

Immune response of the atopic woman and foetus: effects of high- and low-dose food allergen intake during late pregnancy

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Summary

The influence of the mother's consumption of cows' milk and hens' egg on the immune response (IgE, IgG) in the mother and foetus was studied in 165 pregnant women with atopic respiratory disease with an allergy to pollen and/or animal dander. The women were randomly allocated to four diets ranging from a diet free from hens' egg and cows' milk to a diet containing intake of one egg and one litre of milk daily during the third trimester. No significant differences in cord blood IgE levels were noted in spite of differences in maternal diet, and no specific IgE antibodies to ovalbumin, ovomucoid and betalactoglobulin were found in the cord blood. The mother's IgG antibody concentrations to ovalbumin, ovomucoid and betalactoglobulin were influenced by her diet, but cord blood IgG antibody levels to the selected food allergens were unaffected. The data presented on the IgE and IgG antibody levels to ovalbumin, ovomucoid and betalactoglobulin in cord blood suggest that changes in maternal diet during the last trimester of pregnancy in order to prevent atopic sensitization *in utero* are less likely to affect the foetus than previously supposed.

Introduction

The cumulated incidence of atopic disease is 15–18% among Swedish children up to 7 years of age [1]. The aetiology of atopic disease is multifactorial, both genetic [2] and environmental factors being important.

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Reports of positive skin-prick tests in newborns [3] and symptoms of atopic disease during the first months of life [4] have, in the light of several studies on cord blood IgE [5–8] and the occasional occurrence of specific IgE antibodies (IgE-Ab) in cord blood [6, 7, 9, 10], raised a question about intrauterine sensitization of the foetus. The foetus has been thought to have the immunological ability to produce IgE from the eleventh week of pregnancy [11]. Since cord blood IgE seems to be of foetal origin, and elevated levels seem to predict subsequent atopic disease [6–8, 12], the avoidance of potent food allergens in the diet during late pregnancy has been recommended when there is a family history of atopic disease [13–15].

Conversely, experiments in animals show the importance of antigen exposure during pregnancy and after birth for the induction of tolerance in the offspring [16, 17]. The IgG response in the foeto-maternal relationship and its role in the suppression of IgE synthesis has been studied in rats [18].

In man a protective role of maternal IgG-Ab against sensitization of the newborn has been suggested [19–21]. It has been reported [22] that when women with hay fever were given immunotherapy with grass pollen extract during pregnancy, the incidence of grass pollen allergy was lower in their children than in infants who were born after a pregnancy in which the allergic woman did not receive immunotherapy. Thus, there are conflicting opinions as to whether allergen exposure during pregnancy is an advantage for the foetus.

Therefore, the aim of the present study was to determine whether diets containing different amounts of common food allergens—cows' milk and hens' egg—ingested by atopic women during the third trimester of pregnancy might influence the IgE and IgG immune response in both the mother and the foetus.

Subjects and methods

A total of 183 pregnant atopic women with a history of respiratory symptoms after exposure to animal dander and/or tree or grass pollen were selected for the study. Women in the first half of pregnancy who were attending maternity clinics in three cities, Stockholm–Uppsala ($n=99$) and Linköping ($n=84$), were asked to participate. Eighteen pairs of mothers and their newborns were excluded at delivery because of contamination of the cord blood by maternal blood (see study design). This left 165 cases to be evaluated (Table 1).

Before changing their diet all the women were ingesting 'normal' amounts of hens' egg and cows' milk, except one woman who avoided large amounts of hens' egg.

Atopic disease among other family members was not a contra-indication for entering the study. In order to elucidate the atopic heredity a 'family allergy score' was calculated among the first-degree relatives. Obvious atopic disease was given two points, suspected atopic disease one point and no atopic disease 0 points. The 'family allergy score' was the sum of the points of mother, father and sibling but limited to a maximum score of six points.

The pregnant women in the Linköping area were randomly assigned to two groups with different diets. During the last 3 months of pregnancy one group of women had a diet without hens' egg and cows' milk. The other group continued on a 'normal' diet consisting of about 0.5 l cows' milk daily and three hens' eggs weekly. The two groups will be called the free group ($n=37$) and the normal group ($n=39$).

