

Current topics

Does infant feeding affect the risk of allergy?

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SUMMARY For nearly 50 years the hypothesis has been debated that withholding cows' milk from babies reduces the risk of allergic disease. Numerous studies have been conducted of varying design, size, and quality, and with conflicting results. Evidence tends to favour the hypothesis, but the only firm conclusion that can be drawn is that random controlled trials with blind assessment are needed to settle the issue.

In 1936 Grulee and Sanford¹ wrote with regard to infantile eczema, 'We believe, however, that the effect of diet on these infants, once so stressed, has been largely lost sight of recently'. They then described a study designed to answer the question. Forty-seven years later the issue is still hotly debated, despite numerous papers which have appeared on the subject in the meantime. This paper reviews some of the studies which have been conducted, grouped according to their design.

Prospective observational studies

In these studies infants were followed up to see whether the type of feeding bore any relation to the subsequent incidence of disease.

Infants not selected by medical history. The first and largest of all the studies on this topic was that of Grulee and Sanford.¹ In the study 20 061 infants were followed up from birth to age 9 months and a striking association was found between bottle feeding and eczema. In comparison with the breast fed babies, eczema was twice as common in the partially breast fed, and seven times as common in the bottle fed.

Gerrard *et al.*² followed up a consecutive series of 787 babies for 1-3 years. Those with possible allergic symptoms were investigated by repeated challenge tests for cows' milk allergy, the most common symptoms of which were eczema and diarrhoea. Among the babies with cows' milk allergy, the proportion who were 'brought up on the breast for a few months' was similar to that in the cohort as a whole, showing no evidence of any protective effect of breast feeding. The authors did not distinguish between exclusive and partial breast feeding nor did

they define 'a few months', although they did show that symptoms often began within a week of the baby's first introduction to cows' milk, even as an occasional supplement.

Saarinen *et al.*³ followed up 256 infants for 3 years. They found fewer atopic diseases in those solely breast fed for 6 months than in those given cows' milk before 2 months, but the difference was significant only in the subgroup with an atopic family history. Otherwise the paper tended to over-interpret the results; thus $P < 0.10$ was termed significant.

Jakobsson and Lindberg⁴ followed up 1079 infants during the first year of life. Symptoms which could have been due to allergy (including gastrointestinal disturbances, eczema, and recurrent bronchitis) were investigated for cows' milk allergy by repeated withdrawal and challenge, and 20 cases were finally diagnosed. The mean duration of exclusive breast feeding was 13 weeks in these infants compared with 12 weeks in the others, implying no relationship with milk allergy. But in 751 of the cohort the information was obtained solely from clinic and hospital records, and was almost certainly incomplete.

A birth cohort of 1123 babies was followed up for 2 years by Fergusson *et al.*⁵ Infantile eczema was associated with early solid feeding and the risk was proportional to the number of different foods in the first 4 months; there was no specific effect of breast feeding *per se*.

Hide and Guyer⁶ followed up 843 infants for 2 years. Breast feeding was associated with a reduced incidence of allergy overall, and of asthma and bronchitis in those without parental atopy. No relationship with eczema was found.

A preliminary report by Golding *et al.*⁷ has the distinction of providing the only evidence that breast feeding actually increases the risk of eczema. A national cohort of 13 135 children was followed up for 5 years and the parents were asked about eczema, asthma, and wheezing. Breast feeding was positively associated with eczema ($P < 0.01$) after standardising for social class. No relationship was found between feeding practice and asthma or wheezing.

Juto *et al.*⁸ followed up 70 infants for one year and reported a favourable effect of breast feeding. The method of enlisting the subjects was perhaps open to bias: out of 400 eligible mothers only 68 agreed to participate, and an extra 2 volunteered 'by their own initiative' when their babies were 3 months old. Babies who were breast fed for longer than a month had significantly lower 'symptom scores' than the others at both 6 and 12 months. These scores comprised various symptoms, chiefly eczema, wheezing, and diarrhoea, plus others that were not necessarily allergic; an effect on allergic status was suggested in that the bottle-fed babies had a higher lymphocyte responsiveness, although this was unrelated to symptom scores.

