

# Development of atopic disease after early administration of cow milk formula

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We prospectively studied the incidence of atopic disease in healthy term infants with a birth weight between  $-1$  and  $-2$  SD who were fed a cow milk formula during the first few days of life. A total of 216 infants were randomized to receive either early feeding with formula before normal breastfeeding was started ( $n = 112$ ) or "normal feeding" with breastmilk ( $n = 104$ ). Symptoms of allergy developed in 18 % of the infants before 18 months of age in the formula fed group, as compared to 33 % in the breastfed group ( $P < 0.05$ ). The difference was confined to the group of infants with a history of allergy in two family members. Thus, 11 % of the formula-fed infants developed allergy symptoms, as compared to 61 % of the control infants ( $P < 0.01$ ). Our study implies that early feeding during the first days of life with a cow milk formula, before the introduction of breastmilk, may reduce the incidence of allergy symptoms before 18 months of age in infants with a family history of allergy.

*Key words:* allergy; cow milk; early feeding.

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Much controversy still exists concerning the type of feeding and the development of allergy (2). Several authors have shown that the introduction of a cow milk formula during the first months of life has a detrimental effect (4, 9, 13). Others (3, 5, 17) have failed to show any difference in the development of allergy symptoms related to the type of feeding. During the late 1970s, some reports suggested that the infants might suffer a more harmful effect if they were given one or a few doses of a foreign protein during the *first weeks* of life (15).

At the beginning of the 1970s early feeding of a cow milk formula to infants with a moderately low birth weight was introduced on our maternity wards. This was done in order to reduce the starvation period for these infants and, consequently, the risk of hypoglycemia and hyperbilirubinemia.

In evaluating the possible advantages or disadvantages of this practice, we also carried out a prospective study on the development of allergy. The latter forms the basis of this report. To

our knowledge no previous prospective study has been published about briefly giving infants a cow milk formula almost immediately after birth and studying its effect on the development of allergy symptoms.

## MATERIAL AND METHODS

Infants born at Danderyd Hospital between June 1981 and January 1983 with a birth weight between  $-1$  SD and  $-2$  SD (14), a gestational age of 37–42 weeks, and without any major initial neonatal problems, participated in the study. Cord blood for IgE determinations were taken. Following a predetermined protocol, the maternity wards changed their feeding routine the first day of every other month between breastfeeding and early feeding with an adapted cow milk formula (Milkotal®). The infants who were given formula (F) as their first meal at 6 h of age, thereafter received increasing amounts of this formula every 4 h up to a maximum of 60 ml per meal. As soon as the

mother's lactation started, the cow milk formula was gradually replaced by breastmilk. The infants who were given breastmilk (B) received their first meal when the mother's breastmilk production started and no effort was made to adjust the amount of each feeding. During their stay on the maternity ward standard blood tests were regularly taken to exclude the presence of hypoglycemia and hyperbilirubinemia. The parents also filled in a questionnaire about the presence of allergy in the family. No effort was made to standardize the age at which the infants were weaned or given solid foods.

The infants were then regularly followed up by the pediatrician at the child welfare center. About 20 pediatricians participated in the study and were unaware of the feeding regimen. They examined each child at the ages of 3, 6, and 18 months, scrutinized the history, and then filled in a detailed form concerning feeding and allergy, if any. Obvious and probable symptoms of atopic disease (11), such as atopic eczema, asthma or wheezing on more than two occasions, allergic urticaria, recurrent gastrointestinal allergic reactions to the same food, such as colicky pain, vomiting or diarrhea, were recorded as allergy symptoms. No diagnostic "challenges" or other tests were performed, neither was the incidence of specific food allergy registered. During the follow-up period notes were also made, in accordance with the protocol, at 3, 6, and 18 months, about the duration of breastfeeding.

The F-group comprised 112 infants and the B-group 104 infants. One infant with a family history of cow milk allergy was transferred to the B-group. Three infants in the F-group and six in the B-group were lost to follow-up at 18 months. Three of the latter were excluded because they had been given one or more meals with formula outside the schedule. Thus, at 18 months 109 infants (59 boys, 50 girls) in the F-group and 98 (49 boys, 49 girls) in the B-group completed the study.