The fourteen maternity clinics associated with Sachs' Children's Hospital in Stockholm and the University Hospital in Uppsala were arranged in pairs with regard

Table 1. Characteristics of 165 atopic women allocated to four diet groups during the last trimester of pregnancy. The diets (from a free to a high group) differ with respect to their content of cows' milk and hens' egg

	Free (n = 37)	Reduced (n = 32)	Normal (n = 39)	High (n = 57)
<i>Age at delivery (years)</i>				
Mean	28.4	28.7	27.7	28.4
Range	20.5-36.8	21.4-36.3	21.2-37.3	19.5-40.3
<i>Atopic disease (%)</i>				
Bronchial asthma	22	47	23	46
Rhinoconjunctivitis	97	94	100	97
Atopic eczema	22	41	28	33
<i>Allergy history (%)</i>				
Pollen	83	85	80	70
Animal dander	53	82	40	89
<i>Smokers (%)</i>				
	11	9	10	19
<i>Family allergy score</i>				
Mean $\pm$ s.d.	3.0 $\pm$ 1.3	3.5 $\pm$ 1.2	3.1 $\pm$ 1.2	3.3 $\pm$ 1.3

to differences in socio-economic background. Maternity clinics in the central parts of the cities were paired, as also were the maternity clinics in the more peripheral parts. All mothers of a pair, belonging to a particular maternity clinic, were randomly allocated to one of two diets. One group of women had a 'reduced' intake of eggs and cows' milk (no 'apparent' intake of egg and cows' milk) but their diet was not completely free from these two nutrients; this was the reduced group ($n = 32$). The other group, high group ($n = 57$) had a high intake, corresponding to one hen's egg daily and about 1 l cows' milk daily during the study.

The four groups were comparable with respect to basic demographic data, except for the incidence of asthma (Chi-square analysis, $P < 0.05$) and allergy to animal dander (Chi-square analysis, $P < 0.01$) (Table 1).

One hundred and seventy infants were born, including five pairs of twins. There were significantly more boys ($n = 110$) than girls ($n = 60$) (Chi-square analysis, $P < 0.001$). Atopic women seem to give birth to more boys than girls, which also has been observed by others [23]. No other group differences in the distribution of sexes were seen. One child in the free group and two children in the reduced group were premature. There were no significant group differences in the birth weights, and the month of birth was evenly distributed over the year within each study group.

Methods

IgE concentrations were determined by Phadebas IgE PRIST (Pharmacia Diagnostics AB, Sweden), according to the manufacturer's recommendations. The following modification was introduced for analyses of cord serum samples in order to increase the sensitivity. Undiluted serum (50 μ l) was incubated with one regular PRIST disc in a test-tube shaker (Buhler, Claesson and Skafte, Sweden) at room temperature, overnight. After washing, using the standard procedure, 100 μ l of ^{125} I-labelled anti-IgE (Phadebas RAST Anti-IgE Tracer, Pharmacia Diagnostics AB, Sweden) were added.

This was followed by incubation and washing using the standard procedure. The Phadebas IgE PRIST reference solutions were further diluted in the enclosed diluent to cover the range 0.12–4.0 kU/l.

IgE-Ab were determined by RAST (Phadebas RAST, Pharmacia Diagnostics AB, Sweden) using the manufacturer's recommendations. The RAST allergen discs were obtained from Pharmacia Diagnostics AB, except those with ovomucoid, which were kindly supplied by MIAB, Sweden. All samples were tested in duplicate and the results were expressed in PRU/ml, as derived from the Phadebas RAST reference system.

A modified RAST was used for cord serum samples. The ordinary reference was further diluted in a pool of IgE-Ab negative serum samples and ranged between 0.022 PRU and 3.5 PRU. The sample volume was 50 μ l and the serum incubation step was made as in the modified PRIST. The rest of the procedure was similar to ordinary RAST.

