

Association between Caesarean Delivery and Isolated Doses of Formula Feeding in Cow Milk Allergy

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Keywords

Cow milk allergy · Caesarean delivery · Breastfeeding · Formula feeding

Abstract

Background: Cow milk allergy (CMA) is the most common food allergy in breastfed infants. The aim of this study is to verify whether certain perinatal factors may influence the development of CMA immunoglobulin E (IgE)+. **Methods:** A retrospective, observational study of case and control groups was carried out. Information was collected of patients with CMA IgE+ from our department during the years 1990–2013. Patients of the same age and sex were recruited for the control group. Information on the following variables was collected: sex, age, pregnancy tolerance, duration of pregnancy, type of delivery, isolated doses of formula feeding in hospital (FFH), duration of breastfeeding, and family history of allergy (defined as ≥ 1 first-degree family member with allergic disease). Statistical analysis was performed using multivariate logistic regression techniques. **Results:** A total of 211 cases were included in this study. Multivariate analysis showed an influence of duration of breastfeeding, FFH to be a risk factor (OR 4.94; 95% CI 2.68–9.08), especially in caesarean delivery (OR 11.82; 95% CI 2.64–47.50), and prematurity

(OR 0.29; 95% CI 0.09–0.92) to be a protective factor. **Conclusions:** Perinatal factors play a key role in the development of CMA IgE+, with an influence of breastfeeding duration, FFH and caesarean delivery as risk factors and prematurity as a protective factor. While family history had no important role, environmental factors were more decisive.

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Introduction

Cow milk allergy (CMA) is the most common food allergy in breastfeeding (BF) infants and young children and it can affect 2% of children under 5 years of age and 0.9% of the general population [1–3]. CMA presents a wide variety of clinical symptoms as immune responses to cow's milk proteins (CMP) can be mediated by immunoglobulin E (IgE) and not mediated by IgE, fundamentally type III (immune complex) and type IV reactions (mediated by T cells or a delayed type) [4, 5]. The diagnosis is based on clinical and allergy studies, with provocation testing being the gold standard for diagnosis [6]. The treatment of choice is initially a diet free from CMP [4, 6].

CMA is a disease that generates high health care costs [7–10]. In primary prevention strategies recommended

by clinical guidelines, children at risk are defined as those whose parents or siblings have a history of allergic disease [6]. These strategies have been based mainly on dietary restrictions for mothers during pregnancy and lactation, suggesting that they avoid or delay introducing certain foods that are considered allergenic [6]. However, such recommendations have been found to not be effective [11–14]. BF has been postulated as a protective factor against the development of CMA, although evidence levels are somewhat inconsistent [14]. There is also not much evidence regarding the use of special formulas [15, 16], probiotics [17], or prebiotics [18] by patients at risk. Other factors that have been studied are caesarean delivery [19–23] and perinatal exposure to small amounts of CMP [24–27], though the results are conflicting. Other factors such as duration of BF [14, 28, 29], prematurity, threatened premature delivery, preeclampsia [30], hypertension, gestational diabetes [31], and antibiotics [21] during labor have been much less studied. The purpose of this study is to analyze the impact different perinatal factors may have on the development of IgE-mediated CMA.

Materials and Methods

A retrospective, observational case-control study was conducted in Navarra, Spain, after receiving approval from the Clinical Research Ethics Committee. The cases were recruited in the Pediatric Gastroenterology and Nutrition Unit of the Hospital of Navarra, the tertiary referral hospital of the Navarra Health Service, which offers universal assistance to the people of Navarra (Autonomous Community of Spain, estimated population: 640,154) [32]. All patients were recruited in the outpatient pediatric gastroenterology consult at the time of diagnosis in the first year of life, and any refusal to be included in this observational study was registered. Clinical data of all of the patients diagnosed with CMA were collected from June 1990 to June 2013 via consultation of medical records and a recruitment questionnaire. The inclusion criteria for the cases were: previously healthy patients with a clinical profile suggestive of CMA (anaphylactic shock, urticaria, angioedema, perioral syndrome, atopic dermatitis, vomiting, diarrhea, rejection of feeding, spasmodic cough, allergic rhinitis, otitis, and other compatible symptoms) who also presented specific IgE antibodies to CMP (IgE specific to casein, β -lactoglobulin and α -lactalbumin, IgE cutoff >0.35 kU/L) in the initial evaluation with confirmation via a positive provocation test (except for those cases in which a provocation test was considered contraindicated). Provocation tests were performed on all of the patients, except those with a history of anaphylaxis or severe allergic reaction after exposure to CMP or who presented very high levels of specific IgE in the initial determination (>2.5 kU/L). We excluded all patients with a history of chronic digestive diseases and patients who had already been diagnosed with CMA IgE+ who had undergone previous treatments.

