

Is delivery by cesarean section a risk factor for food allergy?

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Background: Cesarean delivery might delay the colonization of the newborn intestine. A delayed or aberrant colonization process has been offered as an explanation for the increase in allergic diseases.

Objective: The aim of this study was to examine whether cesarean delivery and the use of antibiotics were associated with subsequent food allergy.

Methods: In a population-based birth cohort of 2803 children, information regarding mode of delivery, maternal or infant use of antibiotics, and information on potential confounders was obtained prospectively from parental reports and the Norwegian Birth Registry. Parentally perceived reactions to egg, fish, or nuts, as well as objectively confirmed reactions to egg at the age of 2½ years, were chosen as outcomes.

Results: Among children whose mothers were allergic, cesarean section was associated with a 7-fold increased risk of parentally perceived reactions to egg, fish, or nuts (odds ratio, 7.0; CI, 1.8-28; $P = .005$) and a 4-fold increased risk of confirmed egg allergy (odds ratio, 4.1; CI, 0.9-19; $P = .08$) in a logistic regression analysis, adjusting for pregnancy complications, birth weight, gestational length, and socioeconomic factors. Among children whose mothers were not allergic, the association was much weaker and not significant. Maternal or infant use of antibiotics was not associated with an increased risk of food allergy.

Conclusion: The results indicate that in predisposed children cesarean section might increase the risk of development of food allergy, which supports the theory that factors interfering with the colonization process might play a role in the development of food allergy. (*J Allergy Clin Immunol* 2003;112:420-6.)

Key words: Food hypersensitivity; egg allergy; double-blind, placebo-controlled food challenge; risk factors; cesarean section; antibiotics; hygiene

Allergic disease has, since first described at the beginning of the 19th century, been the disease of the advanced within a society. Furthermore, the epidemic increase in allergic diseases is mainly observed in westernized countries. Another consistent finding in epidemiologic

Abbreviation used

DBPCFC: Double-blind, placebo-controlled food challenge

OR: Odds ratio

SPT: Skin prick test

research has been that having older siblings seems to convey some sort of protection for the child. Improved hygiene has been offered as a hypothesis for these findings,¹ and in the last decades, this hypothesis has gained much support. Although the focus of the hypothesis initially was on the role of early infections, it has recently been directed more to the total microbial burden in general and to the normal intestinal colonization in particular.^{2,3}

A close interplay between the colonization of the intestine and the maturation and differentiation of the immune system has recently been revealed. Through different immunostimulatory mechanisms, microbes stimulate the immune system toward a T_H1 nonallergic response.^{4,5} Among other responses, a specific downregulation of IgE synthesis occurs through several mechanisms. Studies on germ-free animals indicate that a successful colonization of the intestines is a prerequisite for the development of a normal immune response system.⁶

Because of our good hygiene and other lifestyle factors, major alterations have occurred in the composition of the intestinal flora. The flora reported in western babies at the beginning of the 19th century had a high count of *Bifidobacterium* and *Lactobacillus* species,⁷ which resembles the flora found in babies from undeveloped countries today.⁸ A variety of hospital-acquired organisms have partially replaced these organisms in western babies. Moreover, the colonization process occurs at a slower pace.⁹ Among western babies, children delivered by means of cesarean section are reported to have an even more pronounced delayed and differential colonization.¹⁰⁻¹² Moreover, it has been shown that the differential colonization of the gut in these children is of a long-lasting character, lasting up to 6 months of age.¹³ Consequently, if a delayed or aberrant colonization does interfere with the development of the immune system and cause allergic disease, children delivered by means of cesarean section should be at increased risk of development of allergy.

The use of antibiotics has also been reported to alter the colonization. The effect probably depends on the relative germ-free status of the environment because larger effects of antibiotics have been reported in Swedish children than in African children.¹⁴

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The aim of this study was therefore to investigate whether factors that might delay or alter the quality of the bacterial colonization of the intestine are associated with allergic diseases. Specifically, we wanted to study whether children who had been delivered by means of cesarean section and had received antibiotics in their first 6 months of life or whose mothers had taken antibiotics during pregnancy were at higher risk of development of food allergy than children who had not been subjected to these measures.