The family history for allergy was evaluated. A *single* heredity meant that the infant had one parent or a sibling with a positive history of allergy. A *double* heredity meant that both par-

ents, or one parent and a sibling, had a positive history of allergy, as defined by Kjellman (11). In the F-group 31 children (29%) had a single and 19 (17%) a double heredity. In the B-group 39 infants (40%) had a single and 18 (18%) a double family history of allergy. A single maternal, a single paternal and biparental heredities were also noted.

Serum IgE concentrations in cord blood were determined by the Phadebas® PRIST standard method (Pharmacia Diagnostics, Uppsala, Sweden), using undiluted samples, in 82 infants in the F-group and 72 infants in the B-group. The IgE level was classified as *high* when the concentration was above 0.6 kU/l ( $> + 1$  SD in cord blood (10)), and as *normal* when the concentration was 0.6 kU/l or less.

The Chi-square test and Fisher's exact test were used in the statistical analyses of the results.

A protocol for the study was accepted by the Ethics Committee at Karolinska Institute. After delivery, the mothers were informed verbally and in writing about the study; they were told that any positive or negative effects of their infants' diet would be evaluated during the following 18 months. Their informed consent was thus obtained.

## RESULTS

The durations of breastfeeding were similar in the two groups. The only difference – and it was not significant – was found during the first 2 months when a slightly higher proportion of infants in the B-group were only fed breastmilk. After 2 months of age there was no difference between the two groups (Fig. 1).

When comparing infants in the two groups with or without a family history of allergy, no difference was found in durations of breastfeeding. This was also true of the subgroups with symptoms of allergy. The number of infants who were fed only breastmilk for 4 months or more were evenly distributed in both groups. The only tendency noted was that the infants in the B-group who developed allergy symptoms had been breastfed for a slightly longer period. Thus the age at the introduction of cow milk

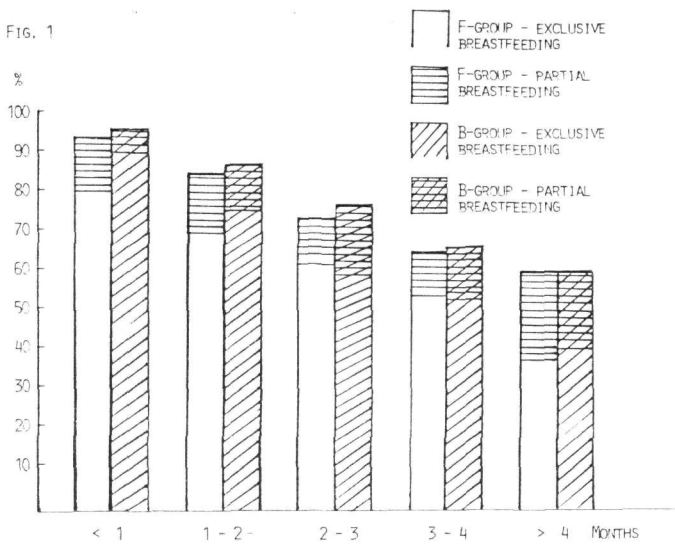


Fig. 1. Percentage of infants who were partly or wholly breastfed at different ages in groups F and B. F: fed formula early; B: only fed breastmilk.

protein after the first week of life was similar in the two groups (Table 1). At the end of the follow-up period, significantly more infants in the B-group had shown obvious or probable symptoms of atopic diseases, such as atopic eczema, wheezing or asthma, urticaria, gastrointestinal allergy, as well as multiple symptoms of allergy (Table 2). A total of 20/109 (18%) in the F-group, compared to 32/98 (33%) in the B-group developed one or more allergy symptoms ( $P < 0.05$ ). No cluster-

ing of infants with a diagnosis of allergy was confined to any particular pediatrician, nor was there any cluster of symptoms attributable to the season of birth. Among the infants with a negative family history for allergy there were more infants who developed allergy symptoms in the B-group than in the F-group 11/41 (27%) vs. 10/59 (17%) (Table 2). In the groups with single heredity the frequency for infants with allergy symptoms was similar in the F-group and B-group, 8/31 (26%) vs. 10/39 (26%). Among those with double heredity, 2/19 (11%) in the F-group, compared to 11/18 (61%) in the B-group, developed allergy symptoms ( $P < 0.01$ ). In 53 of the 207 infants no samples were taken for IgE determinations, either because of technical difficulties or failure to obtain a specimen, especially when there was a heavy workload on the delivery ward. Thus cord IgE levels were determined in only 154 infants and were found to be high in 12 (8%). The proportions of infants with high values, normal values and “drop-outs” were similar in the F-group and the B-group. Most of the allergic infants had normal IgE values, but the incidence was higher in the B-group than in the F-group, 23/67 (34.3%) vs.