Table 1. Descriptive analysis of age and gender in the CMA and control groups

	CMA IgE+	Control	<i>p</i>
Age, years	14.41 $\pm$ 5.42	14.59 $\pm$ 4.09	0.713 ^a
Male gender	128/211 (60.7)	128/211 (60.7)	1.000 ^b

Values are presented as means $\pm$ SD or numbers/total (%) unless otherwise stated. CMA, cow milk allergy; IgE, immunoglobulin E. ^a Student *t* test for independent samples. ^b Pearson χ^2 test.

The control sample was found in the same healthy reference population according to a criterion of no difference in the distribution of basic biological variables (age and gender) from the study cases. The control sample was recruited using a direct questionnaire at schools and health centers. Control recruitment was performed after planning stratification by gender and age, with different numbers of participants in every group according to the case distribution. They were collected unselectively in order of arrival to complete every stratum previously established and then the recruitment was stopped, so a database of the excluded controls was not generated. The inclusion criteria were: individuals from the same reference population who regularly tolerated the consumption of dairy products, excluding patients with a previous or current history of CMA.

The following variables were collected for both the case and the control groups: date of birth, pregnancy tolerance (poor pregnancy tolerance was defined as presence of any of the following conditions in the mother during pregnancy: hypertension, preeclampsia/eclampsia, and threatened preterm birth or gestational diabetes; the absence of these conditions was the reference category), duration of pregnancy (pregnancy was defined as premature when the baby was born at a gestational age of less than 37 weeks and as term when they baby was born at a gestational age of more than 37 weeks, with term delivery being the reference category), type of delivery (categorized as vaginal birth or caesarean delivery, with vaginal birth being the reference category), formula feeding in hospital (FFH) (categorized as patients who received some isolated doses of formula during maternity and then continued with BF exclusively; the reference category was comprised of patients who received no formula supplement and were discharged with exclusive BF or those who were discharged with formula feeding or mixed BF), duration of BF (categorized as less than 1 month, from 1 to 4 months, from 4 to 6 months, and more than 4 months, with BF duration longer than 6 months as the reference category), family history of allergy (FH) (defined as one or more first-degree relatives with a history of allergic disease; no first-degree relatives with a history of allergic disease was the reference category). Additionally, for the cases, age and clinical manifestations when diagnosed were collected.

For statistical analysis, the Pearson χ^2 test was used for dichotomous variables for comparison of proportions. To calculate OR and 95% CI, logistic regression was used. A multivariate logistic regression model was employed for different predictor variables (i.e., pregnancy tolerance, duration of pregnancy, type of delivery, FFH, duration of BF, and FH, tested a priori for confusion and interaction), performing calibration and adjustment with ROC curves and the Hosmer-Lemeshow test.

Table 2. Perinatal variables for the CMA and control groups

	CMA	Control	OR ^a (CI 95%)	<i>p</i> ^b
PPT	24 (11.5)	37 (18)	0.59 (0.34–1.03)	0.062
Prematurity	9 (4.3)	27 (13.2)	0.29 (0.13–0.64)	0.001
Caesarean	94 (45)	33 (15.9)	4.33 (2.73–6.87)	<0.001
FFH	134 (73.6)	35 (17.9)	12.76 (7.79–20.88)	<0.001
FH ^c	100 (42.1)	89 (47.3)	1.23 (0.84–1.81)	0.282
BF duration				
<1 month	41 (19.4)	25 (11.8)	1.79 (1.04–3.07)	0.034
1–4 months	69 (32.7)	66 (31.3)	1.06 (0.70–1.60)	0.754
4–6 months	65 (30.8)	39 (18.5)	1.96 (1.24–3.09)	0.004
>6 months	30 (14.2)	57 (27.0)	0.44 (0.27–0.73)	0.001

Values are presented as numbers (%) unless otherwise stated. CMA, cow milk allergy; PPT, poor pregnancy tolerance; FFH, formula feeding in hospital; FH, family history of allergy; BF, breastfeeding. ^a The control group was used as reference. ^b Pearson χ^2 test. ^c One or more family members with an allergic disease.

