

Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to 18 months of age—*in-vivo* results

G. LILJA*, A. DANNAEUS†, T. FOUCARD†, V. GRAFF-LONNEVIG*,
S. G. O. JOHANSSON‡ and H. ÖMAN‡

*Sachs' Children's Hospital, Stockholm, †Department of Paediatrics, University Hospital, Uppsala, and

‡Department of Clinical Immunology, Karolinska Hospital, Stockholm, Sweden

Summary

One hundred and sixty-two women with respiratory allergy to animal danders and/or pollens were randomly allocated to a diet consisting of either a very low ingestion of hens' egg and cows' milk or a daily ingestion of one hens' egg and about 1 l of cows' milk during the last 3 months of pregnancy. One hundred and sixty-three infants were followed prospectively up to 18 months of age when the cumulated incidence of atopic disease in each child was evaluated blindly. No significant differences in the distribution of atopic disease were found among the infants in relation to the maternal diet during late pregnancy. The numbers of skin-prick tests positive to ovalbumin, ovomucoid, β -lactoglobulin and cows' milk were likewise not influenced by differences in the maternal diet during late pregnancy. Genetic factors rather than maternal diet during the perinatal period probably have a greater effect on the incidence of atopic diseases during early infancy.

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Introduction

During recent decades much interest has been focused on the possibility of predicting and preventing atopic diseases during infancy [1]. Prevention has mostly focused on the beneficial effect of breast-feeding [2]. The findings of specific IgE antibodies in cord blood [3–5], positive skin-prick tests [6] and symptoms of atopic disease during the first months of life [7] have raised the question of intrauterine sensitization of the foetus. Some authors have found that avoidance of potent food allergens in the diet during late pregnancy, when there is a family history of atopic disease, diminished the number of atopic manifestations during infancy [8,9]. Others have not found any beneficial effect of such diets [10,11].

The importance of antigen exposure during and after pregnancy for the induction of tolerance in the offspring [12,13] as well as for modulating the IgE response in the newborns [14] has been studied in animals. The beneficial

effect of exposure to allergens during pregnancy in man has also been reported [15–17].

The purpose of the present study was to determine whether the ingestion of food allergens by atopic women during the last 3 months of pregnancy may influence the risk of atopic disease among their infants. The *in-vivo* results of skin-prick tests and signs of atopic diseases in the infants up to 18 months of age are reported.

Subjects and methods

Women

One hundred and seventy-one pregnant women, with a history of respiratory allergy symptoms after exposure to animal danders (cat and dog) and/or tree or grass pollens, participated in the study. They all attended maternity clinics in Stockholm and Uppsala.

Eighty-four women were allocated to a diet with a strictly reduced ingestion of egg and dairy products (milk, yoghurt, butter, cheese, etc.). No foods obviously containing egg or cows' milk were allowed, but small amounts of these foods, such as bread brushed with egg or

ordinary margarines, were allowed. Five women discontinued the diet and were considered to be drop-outs. This left 79 women to be evaluated and they will be presented as the 'reduced' group.

Eighty-seven women were assigned to a diet with an ingestion of one hens' egg and dairy products corresponding to about 1 l of cows' milk daily during the third trimester. Four women dropped out of the study, leaving 83 to be evaluated and these are presented as the 'high' group.

The two groups of women were comparable except for a significantly higher incidence of atopic eczema and higher IgE levels before week 28 in the 'reduced' group (Table 1).

Infants

One hundred and sixty-six infants were born, 104 boys and 62 girls, including four pairs of twins. There were two premature infants in the 'reduced' group. No significant differences in birth weight, month of birth or sex were detected between the two study groups. All 81 infants in the 'reduced' group were followed up to 18 months of age.

In the 'high' group ($n=85$) two children were excluded from the study immediately after delivery, one for social reasons and one because of a cerebral haemorrhage. A third child developed infantile spasms at 6 months of age and was therefore excluded from the study, leaving 82 infants up to 18 months of age to be examined.

In-vitro tests

Serum IgE levels and IgE antibody concentrations were determined with PRIST®, Phadebas RAST® and Phadiatop® [18] (Pharmacia, Uppsala, Sweden) in accordance with the recommendations of the manufacturer. For the determination of low IgE levels a sensitive PRIST method was used [10].

Skin-prick test

Food allergens. Reagents for skin-prick testing (SPT) were made by dissolving 90 mg of the proteins, ovalbumin (OA), ovomucoid (OVO) and β -lactoglobulin (BLG) in 9 ml of 0.9% saline containing 0.3% phenol as preservative. The food allergens were supplied by Sigma (St Louis, U.S.A.).