Infants selected by medical history. Danaeus *et al.*⁹ followed up 36 children of atopic mothers for 2 years from birth and found clear or possible atopic symptoms in 18 of them. There was no relationship between the development of allergic symptoms and the time that artificial feeding started.

Kaufman and Frick¹⁰ identified 94 infants who were born to allergic mothers and followed them up for 2 years. Asthma developed in 10 out of 56 bottle fed and in 2 out of 38 breast fed infants ($P < 0.06$). The authors said that their results showed clearly that breast fed infants were less likely to develop asthma or atopic dermatitis than bottle fed infants. This conclusion is questionable regarding asthma and entirely unsupported by data regarding atopic dermatitis. They also compared strangely-defined subsets, with dubious consequences.

In a preliminary communication Lucarelli *et al.*¹¹ reported a follow-up study of 75 infants born to atopic parents. The incidence of atopic dermatitis was significantly lower in the breast fed group ($P < 0.01$).

Gordon *et al.*¹² identified 250 infants with a history of eczema or asthma in a parent or sibling. On following up the infants for 2 years they found no difference in the incidence of eczema or asthma between babies who were breast fed and those who were bottle fed.

A different kind of follow-up study, concerned with the prognosis rather than the incidence of asthma, was conducted by Blair.¹³ He followed up

244 asthmatic children for longer than 20 years and found that those who had been breast fed for at least 8 weeks had on average an appreciably better prognosis than those who had never been breast fed. Breast feeding even for less than a week seemed to confer some prognostic advantage, at least for the first 5 years; no data were presented on the effects of breast feeding for 1–8 weeks.

In a preliminary report, Cogswell and Alexander¹⁴ described a 3 year follow-up study of 80 infants with a family allergic history. They 'found that babies breast fed for over 3 months had a slightly greater incidence of eczema and positive cutaneous allergy tests than did babies fed on cows' milk alone', and attributed the difference to food antigens in breast milk. But the numbers were small—eczema occurred in 11 out of 23 babies breast fed for 3 months and in 5 out of 13 never breast fed—so that no conclusions should be drawn about the relative incidence of eczema in the two groups.

Comment

The main drawback to this type of study is that the mothers who decide to breast feed are likely to differ from other mothers in ways which could conceivably affect their children's risk of allergic disease. The original study by Grulee and Sanford is especially important, not only because of its size but because at that time a relationship between bottle feeding and eczema was not generally suspected, so that the mothers were presumably unbiased in their decisions about breast feeding and in their reporting of it. The other studies showed conflicting results, one actually suggesting a harmful effect of breast feeding which the authors attribute to chemical contaminants in breast milk. The full report of this study may shed some light on this puzzling observation; meanwhile it seems reasonable to say that the conclusions of Grulee and Sanford have been challenged but not rejected.

Retrospective studies

Such studies enquired into the feeding history of allergic patients and a control group.

In Murray's survey¹⁵ of 321 Canadian primary schoolchildren the mothers were asked whether their children had received any food other than breast milk during the first month of life. Among the children with an immediate family history of allergy, exclusive breast feeding was significantly associated with a lower prevalence of nasal-secretion eosinophilia, which was regarded as a diagnostic sign of allergic rhinitis. No significant association was found in those without a family history.

Stintzing and Zetterström¹⁶ found that 22 out of

25 infants with cows' milk allergy had received cows' milk during the first month of life compared with (apparently) 25 out of 47 control infants ($P < 0.01$). The infants with cows' milk allergy were aged 5–26 weeks whereas the controls were all aged 12 months when their mothers were interviewed, so the information was probably less accurate for the control group. But cows' milk allergy was still associated with exposure to cows' milk during the first week of life as recorded in the hospital notes, which were available in every case for this period ($P < 0.05$).