Results

A total of 211 cases were included. The gender distribution was 128 (60.7%) men and 83 (39.3%) women. The age at diagnosis was 5.07 ± 2.67 months and the current mean age (June 2015) was 14.41 ± 5.42 years. The 211 healthy controls showed no significant differences in gender or age compared to the cases (Table 1).

Table 2 shows the univariate analysis of the different perinatal variables that were studied in the case and control groups. Generally, a higher proportion of poor pregnancy tolerance, increased prematurity, and a higher proportion of BF duration >6 months were observed in the control group compared to the CMA group. Conversely, a higher proportion of caesarean deliveries, FFH, BF duration <1 month, and BF for 4–6 months in the CMA group was evident.

When performing the multivariate analysis on patients with CMA and the control group of independent predictors of CMA, the model shown in Table 3 was obtained. A strong association of CMA with FFH as a risk factor was observed, and it also interacted with caesarean delivery, in the presence of which the OR value was significantly multiplied. Other factors such as prematurity were negatively associated. With respect to BF duration (used BF longer than 6 months as the reference category [33]), we observed that BF duration <1 month as well as BF for 4–6 months were associated with a higher risk of CMA, while there were no differences in BF from 1 to 4 months. The model showed goodness of fit, with an area under the curve of 0.852 and a nonsignificant Hosmer-Lemeshow test result ($p = 0.816$).

Table 3. Multivariate analysis model for the variable outcome CMA

	OR (95% CI)	<i>p</i>
FFH ^a	4.94 (2.68–9.08)	<0.001
Caesarean	0.91 (0.36–2.31)	0.857
FFH $\times$ caesarean	11.62 (2.84–47.50)	0.001
Prematurity	0.29 (0.09–0.92)	0.037
BF duration		0.005
<1 month	3.87 (1.58–9.50)	0.003
1–4 months	1.81 (0.84–3.90)	0.127
4–6 months	3.54 (1.58–7.89)	0.002
>6 months	Ref.	
FH	0.86 (0.49–1.48)	0.594
Constant	0.17	<0.001

FFH, formula feeding in hospital; BF, breastfeeding; FH, family history of allergy; CMA, cow milk allergy. ^a Isolated formula feeding during maternity with subsequent exclusive BF.

Discussion

Comparison of the different perinatal variables analyzed between the CMA IgE+ and control groups suggests a number of interesting considerations. The most significant is the strong association of this disease with isolated administration of FFH in women who subsequently continued to exclusively breastfeed their children. Among the patients with CMA IgE+, 73.6% reported having consumed isolated doses of formula during maternity, compared to only 17.9% of the healthy control group. Similar data have been reported in case and control studies [34],

a series of case studies [25], and cohort studies [24, 35–36]. However, De Jong et al. [26] refuted this association in a double-blind randomized trial of 1,533 infants who were given either CMP or a placebo for 3 days and were monitored for the occurrence of atopic diseases for 2 [26] and 5 years [27]. The authors concluded that early exposure to CMP was not associated with atopic diseases. Despite this, the infants randomized into the CMP group from that study were BF exclusively for a very short period (33.4% were exclusively BF for less than 2 weeks, 48% were exclusively BF for less than 6 weeks, and more than 70% were exclusively BF for less than 3 months), in contrast to our study in which the mean period of exclusive BF in the CMA group was more than 4 months. The fact that the rate of exclusive BF was so low in such a high percentage of cases may have contributed to inducing tolerance in these patients, as occurred in patients who consumed breastmilk mixed with formula or those who only consumed formula. Not considering the duration of the BF period may have led to underestimation of the association between FFH and CMA, which in our study was very strong, with an OR in the multivariate analysis of 4.94 for vaginal delivery and 11.62 for caesarean delivery, as has been noted by various authors. Katz et al. [37] published a study of a cohort of more than 13,000 children and found that children who consumed formula from an earlier age were less likely to develop IgE-mediated CMA. Possibly the key problem is isolated consumption of formula and a subsequent extended period of exclusive BF.