The solutions were sterile-filtered through 0.22- μ m filters (Millipore, Molsheim, France) and kept at 4°C for a maximum of 6–9 months. The proteins were analysed with PHAST SDS-PAGE (Pharmacia, Uppsala, Sweden) and were found to be mainly single-banded, indicating a high degree of purity. The potency of the extract was

Table 1. Demographic data in the two groups of women

	'Reduced' ($n=79$)	'High' ($n=83$)	<i>P</i>
Mothers			
Age (yr)*	28.5 $\pm$ 3.9	28.8 $\pm$ 4.7	n.s.
Atopic disease			
Bronchial asthma (%)	44	42	n.s.
Rhinoconjunctivitis (%)	95	96	n.s.
Atopic eczema (%)	64	46	<0.05
Allergy history			
Pollen (%)	79	70	n.s.
Animal dander (%)	82	83	n.s.
Egg allergy (n)	2	0	
Immunological parameters			
IgE levels before week 28 (Geometric mean, range)	110 2.5–2400	61 2.5–3200	<0.01
Positive RAST†/ positive Phadiatop/ positive SPT‡ (%)	83	82	n.s.
Fathers			
Atopic disease (%)	33	41	n.s.
Bronchial asthma (%)	6	10	n.s.
Rhinoconjunctivitis (%)	24	26	n.s.
Atopic eczema (%)	16	23	n.s.
Siblings			
Atopic disease (%)	33	31	n.s.
Bronchial asthma (%)	10	8	n.s.
Rhinoconjunctivitis (%)	11	11	n.s.
Atopic eczema (%)	24	19	n.s.
Food allergy (egg, fish, milk, nuts) (%)	14	14	n.s.
Environmental factors			
Mother smokes (%)	16	20	n.s.
Father smokes (%)	22	23	n.s.
Animal in home (%)	5	2	n.s.

* Mean $\pm$ SD.

† Cat, dog, birch and timothy.

‡ *Dermatophagoides pteronyssinus*, *Aspergillus*, *Cladosporium*, cat, dog, horse, birch, timothy and mugwort.

n.s. = not significant.

tested in six infants with verified hens' egg allergy and in five infants with verified cows' milk allergy. A fresh preparation of the extract was tested against 1.5-year-old extract and the skin reactions were identical, indicating that the extracts used were stable during the observation period. In addition to these allergens, whole cows' milk (3% fat) was used for testing.

Histamine chloride (1 mg/ml) served as a positive reference and the diluent was used as the negative control.

The allergen SPT was regarded as positive if the weal was greater than or equal to the histamine skin reaction [19]. All SPTs were performed singly on the forearm, using a lancet with a 1 mm tip.

Statistical analyses

Chi-square analyses, Fischer's exact test and the Student's *t*-test (for two samples) were used to determine differences between the study groups.

Ethics

The study was approved by the Human Research Ethics Committee of the Karolinska Institute, Stockholm. Informed consent was given by all the women before they were included in the study.

Study design

Assignment of patients—maternal feeding instructions.

The pregnant women selected for the study were randomly assigned to one of the two study groups ('reduced' or 'high'), according to the location of the maternity clinic. The 14 maternity clinics were arranged in pairs with respect to differences in the socio-economic character of their uptake areas. Maternity clinics in the central parts of the cities were paired, as were the maternity clinics in the suburbs. In this way all the women habitually visiting a particular maternal clinic were assigned to one of the two diets ('reduced' or 'high') during the last 3 months of pregnancy.

Before entering the study the women were characterized with respect to basic demographic data, and to levels of IgE and IgE antibodies to pollen (birch and timothy) and animal danders (cat and dog) (Table 1). Women with a negative RAST to pollens and/or animal danders were analysed with Phadiatop, and SPTs were performed using a panel of representative inhalation allergens (*Dermaphagoides pteronyssinus*, *Aspergillus fumigatus*, *Cladosporium herbarum*, cat, dog, horse, birch, timothy and mugwort; 3 HEP; ALK®, Copenhagen, Denmark).

Before changing their diet all the women ingested 'normal' amounts of hens' egg and cows' milk, except two who were allergic to hens' egg and one who avoided any larger amounts of hens' egg. All the women in the 'reduced' group were given 1 g calcium phosphate daily. In both groups the women's diet was supervised by a dietitian during the study.

After delivery and by their own decision 25 women in the 'reduced' group continued to ingest very low amounts of the two nutrients during the first two months of lactation, thus forming the 'reduced' A-group. The

remaining 54 women in the 'reduced' group 'normalized' their ingestion of hens' egg and cows' milk after delivery, forming the 'reduced' B-group. The women in the 'high' group all 'normalized' their ingestion of the two nutrients after delivery.

