

REGULAR ARTICLE

Is there an increased frequency of food allergy in children delivered by caesarean section compared to those delivered vaginally?

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Abstract

Aim: Allergic diseases are increasing. At the same time an increasing number of children are delivered by caesarean section. These children do not get the same contact with their mother's gut flora as babies delivered vaginally. Theoretically, lack of exposure to maternal vaginal and perineal bacteria might change the gut flora, with secondary changes in the immune system. The aim of this study was to investigate whether children delivered by caesarean section were more prone to develop food allergy.

Methods: Six hundred and nine children were included at birth. At 2-year follow-up, 512 children participated, 171 delivered by caesarean section, 341 born vaginally. The children reported to have symptoms consistent with possible food allergy, were examined at the outpatient clinic. The diagnosis was based on the history, skin prick test (SPT), specific IgE, elimination/challenge test and double blind placebo controlled challenge.

Results: Thirty-five (6.8%) children were diagnosed with adverse reactions to food, 27 with non-IgE-mediated and eight with IgE-mediated allergy. There was no over representation of children born by caesarean section.

Conclusion: In this study there seems to be no increased risk for food allergy in the first 2 years of life in children delivered by caesarean section.

INTRODUCTION

Allergic sensitization and allergic diseases have increased markedly over the last 100 years in industrialized countries, from occurring seldom to becoming one of the most common diseases in childhood. Currently, approximately 20% of Norwegian children have or have had a diagnosis of asthma (1), other investigators report nearly 20% with allergic rhinitis (2,3) and about 6–8% of children < 3 years of age have food allergy (4,5), defined as an abnormal or exaggerated immunological response to food proteins that may be IgE or non-IgE mediated (6).

One leading theory for the last few decades has been 'The hygiene hypothesis' (7). It postulates that the time of introduction and composition of the microbial flora in the intestine is of great importance for the development of allergic diseases. Environmental factors, such as mode of delivery, antibiotics and possibly probiotics may affect a child's intestinal flora, as well as genetic factors (8–10).

In the last few decades the frequency of caesarean sections has increased in industrialized countries, in Norway now accounting for about 15% of deliveries (11), whereas the frequency in 1930 was about 1.5% and in 1960 about 6%. (12) This fact could, according to the theory above, explain some of the increases in the frequency of allergy. Previous publications have found support for this hypothesis, and discussed maternal allergy as an additional risk factor (13–15).

However, studies have been published in which there were no association between food allergy/other atopic diseases and mode of delivery (16–18). The aim of this study was to investigate whether there is an increased risk of food allergy during the first 2 years of life in children delivered by caesarean section compared to children delivered vaginally.

PATIENTS AND METHODS

Study population

One hundred and ninety-three premature infants born consecutively at the maternity clinic of Ostfold Hospital Trust (OHT) were included, with a gestational age of 28 to 35 weeks and mean birth weight 2224 (1214–2880) g. Additionally, the two following children born at term, with mean birth weight 3648 (2650–5050) g. were included, giving a total number of 609 participants. At the 2-year follow-up, 512 children (84% of the total population) participated, 161 (83.4%) premature and 351 (84.3%) term children. Of the 609 included children, 195 were born by caesarean section (48.2% of the premature and 24.5% of the term children), 414 were born by vaginal delivery. At the 2-year follow-up the numbers were 171 (50% of the participating premature and 26% of participating term children) and 341, respectively.

The parents were asked to participate during the first 4 days after delivery. Verbal and written information were

given, and a written consent was collected from those who agreed to participate. All the families were given the cell phone number of the investigator, and were instructed to call if there was any sign of illness.

Exclusion criteria: Families unable to communicate in Norwegian, and children presenting with other serious diseases, were excluded.

Questionnaires and interviews

A written questionnaire was filled out by the parents at the time of inclusion, and at the 6, 12, 18 and 24 months follow-up. Additionally, one parent was interviewed by phone at 1, 4 and 12 months after inclusion, and was specifically asked for abdominal and respiratory symptoms, skin rashes and pain behaviour.

