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Complementary bottles during the first month and risk of cow's milk allergy in breastfed infants

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Abstract

Aim

To assess the impact of complementary feeding bottles given at maternity hospital and/or over the first month after discharge from the maternity ward on cow's milk allergy (CMA) risk in breastfed infants.

Methods

Case-control study involving infants aged 6–9 months and who were breastfed for at least 1 month.

Results

In 554 cases with a diagnosis of CMA and 211 controls, feeding bottles at maternity hospital, feeding bottles during the first month of life, avoidance of dairy products during pregnancy or breastfeeding, family history of allergy, intake of antibiotics and consumption of proton-pump inhibitors or antacids by the infant during the first month of life were associated with increased risk of CMA in a univariate model. In a multivariate model, only feeding bottle at maternity hospital (OR = 1.81 [1.27; 2.59]), family history of allergy (OR = 2.83 [2.01; 3.99]) and avoidance of dairy products during pregnancy or breastfeeding (OR = 5.62 [1.99; 15.87]) were independent risk factors of CMA.

Conclusion

Complementary bottles given at maternity hospital to newborns who will be exclusively breastfed increases the later risk of CMA. Similarly, avoidance of dairy products during pregnancy or breastfeeding should be discouraged.

Abbreviations

95% CI

95% 2-sided confidence interval

CMA

cow's milk allergy

CMF

cow's milk formula

CMP

cow's milk proteins

OR

odds ratio

PPI

proton-pump inhibitor

Key notes

Complementary bottles given at maternity hospital to newborns who will be exclusively breastfed was associated with later risk of cow's milk allergy.

In breastfed infants, complementary bottles during the first month of life after discharge from the maternity ward were not associated with the risk of developing cow's milk allergy.

Avoidance of dairy products during pregnancy or breastfeeding were associated with later risk of cow's milk allergy.

1 INTRODUCTION

Food allergies affect 1%–4% of infants in developed countries,¹ a proportion that has increased in the last decades.² Cow's milk allergy (CMA) counts as one of the most frequent food allergies in children. Self-reported prevalence ranges from 1.2% to 17% with a marked heterogeneity between the studies.³ Medically confirmed prevalence is 2%–6%.^{4, 5}

Numerous factors that may affect the risk of CMA have been suggested. Among them, isolated bottles of formula in maternity hospital in neonates who will be later exclusively breastfed have been considered.⁶ A well-conducted study showed that exposure to isolated

formulas with cow's milk proteins (CMP) significantly increased subsequent risk of CMA when compared with neonates who received extensively hydrolysed proteins formulas or human milk.⁷ Some studies confirmed this risk,⁸⁻¹⁰ whereas others did not.^{11, 12} Neonates who will be exclusively breastfed should not receive complementary bottles of formula at maternity hospital. However, more than 80% of them did receive 1 or 2 bottles, especially during the first night after delivery.^{7, 9} In most cases, these bottles contain nonextensively hydrolysed CMP.

This study aimed to assess the impact of complementary feeding bottles given at maternity hospital and/or over the first month on CMA risk in breastfed infants after adjustment on other predictors.

2 METHODS

This was a case-control study conducted in 2018 in France. The study was proposed by mail and phone call to a random sample of French paediatricians working in their private practice. Centre sampling was stratified on the geographical area to ensure representativeness. Subjects were recruited during a routine visit recommended in France during the sixth or the ninth months of life. Exposure to risk factors of CMA was retrospectively collected from subjects' medical files and from the parents. Parents were instructed on the aims and constraints of the study, had the opportunity to refuse the data collection regarding their infant and signed a consent form.

Eligible subjects were 6–9 months old when recruited and should have been breastfed for at least 1 month. Subjects investigated for CMA suspicion at the time of the study could not enter the study. Cases were infants with a diagnosis of CMA based on an evocative clinical history of CMA⁴ associated with at least 1 of the following: positive skin prick tests, positive CMA-specific IgE testing, history of anaphylactic reaction, improvement of symptoms under elimination diet or positive oral challenge test. Controls were not suspected of CMA after finishing breastfeeding for at least 1 month. Such a delay was deemed enough to ensure that controls did not present CMA-related symptoms that otherwise would potentially result in misclassification bias. Each participating paediatrician was asked to include 3 cases and 1 control.