Table 1

| Mean duration of breastfeeding, exclusive (E) or partial (P), in relation to family history and allergy symptoms. Percentage exclusively breastfed ≥ 4 months is also given |                  |          |          |      |          |          |      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|----------|----------|------|----------|----------|------|
| Family history of allergy                                                                                                                                                   | Allergy symptoms | F-group  |          |      | B-group  |          |      |
|                                                                                                                                                                             |                  | E months | P months | %    | E months | P months | %    |
| Negative                                                                                                                                                                    | present          | 3.38     | 5.55     | (44) | 3.35     | 5.60     | (50) |
|                                                                                                                                                                             | absent           | 3.34     | 5.51     | (49) | 3.45     | 5.25     | (48) |
| One relative                                                                                                                                                                | present          | 3.50     | 6.10     | (38) | 3.60     | 5.60     | (50) |
|                                                                                                                                                                             | absent           | 2.86     | 4.77     | (44) | 3.13     | 4.89     | (52) |
| Two or more relatives                                                                                                                                                       | present          | 2.00     | 5.50     | (50) | 3.50     | 5.45     | (64) |
|                                                                                                                                                                             | absent           | 2.63     | 3.93     | (38) | 2.36     | 4.14     | (29) |

F: fed formula early; B: fed only breastmilk

12/75 (16.0 %) ( $P < 0.05$ ). The same tendency, though not significant, was found among those whose IgE values were not measured. Only a few of the allergic infants had high IgE values. Of the five allergic infants with a high cord IgE level three were in the F-Group and two in the B-group (Table 3).

DISCUSSION

Like most other investigators we have recorded the family history of allergy on the basis of the parent's answers to a questionnaire and have not tried to verify this information. However, the frequencies of an allergy history single or double, as well as of high IgE-levels, were simi-

lar in the F- and B-groups. Thus, in this sense the two groups may be considered comparable. The allergy symptoms recorded in infancy are not entirely reliable. The diagnoses, however, were made by different pediatricians who were not aware of the feeding procedure on the maternity ward, and therefore there should be no bias in their judgements. Moreover, no particular allergy symptom was diagnosed more often by any particular pediatrician. The frequency of "drop-outs" was very low.

The type of feeding given during the first week of life was carefully documented on the maternity wards. The duration of breastfeeding during infancy was recorded by regular questioning at the child welfare center. There were

Table 2  
Number of children with allergy symptoms correlated to type of family history of allergy and type of feeding in early neonatal period

| Symptoms of allergy               | Positive (one relative) |                     | Positive (two relatives) |                     | Negative            |                     | Total                |                     |
|-----------------------------------|-------------------------|---------------------|--------------------------|---------------------|---------------------|---------------------|----------------------|---------------------|
|                                   | F-group<br>(n = 31)     | B-group<br>(n = 39) | F-group<br>(n = 19)      | B-group<br>(n = 18) | F-group<br>(n = 59) | B-group<br>(n = 41) | F-group<br>(n = 109) | B-group<br>(n = 98) |
| All infants with allergy symptoms | 8                       | 10                  | 2 <sup>b</sup>           | 11                  | 10                  | 11                  | 20 <sup>a</sup>      | 32                  |
| Atopic eczema                     | 3                       | 6                   | 0                        | 5                   | 7                   | 7                   | 10                   | 18                  |
| Wheezing                          | 2                       | 2                   | 1                        | 3                   | 3                   | 3                   | 6                    | 8                   |
| Urticaria                         | 2                       | 5                   | 1                        | 4                   | 5                   | 2                   | 8                    | 11                  |
| GI allergy                        | 3                       | 1                   | 0                        | 3                   | 1                   | 2                   | 4                    | 6                   |
| Multiple allergies                | 2                       | 4                   | 0                        | 3                   | 4                   | 2                   | 6                    | 9                   |

F: fed formula early; B: fed only breastmilk.  
<sup>a</sup>  $P < 0.05$  ( $\chi^2$ -test). <sup>b</sup>  $P < 0.01$  (Fisher's exact test).