The mothers were asked to give a blood sample for IgE analysis at the time of inclusion. All blood samples were analysed for food specific IgE (cow's milk, eggs, soy, fish, peanuts, hazelnuts and wheat) and inhaled allergens (birch, timothy, mugwort, dog, cat, house dust mite and mould) (ALAstat DPC, California, USA) at the Clin. Chem. Laboratory, OHT.

Examinations

Children with symptoms consistent with possible food allergy, reported either by phone or by questionnaire, were invited to a clinical examination at OHT within the following 4–5 days. The visit included a case history and a general clinical examination, with special attention to skin, mucosal, lung and abdominal conditions.

A skin prick test (SPT) was performed on both lower arms with a lancet, 1 mm tip, (ALK-Abello, Copenhagen, Denmark), using allergen extracts from milk, egg, cod, hazelnuts, peanuts, wheat and soy, histamine chloride 10 mg/mL was used as positive control (ALK-Abello, Copenhagen, Denmark). As negative control NaCl 0.9% was used. The SPT was read after 13 min. The contours of the wheals were encircled by a pen, the two diameters perpendicular to each other were measured in mm, added and divided by 2. The result was presented in mm. SPT equal to or greater than the positive control was considered positive.

Blood was drawn to determine total and specific IgE against food (cow's milk, eggs, fish, soy, peanuts, hazelnuts and wheat) and inhaled allergens (birch, timothy, mugwort, dog, cat, house dust mite and mould) (AlaStat, DPC, California, USA). The analyses were performed at the Clin. Chem. Laboratory, OHT.

Elimination/challenge test: The infant and/or the mother had a diet totally free from the suspected food allergen for 14 days. Detailed dietary instruction was given. A symptom score diary card was filled out daily by one of the parents. The challenge was performed by introducing the suspected food allergen to the infant or to the breastfeeding mother. Reappearance of symptoms was noted. The challenge was considered positive when symptoms reappeared with reintroduction of the allergen, but had to be reproducible and thus the elimination/challenge test was repeated at least once.

Double blind placebo controlled challenge (DBPC): The challenge was performed at the paediatric clinic: The hospital kitchen made food with and without the suspected allergen. The blinded investigator was responsible for giving the food to the child. Beginning with a minimal dose, the amount was increased 3, 10, 30, 100, 300, 1000 fold every 20 min until an adverse reaction appeared or the last dose was reached. The child was observed for two h after the last challenge dose, and a symptom score diary card was filled out by the parents the following days. The alternative challenge was performed the following week.

In the cases with suspected delayed symptoms the parents brought home food for seven days, with and without the food allergen in question, and a symptom score diary card was filled out every day.

The diagnosis of food allergy

The diagnosis was based on the following criteria:

- (1) A history of an immediate reaction to a food allergen, a positive SPT and an elevated IgE to that food allergen.
- (2) A history of suspected food allergy, with no immediate reaction and
 - for children less than 12 months of age: An open elimination/challenge test performed twice, both positive.
 - for children more than 12 months of age: A positive DBPC test.

Statistical analysis

For continuous variables the mean was used as index of location and standard deviation (SD) as index of dispersion. Counts with percentage were used for categorical variables. Pearson's chi-square test was used to assess group differences for categorical variables. The analysis was performed using Statistical Package for Social Sciences version 15 (SPSS Inc. Chicago, Illinois). p-values below 0.05 were considered significant. Odds ratios (OR) were calculated.

RESULTS

Of the 512 children at the 2-year follow-up, 198 (38.6%) children reported symptoms and were examined at the hospital. Sixty-two of these children were delivered by caesarean section, (62/171, 36.2%) and 136 children were delivered vaginally (136/341, 39.8%). Thirty-five children were diagnosed with food allergy (Fig. 1).

Twenty-eight of these children had allergy to cow's milk, only one was IgE-mediated. All the children had onset of symptoms before six months of age, but one child was not diagnosed until the second year of life. This child had onset of symptoms at one month, but the parents did not report this until 18 months. The child then was positive on DBPC challenge.