IgG-Ab were assayed by antigen ELISA [24]. Commercial preparations of ovalbumin, ovomucoid and betalactoglobulin (Sigma, St Louis, U.S.A.) were diluted to a concentration of 10 μ g/ml in 0.1 M carbonate-buffer pH 9.6. 100 μ l of the solution were added to each well in microtitre plates (Nunc, Immunoplate IIF, Denmark) and incubated overnight at +4°C. The microtitre plates were excessively washed with washing buffer (5 mM phosphate-buffered saline, pH 7.4, containing 0.1% Tween). The patients' serum samples in duplicates and diluted 1/100 in assay-buffer (50 mM phosphate-buffered saline, pH 7.4, containing 0.1% Tween and 0.2% bovine serum albumin) were then added to the plates and incubated for 3 hr at room temperature. The plates were, after another washing, incubated overnight with anti-IgG (Dako, Denmark), conjugated to alkaline phosphatase by a one-step glutaraldehyde method [25]. After conventional development with p-nitrophenylphosphate (Sigma, U.S.A.) in 1 M diethanolamine (pH 9.8), the measurements were made on a SLT 210 photometer (Kontron, Sweden) and, by computer-calculated spline curvefit, related to serial dilutions of standard serum samples (Sinus Data AB, Sweden). The results are expressed in Arbitrary Units (AU) per ml.

IgA concentrations of cord serum samples were determined by a double-antibody ELISA. Rabbit anti-human IgA (Pharmacia, Sweden) was used to coat microtitre plates as described above. The samples were diluted 1/100 in assay-buffer and run in duplicates. Bound IgA was detected by alkaline phosphatase conjugated primary antibody. Serial dilutions in assay-buffer of an Immunoglobulin Standard Set (Boehringer Mannheim GmbH, Sweden) were used as a reference, and the results are expressed in μ g/ml. Incubation times, washings, curvefit and buffers were the same as in the assays for IgG-Abs.

Statistical methods

In the testing of differences between the study groups, the Kruskal Wallis one-way analysis of variance by ranks was used. Changes within the study groups were tested by the Wilcoxon matched paired rank sum test. Differences between maternal IgG-Ab levels at delivery and the concentrations of cord blood IgG-Ab to ovalbumin, ovomucoid and betalactoglobulin were tested by the Mann-Whitney *U*-test. The non-parametric Spearman Rank correlation test was employed to determine the correlations between the maternal IgE levels at delivery and the cord blood IgE levels, as well as between the serum concentrations of the maternal IgG-Ab at delivery and the levels of cord blood IgG-Ab to selected food allergens.

Ethics

The study was approved by the Human Research Ethics Committees at the University Hospital, Linköping, and the Karolinska Institute, Stockholm. Informed consent was given by all the women before entering the study.

Study design

During the second trimester of pregnancy the atopic women selected for the study were randomly assigned to the four diet groups. They were characterized with respect to demographic data, serum IgE concentrations and IgE-Ab levels to birch and timothy pollens, cat and dog danders, and food allergens such as ovomucoid and betalactoglobulin. Serum levels of IgG-Ab to selected food allergens were determined.

Before and during the trial all the women discussed their diet with a dietician at regular intervals. All women who were on a diet that contained little or no egg and milk (reduced group and free group) were given 1 g calcium daily. Most of the women in the free group were also given a supplement of casein hydrolysate (Nutramigen®).

On delivery, a second blood sample was taken from all the women for the determination of the serum levels of IgE, IgE-Ab and IgG-Ab.

Samples of cord blood were obtained at delivery and analysed for the concentrations of IgE, IgE-Ab (ovomucoid and betalactoglobulin) and IgG-Ab (ovalbumin, ovomucoid and betalactoglobulin). Analyses of the levels of IgA and IgE-Ab to major maternal allergens (pollen or animal dander) in cord blood were performed when the cord blood IgE was >0.5 kU/l. Maternal contamination of the cord blood was suspected when the cord blood IgA level was found to be ≥ 14.1 $\mu\text{g/ml}$ and/or IgE-Ab concentrations of the major maternal allergens (pollen or animal dander) were ≥ 0.15 PRU. The upper limit for cord blood IgA was taken as 14.1 $\mu\text{g/ml}$ because this value corresponds to the geometric mean $+3$ s.d. in twenty newborns, selected at random, who had a cord blood IgE <0.12 kU/l. The detection limit of IgE-Ab to the major maternal allergens was taken as 0.15 PRU and corresponds to twice the background in a pool of serum samples from healthy, non-atopic individuals. The serum samples that fulfilled any or both of these criteria, elevated levels of IgA and/or IgE-Ab, were excluded ($n=18$).