Maternal compliance. In order to evaluate the compliance with the dietary regime 136 women, recruited from Stockholm, recorded their intake of hens' egg and cows' milk. In the 'high' group, daily records were kept by 65 women during the third trimester of pregnancy and all except four records were complete and available for analyses. Their mean weekly ingestion of hens' egg was 7.0 per woman. The corresponding value for cows' milk and yoghurt was 7.4 dl daily. The cows' milk protein in cheese, butter and other dairy products was calculated to be at least 1–2 dl of cows' milk daily.

The 71 women in the 'reduced' group recorded their intake every 10th day. Ninety per cent of the dietary records were analysed and all were found to be in agreement with the prescribed diet.

Infant feeding. The women were encouraged to practise breast-feeding alone for as long as possible and preferably for 6 months. If breast-feeding proved impossible, soy formula (Soja-Semp®, Semper AB, Stockholm, Sweden) was given until the child reached 6 months of age, when cows' milk-based formula was introduced. However, if the child refused to take soy formula, or was not satisfied with it, cows' milk-based formula was given instead. The weaning age (after which no further breast-milk was given) was the same in both groups ('reduced' 7.1 ± 4.0 months, 'high' 7.1 ± 3.7 months (mean $\pm$ SD). Eight children in the 'reduced' group and five in the 'high' group received cows' milk-based formula. However, all the children were more than 3 months old when cows' milk-based formula was introduced.

Solid foods—starting with vegetables, mainly potatoes—were not given until the children were 3–4 months old. Citrus and other fruits, meat, cereals and tomatoes were not given before 6 months of age and fish and hens' egg not before 9–12 months of age.

Physical examination. All children were examined at 2, 6, 12 and 18 months of age (Fig. 1). The physicians who performed the physical examination at 18 months of age (V.G-L and T.F.) were unaware of the mothers' diet during the trial and of previously performed SPT and *in-vitro* analyses in the mother and child. The cumulative incidence of signs of atopic diseases up to 18 months of age was evaluated by means of a questionnaire and the physical examination. According to a classification pro-

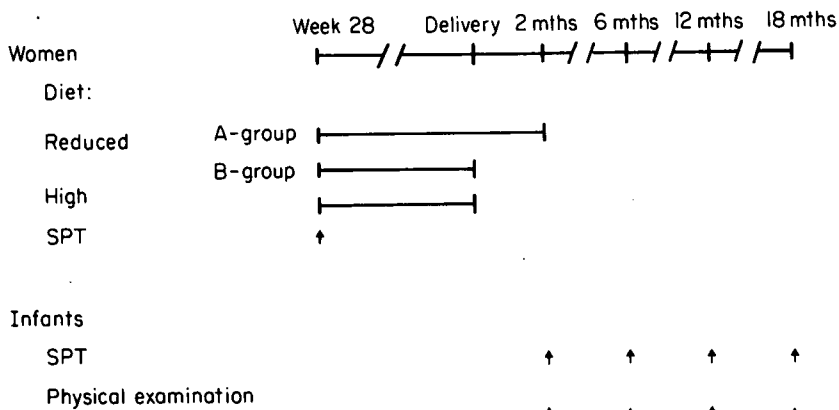


Fig. 1. Study design in 162 atopic women randomly allocated to two diet groups, the 'reduced' group ($n=79$) and the 'high' group ($n=83$), and clinical investigation of their infants up to 18 months of age. SPT = skin-prick test.

cedure [20] the examiner assigned the child to one of the groups: obvious atopic, probable atopic, possible atopic or non-atopic, and the type of atopic symptom was noted.

In-vivo and in-vitro tests. The infants were followed with SPTs (OA, OVO and BLG and cows' milk) and with serum samples for analyses of the levels of IgE, IgE and IgG antibodies to selected food allergens (Fig. 1). The results of *in-vitro* tests will be presented elsewhere.

Results

Skin-prick tests

No significant differences between the 'reduced' A- and B-groups were recognized either in the results of SPTs or in the incidence of atopic diseases. Thus the results in the A-group and B-group will be considered together and presented as the 'reduced' group.

A comparison of the 'reduced' group with the 'high' group revealed no significant differences in the number of positive SPTs to OA, OVO and BLG and cows' milk (Fig. 2) (Fischer's exact test, $P>0.05$).