Five children were diagnosed with IgE-mediated allergy to eggs, of whom two were diagnosed solely with allergy to eggs. One of these children had no history of suspected allergy to eggs, but was positive on DBPC challenge. Two of the children with allergy to eggs were allergic to cow's milk

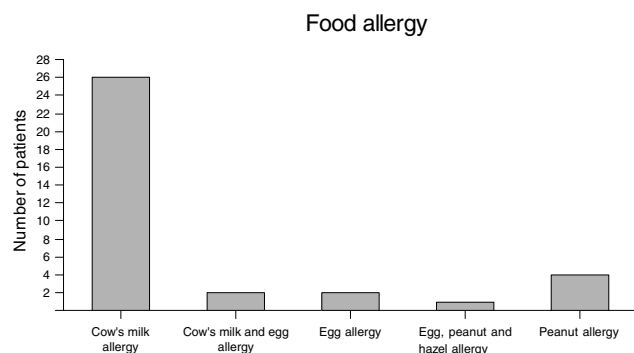


Figure 1 The different food allergies in the first 2 years of life.

Table 1 Immunologic reactions to foods/elevated IgE in children born vaginally and by caesarean section, respectively

	N	Food allergy (%)	IgE-mediated allergy (%)	Any elevated IgE (%)
Vaginally	341	22 (6.5)	7 (2.1)	35 (10.3)
Caesarean	171	13 (7.6)	2 (1.2)	6 (3.5)

as well, one of these was the child with the IgE-mediated allergy to cow's milk. One child had allergy to peanuts and hazelnuts as well.

Five children were diagnosed with peanut allergy. Two of these children had no history of suspected peanut allergy. Both were positive on DBPC challenge (Fig. 1).

Thirteen out of 171 (7.6%) children born by caesarean section and 22 out of 341 (6.5%) born by vaginal delivery were diagnosed with food allergy (Table 1). OR 0.84.

All together nine children (9/512, 1.8%) were diagnosed with IgE-mediated food allergy, seven of these were delivered vaginally and two by caesarean section (Table 1).

Six out of 171 (3.5%) children born by caesarean section and 35 out of 341 (10.3%) children born vaginally had an elevated IgE to any allergen (Table 1).

Four food allergic children (4/171, 2.3%) born by caesarean section, and seven food allergic children (7/341, 2.1%) born by vaginal delivery had a mother with an elevated IgE to any allergen.

The use of antibiotics was the same in the two groups.

Food allergy was diagnosed in ten premature children and 25 term children, 6.2% and 7.1%, respectively, OR 0.86. Six of out the ten premature (60%) and six out of the 25 term (24%) children with food allergy were delivered by caesarean sections.

DISCUSSION

In the present study 35 out of 512 children were diagnosed with food allergy during the first 2 years of life, giving 6.8% with food allergy during the first 2 years of life. This is in accordance with other investigators (4,5).

Of the food allergic children 7.6% were born by caesarean section, compared to 6.5% born vaginally. The difference is not significant, OR 0.84. This is in contrast to some previous findings, where children born by caesarean section were

three times more likely to develop food allergy (13). However, in this retrospective study with 2803 children included, the diagnosis was based on parentally perceived reactions to eggs, nuts and fish, objectively confirmed reactions to eggs only, at 2.5 years of age (13). The explanation of the diverging results might be that the diagnostic procedure in our study was different, and there was an over representation of non-IgE-mediated allergy in our cohort, as allergy to eggs, fish and nuts mainly are IgE-mediated allergy (13). As the proportion of IgE-mediated food allergy in our cohort was small, we studied the children with an IgE-mediated food allergy, as well as all children with an elevated specific IgE to any allergen, sensitized or allergic. We did not, however, find any over representation of elevated IgE in children born by caesarean section. On the contrary, we found elevated specific IgE in 3.5% of the children delivered by caesarean section compared to 10.3% of those delivered vaginally. The investigators found an even higher risk in children with an allergic mother (13), which we cannot verify. However, we did not examine the mothers with respect to clinical allergy; we looked at sensitization, knowing that this is not comparable to allergy, whereas the other investigators based the diagnosis on self reported allergy. This fact might explain the difference.