Collected data included demographics and biometrics, birth conditions, duration of exclusive breastfeeding (defined as breastfeeding without any regular complementary bottle) and the presence of atopic manifestations. Supplementary feeding bottles at maternity hospital and/or during the first month of life were reported including the type of formula, age at first intake and frequency of exposure. Other potential risk factors for CMA were investigated. Parents were asked about family history of atopic diseases or allergy, maternal consumption of antibiotics or proton-pump inhibitor (PPI) during the last 2 months of pregnancy and the 2 weeks following delivery, eviction of dairy products by the mother during pregnancy and/or breastfeeding, maternal smoking habits during pregnancy.

Regarding the infant, vitamin D supplementation, intake of antibiotics, antacids or PPI during the first month of life, exposure to passive smoking, rural or urban environment and the presence of pets at home were collected.

For cases, additional information regarding symptoms related to CMA, delay of occurrence after formula intake, associated signs such as irritability, crying, sleep disorders and insufficient weight gain were collected. The investigators were asked about the suspected underlying mechanism of CMA (IgE-mediated or non-IgE-mediated, unknown).

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and has been approved by the French Ethics Committee, *Comité de Protection des Personnes Sud-Est II* (N° ID-RCB: 2017-A1138-45). This work was supported by NHS.

3 STATISTICAL ANALYSIS

Based on a prospective study conducted by Saarinen et al.,⁷ the proportion of controls exposed to supplementary feeding bottles at maternity hospitals or during the first month of life was assumed to be 80%. A total of 1405 cases and 464 controls were required to put in evidence an odds ratio of at least 1.5, assuming a type 1 error rate of 5%, a power of 80% and a 3:1 ratio between cases and controls. As planned in the protocol, a revision of the sample size calculation was performed after the inclusion of 500 infants based on the observed proportion of controls exposed. As 40% of newborns received feeding bottles, only 783 cases and 259 controls were required to highlight an odds ratio of at least 1.5 without loss of power.¹³

Cases and controls have not been matched. Missing data were not replaced. Bottles at maternity hospital and at home during the first month of life were distinguished as 2 separate risk factors. The odds ratio associated with each risk factor was estimated in logistic regression models. In order to make sure that models were specified correctly, interactions between potential risk factors were tested. If the interaction was not statistically significant, a final model was built without interaction. All bivariate models were adjusted for the use of bottle at maternity hospital or at home. Other potential risk factors investigated included elimination of dairy products during pregnancy and/or breastfeeding, history of allergy in at least 1 parent, intake of PPI by the mother during pregnancy and/or breastfeeding, intake of antibiotics by the mother during pregnancy or at delivery, caesarean delivery, premature birth, intake of antibiotics by the infant during first month of life, intake of PPI or antacids by the infant during the first month of life, vitamin D supplementation during the first month of life and the presence of pets at home. Finally, factors associated with the risk of CMA ($p < 0.20$) were introduced in a multivariate logistic regression model. Results were expressed as odds ratios (OR), 95% 2-sided confidence interval (95% CI) and p -value. Fitness of the model was assessed by the Hosmer-Lemeshow test. Models were run twice: regardless of the supposed CMA mechanism and in the subset

of IgE-mediated CMA. In order to take into account the matching between infants recruited by the same physician, a sensitivity analysis using a conditional logistic regression model was fitted. This model was used to estimate the effect of the risk of at least 1 feeding bottle at maternity hospital, elimination of dairy products during pregnancy and/or breastfeeding and history of allergy in at least 1 parent on the odd of being a case (either CMA or IgE-mediated CMA).

4 RESULTS

Due to recruitment difficulty, the study was prematurely terminated and the expected sample size was not full reached. The analysis involved 765 subjects (554 cases and 211 controls) who met the inclusion criteria. They were recruited by 295 physicians. The characteristics of the population are summarised in Table 1. Briefly, history of allergy (food allergy, asthma, eczema or allergic rhino-conjunctivitis) in at least 1 parent was more frequent in cases. In parents, asthma, food allergy and eczema were more frequent in cases than in controls (42.6% vs 20.6%, 12.6% vs 2.9% and 43.9% vs 30.9% respectively) but no difference was found in the prevalence of allergic rhino-conjunctivitis. A small number of mothers eliminated dairy products during pregnancy or breastfeeding with a larger proportion in cases (5.4% vs 0.9% during pregnancy and 10.3% vs 1.9% during breastfeeding).