There was a tendency towards an increase in the numbers of positive SPTs up to 12 months of age which was most pronounced for OA and OVO (Fig. 2). Of the infants with positive SPTs to the two egg proteins, 53% were positive only to OA and 12% only to OVO. Between 12 months and 18 months only seven developed a positive SPT to OA, OVO or BLG. Reductions or a complete disappearance of the SPT reactions to the three food allergens were noted after 6 months of age. These changes were most pronounced between 12 months and 18 months of age. Fourteen per cent of 128 positive skin reactions to OA, OVO and BLG completely disappeared and 10% of the positive SPT reactions were reduced. The observed changes in SPTs, disappearance and reduction of the reactions were found in 15 and 12 infants respectively, and 61% of these changes occurred in infants classified as non-atopic.

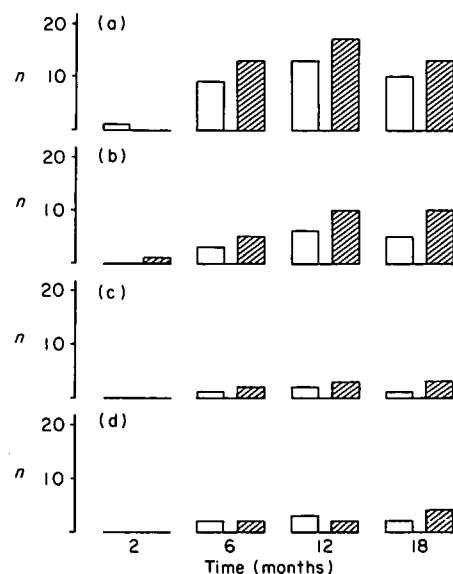


Fig. 2. Number of skin-prick tests positive to (a) ovalbumin, (b) ovomucoid, (c) β -lactoglobulin and (d) cows' milk at 2, 6, 12 and 18 months of age among the infants in the 'reduced' group ($\square$) and in the 'high' group ($\blacksquare$).

Table 2. Classification of past or present atopic disease at 18 months of age

	'Reduced' ($n=81$)	'Reduced'-A ($n=26$)	'Reduced'-B ($n=55$)	'High' ($n=82$)
Obvious	11 (14)*	5 (19)	6 (11)	16 (19)
Probable	4 (5)	3 (12)	1 (2)	4 (5)
Possible	17 (21)	7 (27)	10 (18)	8 (10)
Non-atopic	49 (60)	11 (42)	38 (69)	54 (66)

* Values represent number within each group, with percentages shown in parentheses.

No significant differences between the groups were present.

There were 21 infants with persistently positive SPTs to OA, OVO and BLG during the observation period and 57% of these infants were classified as atopic (obvious or probable). Negative SPTs to the three food allergens and to cows' milk were found in 123 infants of whom 11% were classified as atopic.

Physical examination

One hundred and sixty-three infants were available for atopic classification at 18 months of age (Table 2). Twenty-seven (16%) were considered to be obviously atopic, 8 (5%) probably atopic, 25 (15%) possibly atopic and 103 (64%) non-atopic. No significant difference in the atopic classification of the infants was noted between the two investigators (V.G-L, T.F.).

There were also no significant differences between the

'reduced' and the 'high' groups in the distribution of infants according to the atopic classification. This was also true when the infants classified as atopic (obvious or probable) were grouped together, and those classified as possible or non-atopic were also grouped together, and compared.

The kind of atopic manifestation in the child was not influenced by the mother's diet (Table 3). Nor was the distribution of the children as, obvious, probable, possible or non-atopic, influenced by the different feeding methods during the first 6 months of life (Table 4).

Despite the relatively high number of positive SPTs to OA and OVO, obvious egg allergy (acute symptoms—urticaria, vomiting, wheezing—when eating hens' egg) was seen in only two children in the 'reduced' group and one in the 'high' group. Four children, two in each group, had similar allergy symptoms after the intake of cows'

Table 3. Incidence of different types of atopic diseases up to 18 months of age

	Asthma		Rhino-conjunctivitis		Atopic eczema		Urticaria	
	'Reduced' (n=81)	'High' (n=82)	Reduced (n=81)	High (n=82)	Reduced (n=81)	High (n=82)	Reduced (n=81)	High (n=82)
Obvious	1	1	0	0	10	14	2	1
Probable	0	0	0	0	3	4	1	2
Possible	3	6	1	1	14	5	0	0

Values are the number of subjects within each category.