The other risk factor in our study associated with CMA was caesarean delivery. There is some controversy regarding this in the literature, and mixed results have been published [19–23]. The univariate analysis of our study showed that a caesarean delivery is a very significant risk factor. However, when performing the multivariate analysis this association was only observed for interactions with the variable FFH, such that the OR increased significantly in the group of patients born by caesarean who consumed FFH, while in the group of patients born by caesarean who did not consume FFH it was not shown to be a risk factor. In the studies mentioned above, FFH was not considered as a variable, and perhaps this could explain the contradictory results found in previous studies. It therefore seems that both early and isolated introduction of CMP with a subsequent period of prolonged BF and the presumable changes in the intestinal microflora produced by a caesarean delivery [38] (in addition to the concomitant use of antibiotherapy [39]) act together, with the latter being a predisposing factor while the first would be the trigger.

In our study the duration of BF was shown to have a significant influence on the occurrence of CMA. The duration of BF was longer in the control group. We found a lower risk of CMA in infants who were BF for longer than 6 months, which we used as the reference category, but in fact over 90% of patients with CMA are diagnosed before the age of 6 months, so we stratified the BF duration variable into 4 categories. We found a higher risk of CMA in infants with a very brief BF duration (less than 1 month) and in those with a BF duration of 4–6 months, but no significant differences were identified in infants with a BF of 1–4 months. Liao et al. [40] reported a lower risk of CMP sensitization in infants with prolonged BF, although their cutoff was 4 months. The results of a meta-analysis [41] addressing BF as a protective factor against allergic diseases also suggested that prolonged BF is a protective factor for the development of CMA IgE+. Regardless of the effects of BF, the special bimodal distribution of risk in the duration of BF points to an important effect of time of introduction of CMP in these patients. Clinical experience has shown us that most mothers who discontinue BF do so during the first month (due to BF problems) or at 4–6 months (coinciding with the end of their maternity leave). These medical and socioeconomic reasons could condition the time of introduction of CMP and, at the same time, the duration of BF. Different factors such as the benefits of BF, the time of introduction of CMP, and others like the maturity of the digestive and immune systems could explain the effects we found to be associated with BF duration in our study.

Prematurity also appeared to be a protective factor against CMA in the multivariate analysis. The relevant fact is that only 4.3% of patients with CMA were premature, and this figure is much lower than the proportion in the general population (13.2% in the control group). This fact has already been pointed out by Zachariassen et al. [29] who, when studying the incidence of allergic disease in a cohort of extremely premature infants, did not find a single case of food allergy. The explanation for this is possibly immunological: the premature patient's immune system is most likely not developed enough to generate IgE-mediated reactions to allergens through the digestive tract, a fact that was already observed in a study published in 1975 by Rieger and Rothberg [42] in which it was found that up until 35–36 weeks newborns exposed to CMP are not able to generate specific IgE antibodies.

It is worth mentioning that FH was not a significant risk factor for IgE-mediated CMA, even in the univariate analysis. Although a family history of atopy is a universally accepted risk factor [6, 14, 41] in the development of

allergic diseases, in view of the current results we could hypothesize that the development of CMA in our context has a greater association with environmental factors. Consumption of FFH has been (and remains) a very common practice in our context, especially in caesarean deliveries, where the mother is separated from the child for a few hours, and it is in these situations in which patients usually receive the first doses of formula. This, combined with subsequent more or less prolonged exclusive BF, is largely responsible for many of these children developing IgE-mediated CMA. It seems that the development of CMA is more related to this “iatrogenic care” than to a high genetic or familial risk. Thus, in our opinion isolated doses of formula should be avoided in newborns whose mothers wish to give exclusive BF, especially in children born by caesarean. If isolated doses are necessary for medical reasons, extensively hydrolyzed formulas could be a good option to avoid sensitization in these children.