Results

Maternal IgE

The differences in maternal serum IgE concentrations between the groups at week 28 and on delivery were not significant (Table 2). Measurements of the maternal IgE levels before the trial and at delivery showed no significant differences within the free and the normal groups. However, in the reduced group and in the high group the IgE levels were around 20% higher at delivery than in week 28 ($P<0.01$) (Table 2).

Before the diet, IgE-Ab to betalactoglobulin were found in four women, and IgE-Ab to ovomucoid in one woman. Three of these women were in the free group and one in the high group. During the observation period the IgE-Ab to betalactoglobulin disappeared in one woman in the high group. In the other women IgE-Ab to ovomucoid and betalactoglobulin remained unchanged and no new IgE-Ab appeared at the end of the observation period.

Table 2. Serum IgE levels (kU/l) in 165 atopic women at the 28th week of pregnancy and at delivery

	Free (n = 37)	Reduced (n = 32)	Normal (n = 39)	High (n = 57)
Week 28	71 2.8-12 300*	89 2.5-2100	73 2.5-1100	72 2.5-1400
Delivery	70 3.6-15 300	160 4.5-2900	57 2.5-940	84 2.5-1700
Significance	n.s.	$P < 0.01$	n.s.	$P < 0.01$

* Values are medians and range.

† n.s. = Not significant.

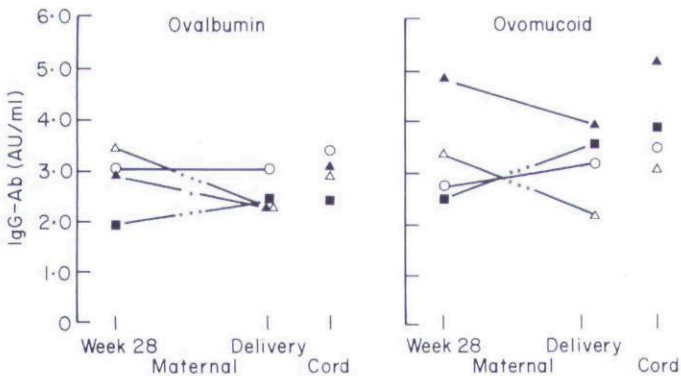


Fig. 1. Serum levels of maternal IgG-Ab to ovalbumin and ovomucoid and IgG-Ab levels in cord blood. The geometric means and arbitrary units (AU) per ml are presented. The symbols represent the findings in the four study groups: (Δ) free, (▲) reduced, (○) normal and (■) high. * = $P < 0.05$, ** = $P < 0.01$, *** $P < 0.001$.

Maternal IgG-Ab

There was a wide range in maternal IgG-Ab concentrations to the three food allergens before the women's diet was changed. The range for ovalbumin was 0.4-24.6 arbitrary units (AU)/ml, for ovomucoid 0.4-83.7 AU/ml and for betalactoglobulin 0.4-220.0 AU/ml. No significant differences between the study groups with respect to IgG-Ab levels to selected food allergens were found before the trial. At delivery the maternal concentrations of IgG-Ab also showed a wide range (ovalbumin 0.4-37.7 AU/ml, ovomucoid 0.4-106.0 AU/ml and betalactoglobulin 0.4-113 AU/ml), and no significant group differences were found.

However, there were significant changes in maternal IgG-Ab levels to the three food allergens within the groups from week 28 to delivery. There were significant reductions in the concentrations of IgG for the three food allergens in the free group (Figs 1 and 2). In the reduced group there were significant reductions in the IgG-Ab levels to ovalbumin and to betalactoglobulin. There was a tendency of decreasing IgG-Ab levels to ovomucoid but this was not statistically significant. IgG-Ab levels were unchanged in the normal group. In the high group there were significant increases in