METHODS

Study population

The study population included children consecutively born at the 2 main maternity clinics in Oslo, Norway, in which approximately 90% of all births in the capital take place. The study population and methods for collection of data are described in more detail elsewhere (Oslo Birth Cohort).^{15,16} Briefly, the families of the children were recruited by the midwives at the maternity wards during 1992 and part of 1993 and were followed until the child was 2 years of age. Of the 4973 eligible families, 75% participated in the study. The present study is based on the 2803 (77.4%) families of the participants who responded to the questionnaires at birth and 12, 18, and 24 months of age. The Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research approved the study.

Data collection

Information was collected on both nonparticipating and participating families by the midwives on the basis of the hospital record at the birth clinics regarding mode of delivery, maternal allergy, maternal age, and the infant's birth weight.

Information regarding maternal education in years, whether there had been any pregnancy complications (in which case the complications were required to be specified), whether the infant was the mother's firstborn child, and whether there had been maternal use of antibiotics during pregnancy was obtained from the questionnaire completed by the participating families at the maternal ward and categorized, as shown in Table I.

Information regarding infant use of antibiotics during the first 6 months was obtained from the questionnaire completed by the families when the child was 6 months of age.

Information on parentally perceived reactions to food were obtained from questionnaires sent to the families when the child was 12, 18, and 24 months of age.

Information on gestational age was obtained from the Norwegian Medical Birth Registry, which is a national registry containing information on all children born in Norway since 1967.¹⁷

Outcomes: Food allergy

Two main outcomes for food allergy were chosen. Information regarding the occurrence and type of any reaction to food was obtained at 12, 18, and 24 months from the questionnaires filled in by the parents. The operational definition of the first outcome was parentally perceived reactions to egg, fish, or nuts consistently reported at all age points (eg, 12, 18, and 24 months of age).¹⁵ Reported reactions to egg, fish, or nuts were categorized together because the bivariate analysis revealed similar associations between each of these outcomes and cesarean delivery.

The second outcome chosen was objectively confirmed reactions to egg. A reaction to egg was considered confirmed when one of the 3 following criteria were fulfilled: a history of an immediate reaction and corresponding high levels of specific IgE, an objective

reaction to an open food challenge, or a reaction verified by means of double-blind, placebo-controlled food challenge.¹⁸ Symptoms and conditions had been given a preset score in a ranking system. Each symptom was graded on a scale, ranging from 0.5 to 4, with the highest grade corresponding to the highest severity of the symptoms. Before opening the blinded code, ratings were completed to indicate whether there was a substantial difference in reactions between the 2 challenges. The details of the procedure and the symptoms recorded have been reported in detail previously.¹⁸

The first outcome measure has the advantage of avoiding potential selection bias associated with participation in the diagnostic examination. The second outcome measure has the advantage of avoiding misclassification as a result of parental misconception. Nine of 52 children were in both outcome groups.

Statistical analysis

The data were categorized and presented in contingency tables, and independence was tested by means of the Pearson χ^2 test. Odds ratios (ORs) were used as a measure of association and effect. Adjusted ORs were obtained by means of logistic regression analysis. All data were entered and analyzed by means of SPSS software (release 10).

First, to find potential confounders, we assessed the crude and adjusted relationship between covariates and cesarean delivery (Table I). Those covariates that were significantly associated with cesarean delivery plus important potential confounders were included in the multivariate analysis, with food allergy as the outcome. Gestational length and preeclampsia were the 2 factors most strongly associated with cesarean delivery, as can be seen in Table I. Stratified analyses were performed on allergic and nonallergic mothers.

RESULTS

Repeatedly parentally reported reactions to egg, fish, and nuts

For 32 children, a reaction to either eggs, fish, or nuts had been consistently reported by the parents at all age points (eg, when they were 12, 18, and 24 months of age). Repeatedly, reported reactions were 3-fold more common among children delivered by means of cesarean section (Table II). Adjustment for a broad number of potential confounders only slightly altered the associations (Table II).