TABLE 1. Characteristics of subjects

	Cases <i>N</i> = 554	Controls <i>N</i> = 211	<i>p</i> -value
Age (months)	7.2 ± 1.0 [min 6.0; max 9.0]	7.2 ± 1.0 [min 6.0; max 9.0]	0.703
Males	277 (51.1%)	119 (57.5%)	0.118
Premature birth (<37 WA)	28 (5.1%)	6 (2.9%)	<0.0001
Caesarean delivery	98 (18.0%)	26 (12.4%)	0.064
Duration of exclusive breastfeeding (days)	92.9 ± 47.2 [min 30.0; max 270.0]	99.4 ± 40.5 [min 30.0; max 189.0]	0.083
Age of onset suggesting CMA (weeks)	15.6 ± 6.9 [min 2.0; max 38.0]	N/A	—
History of allergy in at least 1 parent	326 (58.8%)	68 (32.2%)	<0.0001
Elimination of dairy products during pregnancy and/or breastfeeding	59 (10.7%)	4 (1.9%)	<0.0001

Cases	Controls	<i>p</i> -value
<i>N</i> = 554	<i>N</i> = 211	

Abbreviations: PPI, proton-pump inhibitor; WA, weeks of amenorrhea.

Results are expressed as mean $\pm$ standard deviation and number (percentage).

Infants have been exclusively breastfed for 94.7 ± 45.5 days and duration of exclusively breastfeeding was similar between cases and controls. At maternity hospital, 296 (39.0%) infants received at least 1 complementary feeding bottle (235 (42.7%) cases and 61 (29.2%) controls). Among them, the majority received a formula containing nonhydrolysed CMP (62.2%). A minority received either partially hydrolysed formula (7.4%), amino acid formula (0.7%) or mother's milk from an official milk collecting centre (1.0%). All infants receiving either partially hydrolysed, amino acids or mother's milk from a milk-collecting centre at maternity hospital were cases. Finally, 28.4% of infants were fed with an unknown type of bottle at the maternity hospital.

While breastfed, 27.6% of cases and 19.4% of controls received at least 1 complementary bottle during the first month of life. Most of them (74.9%) were given a nonhydrolysed formula. Few received either partially hydrolysed formula (7.9%), amino acids formula (1.1%) or rice protein-based infant formula (1.6%). Nature of the complementary bottle was unknown for 14.5% of the infant.

Prevalence of eczema was 59.0% in cases and 5.7% in controls and asthma was reported in 9.6% of cases and 1.9% of controls. Cases reported various manifestations dominated by digestive signs: regurgitations (55.4%), irritability (46.5%), vomiting (40.3%), diarrhoea (38.1%), sleep disorders (36.5%), urticaria (24.2%), rectal bleeding (10.5%), wheezing, breathing discomfort or cough (9.6%), rhinitis (8.1%), conjunctivitis (2.4%), angioedema (4.0%) and anaphylaxis (1.4%). The diagnosis has been based on an allergy assessment (56.4%), or CMP elimination diet (83.9%) followed by a challenge test (29.2%). Complete disposition of the diagnosis workflow reported is provided in Figure [S1](#). In the physician's opinion, CMA was IgE-mediated in 37.0% of cases, non-IgE-mediated in 33.6% and the mechanism remained unclear in 29.4%. Immediate cutaneous symptoms such as urticaria or angioedema were reported in 42.3% of IgE-mediated CMA.

The distribution of potential risk factors for CMA in breastfed infants is summarised in Table [1](#). Results of the univariate analyses are detailed in Table [2](#). Risk of CMA was not significantly impacted by vitamin D supplementation during the first month of life ($p = 0.55$), intake of antibiotics by the mother during pregnancy or at delivery ($p = 0.10$), the presence of pets at home ($p = 0.40$), premature birth ($p = 0.19$), caesarean delivery ($p = 0.066$) and

intake of PPI by the mother during pregnancy or breastfeeding ($p = 0.054$).