The limitations of this study come from its own methodological design. This was a retrospective study of case and control groups, and there may have been bias with regard to memory, i.e., the parents of the cases may have remembered certain details about the risk factors better than those of the controls. In some cases, such as for the variable type of delivery, this bias is irrelevant, but it may have affected this study in terms of other variables. However, as the birth of a child is a vital event, parents tend to remember all of the details surrounding the event well. Furthermore, the responses given in the questionnaire were verified via the available medical record register and

the correlation was correct. Selection bias in the controls is possible, because parents with allergies could have been more motivated to participate in this study, but the prevalence of FH among cases and controls was similar to the allergy prevalence described in developed countries [43], so despite this we think that our results can be applied to the general population. Another limitation of this study was the frequency of disease in our context, which meant that an extended recruitment period was needed to reach a sufficient sample size. Finally, some important conditions, like the socioeconomic or educational level of the mothers, have not been studied and could be related to other variables like BF duration. A lack of these variables could make the current results subject to residual confounding.

Conclusions

Sporadic FFH consumption during the first days of life is a key risk factor in the development of CMA, especially in those patients born by caesarean delivery, such that its consumption should be avoided. Prolonged BF has been shown to be a protective factor against the development of CMA and should therefore be encouraged.

Disclosure Statement

The authors confirm that they have no conflict of interest regarding the content of this article.

References

- ▶ 1 Rona RJ, Keil T, Summers C, et al: The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638–646.
- ▶ 2 Sicherer SH: Epidemiology of food allergy. *J Allergy Clin Immunol* 2011;127:594–602.
- ▶ 3 Liu AH, Jaramillo R, Sicherer SH, et al: National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2010;126:798–806.
- 4 Plaza Martín AM: Alergia a proteínas de leche de vaca. *Protoc Diagn Ter Pediatr* 2013;1:51–61.
- ▶ 5 Host A, Halken S: Cow's milk allergy: where have we come from and where are we going? *Endocr Metab Immune Disord Drug Targets* 2014;14:2–8.
- ▶ 6 Martorell-Aragónés L, Echeverría-Zudaireb E, Alonso-Lebreroc J, et al: Position document: IgE-mediated cow's milk allergy. *Allergol Immunopathol (Madr)* 2015;43:507–526.
- ▶ 7 Sladkevicius E, Nagy E, Lack G, Guest JF: Resource implications and budget impact of managing cow milk allergy in the UK. *J Med Econ* 2010;13:119–128.
- ▶ 8 Sladkevicius E, Guest JF: Budget impact of managing cow milk allergy in the Netherlands. *J Med Econ* 2010;13:273–283.
- ▶ 9 Sladkevicius E, Guest JF: Modelling the health economic impact of managing cow milk allergy in South Africa. *J Med Econ* 2010;13:257–272.
- ▶ 10 Guest JF, Nagy E: Modelling the resource implications and budget impact of managing cow milk allergy in Australia. *Curr Med Res Opin* 2009;25:339–349.
- ▶ 11 Kramer MS, Kakuma R: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2012;3:CD000133.
- ▶ 12 Lovegrove JA, Hampton SM, Morgan JB: The immunological and long-term atopic outcome of infants born to women following a milk-free diet during late pregnancy and lactation: a pilot study. *Br J Nutr* 1994;71:223–238.
- ▶ 13 Fiocchi A, Burks W, Bahna SL, et al: Clinical use of probiotics in pediatric allergy (CUPA): a world allergy organization position paper. *World Allergy Org J* 2012;5:148–167.
- ▶ 14 Von Berg A: Dietary interventions for primary allergy prevention – what is the evidence? *World Rev Nutr Diet* 2013;108:71–78.