Table 4. Classification of past or present atopic disease at 18 months of age in relation to feeding during 0–6 months

	Breast-fed > 6 months	Breast-fed > 2/ < 6 months + soy formula	Breast-fed > 2/ < 6 months + cows' milk/soy formula	Breast-fed < 2 months + soy formula
'Reduced' (n=81)				
Obvious	6	4	0	1
Probable	2	0	1	1
Possible	10	1	4	2
Non-atopic	25	11	3	10
'High' (n=82)				
Obvious	8	3	1	4
Probable	3	0	0	1
Possible	4	2	0	2
Non-atopic	30	12	4	8

Values represent the number of subjects within each category.
No significant differences between the groups are present.

milk. The six children with obvious egg and cows' milk allergies all had very strong positive SPTs to hens' egg and cows' milk proteins, respectively. Six other children gradually developed mild diarrhoea after they were started on cows' milk. They were classified as possible cases of cows' milk allergy; two were in the 'reduced' and four were in the 'high' group. Two of them had a moderately positive SPTs to BLG. The development of type I reaction to cows' milk and hens' egg was not preceded by gastroenteritis in any child.

Discussion

A modification of the maternal diet during pregnancy and early lactation has been suggested as a means of preventing perinatal sensitization [8,9] or inducing tolerance [12–14] in the foetus and newborn. However, the present study comparing high and low ingestion of hens' egg and cows' milk during late pregnancy showed no preventative effect on the development of atopic diseases in infants up to 18 months of age. Avoidance of the two nutrients during the first 2 months of lactation also did not influence the cumulated incidence of atopic disease. The duration of breast-feeding [2] and the time for the introduction of solid foods [21] have been thought to influence the incidence of atopic disease during infancy. However, this study showed no differences between the two study groups with regard to the feeding regimen up to 6 months of age.

Much interest has been focused on the antigen dose and the IgE antibody response [22]. It has been proposed that a low antigen dose in connection with a defect in T-suppressor function predisposes to synthesis of IgE [22,23]. Some experimental studies in rats have reported a suppressive effect on IgE synthesis in the offspring after a high ingestion of hens' egg during pregnancy [14]. However, the rats' diet was introduced at the very beginning of the pregnancy and the animals were genetically identical. Our study might have given different results if the maternal diet had been changed earlier during pregnancy. One may also wonder whether the amounts of hens' egg and cows' milk proteins were high enough to induce a protective effect on the foetal (newborns) IgE synthesis.

Similarly, the diet in the 'reduced' group may not have been sufficient to minimize intrauterine sensitization and subsequent atopic disease during infancy. However, other studies of an 'avoidance diet' during pregnancy have shown different effects on the development of atopic disease during infancy. In one study a strict avoidance diet had no effect [11]. Chandra [8], on the other hand, reported that the avoidance of potent food allergens in the maternal diet during pregnancy and lactation had a

beneficial effect. However, he excluded not only cows' milk and hens' egg but also other food allergens, e.g. fish and peanuts. In the present study cows' milk and hens' egg were chosen as being the two commonest allergens and therefore they have been the most extensively studied food allergens during infancy [17]. The beneficial effect of an 'avoidance diet' during pregnancy was not very pronounced in Chandra's study and the results do not seem to justify the recommendation of this diet during pregnancy.

The women in the 'reduced' group at the start of the study had a higher incidence of atopic eczema than the women in the 'high' group (Table 1), which may explain the higher IgE levels in the 'reduced' group. These differences were regarded as resulting from chance. The discrepancy in IgE levels between the two study groups indicates that the women in the 'reduced' group were more atopic, and this might have obscured a possible beneficial effect of the diet in the 'reduced' group.

Positive skin-prick tests to different allergens—not only to food allergens but also to inhaled allergens [24, 25]—have been found in infants during the first year of life. In this study two children with positive SPTs to hens' egg proteins at 2 months of age were found, as well as an increasing number of positive SPTs, especially to OA and OVO up to 12 months of age. An increase in the number of positive SPTs up to 12 months is in agreement with studies by other authors [26,27]. Changes in skin reactivity and the disappearance or reduction in positive SPTs with time were found among infants both with and without signs of atopic disease. The occurrence of serum IgE antibodies to egg-white and cows' milk allergens during infancy, without clinical food allergy or other atopic manifestations, has been found to be a risk factor for future atopic allergy [27]. The question of whether the transient occurrence of skin-fixed food-specific IgE antibodies in our study, especially among infants without concomitant food allergy or other signs of atopic disease up to 18 months of age, predicts the development of future atopic disease can only be answered by a continued follow-up of the children.

The high incidence of positive skin-fixed specific IgE to hens' egg at 6 months of age, at a time when the child had not yet received this nutrient, implies that it might have been sensitized by mechanisms other than its own food intake. Sensitization *in utero*, via breast-milk or by inhalation of egg allergens [27–29] are other possible mechanisms.

In summary, genetic factors probably have a greater influence on the incidence of atopic disease during infancy than environmental factors, including the manipulation of maternal diet during late pregnancy and the early lactation period.

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