Stratifying the sample according to whether the mother was allergic ($n = 571$) or not ($n = 2227$) revealed that the effect of cesarean delivery on subsequent food allergy was larger among children whose mothers were allergic (OR, 7.0; CI, 1.8-28; $P = .005$) than among mothers who were not allergic (OR, 1.8; CI, 0.5-6; $P = .3$). Because of the small strata of allergic mothers, the effect of maternal allergy and cesarean delivery is presented as 4 categories for the combinations of maternal allergy (yes-no) and cesarean delivery (yes-no) in the total sample (Table III). The risk of reported allergy to egg, fish, and nuts is 9-fold in children delivered by means of cesarean section whose mothers are allergic compared with vaginally delivered children of nonallergic mothers (Table III).

In a multivariate analysis in which an interaction term had been included, there was no significant interaction between maternal allergy and cesarean delivery (OR, 3.6; CI, 0.7-19; $P = .16$), however.

TABLE I. Percentage of children delivered by means of cesarean section and crude and adjusted ORs for section in a population-based cohort of 2803 children separated according to gestational age, birth weight, pregnancy complications, and socioeconomic factors

	n	%	P value	Crude		Adjusted	
				OR	CI	OR	CI
All	2803	11.7					
Maternal age (Y)			.003				
16-25	406	7.6		0.4	0.3-0.7	0.4	0.2-0.7
26-30	2047	11.8		0.7	0.5-1.0	0.7	0.5-1.0
>35	350	15.7		1.0		1.0	
Maternal education (Y)			.376				
9-12	1204	12.0		1.0	0.7-1.3	1.0	0.7-1.3
13-15	873	10.4		0.8	0.6-1.1	0.8	0.6-1.1
>15	712	12.5		1.0		1.0	
Birth weight (g)			<.001				
2010-3000	367	22.6		2.3	1.5-3.6	1.1	0.6-1.8
3005-3500	884	10.5		0.9	0.6-1.4	0.7	0.4-1.1
3505-3795	655	9.5		0.8	0.5-1.3	0.7	0.4-1.1
3800-4200	611	9.7		0.8	0.5-1.3	0.7	0.4-1.2
4210-5600	276	11.2		1.0		1.0	
Gestation length (wk)			<.001				
<38	209	25.4		4.0	2.7-5.9	2.6	1.6-4.3
38	259	17.0		2.4	1.6-3.6	1.9	1.2-2.9
39	533	14.3		1.9	1.4-2.7	1.7	1.2-2.5
40	728	8.1		1.0	0.7-1.5	1.0	0.7-1.5
>40	925	7.9		1.0		1.0	
Preeclampsia			<.001				
Yes	68	26.5		2.8	1.6-4.9	2.9	1.6-5.4
No	2735	11.3		1.0		1.0	
High blood pressure			.088				
Yes	52	19.2		1.8	0.9-3.7	1.9	0.9-4.2
No	2751	11.6		1.0		1.0	
Pregnancy bleeding			.006				
Yes	67	22.4		2.2	1.2-4.0	1.6	0.8-3.2
No	2736	11.4		1.0		1.0	
Intrauterine growth restriction			<.001				
Yes	34	41.2		5.5	2.7-10.9	2.9	1.3-6.4
No	2769	11.3		1.0		1.0	
Hyperemesis gravidarum			.554				
Yes	45	8.9		0.7	0.3-2.1	0.6	0.2-1.7
No	2758	11.7		1.0		1.0	
Threatening premature labor			.827				
Yes	39	12.8		1.1	0.4-2.9	0.7	0.3-2.0
No	2764	11.7		1.0		1.0	
Maternal smoking			.468				
Yes	622	12.5		1.1	0.8-1.5	1.1	0.8-1.5
No	2178	11.5		1.0		1.0	
Breast milk			<.001				
≤1 mo	122	21.3		2.1	1.4-3.3	1.9	1.1-3.1
>1 mo	2615	11.3		1.0		1.0	
Pregnancy complications			.025				
Yes	115	18.3		1.7	1.1-2.8	1.3	0.8-2.4
No	2688	11.4		1.0		1.0	

Adjustment was made for the factors listed.

There was no significant association between maternal use of antibiotics during pregnancy and infant's use of antibiotics one or more times during the first 6 months compared with no use of antibiotics on the risk of subsequent parentally reported reactions to egg, fish, or nuts (Table II).

