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Risk of developing atopic disease after early feeding with cows' milk based formula

D Gustafsson, T Löwhagen, K Andersson

Abstract

A follow up of a cohort of 736 healthy full term children with exposure to cows' milk based formula and breast milk from donors on the maternity ward was performed. The children were divided into three exposure groups according to the feeding patterns on the maternity ward. Group 1 received only mother's milk, group 2 mother's milk and human donors' milk, and group 3 received mother's milk, donors' milk and cows' milk based formula. The children were investigated at 7 years of age, by examining their medical files, and at 11 and 14 years, by questionnaires regarding symptoms of atopic disease.

No significant differences between the three groups at follow up were found in the cumulative incidences of atopic diseases. The amount of formula given did not affect the risk of developing atopic disease. Children with a family history of such diseases ran the same risk of subsequent atopic disease whether they were fed formula or breast milk alone. Cows' milk based formula given on the maternity ward does not seem to increase the risk of developing atopic disease.

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The newborn child is immature as regards certain immunological functions and has a low production of secretory IgA. The child receives large quantities of IgA antibodies in mother's milk, some of which are directed against food proteins in the mother's diet. This creates an 'antigen-avoidance system' by preventing contact between the mucosal lining of the newborn's gut and the food given.[1] In animal models the response of the immunological system of the newborn depends on the dose of foreign protein.[2] The newborn infant has a high macromolecule absorption because the gut mucosa is immature. Hence the administration of even small amounts of foreign proteins may result in activation of the immunological system.[3] A minimal amount of cows' milk secreted in breast milk may result in antigen-antibody complexes in the newborn's blood. The role of this process in the genesis of the later development of conditions such as allergies and infections is reviewed elsewhere.[3]

The clinical importance of the early introduction of cows' milk proteins has been extensively studied, but the results have been conflicting.[4–6] Children with a family history of atopic disease have been shown to run a greater risk of developing atopic symptoms when exposed to cows' milk protein than do children without heredity.[7] However, only a few of the studies performed have focused on the very early introduction of cows' milk formula,[7–9] and for ethical reasons such studies have been difficult to perform on term neonates.[7]

The aim of this study was to evaluate the effect of the administration of cows' milk based formula, given in the maternity ward, for later development of atopic diseases.

Subjects and methods

The investigation was performed in Karlskoga, an industrial town in the middle of Sweden with small social class differences and little industrial pollution. All children were born in the town, were nursed on the local maternity ward during 1970, 1973, and 1976, attended the 1st, 4th, and 7th grades at the compulsory school in 1984; a total of 952 children were included. The children's feeding patterns up to the eighth day of life were determined by examining the files from the maternity ward. The children stayed at the maternity ward from birth up to six to eight days of life. Data concerning supplementary feeding to breast milk after leaving the maternity ward was not collected. The feeding patterns were available for 754 children. No data were available for 198 children, mostly because the files from the maternity ward could not be found or because no notes had been made or because the children had been transferred to a regional paediatric centre. The study group therefore consists of healthy full term children without any apparent abnormalities.

The children were divided into three groups based on the neonatal feeding patterns: group 1=mother's milk only (n=219), group 2= mother's milk and human donor milk (n=277), and group 3=mother's milk, human donors' milk, and cows' milk based formula (n=240). Eighteen infants had feeding patterns that diverged from those of the three groups, some did not get mother's milk at all, some received mother's milk and formula but not donor's milk, and they were therefore excluded. A total of 282 infants born in 1970, 215 born in 1973, and 239 born in 1976 were included. At the time of their birth, the feeding routines were based on a fixed feeding schedule with a meal every fourth hour. If the mother did not produce enough milk, formula or human milk from donors was given without regard to a family history of atopic disease. The donors were other mothers on the ward; their milk was not pasteurised and it was stored in a refrigerator for no longer than 24 hours. The formula used

Örebro Medical Centre Hospital, Sweden, Department of Paediatrics
D Gustafsson

Department of Occupational Medicine
K Andersson

Department of Paediatrics, Karlskoga County Hospital, Sweden
T Löwhagen

Correspondence to:
Dr Dan Gustafsson, Department of Paediatrics, Örebro Medical Centre Hospital, S-70185 Örebro, Sweden.

