

Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A prospective study of 6209 infants

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Background: Early feeding with cow's milk (CM) may increase the risk of cow's milk allergy (CMA).

Objective: We sought to examine prospectively whether supplementary feeding of CM at the maternity hospital would increase the risk when compared with feeding with pasteurized human milk or hydrolyzed formula.

Methods: We studied 6209 unselected healthy, full-term infants, of whom 5385 (87%) required supplementary milk while in the hospital. The infants were randomly assigned to receive CM formula (1789 infants), pasteurized human milk (1859 infants), or whey hydrolysate formula (1737 infants). The comparison group (824 infants) was composed of infants who were exclusively breast-fed. The infants were followed for 18 to 34 months for symptoms suggestive of CMA. The primary endpoint was a challenge-proven adverse reaction to CM after a successful CM elimination diet.

Results: The cumulative incidence of CMA in the infants fed CM was 2.4% compared with 1.7% in the pasteurized human milk group (odds ratio [OR], 0.70; 95% confidence interval [CI], 0.44-1.12) and 1.5% in the whey hydrolysate group (OR, 0.61; 95% CI, 0.38-1.00). In the comparison group, CMA developed in 2.1% of the infants. Among the infants who required supplementary feeding at hospital, both exposure to CM while in the hospital (OR, 1.54; 95% CI, 1.04-2.30; $P = .03$) and obvious parental atopy (OR, 2.32; 95% CI, 1.53-3.52; $P < .001$) increased the risk of CMA.

Conclusions: Our data indicate that feeding of CM at maternity hospitals increases the risk of CMA when compared with feeding of other supplements, but exclusive breast-feeding does not eliminate the risk. (*J Allergy Clin Immunol* 1999;104:457-61.)

Key words: Cow's milk, formula, breast milk, food allergy, infant, maternity hospital

The gastrointestinal tract of newborn infants is deficient of both nonspecific and specific defense factors, and its digestive capacity is not fully developed.¹ Many properties of breast milk compensate for these deficiencies because it contains many immunologic and nonspecific defense factors² and digestive enzymes.³ In contrast, supplementary feedings, most of which contain cow's milk (CM) proteins, may provoke an immune reaction and retard gut closure to macromolecules.⁴⁻⁶ Nevertheless, the great majority of healthy infants tolerate these supplements with no deleterious effects.

Early feeding with CM was a risk factor for development of cow's milk allergy (CMA) in one study,⁷ but in another study⁸ it reduced the emergence of atopic symptoms during the first 18 months, suggesting the development of tolerance. This inconsistency concerning the effect of early supplementary feeding with CM during the first days of life prompted us to perform this clinical study in which we examined prospectively whether the risk of CMA could be reduced by feeding newborn infants either pasteurized human milk or extensively hydrolyzed formula compared with feeding them CM formula. Infants who had been exclusively breast-fed while in the hospital were followed up as a comparison group.

METHODS

Study groups and randomization procedure

The study was explained to 15,400 mothers of healthy, full-term infants immediately after delivery between August 1994 and November 1995 in 3 maternity hospitals in the Helsinki region. Within 12 hours after delivery, 6267 (41%) of them agreed to participate. Of these mothers, 58 (0.9%) were lost for various reasons (withdrawal, infant death or disease, or no questionnaires returned), leaving a final cohort of 6209 infants. Although breast-feeding was strongly encouraged in these hospitals, 5385 (87%) of the infants required supplementary milk at hospital because of insufficient secretion of breast milk. These infants were randomly assigned to one of 3 study groups according to the supplement given: liquid CM formula (Tutteli; Valio, Finland); pasteurized human milk (a mixture of milk from multiple donors expressed 1 to 6 months after delivery); and extensively hydrolyzed whey formula (Pepti-Junior;

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Abbreviations used

CI: Confidence interval
 CM: Cow's milk
 CMA: Cow's milk allergy
 OR: Odds ratio

Nutricia, The Netherlands). The supplements were supplied to the maternity wards in color-coded bottles; only one of the authors (LL), who was not in contact with the ward personnel or the infants, was aware of the code. The supplements were changed monthly, with the 3 hospitals each using a different supplement, and thus the supplement that an infant received depended on the month of birth and the hospital in which he or she was born. The time and amount of every feeding was recorded in the delivery ward. The comparison group was composed of 824 exclusively breast-fed infants. The infants were kept in the hospital for a mean of 4 days. The ethics committee of each hospital approved the study protocol, and written informed consent was obtained from the mother of each infant entering the study.