Our results are consistent with those by the Renz-Polster et al. (16), who found no relation between caesarean section and food allergy. Renz-Polster and co-workers found in a retrospective study, which included 8953 children, 3–10 years of age, an increased risk of allergic rhinoconjunctivitis in children delivered by caesarean section, but no increased risk of food allergy (16). Other studies have shown no association between any atopic diseases and mode of delivery (17,18).

Adlerberth et al. found in a prospective study no association between food allergy and lack of any particular culturable bacteria (19), which weakens the hypothesis that food allergy is associated with diverging intestinal microbial colonization and thus in accordance with our findings.

It might be argued that our findings could be due to the large number of premature children in our cohort, as they more often are delivered by caesarean section, but according to some investigators are less prone to develop allergy (20). In this cohort, however, there was no statistical difference in prevalence of food allergy in premature compared to term children, not even when adjusted for mode of delivery.

In conclusion, we cannot confirm an increased risk for food allergy in the first 2 years of life in children born by caesarean section compared to those delivered vaginally.

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References

1. Lödrup Carlsen KC, Haaland G, Devulapalli CS, Munthe-Kaas M, Pettersen M, Granum B, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006; 61: 454–60.
2. Mortz CG, Lauritsen JM, Bindselev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 2001; 144: 523–32.
3. Asher MI, Barry D, Clayton T, Crane J, D'Souza W, Ellwood P, et al. The burden of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema in children and adolescents in six New Zealand centres: ISAAC Phase One. *N Z Med J* 2001; 114: 114–20.
4. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2006; 117: 470–5.
5. Sampson HA. Food allergy—accurately identifying clinical reactivity. *Allergy* 2005; 79: 19–24.
6. Baral VR, Hourihane JO. Food allergy in children. *Postgrad Med J* 2005; 81: 693–701.
7. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299: 1259–60.
8. Kirjavainen PV, Gibson GR. Healthy gut microflora and allergy: factors influencing development of the microbiota. *Ann Med* 1999; 31: 288–292.
9. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* 2001; 107: 129–34.
10. Kalliomäki M, Isolauri E. Role of intestinal flora in the development of allergy. *Curr Opin Allergy Clin Immunol* 2003; 3: 15–20.
11. Hager R, Oian P, Nilsen ST, Holm HA, Berg AB. The breakthrough series on Caesarean section. *Tidsskr Nor Laegeforen* 2006; 126: 173–75.
12. Bordahl PE, Hem E. Changes in Norwegian obstetric practices, 1915–1961. *Tidsskr Nor Laegeforen* 2004; 124: 3231–34.
13. Eggesbø M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 2003; 112: 420–26.
14. Negele K, Heinrich J, Borte M, von Berg A, Schaaf B, Lehmann I, et al. Mode of delivery and development of atopic disease during the first 2 years. *Pediatr Allergy Immunol* 2004; 15: 48–54.
15. Laubereau B, Filipiak-Pittroff B, von Berg A, Grubl A, Reinhardt D, Wichmann HE, et al. Caesarean section and gastrointestinal symptoms atopic dermatitis, and sensitisation during the first year of life. *Arch Dis Child* 2004; 89: 993–97.
16. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connor EA, Frazier EA, et al. Caesarean section delivery and the risk of allergic disorders in childhood. *Clin Exp Allergy* 2005; 35: 1466–72.
17. Maitra A, Sherriff A, Strachan D, Henderson J, ALSPAC Study Team. Mode of delivery is not associated with asthma or atopy in childhood. *Clin Exp Allergy* 2004; 34: 1349–55.
18. McKeever TM, Lewis SA, Smith C, Hubbard R. Mode of delivery and risk of developing allergic disease. *J Allergy Clin Immunol* 2002; 109: 800–2.
19. Adlerberth I, Strachan DP, Matricardi PM, Ahrne S, Orfei L, Aberg N, et al. Gut microbiota and development of atopic eczema in 3 european birth cohorts. *J Allergy Clin Immunol* 2007; 120: 343–50.
20. Siltanen M, Kajosaari M, Pohjavuori M, Savilahti E. Prematurity at birth reduces the long-term risk of atopy. *J Allergy Clin Immunol* 2001; 107: 229–34.