Kramer and Moroz¹⁷ conducted a retrospective case-control study in 470 children aged 1 month to 20 years attending a dermatology clinic. The children were classified as having atopic eczema (cases) or a non-atopic skin condition (controls). A history of feeding in infancy, together with other details, was then obtained 'blind'. The raw data showed a small positive association between breast feeding and eczema, but this disappeared when age, race, and ethnic origin were allowed for as confounding factors. There was then no significant association, positive or negative, between breast feeding and eczema.

Comment

In addition to other weaknesses of the observational method, the retrospective approach has the disadvantage of relying on the mother's memory. Stintzing and Zetterström showed that this can be very unreliable: in 8 out of 19 cases for whom hospital notes recorded an early milk feed, the mother did not remember it at 12 months. It is therefore very likely that some early supplementary feeds were not reported in the study by Kramer and Moroz despite their attempts to check the mothers' accounts. Thus the first two retrospective studies support the hypothesis under consideration, and the third does not provide strong evidence against it.

Random controlled trials

Random allocation of mothers to the intervention and control groups ensures that the two groups are entirely comparable. It is, however, very difficult to ensure compliance in the intervention group, while some of the control mothers may follow spontaneously the 'intervention' regimen.

In Johnstone and Dutton's trial¹⁸ 292 infants with a family history of allergy were randomly chosen to receive either a soya preparation or a cows' milk formula. Only 13 in the soya group and 12 in the cows' milk group were breast fed, and they were given their respective preparations as supplementary feeds or on weaning. The degree of compliance was

exceptional; only 8 dropped out of the soya group and 6 out of the control. Otherwise no child in the soya group received milk, egg, wheat, or beef before age 7 months. Ten years later 235 of the children were examined by a physician. Allergic disease had occurred in 18% of the soya group and in 50% of the controls ($P < 0.0001$), the difference being due to asthma and perennial allergic rhinitis. No significant difference occurred in the incidence of eczema, which was very low in both groups (6 cases in the soya and 2 in the control groups).

In the trial by Brown *et al.*¹⁹ 379 unselected babies were randomly given to soya or cows' milk and followed up for one year. Compliance was poor; only 46% of those allocated to the soya diet actually started using it, and the drop-out rate after that was not stated. Allergy occurred in 10% of those allocated to the soya group and in 13% of the controls; the difference was not statistically significant.

A much smaller trial among specially high-risk infants was conducted by Kjellman and Johansson.²⁰ Forty-eight infants with a bi-parental history of atopy were randomised to receive soya or cows' milk from weaning to age 9 months. Two-thirds of the children developed atopic disease and there was no significant difference between the groups.

Comment

The random controlled trial is undoubtedly the best way of investigating a hypothesis of this kind. These three trials gave conflicting results, but the second was invalidated by non-compliance, the third was very small, and in none was the assessment apparently 'blind'. In other respects the first trial was a remarkable achievement and arguably the best study so far. Its results provide important evidence for the hypothesis, although the lack of blind assessment leaves open the possibility of bias.

Other intervention studies

These studies represent a compromise between the observational and intervention methods.

Glaser and Johnstone²¹ selected 96 infants who had an allergic parent or sibling. Cows' milk was withheld from these infants from birth, all but 8 being given a soya-based substitute. They were followed up for periods varying from 7 months to 10 years, and their incidence of allergy was compared with that occurring in two historical control groups. One of these comprised siblings of the experimental group while the other was a group with family histories similar to those of the experimental subjects. Major allergy occurred in 15% of the experimental group and in 64% and 52% of the control groups respectively. The sibling control group was inevitably

weighted with children who had allergic disease in that an allergic sibling was one of the criteria used for selecting the index cases, thereby invalidating comparisons made with this group.