Confirmed reactions to egg

Confirmed reactions to egg were not significantly associated with cesarean delivery (Table IV). However, among allergic mothers, a 4-fold increased risk was observed in children delivered by means of cesarean sec-

TABLE II. Children with repeatedly reported reactions to egg, fish, or nuts in a population-based cohort of 2803 children separated according to cesarean delivery, use of antibiotics, short-term breast-feeding, maternal allergy, and older siblings and adjusted for potential confounders

	n	%	P value	Crude		Adjusted	
				OR	CI	OR	CI
All	2803	1.1					
Cesarean delivery			<.001				
Yes	328	2.7		3.1	1.4-6.9	3.2	1.4-7.3
No	2475	0.9		1		1	
Maternal antibiotic use			.5				
Yes	272	0.7		0.6	0.2-2.7	0.8	0.2-3.3
No	2531	1.1		1		1	
Child received antibiotics in first 6 mo			.7				
Yes	963	1.2		1.2	0.6-2.4	1.1	0.5-2.4
No	1796	1.1		1		1	
Breast milk			.6				
≤1 mo	122	1.6		1.5	0.4-6.5	1.5	0.3-7
>1 mo	2615	1.1		1		1	
Maternal allergy			<.05				
Yes	571	1.9		2.2	1-4.6	2.0	0.9-4.4
No	2227	0.9		1		1	
Older siblings			.4				
Yes	1063	1.3		1.4	0.7-2.8	1.3	0.6-2.8
No	1740	1.0		1		1	

Adjusted for birth weight, gestational age, preeclampsia, restricted growth of the fetus, pregnancy bleeding and other pregnancy complications, maternal age, maternal education, and maternal smoking. Two hundred seventy-two children were not included in the adjusted analysis because of missing values on covariates.

TABLE III. Children with repeatedly reported reactions to egg, fish, or nuts in a population-based cohort of 2803 children separated according to cesarean delivery, maternal allergy, or both cesarean delivery and maternal allergy

	n	%	P value	Crude		Adjusted	
				OR	CI	OR	CI
All	2803	1.1					
Maternal allergy, cesarean section, or both			<.000				
Allergy -/section -	1969	0.8		1.0		1.0	
Allergy -/section +	263	1.5		1.9	0.6-5.7	1.9	0.6-6.0
Allergy +/section -	506	1.2		1.5	0.6-3.8	1.4	0.5-3.6
Allergy +/section +	65	7.7		10.2	3.6-29	9.3	3.1-28*

Adjusted for birth weight, gestational age, preeclampsia, restricted growth of the fetus, pregnancy bleeding and other pregnancy complications, short-term breast-feeding, older siblings, maternal age, maternal education, and maternal smoking. Two hundred thirty-six children were not included in the adjusted analysis because of missing values with regard to covariates.

**P* < .001.

tion, although the CI is wide and reaches less than 1 (OR, 4.1; CI, 0.9-19; *P* = .08). Among nonallergic mothers, there was no association between cesarean delivery and subsequent egg allergy (OR, 0.6; CI, 0.07-5.6; *P* = .7).

Because of small numbers and to adjust for potential confounders, the results are shown in the total sample by using 4 categories for the combinations of maternal allergy (yes-no) and cesarean delivery (yes-no; Table V). The risk of having a confirmed allergy to egg is 7-fold increased in children delivered by means of cesarean section whose mothers are allergic compared with vaginally delivered children of nonallergic mothers (Table V). Vaginally delivered children of allergic mothers are also at significantly increased risk. There was no significant associa-

tion between maternal use of antibiotics during pregnancy and infant's use of antibiotics one or more times during the first 6 months compared with no use of antibiotics on the risk of subsequent egg allergy (Table IV).

DISCUSSION

Cesarean section was associated with subsequent food allergy, especially among allergy-predisposed children. Among children whose mothers were allergic, cesarean section was associated with a 7-fold increased risk of parentally perceived reactions to egg, fish, or nuts and a 4-fold increased risk of confirmed egg allergy, although in the latter the CI is wide and reaches less than 1.