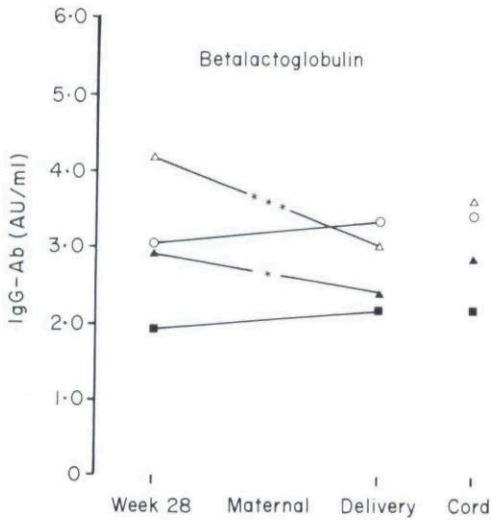


Fig. 2. Serum levels of maternal IgG-Ab to betalactoglobulin and corresponding IgG-Ab levels in cord blood. For further explanation see Fig. 1.

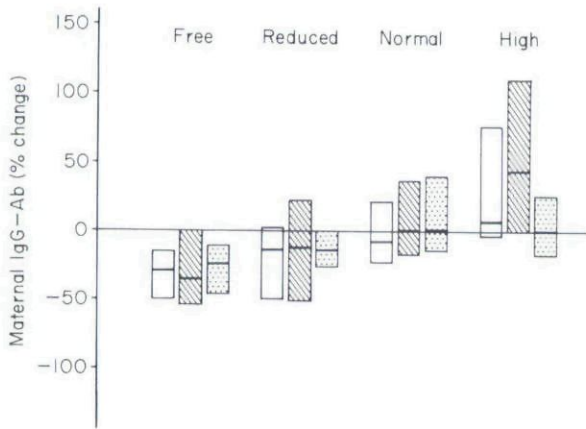


Fig. 3. Changes in maternal serum levels of IgG-Ab to ovalbumin, ovomucoid and betalactoglobulin from week 28 to delivery in the four diet groups. The three food allergens are presented: (□) ovalbumin, (■) ovomucoid and (▨) betalactoglobulin. Only the median (horizontal line), 25th and 75th percentiles are shown.

the IgG-Ab concentrations to ovomucoid and to ovalbumin, but no significant changes in the IgG-Ab levels to betalactoglobulin.

The relative changes in maternal IgG-Ab concentrations to ovalbumin, ovomucoid and betalactoglobulin between week 28 and the time of delivery were calculated. The results are presented in Fig. 3. A comparison of the relative changes in the maternal IgG-Ab levels and the individual allergens revealed significant differences between the groups ($P < 0.001$).

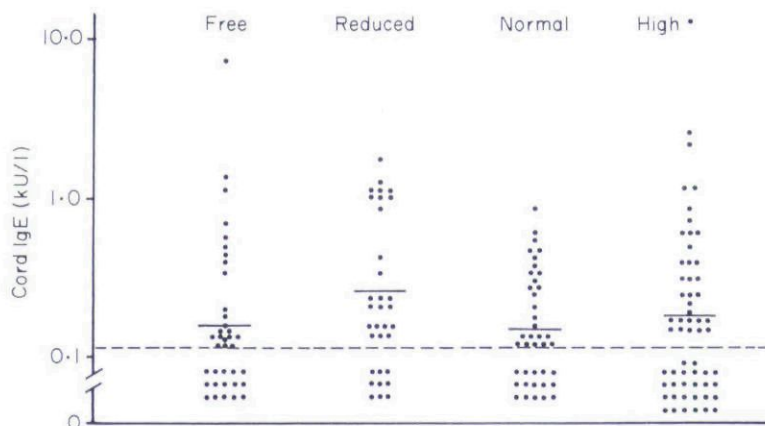


Fig. 4. Cord blood IgE levels in the four groups of children. Horizontal lines correspond to the geometric means. The cut-off value (0.12 kU/l) is indicated by the interrupted line.

Cord blood IgE

The cord blood IgE results are presented in Fig. 4. Two values, one in the reduced group and one in the high group, are missing. No significant differences were found between the study groups.