- ▶ 15 Osborn DA, Sinn J: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006; p CD003664.
- ▶ 16 Osborn DA, Sinn J: Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;4: CD003741.
- ▶ 17 Osborn DA, Sinn JK: Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007; p CD006475.
- ▶ 18 Osborn DA, Sinn JK: Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev* 2013;3:CD006474.
- ▶ 19 Eggesbø M, Botten G, Stigum H, Samuelsen SO, Brunekreef B, Magnus P: Cesarean delivery and cow milk allergy/intolerance. *Allergy* 2005;60:1172–1173.
- ▶ 20 Metsälä J, Lundqvist A, Kaila M, Gissler M, Klaukka T, Virtanen SM: Maternal and perinatal characteristics and the risk of cow's milk allergy in infants up to 2 years of age: a case-control study nested in the Finnish population. *Am J Epidemiol* 2010;171:1310–1316.
- ▶ 21 Toro Monjaraz EM, Ramírez Mayans JA, Cervantes Bustamante R, et al: Perinatal factors associated with the development of cow's milk protein allergy. *Rev Gastroenterol Mex* 2015;80:27–31.
- ▶ 22 Sánchez-Valverde F, Gil F, Martínez D, et al: The impact of caesarean delivery and type of feeding on cow's milk allergy in infants and subsequent development of allergic march in childhood. *Allergy* 2009;64:884–889.
- ▶ 23 Bager P, Wohlfahrt J, Westergaard T: Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy* 2008; 38:634–642.
- ▶ 24 Høst A, Husby S, Osterballe O: A prospective study of cow's milk allergy in exclusively breast-fed infants: incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. *Acta Paediatr Scand* 1988;77:663–670.
- ▶ 25 Cantani A, Micera M: Neonatal cow milk sensitization in 143 case-reports: role of early exposure to cow's milk formula. *Eur Rev Med Pharmacol Sci* 2005;9:227–230.
- ▶ 26 De Jong MH, Scharp-van der Linden VT, Aalberse RC, Oosting J, Tijssen JG, de Groot CJ: Randomised controlled trial of brief neonatal exposure to cows' milk on the development of atopy. *Arch Dis Child* 1998;79:126–130.
- ▶ 27 De Jong MH, Scharp-van der Linden VT, Aalberse R, Heymans HS, Brunekreef B: The effect of brief neonatal exposure to cows' milk on atopic symptoms up to age 5. *Arch Dis Child* 2002;86:365–369.
- ▶ 28 Lodge CJ, Tan DJ, Lau M, et al: Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* 2015;104: 38–53.
- ▶ 29 Zachariassen G, Faerk J, Esberg BH, et al: Allergic diseases among very preterm infants according to nutrition after hospital discharge. *Pediatr Allergy Immunol* 2011;22:515–520.
- ▶ 30 Byberg KK, Oglund B, Eide GE, Oymar K: Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood: a historically matched cohort study. *BMC Pediatr* 2014;14:101.
- ▶ 31 Kumar R, Ouyang F, Story RE, et al: Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. *J Allergy Clin Immunol* 2009;124:1031–1038.
- ▶ 32 Instituto de Estadística de Navarra: Población y demografía. <http://www.navarra.es/Apps-Ext/GN.InstitutoEstadistica.Web/informacionestadistica.aspx?R=1&E=1> (accessed September 16, 2015)
- ▶ 33 World Health Organization: Global strategy for infant and young child feeding. 2003. http://www.who.int/maternal_child_adolescent/documents/9241562218/en/ (accessed February 28, 2017).
- ▶ 34 Stintzing G, Zetterström R: Cow's milk allergy, incidence and pathogenetic role of early exposure to cow's milk formula. *Acta Paediatr Scand* 1979;68:383–387.
- ▶ 35 Høst A: Importance of the first meal on the development of cow's milk allergy and intolerance. *Allergy Proc* 1991;12:227–232.
- ▶ 36 Saarinen KM, Savilahti E: Infant feeding patterns affect the subsequent immunological features in cow's milk allergy. *Clin Exp Allergy* 2000;30:400–406.
- ▶ 37 Katz Y, Rajuan N, Goldberg MR, et al: Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;126:77–82.
- ▶ 38 Salminen S, Gibson GR, McCartney AL, Isolauri E: Influence of mode of delivery on gut microbiota composition in seven year old children. *Gut* 2004;53:1388–1389.
- ▶ 39 Azad MB, Konya T, Persaud RR, et al: Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG* 2016;123:983–993.
- ▶ 40 Liao SL, Lai SH, Yeh KW, et al: Exclusive breastfeeding is associated with reduced cow's milk sensitization in early childhood. *Pediatr Allergy Immunol* 2014;25:456–461.
- ▶ 41 Van Odijk J, Kull I, Borres MP, et al: Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003;58:833–843.
- ▶ 42 Rieger CH, Rothberg RM: Development of the capacity to produce specific antibody to an ingested food antigen in the premature infant. *J Pediatr* 1975;87:515–518.
- ▶ 43 Pawankar R, Canonica GW, Holgate ST, Lockey RF: World Health Organization White Book on Allergy: 2011–2012 Executive Summary. Milwaukee, WAO, 2011.