Feeding of infants at home

Mothers were advised to give infants supplementary CM formula when required and to start solid foods at the age of 4 to 6 months. During the first 8 weeks, the mothers were asked to record the infant-feeding regimen daily and then return the records. All 118 mothers of infants subsequently found to be hypersensitive to CM and 4543 (76%) of the mothers of tolerant infants (similar proportions in all 4 groups) returned the records.

Definition of CMA

Before leaving the hospital, the mothers were given written information about symptoms suggestive of CMA. If an infant had any such symptoms, the parents were asked to call one of the authors (KMS). The well-baby clinics of the area, in which every infant is seen an average of 8 times during the first 12 months of life, were also informed of the study.

If, after a comprehensive interview, the symptoms were compatible with CMA, CM was eliminated from the infant's diet for 2 to 4 weeks. If the symptoms subsided, a CM challenge test was done. For this test, CM formula was given in quantities of 1, 10, 50, and 100 mL at intervals of 30 to 60 minutes. On the next day, those infants without symptoms continued to receive the formula at home. All the infants were examined for delayed symptoms 5 days after the challenge test. The test result was considered positive if one or more of the following symptoms had appeared in the interim: urticaria, exanthema, atopic dermatitis, vomiting, diarrhea, wheezing, or allergic rhinitis. Those infants reacting adversely to the challenge were fed a milk-free diet, and those with no symptoms were fed formula. One month later, all infants were examined to confirm the challenge result.

Trial end point

The primary end point was an adverse reaction to challenge with CM. The number of contacts with the mothers of infants with symptoms suggestive of CMA diminished spontaneously. The last new contact was made in mid-October 1996, and the last challenge test was performed in November 1996. The milk code was broken in December 1996.

In May 1997, when the mean age of participants was 27 months (range, 18 to 34 months), the number of infants diagnosed as having CMA was obtained from the Social Insurance Institution. This

TABLE I. Cumulative incidence of CMA and ORs for the risk of development of CMA according to the type of feeding in the hospital after delivery

Feeding group	Total	Infants with positive CM challenge result	
		n (%)	OR (95% CI)
CM formula	1758	43 (2.4)	1.0
Pasteurized human milk	1844	32 (1.7)	0.70 (0.44-1.12)
Whey hydrolysate formula	1715	26 (1.5)	0.61 (0.38-1.00)

national organization maintains a complete register of infants under 2 years of age who are allergic to CM.

Family history of atopy and environmental factors

While in the hospital, mothers filled in a questionnaire about parental history of atopy. Atopy was defined as asthma, atopic dermatitis, allergic rhinitis, or conjunctivitis. The data were categorized as follows: no atopy and obvious atopy (asthma or symptoms from 2 different organs). Data on parental smoking, numbers of siblings, and furred household pets also were recorded.

Skin tests

A skin prick test with liquid CM formula was performed according to a standard technique.⁹ Histamine dihydrochloride (10 mg/mL) served as a positive control, and 50% glycerol solution (Soluprick; ALK, Denmark) served as a negative control.

Statistical analyses

We used logistic regression analysis to analyze the effect of the type of early feeding on CMA and the independent contribution of environmental and genetic factors to the risk of its development by including all risk factors in the model and testing the significance of each one with control for all other factors. Pearson's chi-square test was applied for categorical variables, and the Kruskal-Wallis test was applied for continuous data. Statistical significance was defined as a *P* value of .05 or less. Two-sided tests of significance were used throughout. Analyses were performed with SAS software (SAS Institute, Cary, NC).

Sample size calculations were based on a prediction of a 3.5% cumulative incidence of CMA.¹⁰ The trial was designed to detect a 60% lower cumulative incidence in the pasteurized human milk or whey hydrolysate groups than in the CM group, with a power of 80% and an α value of 0.05. The projected sample size for a group was 1640 infants.