Another part-intervention study was that of Halpern *et al.*²² on 1753 unselected infants. Only a subgroup was randomly fed breast milk, soya, or cows' milk; the original groupings were not adhered to in the analysis but the babies were reallocated according to what they actually received. Breast fed, soya fed, and milk fed infants had a similar incidence of allergy, which was not apparently assessed 'blind'. The onset of allergy occurred on average 6 months later in the breast fed group than in the cows' milk group ($P < 0.05$), the soya group being intermediate.

The small part-intervention study by Matthew *et al.*²³ started with 62 infants who had a parental allergic history. Twenty-three mothers volunteered for and adhered to a dietary regimen for their infants from which dairy products, fish, and eggs were excluded for 6 months, the babies being breast fed with some soya supplements. Nineteen mothers who declined this advice formed the control group and the others were excluded because of non-compliance. The incidence of eczema was significantly lower in the 'regimen' groups at both 6 and 12 months. The diagnosis of eczema was not 'blind' with regard to dietary grouping.

It is not clear what degree of intervention entered into the study by Chandra²⁴ which may be conveniently considered here. He compared 37 infants who were exclusively breast fed for at least 6 weeks with 37 bottle-fed infants; all the infants had an older sibling with atopic disease. They were examined at 3-monthly intervals for the first year and then 6 monthly until age 3 years. Eczema occurred in 4 breast fed and 21 bottle fed infants ($P < 0.001$), while 1 breast fed infant and 8 bottle fed infants had recurrent wheezing ($P < 0.01$), suggesting a protective effect of breast feeding.

Comment

Of these four studies, three showed a relation between cows' milk and allergic disease, and one showed an apparent effect on the age of onset of allergy. It is difficult to assess the strength of this evidence, but so far as it goes it tends to support the hypothesis.

Discussion

Thus in 13 of these 24 studies allergic disease was positively associated with cows' milk or mixed feeding in early infancy; in one it was positively associated with breast feeding; while 10 showed no convincing relationship with infant feeding. Other

papers are known to be in preparation, confirming²⁵ or failing to confirm²⁶ an association between cows' milk and allergy. The 24 studies differ in size and quality and their results should not be given equal weight. Very few state that the clinical assessment was carried out 'blind' with regard to the feeding history, so some bias may have unintentionally affected the findings. The mothers who opt for different feeding practices are likely to differ in various ways which may affect their offsprings' risk of disease. Thus in Halpern's study the babies with an allergic family history (and therefore a greater liability to allergy) were much more likely to be fed on breast or soya milk than were babies with no family history. Similarly Brown's special diet was most readily accepted among the families with bilateral allergic backgrounds. Presumably if mothers with an allergic family history now believe that cows' milk increases the risk of allergy they will tend to avoid it for their babies. This may explain the paradoxical finding by Golding *et al.* of an association between allergy and breast feeding.

A serious defect in many studies is the failure to monitor early supplementary feeds in breast fed infants. It seems likely that quite small amounts of foods could influence the development of allergy. Mothers can hardly be expected to remember (or even to have known) everything that their babies received, especially while they were in the maternity hospital. Considerable reservations are needed in assessing studies if the relevant information was obtained long afterwards. Intervals of 6 weeks,⁶ 3 months,¹¹ 6 months,¹² a few years,¹⁵ and up to 20 years¹⁷ occur in different studies; several authors do not state whether, when, or how information was obtained about supplementary feeding. The only reliable information is that collected at the time as part of a system designed in advance to detect the occasional milk supplement.

Overall it may be concluded that the issue is not settled but the balance of evidence tends to favour the hypothesis that giving infants cows' milk or solids increases the risk of allergic disease. There seems little point in mounting any more observational studies. Two or three random controlled trials, carefully conducted with reasonable numbers and 'blind' assessment, should give a convincing answer to our question. Otherwise, if papers continue to be published at the current rate, we shall end up in a state of total confusion.

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