

Original article

Cesarean delivery and cow milk allergy/intolerance

The present study provides support for a positive association between cesarean delivery and persistent cow milk allergy/cow's milk intolerance. Correspondingly, a negative association was seen between cesarean delivery and early outgrown cow milk allergy/intolerance. A possible explanation is that cesarean delivery, rather than increasing the overall risk of food allergy, increases the risk of persistency of disease among food allergic children.

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Reduced microbial encounter has been hypothesized to play a role in the development of allergies. Cesarean delivery limits the input of maternal bacteria during birth and may thus be a risk factor.

Previously we reported a positive association between cesarean section and egg, fish and nut allergy (1). Here, the more complex associations with cow milk allergy/intolerance (CMA/CMPI) are reported.

Methods

The present study is based on 2656 participants in Oslo Birth Cohort, omitting children with reactions to egg, fish or nuts, and nonresponders to questionnaires used in the study. The outcomes chosen were parentally perceived reactions reported at 12, 18 and 24 months, and reactions objectively verified at the age of 2½. Confirmed and probable CMA/CMPI were grouped together as 'verified', because bivariate analysis revealed the same associations to cesarean delivery. All details of the study have been reported previously (2). Odds ratio (OR) were obtained by logistic regression

(SPSS Release 11), adjusting for variables listed in Table 1, 95% confidence intervals (CI) are given.

Results

There was no association between parentally perceived reactions to milk reported at three occasions and mode of delivery (crude OR, 0.5, CI: 0.2–1.4), or any interaction with maternal allergy, whether analyzed crude or adjusted.

In contrast 'verified' CMA/CMPI is twice as common among children who had been delivered by a cesarean section compared with children who had been vaginally delivered (adjusted OR: 2.5, CI: 0.8–7.5). Cesarean delivery is associated with a larger percentage increase in allergic children among allergic mothers than among nonallergic mothers, indicating an additive interaction (Table 1).

Among children classified as earlier CMA/CMPI grown tolerant, either based on parental reports or observed at the examination at 2½ years, none had had a cesarean, indicating a negative association between becoming tolerant before the age of 2½ year and cesarean section ($P = 0.05$).

Abbreviations: SPT, skin prick test; CMA/CMPI, cow milk allergy/intolerance.

Table 1. Children with verified cow's milk allergy/intolerance (CMA/CMPI) in a population-based cohort of 2656 children, according to caesarean delivery, maternal allergy, or both caesarean delivery and maternal allergy

	Healthy	CMA/CMPI		Crude		Adjusted	
	<i>n</i>	<i>n</i> (%)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
All	2634	22					
Maternal allergy ± caesarean							
None	1868	7 (0.4)	>0.001	1		1	
Only caesarean delivery	244	3 (1.2)		3.3 (0.8–12.8)	0.09	3.3 (0.8–14.1)	0.10
Only maternal allergy	467	10 (2.1)		5.7 (2.2–15.1)	0.000	5.6 (2.1–15.0)	0.001
Both	55	2 (3.6)		9.7 (2.0–47.8)	0.005	9.6 (1.8–52.4)	0.009

Adjusted for maternal age, education and smoking, children's birth weight, gestation length, pregnancy complications, short-term breast feeding (<1 month), being a firstborn child, maternal use of antibiotics during pregnancy and finally infant use of antibiotics during the first 6 months of life.

About 255 children not included in the adjusted analysis due to missing values.

CI, confidence interval.

Discussion

The association between cesarean section and verified CMA/CMPI is consistent with our previous study on egg allergy and with a study on sensitization to food allergens (3). For asthma, although more inconsistent results are reported, a pooled analysis favors an association (4). Furthermore, differences have been observed in the intestinal microflora between food allergic and healthy children (5). However, these differences may not be causal but rather a consequence of the disease. The results of the present study cannot be explained by differences between predisposed and not predisposed children and thus provides support for early intestinal colonization playing a role in the etiology of food allergy.

The lack of an association between cesarean delivery and reported reaction to milk was unexpected, as was the negative association with growing tolerant before 2½ years. In order to investigate whether this could be explained by misclassification associated with parental reports, we performed a mathematic simulation. Only when assuming an extreme degree of differential misclassification, with all misclassification taking place among

children without a cesarean was it possible to move OR below 1.

An alternative explanation is that cesarean delivery does not increase the risk of food allergy but the risk of persistent disease among food allergic children. This could explain the lack of association to parentally reported reactions to milk, because this is a mix of children with nonpersistent and persistent allergy. In contrast, all children with verified CMA/CMPI had persistent allergy, as the diagnosis was set when they were 2½ years old. The finding of not one cesarean section among the children that had become tolerant, support this explanation.

The small sample size and the wide and overlapping CI limits the interpretation and larger studies are required to confirm these findings. However, the possibility that mode of delivery influences persistence of allergic disease, may be worth considering in future research.

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References

1. Eggesbo 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**: 420–426.
2. Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy* 2001;**56**:393–402.
3. 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 of life. *Pediatr Allergy Immunol* 2004;**15**:48–54.
4. Maitra A, Sherriff A, Strachan D, Henderson J. Mode of delivery is not associated with asthma or atopy in childhood. *Clin Exp Allergy* 2004;**34**:1349–1355.
5. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001;**108**:516–520.