TABLE 2. Factors increasing the risk of cow's milk allergy in breastfed infants

	Univariate analysis		Analysis adjusted on feeding bottle at maternity hospital or at home	
	Odd ratio [95% CI]	<i>p</i> -value	Odd ratio [95% CI]	<i>p</i> -value
At least 1 feeding bottle at maternity hospital	1.81 [1.29; 2.55]	0.0007	—	—
At least 1 feeding bottle at home during first month of life	1.58 [1.07; 2.34]	0.02	—	—
Elimination of dairy products during pregnancy and/or breastfeeding	6.17 [2.21; 17.24]	0.0005	6.80 [2.43; 19.23]	0.0003
Intake of antibiotics by the infant during first month of life	4.31 [1.00; 18.49]	0.049	4.05 [0.94; 17.49]	0.061
History of allergy in at least 1 parent	3.00 [2.15; 4.20]	<0.0001	2.90 [2.06; 4.07]	<0.0001
Intake of PPI by the mother during pregnancy and/or breastfeeding	2.37 [0.99; 5.72]	0.054	1.99 [0.82; 4.85]	0.129
Intake of PPI or antacids by the infant during the first month of life	9.99 [2.41; 41.42]	0.002	9.08 [2.18; 37.85]	0.002
Caesarean delivery	1.55 [0.97; 2.46]	0.0657	1.51 [0.94; 2.44]	0.0871

Abbreviation: PPI, proton-pump inhibitor.

Univariate analysis was performed using logistic regression model for the risk of CMA using the factor specified in the row as independent predictor. For each factor, a second analysis was run based on multivariate logistic regression model with bottles at maternity hospital and at home during the first month of life as 2 predictors forced in the model.

When adjusted on feeding bottles at maternity hospital, the association of intake of bottle at home was no longer significant ($p = 0.15$) but the elimination of dairy product, history of atopy in at least 1 parent and intake of PPI or antacids by the infant during the first month of life remained risk factors of CMA (Table 2). Finally, a multivariate analysis was run with the factors that displayed a p -value <0.2 along with the bottles at maternity hospital and at home during the first month of life forced in the model. They included elimination of dairy

products during pregnancy and/or breastfeeding, intake of antibiotics by the infant during the first month of life, history of allergy in at least 1 parent, intake of PPI by the mother during pregnancy and/or breastfeeding, intake of PPI or antacids by the infant during the first month of life and caesarean delivery. Of the 765 analysed subjects, 731 could be retained in the analysis. Three factors increased the risk of CMA significantly: feeding bottles at maternity hospital (OR = 1.81 [1.27; 2.59] $p = 0.001$), family history of allergy (OR = 2.83 [2.01; 3.99] $p < 0.0001$) and elimination of dairy products during pregnancy or breastfeeding (OR = 5.62 [1.99; 15.87] $p = 0.001$) (Figure 1). Same factors were retrieved when limiting the analysis to infants with IgE-mediated CMA (397/416 subjects retained in the analysis): feeding bottle at maternity hospital (OR 1.70 [1.10; 2.63] $p = 0.0174$), family history of allergy (OR 3.39 [2.23; 5.13] $p < 0.0001$), elimination of dairy products during pregnancy or breastfeeding (OR = 5.81 [1.90; 17.86] $p = 0.002$) (Table 3). A sensitivity analysis taking into account the form of clustering by matching the subject based on their physician showed similar results (Table S1).