TABLE IV. Children with confirmed reactions to egg in a population-based cohort of 2803 children separated according to cesarean delivery, maternal and infant use of antibiotics, short-term breast-feeding, maternal allergy, and older siblings adjusted for potential confounding factors

	n	%	P value	Crude		Adjusted	
				OR	CI	OR	CI
All	2803						
Cesarean delivery			.3				
Yes	328	1.2		1.8	0.6-5.3	1.6	0.5-5.1
No	2475	0.7		1		1	
Maternal antibiotics			1.0				
Yes	272	0.7		1	0.2-4.2	1.1	0.3-4.9
No	2531	0.8		1		1	
Child antibiotics first 6 mo			.4				
Yes	963	0.9		1.4	0.6-3.3	1.5	0.6-3.7
No	1796	0.7		1		1	
Breast milk			.9				
≤1 mo	122	0.8		1.1	0.1-8.1	1.5	0.2-12
>1 mo	2615	0.8		1		1	
Maternal allergy			<.01				
Yes	571	1.8		3.6	1.5-8.5	3.3	1.4-7.9†
No	2227	0.5		1		1	
Older siblings			.181				
Yes	1063	0.5		0.5	0.2-1.4	0.5	0.2-1.5
No	1740	0.9		1		1	

Adjusted for birth weight, gestational age, preeclampsia, restricted growth of the fetus, pregnancy bleeding and other pregnancy complications, older siblings, maternal age, maternal education, and maternal smoking. Two hundred seventy-two children were not included in the multivariate analysis because of missing values on covariates.

† $P < .01$.

We found no association between the infant's use of antibiotics one or more times during the first 6 months compared with no use of antibiotics or maternal use of antibiotics and subsequent food allergy. However, the effect of antibiotics is likely to be stronger when given perinatally or in the early postnatal period. Unfortunately, we did not have information enabling us to differentiate between antibiotics given perinatally, in the early postnatal period, or later on.

Methodological considerations

The main methodological concern in this study is related to potential confounding factors associated with cesarean section and the relatively small number of cases. We sought to control for a broad range of potential confounders, including pathologic conditions associated with cesarean delivery. The association between cesarean deliveries and reported food reactions was surprisingly stable when the multivariate analysis was performed in a stepwise manner, not indicating any major confounding with any of the variables included in the analysis.

The use of antibiotics in connection with cesarean section is an important confounder for which we were not able to control. Furthermore, a differentiation between elective and emergency cesarean delivery, which could not be done with our data, would also be of interest. Thus further studies are needed that take into account other potential confounders associated with cesarean delivery.

The information is based on hospital reports or maternal self-reports and might be subject to some degree of

misclassification. However, information on pregnancy-related conditions have been shown to have a high degree of validity.¹⁹ Furthermore, the prospective design of the study, in which exposure data were obtained before the outcome, reduces the risk of any systematic error.

Previous studies conducted among the same parents have shown high reliability of repeatedly reported reactions to egg.²⁰ We have assumed that this applies for reported reactions to fish and nuts as well because they are usually IgE mediated, with an immediate onset. The method used to categorize confirmed food reactions is based on a stepwise, well-established diagnostic routine.²⁰ Confirmed reactions to egg should thus not be subject to misclassifications of any substantial degree. On the other hand, there might be selection bias tied to participation in the time-demanding diagnostic procedure. An unequal distribution of characteristics, which could be either preventive or risk factors for disease, between participants and nonparticipants could affect the risk estimate. We have therefore chosen to present the results on the basis of 2 different outcome measures with different potential errors. The consistency in the results in the 2 outcome measures strengthens the validity of the results.

The small groups makes the study prone to type II errors (ie, not detecting factors that might be of importance). This uncertainty affects, among other results, the results concerning antibiotics. Furthermore, it might be the reason why the association between egg allergy and cesarean delivery failed to reach significance in the strata of allergic mothers in spite of the strength of the observed association.