RESULTS

A total of 622 mothers contacted the authors because their infants had symptoms at home, and 247 infants recovered while on the elimination diet. Of those, 118 (48%) reacted adversely to CM in a challenge test performed at hospital at a mean ($\pm$ SD) age of 6.7 ± 2.3 months, giving a cumulative incidence of 1.9% for CMA in the whole cohort. The symptoms provoked by the challenge test were as follows: urticaria or other rash (61 infants), eruption of atopic dermatitis (pruritus, erythema, or oozing; 52 infants), gastrointestinal symptoms (24 infants), respiratory symptoms (18 infants), and 1 anaphylactic reaction; 27 (23%) of the infants had multiple symptoms. The milk skin prick test response was positive in

TABLE II. Median (95% CI) amount of supplementary feedings given to infants in the hospital, age at the first supplementary feeding, and time period over which supplementary feedings were administered

Group	CMA	n	Intake (mL) /infant	Age at first feeding (h)	Administration period (h)
CM formula	Yes	43	110 (55-150)*	15.6 (14.4-18.6)	33.0 (24.0-52.0)
	No	1715	155 (145-170)	14.6 (13.9-15.2)	46.0 (43.0-48.0)
Pasteurized human milk	Yes	32	205 (125-400)	15.0 (10.8-20.4)	56.5 (40.0-67.0)
	No	1812	170 (160-185)	13.5 (12.9-14.0)	46.0 (44.0-48.0)
Whey hydrolysate formula	Yes	26	125 (90-200)	12.5 (11.1-14.8)	42.0 (20.0-59.0)
	No	1689	135 (125-150)	14.8 (14.3-15.5)	42.5 (40.0-45.0)

*P = .03, allergic versus tolerant infants in the CM group.

TABLE III. Percentages of infants exposed to CM formula at home before the age of 8 weeks and the median (95% CI) daily amounts given to exposed infants in each group

Group	CMA	n*	<2 weeks of age		2 to 8 weeks of age		Cumulative Exposed (%)
			Exposure (%)	Daily intake (mL)/ infant exposed	Exposure (%)	Daily intake (mL)/ infant exposed	
CM formula	Yes	43	35	55 (40-105)†	49	110 (35-165)‡	58
	No	1261	43	100 (100-115)	48	200 (170-225)	56
Pasteurized human milk	Yes	32	38	130 (60-190)	34	140 (20-700)	50
	No	1371	40	100 (100-110)	44	220 (200-250)	53
Whey hydrolysate formula	Yes	26	46	140 (30-200)	46	125 (15-250)	54
	No	1285	41	100 (95-115)	49	195 (150-200)	55
Comparison group	Yes	17	0	—	6	20	6
	No	626	8	105 (80-135)	18	125 (100-200)	20

*Number of infants for whom the data on feeding regimens during the first 8 weeks of life were available.

†P = .04 and ‡P = .007, allergic versus tolerant infants in the CM formula group.

70%, 59%, 54%, and 53% of the challenge-positive infants in the CM, pasteurized human milk, whey hydrolysate, and comparison groups, respectively. According to the Social Insurance Institution, CMA was diagnosed elsewhere in 81 infants. However, these infants are excluded from the analyses because of possible heterogeneity in diagnostic criteria.

CMA developed in fewer infants in the whey hydrolysate group than in the CM group (Table I). In the pasteurized human milk group there was a similar trend. Of the 811 exclusively breast-fed infants, CMA developed in 17 (2.1%).

The allergic and tolerant infants had been given similar amounts of supplements for similar durations of time while in the hospital (Table II). Also, their ages at the time of the first supplementary feeding were similar. In the CM group, however, the subsequently allergic infants had received less formula than the tolerant infants.

During the first 8 weeks of life, 54% of the allergic and 55% of the tolerant infants in the randomized groups were given CM at home compared with only 6% and 20% in the comparison group, respectively (Table III). In the CM group the subsequently allergic infants had been given smaller daily amounts of formula than the tolerant infants.

The first symptoms in allergic infants were noticed at the mean ($\pm$ SD) age of 2.9 ± 1.8 months.

The percentage of allergic infants with obvious atopic heredity was almost double that of tolerant infants; the

difference was similarly significant in the 3 groups (Table IV).

A multivariate logistic regression analysis was carried out among the infants in the 3 supplemented groups (Table V). CMA was used as the dependent variable, and environmental and genetic factors were used as independent variables. Both exposure to CM while in the hospital and obvious parental atopy increased the risk of CMA. Factors found not to be significant were maternal and paternal smoking and the presence of siblings and furred pets.