The correlation between the levels of maternal IgE and cord blood IgE in the entire material was $r=0.58$ ($P<0.01$). The corresponding correlation coefficient in each study group varied between 0.52 and 0.62. The probability value for each correlation coefficient was <0.01 . No significant correlation was found between the relative changes in maternal IgE levels during late pregnancy and the cord blood IgE concentrations. IgE-Ab to ovalbumin, ovomucoid and betalactoglobulin were not detected in the cord sera.

Cord blood IgG-Ab

The cord blood IgG-Ab concentrations to ovalbumin, ovomucoid and betalactoglobulin showed wide variations within each study group. IgG-Ab levels to ovalbumin had a range of 0.4–36.0 AU/ml. The corresponding ranges for ovomucoid and betalactoglobulin were 0.4–92.3 AU/ml and 0.4–142.0 AU/ml, respectively. No significant differences in the concentration of cord blood IgG-Ab to the food allergens studied were found between the study groups (Figs 1 and 2).

The IgG-Ab levels to ovalbumin, ovomucoid and betalactoglobulin were, in general, higher in cord blood than in maternal blood on delivery (Figs 1 and 2). The differences were not statistically significant. The correlations between cord blood IgG-Ab and maternal IgG-Ab levels at delivery were of the same magnitude ($r=0.88$ – 0.98) and with the same degree of probability ($P<0.01$), regardless of food allergen and study group.

Discussion

Modification of the maternal diet during pregnancy has been suggested as a method of preventing sensitization [13–15] or inducing tolerance [16, 17] in the foetus. In this prospective randomized study of atopic pregnant women, no significant differences were shown in cord blood IgE or cord blood IgG-Ab concentrations to ovomucoid,

ovalbumin and betalactoglobulin, regardless of the amount of cows' milk and hens' egg consumed by the women during late pregnancy.

During pregnancy the placenta acts as a barrier protecting the foetus against immune complexes and the passage of IgA, IgM and IgE. Conversely, IgG is actively transferred through the placenta to the offspring in several species, including man [26]. However, there is evidence that the pregnant woman and the foetus share immunity to a variety of antigens—for example, those of infectious agents [27]. Food antigens may enter the human circulation [28] and may, therefore, pass through the placenta to the foetus and subsequently induce an immune response, including a rise in IgE levels. Synthesis of IgE and IgE-Ab is dependent on the interaction of T- and B-cells [29, 30]; and, since pregnancy is characterized by a strong suppressor T-cell activity [31], this may explain the low incidence of IgE-specific sensitization *in utero* in this and other studies.

Since the foetus seems capable of IgE-synthesis in early pregnancy, significant differences in cord blood IgE levels in the four study groups might have been recognized if the mother's intake of cows' milk and hens' egg had been changed earlier during pregnancy. It has, however, been suggested that the foetus cannot be regarded as immunologically mature until the seventh month of gestation [32]. Because of this, and to ensure a good compliance, the third trimester was chosen.

The presented results do not support the hypothesis of intrauterine sensitization to food allergens as a cause of an increased cord blood IgE level. It has been suggested that IgE synthesis may be stimulated by the action of anti-idiotypic antibodies that serve as antigens even in the absence of the antigen [33]. IgE synthesis may also result from antigen non-specific stimulation [34]. In subjects with an increased cord blood IgE, genetic factors may play a larger role than the environment.

Contamination with maternal blood can be a possible explanation of increased cord blood IgE level. Analyses of IgA and IgM in cord blood have been recommended when the cord blood IgE exceeds 0.5 kU/l [13]. Contamination with maternal blood was excluded in this study by analyses of the concentrations of both IgA and IgE-Ab to the major maternal allergens (pollen or animal dander) in cord blood. In 10% (18/183) a contamination of the cord blood was found, which is considerably higher than the number (3%) found by Zeiger *et al.* [14]. The higher incidence of maternal contamination of cord blood in this study is believed to result from the use of stricter criteria to exclude such contamination.

Some authors have reported a correlation between the levels of maternal IgE and IgE in cord blood [6, 13], but others have not been able to document this [7, 8]. In this study a correlation of 0.58 ($P < 0.01$) was found between the concentrations of maternal IgE and cord blood IgE. Even if cord blood IgE is considered to be of foetal origin [11], the positive correlation in this study may indicate that IgE can pass through the placenta from mother to foetus. It may also indicate that mothers who are high IgE producers also stimulate the foetus to synthesize IgE *in utero*, or simply that foetuses of 'high IgE'-producers are also 'high IgE'-producers. Further studies on the maternal-foetal interplay with respect to IgE seem necessary.