TABLE V. Children with confirmed reactions to egg in a population-based cohort of 2803 children separated according to cesarean delivery, maternal allergy, or both cesarean delivery and maternal allergy

	n	%	P value	Crude		Adjusted	
				OR	CI	OR	CI
All	2803	0.7					
Maternal allergy, cesarean section, or both			<.001				
Allergy -/section -	1959	0.5		1.0			
Allergy -/section +	262	0.4		0.7	0.1-5.5	0.7	0.1-5.5
Allergy +/section -	499	1.4		2.6	1.0-7.0	2.5	1.0-7.0
Allergy +/section +	62	4.6		7.3	1.7-31.1	7.8	1.9-32*

Adjusted for birth weight, gestational age, preeclampsia, restricted growth of the fetus, pregnancy bleeding and other pregnancy complications, short-term breast-feeding, older siblings, maternal age, maternal education, and maternal smoking. Two hundred thirty-six children were not included in the analysis because of missing values on covariates.

* $P < .01$.

Synthesis with previous knowledge

To our knowledge, there have been no previous studies on the relationship between cesarean delivery and subsequent food allergy. There have been several other studies on the association between cesarean delivery and other atopic outcomes, such as asthma and hay fever, with conflicting results.²¹⁻²⁶ Indeed, in our own study sample no association was observed between cesarean delivery and bronchial obstruction by the age of 2 years or asthma and allergic rhinitis at the age of 4 years.²⁴ However, although there might be some common genetic predisposition, there are probably different environmental risk factors for different atopic conditions.²⁷

If cesarean delivery increases the risk of food allergy by interfering with the colonization process, a differential colonization among children with food allergy and nonallergic children should be observed. There is some support for this because several studies have indeed found an association between food allergy and an aberrant colonization pattern, although there is some inconsistency with regard to which bacteria differ, samples are small, and the outcome is heterogeneous.²⁸⁻³¹ Nevertheless, there seems to be consistency between the studies with regard to a higher colonization rate with *Clostridium difficile* and lower counts of bifidobacteria among children with food allergy or positive skin prick test responses compared with nonallergic children.²⁸⁻³¹ On the other hand, as pointed out by Bjørkstén et al,²⁹ differences in flora between allergic and nonallergic children might not be causal but could be related to other factors associated with atopic diseases, such as mucosa factors or more frequent use of antibiotics.

It might seem unlikely that a single event, such as a cesarean section, should have any major influence on the subsequent turnover of bacteria in the colonization process. On the other hand, the input of maternal bacteria might be especially important because of several factors. First, it has been reported that maternal bacteria are more likely to successfully colonize the child's intestine compared with bacteria from other sources.³² Second, in the

absence of bacterial input from the mother, the infant is more likely to be colonized with hospital bacteria, among which a number of opportunistic and pathogenic bacteria can be found. Opportunistic bacteria are more frequently encountered in children delivered by means of cesarean section than children delivered vaginally. These opportunistic bacteria might have independent negative effects on the immune system. Third, studies have reported that western babies, in contrast to babies from less developed countries, have a reduced turnover of bacteria.³² It has been proposed that a high turnover of translocating bacteria might be necessary to provide the continuous stimulation necessary to prevent allergic diseases.^{4,33} In such a case, any factor further reducing the input of bacteria might have a large effect. For instance, the effect of antibiotics has been reported to result in profound and lasting changes on the flora of Swedish babies, whereas Ethiopian babies quickly restored the lost colonies.¹⁴ Enterobacteria might be among the most potent stimulators. They were ubiquitously present in infants during the first week of life only some decades ago and are ubiquitously present in babies from the third world today, according to previous studies, but are lacking in 25% of Swedish children nowadays.⁹ Enterobacteria are present in the mother's perineum, and this might be one of the few sources for input in western societies because of high hygiene. Thus, taken together, there are several factors that might indicate that the input of bacteria from the birth canal might be of crucial importance in western babies.

Finally, the perinatal period is probably a very important period in life. The first bacteria colonizing the intestine might persist longer compared with bacteria arriving later.³⁴ This might at least partly be due to an ability to induce changes in the host to advantage their survival.^{35,36} Furthermore, once established, the immune system has self-regulatory properties.

Conclusion

The present study indicates that cesarean delivery is associated with subsequent food allergy, especially among predisposed children. The results need to be con-

firmed by others but might be important in several aspects. First, they lend circumstantial support to the importance of microbiologic stimuli in early life. Second, if the association between cesarean delivery and food allergy is confirmed by others, this might be a further factor to consider when mode of delivery is discussed.

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