Table 3  
Number of children with allergy symptoms correlated to cord blood IgE level and type of feeding

| Symptoms of allergy               | $\leq 0.6$ kU/l     |                     | $> 0.6$ kU/l       |                    | Not determined      |                     | Total                |                     |
|-----------------------------------|---------------------|---------------------|--------------------|--------------------|---------------------|---------------------|----------------------|---------------------|
|                                   | F-group<br>(n = 75) | B-group<br>(n = 67) | F-group<br>(n = 7) | B-group<br>(n = 5) | F-group<br>(n = 25) | B-group<br>(n = 27) | F-group<br>(n = 109) | B-group<br>(n = 98) |
| All infants with allergy symptoms | 12 <sup>a</sup>     | 23                  | 3                  | 2                  | 5                   | 7                   | 20 <sup>a</sup>      | 32                  |
| Atopic eczema                     | 7                   | 12                  | 1                  | 2                  | 2                   | 4                   | 10                   | 18                  |
| Wheezing                          | 4                   | 8                   | 2                  | 0                  | 0                   | 0                   | 6                    | 8                   |
| Urticaria                         | 5                   | 9                   | 1                  | 0                  | 2                   | 2                   | 8                    | 11                  |
| GI allergy                        | 0                   | 4                   | 1                  | 1                  | 3                   | 1                   | 4                    | 6                   |
| Multiple allergies                | 3                   | 8                   | 1                  | 0                  | 2                   | 1                   | 6                    | 9                   |

F: fed formula early; B: only fed breastmilk  
<sup>a</sup>  $P < 0.05$  ( $\chi^2$ -test)

no differences in the breastfeeding regimens in the two groups that could explain the discrepancies in the results.

The influences of foods other than formulas and other potential causes of allergies, such as common pets and smoking in the families, have not been evaluated. However, there is no reason to suppose that there is any difference in these respects between the F-group and the B-group. The frequency of allergy in the family history in our study (52 %) is considerably higher than in other Swedish studies, which have reported 30–40 %, and may explain the high incidence of allergy symptoms found in our study (6, 12). We have no simple explanation for this slightly higher frequency of family history of allergy.

Children with a double heredity have been considered a special risk-group for the development of allergy symptoms. However, our results seem to show that in this group a very early period of feeding with cow milk formula significantly reduces the risk.

In a retrospective study Stintzing & Zetterström (15) showed that formula given occasionally during the first 4 weeks induced cow milk allergy in some infants. However, most of the infants may have received breastmilk before the introduction of formula, as this was given in most cases on the fourth day. Moreover, it was not given regularly. Other studies have concerned the effects of early versus late introduction of different foreign proteins on the development of allergy symptoms (3, 4, 5, 9, 13, 17). Experience shows that a late introduction of cow milk protein reduces the risk of developing allergy in high-risk children (2). However, our results indicate that an early initial, but transient, feeding with cow milk protein reduces this risk.

So far as we know, the present study is the only one in which a regular regimen of cow milk formula during the first days of life, has been followed by breastfeeding. No relation was found between the duration of breastfeeding and the allergy symptoms. Thus, the reason for the lower frequency of allergy symptoms in the formula-fed group with double heredity may be found in the feeding regimen.

Jarrett (14) in experimental studies in mice showed that excessive amounts of antigen suppress rather than induce the IgE response when the T-cell function is normal. Juto (8) in a study of infants, reported clinical data which support this finding. Jarrett, moreover, showed that this mechanism also operated in T-suppressor cell-deficient animals. It has also been reported that the development of atopy results from a disturbance in the balance between different sub-populations of T-cells (16).

In our study formula was given before the infants were fed breastmilk. This resembles the method used by Jarrett in her study in mice (7). Jarrett found that the administration of high doses of egg albumin, even in a high-risk mice population, suppressed IgE production. Although we have not serially determined the concentrations of serum IgE or cow milk-specific IgE in the infants, our study suggests that the same mechanism may also operate in humans. Another factor of importance may be that the F-group infants avoided "primary exposure" to their mothers' breastmilk, which may have contained small doses of antigens or lymphokines. According to a recent study by Allardyce & Wilson (1), breastmilk from atopic mothers seems to transfer factors which may increase the IgE synthesis in cord blood lymphocytes. One or the other, or both, of these mechanisms may explain the lower incidence of allergy found in the infants who were put on formula at an early age.

To further evaluate the implications of these results the infants are now being reexamined at the age of 5 years, and a more extensive examination, as well as diagnostic tests, will be performed.

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