The fact that the maternal IgE was significantly higher at delivery than in week 28 in the reduced and in the high groups could not be explained by factors such as a higher incidence of deliveries immediately after the pollen season, or the production of food-specific IgE-Ab. However, the women in these groups had considerably higher incidence of asthma and polyvalent allergy and a higher, although not statistically

significant, family allergy score. This may indicate that they are more 'immunologically active' and therefore, via an antigen non-specific mechanism, react more easily by increasing their immunoglobulin synthesis.

The levels of cord blood IgG-Ab to ovalbumin, ovomucoid and betalactoglobulin showed no significant differences, despite differences in maternal consumption of cows' milk and hens' egg. This may indicate the presence of a regulating mechanism in the distribution of IgG between mother and foetus/newborn in favour of the latter. Most of the IgG in the foetus and in the newborn is said to be transferred through the placenta [26]. The purpose of this maternal-foetal IgG relationship is to protect the newborn during the first months of life while the infant's own immune apparatus matures [35]. The premature infant has been shown to be capable of producing specific IgG to ingested bovine serum albumin (BSA) at an age corresponding to the week 36 of pregnancy [36]. Increased levels of secretory IgA-Ab and IgM-Ab to *Escherichia coli* O and poliovirus type I antigens in amniotic fluid, meconium and saliva have been reported in newborns [37]. It has been suggested that these antibodies, since they do not pass the placenta, are produced by the foetus itself, and that the production of IgA and IgM immunoglobulins may be stimulated by anti-idiotypic antibodies that serve as antigens [37]. However, after stimulation of cord blood B lymphocytes, a significant production of IgM has been demonstrated, but no increase in the concentrations of IgA and IgG [38]. Therefore, it seems reasonable to believe that the IgG-Ab in the newborns were transferred from the mother to the foetus. It also seems probable that the transport mechanisms in the newborns of women in the free and the reduced groups were the same, rather than that the foetus itself was stimulated to synthesize IgG by a mechanism comparable to that described by Hansson *et al.* [33] and Melander *et al.* [37].

The changes in the levels of maternal IgG-Ab to selected food allergens obviously indicate that the IgG response during late pregnancy is influenced by the amount of antigen consumed by the woman. The wide range in individual values of IgG-Ab before the diet was changed indicates a heterogeneity in IgG synthesis ('high and low IgG responders') and is in agreement with earlier studies [19]. An alternative explanation may be the difficulty of standardizing blood sampling in relation to the last intake of milk and egg; this would lead to varying degree of Ab-neutralization by the food antigens absorbed. However, a standardized blood sampling procedure in relation to the last meal was not possible to achieve at delivery. This has probably not given any confounding effect changing the results.

The observed relative changes in the maternal IgG-Ab levels in the four groups of women indicated that the women were keeping to their diet. Changes of food IgG antibody levels has also been suggested by others as a possibility to evaluate the diet compliance [14]. Besides, the women from Stockholm in the reduced and the high groups registered every tenth day and every day, respectively, the ingestion of cows' milk and hens' egg. The results of the dietary registrations confirmed a good maternal compliance.

It has been reported [19] that atopic women seem to transfer larger amounts of milk and egg IgG-Ab to the foetus than do non-atopic women. High levels of IgG-Ab to food allergens have been thought to afford protection against the development of atopic symptoms during the first 2 years of life [20, 21]. Whether the determination of IgG-Ab levels to food allergens in cord serum can be used to predict atopic disease

during childhood is not known. Follow-up studies of these infants may answer that question.

With respect to the data presented on cord blood IgE- and IgG-Ab levels, it is not justifiable to recommend any modifications of the diet during the last trimester of pregnancy. Dieting by itself is a laborious treatment for a pregnant woman and her anxiety to keep to the diet may have a negative influence on the mother-child relationship after birth. A follow-up of the infants in this study may throw further light on the subject of diet during pregnancy in relation to the development of atopic disease during childhood.

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