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was a cows' milk based preparation (Milkotal, Nestlé). No hypoallergenic diets were used. In 1970 only two children received formula, in 1973 there were 35%, and in 1976 there were 68%.

In 1984 the medical files of all the children were examined at the child welfare centres, where all the children were followed up, at the school health units, and at the local hospital. All medical care in the city was provided by the local hospital. When the children were 7 years old the cumulative incidence of asthma, rhinoconjunctivitis, and eczema was determined. The criteria for the diagnosis of asthma was three hospital records showing that the child had had this condition, and for rhinoconjunctivitis and atopic eczema it was the physician's findings at the time of examination.

In 1984 and 1987, questionnaires were sent to the parents about the children's current and previous atopic symptoms, nursing time, family history of atopic disease, etc. Ninety six percent of the parents of 11 and 14 year old children answered the questionnaires. The cumulative incidence of atopic symptoms at 11 and 14 years of age were determined on the basis of the replies. The medical files and the questionnaires were examined without knowledge of the neonatal feeding pattern. The reported time of cessation of breast feeding was validated by notes from the child welfare centre for a subsample (n=47) and was found to be of acceptable quality (r=0·86).

The statistical analyses were based on calculating the crude rate ratio and the 95% confidence interval of the rate ratios.

Table 1 Description of the three milk groups according to birth weight, duration of breast feeding, and family history of atopic disease (n=736)

	Group 1 (n=219)	*Group 2 (n=277)*	*Group 3 (n=240)*
Mean (SD) birth weight (g)	3560 (423)	3521 (509)	3493 (556)
Mean (SD) duration of breast feeding (months)	4·2 (2·9)	4·1 (3·3)	3·9 (3·9)
Family history of atopic disease (%)	33·8	35·0	39·2

Results

The children in the three milk groups were comparable as regards birth weight, duration of breast feeding, and a family history of atopic disease (table 1). The rates of smoking among parents and exposure to animal dander did not differ between the three groups. The cumulative incidence and the crude rate ratios of atopic diseases at the age of 7 years, based on medical files was 9·4% (table 2). The differences between the three milk groups for various types of atopic diseases were not statistically significant.

The cumulative incidence of atopic disease at 7 years of age for children with a family history of atopic disease compared with that for children without a family history is shown in table 3. The incidence was about twice as high in the former group, 14·7% compared with 6·4%. There were no differences in the development of atopic disease between the three feeding groups for children with and without a family history. The cumulative incidence of atopic symptoms at the age of 14 years based on questionnaire responses was 31·4% (table 4). These differences were also

Table 2 Cumulative incidence of atopic disease at the age of 7 years, based on medical files (n=736)

	Group 1		*Group 2*			*Group 3*			*No (%) total*
	No	*Rate ratio*	*No*	*Rate ratio*	*95% Confidence intervals*	*No*	*Rate ratio*	*95% Confidence intervals*	
Asthma	5	1·0	5	0·79	0·2 to 2·7	8	1·48	0·5 to 4·6	18 (2·4)
Rhinoconjunctivitis	9	1·0	10	0·87	0·3 to 2·2	6	0·6	0·2 to 1·7	25 (3·4)
Atopic eczema	9	1·0	13	1·15	0·5 to 2·7	17	1·78	0·8 to 4·0	39 (5·3)
Total									69 (9·4)

Table 3 Cumulative incidence of atopic diseases at the age of 7 years, based on medical files of children with or without a family history for atopic disease (n=736)

	Group 1		*Group 2*			*Group 3*			*No (%) total*
	No	*Rate ratio*	*No*	*Rate ratio*	*95% Confidence intervals*	*No*	*Rate ratio*	*95% Confidence intervals*	
Without family history (n=471)	5	1·0	12	1·66	0·6 to 4·5	12	2·08	0·8 to 5·6	30 (6·4)
With family history (n=265)	11	1·0	15	1·05	0·4 to 2·4	13	0·92	0·4 to 2·2	39 (14·7)

