Wilcoxon rank sum test in each case).

The results of the skin tests at one year were examined according to whether the infants did or did not acquire eczema at some time during their first year of life. The only food antigen which was associated with eczema was egg, for which a positive skin test (weal of 3 mm diameter or more) was obtained in 26 out of 177 babies with a history of eczema (15%), compared with seven out of 288 without eczema (2%) ($p < 0.001$). No other foodstuff produced a positive reaction in more than three infants in either the eczematous or the non-eczematous group.

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.⁷ There was, however, less eczema in breast fed infants, supporting the third hypothesis. An earlier controlled trial tested the first hypothesis⁵: 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.⁸⁻¹¹ Others have shown little or no relation, however,^{12,13} while one paper reported a positive association between breast feeding and eczema.¹⁴ Earlier studies showed a similar lack of agreement.² It is difficult to assess the strength of this evidence as it was seldom clear whether detailed information was collected con-

tinuously 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,²⁰ 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.

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