DISCUSSION

We found that in an unselected group of healthy, full-term newborn infants who required supplementary feeding while in the hospital, feeding of CM for an average of 2 days after birth increased the risk of subsequent CMA. The ill effects of early exposure to CM may be caused by the immaturity of the infants' gastrointestinal tract, which is permeable to macromolecules.¹¹ Conversely, CMA developed less often in infants given whey hydrolysate formula. In many prospective studies the incidence of food allergy in infants at high risk of atopic diseases was lower in those given extensively hydrolyzed formula for several months after birth.¹²⁻¹⁴ These formulas contain hardly any antigenic material,¹⁵ and serum IgE concentrations are lower in the infants given extensively hydrolyzed formula for the first 3 days of life than

TABLE IV. Percentages of infants with a positive history of parental atopy, with 1 or more siblings, and with smoking mothers

Group	CMA (n)	Obvious parental atopy*	P value (χ^2 test)	Siblings	P value (χ^2 test)	Maternal smoking	P value (χ^2 test)
CM formula	Yes (43)	33	.01	51	.88	2	.06
	No (1715)	18		53		11	
Pasteurized human milk	Yes (32)	38	.008	41	.18	16	.46
	No (1812)	19		53		11	
Whey hydrolysate formula	Yes (26)	35	.06	35	.07	12	.8
	No (1689)	20		53		13	
Comparison group	Yes (17)	47	.004	59	.5	0	.22
	No (794)	19		67		8	

*Obvious atopy: asthma or symptoms from 2 different organs in 1 or both parents.

TABLE V. Effects of genetic and environmental factors on the risk of CMA development among infants who required supplementary feeding at the hospital from the multivariate logistic-regression analysis*

Variable	Reference category	OR (95% CI)			
		Crude†	P value	Multivariate‡	P value
Supplementary feeding while in hospital					
CM (43/1758)†	No CM (58/3559)†	1.51 (1.02-2.25)	.04	1.54 (1.04-2.30)	.03
Obvious parental atopy					
Yes (35/1014)†	No (66/4303)†	2.30 (1.51-3.48)	<.001	2.32 (1.53-3.52)	<.001

*Factors tested but found not to be significant were maternal and paternal smoking and the presence of siblings and furred household pets.

†Number of infants with CMA per total number of infants in each category.

‡The variables alone in the model.

§Both variables in the model simultaneously.

in those fed human milk or CM.¹⁶ The extensively hydrolyzed formula proved to be at least as efficient in preventing CMA as pasteurized human milk, which presently is the preferred supplement in Finnish maternity hospitals.

When strict criteria for diagnosis were applied, the cumulative incidence of CMA in the whole cohort was 1.9%, a percentage in good accord with earlier studies on unselected infants using similar criteria for diagnosis.^{7,17} Although a double-blind, placebo-controlled food challenge would be the optimal test,¹⁸ we performed CM challenges openly because in this age group open and double-blind challenges have produced similar reaction rates.¹⁹

Surprisingly, the percentage of infants who were exclusively breast-fed at hospital and in whom CMA developed was similar to that of the infants fed CM. Similarly, in a recent study breast-fed infants who were exposed to either CM or placebo during the first 3 days of life were at similar risk for the development of allergies at 0 to 2 years.²⁰ In contrast, in the study of Høst et al,⁷ CMA developed in none of the 210 infants who were solely breast-fed while in the hospital. In our study all but 1 of the 17 allergic infants in the comparison group were exclusively breast-fed for at least the first 8 weeks of life. In contrast to the randomized groups, this self-selected comparison group was formed on the basis of the mother's ability to breast-feed her infant fully while in the hospital. These mothers were more often multi-

parous and nonsmokers, which are factors associated with reduced risk of atopic diseases^{21,22} that increase the success rate in breast-feeding.²³ On the other hand, a known risk factor, a positive parental history of atopy,²¹ was not more frequent in the comparison group than in the randomized groups. However, in the whole cohort a history of parental atopy was more prevalent among the allergic infants.

The small amounts of CM proteins present in breast milk may elicit a reagenic reaction to CM.²⁴ Furthermore, infants with a positive parental history of atopy react to the minute amounts of food antigens in breast milk,²⁵ and the incidence of food allergies was reduced when both the nursing mother and her infant avoided CM.¹³ Natural tolerance to food antigens will be established if the age at introduction is optimal, depending on the quantity and frequency of intake.²⁶ Our results suggest that larger amounts of CM are more likely to induce tolerance than smaller amounts: in the CM group, the allergic infants had been exposed to smaller amounts of formula at hospital and also at home during the first 8 weeks than the tolerant infants. Oral tolerance may develop during the neonatal period²⁷ or later during the first year of life⁶ and is promoted by administration of large amounts of antigen.²⁴

In conclusion, our results indicate that healthy newborn infants exposed to CM formula while in the hospital immediately after birth are at higher risk of CMA development than those fed other supplements. Never-

theless, exclusive breast-feeding during the first 8 weeks of life did not reduce the risk of CMA.

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