Table 4 Cumulative incidence of atopic disease at the age of 14

	Group 1 (n=213)		*Group 2 (n=190)*			*Group 3 (n=72)*			*No (%) (n=475) total*
	No	*Rate ratio*	*No*	*Rate ratio*	*95% Confidence intervals*	*No*	*Rate ratio*	*95% Confidence intervals*	
Asthma	7	1·0	5	0·80	0·2 to 2·5	3	1·28	0·3 to 5·1	15 (3·2)
Rhinoconjunctivitis	33	1·0	26	0·86	0·5 to 1·5	6	0·50	0·2 to 1·2	65 (13·7)
Atopic eczema	41	1·0	39	1·08	0·7 to 1·8	14	1·01	0·5 to 2·0	94 (19·8)
Total									149 (31·4)

Table 5 Cumulative incidence of atopic disease at the age of 7 years (based on medical files) and 11 years of age (based on questionnaire replies) in relation to the amount of formula given

Amount of cows' milk formula (g)	No	Cumulative incidence: number (%)	
		Atopic disease at 7 years (n=219)	Atopic disease at 11 years (n=217)
10–50	60	7 (11·7)	16 (30·8)
60–125	59	6 (10·2)	15 (28·3)
130–250	54	5 (9·3)	16 (31·4)
≥260	37	5 (13·5)	10 (29·4)

not significant. To evaluate the possible effect of the amount of formula given on the maternity ward on the subsequent development of atopic disease, the cumulative incidence of atopic diseases at the ages of 7 and 11 is related to the dose of formula given. The figures are summarised in table 5. No statistically significant differences could be found.

In order to evaluate the effect of very early formula feeding on the development of atopic disease, the 217 children in group 3 were divided at 11 years of age into three subgroups, according to the day of life the formula was introduced. These results were: formula introduced days 0–1, 23 (21%) had atopic disease; day 2, 16 (16%); and days 3–8, 25 (20%). There were no significant differences.

Only 18 children received formula before breast milk was introduced. The cumulative incidence among these children at 11 years of age was similar to that in the group as a whole.

Discussion

In this study all the children were breast fed and were thus exposed to factors in their mother's milk that could protect them from developing an atopic disease. As these factors are formed by an interaction of immunological 'forces' between the mother and the child,[1] it was desirable that the children who received donor's milk as a supplement should form a separate follow up group. The outcome of this study is based on data from medical files and questionnaires. In medical files only the more obvious symptoms are noted. More discrete symptoms, if not forgotten, may be reported in questionnaires.

The figures presented in this study for a family history of atopic disease are in good agreement with the results of another Swedish epidemiological study.[10] Atopic symptoms was mentioned in the charts of 9·4% of the 7 year old children and in 31·4% of the 14 year old children. Similarly high incidences of atopic disease are reported in other Swedish studies.[10–13] There is no evidence that the healthy full term children who were excluded because of inadequate information about neonatal feeding differed in any respect that might change our conclusions. The statement that the supplementary food was given in a random way is strengthened by the fact that the frequencies of a positive family history of atopy in the three feeding groups were similar. Furthermore, the debate about the possible harmful effects of foreign proteins given at an early age on the maternity ward had not started at the time of the birth of these children.

In some studies a family history of atopic disease was reported to increase the risk of the subsequent development of atopic symptoms when cows' milk was given on the maternity ward.[7 14] We were unable to confirm these results. A family history of atopic disease increased the risk of developing atopic symptoms from 6·4% to 14·7%, This increase, however, was not affected by the kind of food that was given on the maternity ward. Our numbers are too small to permit conclusions regarding children with two parents with a history of atopic disease. It has been suggested that formula has a blocking effect on the immunological system if given before the first meal of breast milk.[8] In our study only 18 children had received formula before breast milk. These children ran the same risk of developing an atopic disease as did the total group. No difference in the development of atopic disease was seen in relation to the day of life when formula feeding was introduced. Small amounts of formula given in the maternity ward have been believed to result in cows' milk sensitisation, and this could be maintained by the cows' milk protein secreted into the breast milk.[14] Despite the evidence suggesting that small doses of foreign proteins may be more likely than larger ones to provoke sensitisation and the development of atopic disease, our data showed no relationship between the dose of cows' milk formula and the subsequent incidence of atopic disease.[2 15]

Despite rather broad confidence intervals for the relative risk this study suggests that the administration of supplements of cows' milk based formula to healthy breast fed term children on the maternity wards does not increase the risk of developing atopic diseases.

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