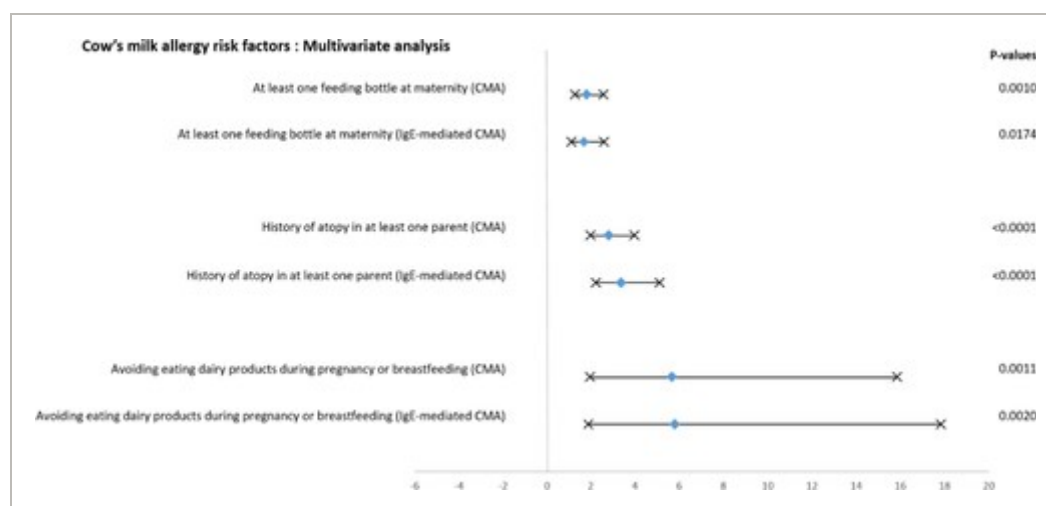


FIGURE 1

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Forest plot showing odds ratio associated with each predictor (multivariate analysis). Results are presented for CMA and for IgE-mediated CMA. Multivariate analysis was based on multivariate logistic regression model for the risk of CMA or IgE-mediated CMA with bottles at maternity hospital and at home during the first month of life as 2 predictors forced in the model and predictors with a p -value < 0.20 in the univariate analysis

TABLE 3. Factors increasing the risk of IgE-mediated cow's milk allergy in breastfed infants

	Univariate analysis		Analysis adjusted on feeding bottle at maternity hospital or at home	
	Odd ratio [95% CI]	<i>p</i> -value	Odd ratio [95% CI]	<i>p</i> -value

	Univariate analysis		Analysis adjusted on feeding bottle at maternity hospital or at home	
	Odd ratio [95% CI]	<i>p</i> -value	Odd ratio [95% CI]	<i>p</i> -value
At least 1 feeding bottle at maternity hospital	1.64 [1.09; 2.48]	0.02	—	—
At least 1 feeding bottle at home during first month of life	1.49 [0.93; 2.37]	0.10	—	—
Elimination of dairy products during pregnancy or breastfeeding	6.54 [2.22; 19.23]	0.0007	7.75 [2.59; 23.25]	0.0002
Intake of antibiotics by the infant during first month of life	3.68 [0.76; 17.91]	0.11	3.42 [0.69; 16.89]	0.13
History of allergy in at least 1 parent	3.57 [2.38; 5.35]	<0.0001	3.57 [2.36; 5.40]	<0.0001

Abbreviation: PPI, proton-pump inhibitor.

IgE-mediated cow's milk allergy was defined according to the investigator's opinion and corresponds to occurrence of immediate symptoms evocating allergy after consumption of cow's milk proteins.

Univariate analysis was performed using logistic regression model for the risk of IgE-mediated CMA using the factor specified in the row as independent predictor. For each factor, a second analysis was run based on multivariate logistic regression model with bottles at maternity hospital and at home during the first month of life as 2 predictors forced in the model.

5 DISCUSSION

This study highlighted the role of feeding bottles at maternity hospital in infants who will be exclusively breastfed later. Early intake of CMP within the first days of life appeared to be strongly associated with a later risk of CMA. Conversely, intake of CMP at any time during the first month (apart from maternity hospital) in breastfed infants was not an independent predictor when analyses were adjusted on supplementary bottles at maternity hospital.

Our results confirm findings by Saarinen et al.⁷ in a prospective cohort of 6,209 exclusively breastfed infants which was followed from birth for symptoms of CMA. Intake of CMP was recorded at the maternity hospital and at home. Significant risk factors for the presence of IgE cow's milk antibodies in allergic infants were long breastfeeding (OR 3.9 [1.6–9.8]), exposure to cow's milk at maternity hospital (OR 3.5 [1.2–10.1]) and breastfeeding during the first 2 months at home either exclusively (OR 5.1 [1.6–16.4]) or combined with

infrequent exposure to small amounts of cow's milk (OR 5.7 [1.5–21.6]). According to our results, the timeframe to develop allergy to CMP could be narrower than 2 months. A recent randomised clinical trial by Urashima et al.⁶ compared strict breastfeeding with occasional supplement of an amino acid-based elemental formula and breastfeeding with an intake of more than 5 ml/day of cow's milk formula (CMF) for at least the first 3 days of life. The main outcome was atopic sensitisation to CMP at 24 months of age. In an intent-to-treat analysis involving 302 infants equally distributed in the 2 groups, the authors found that fewer infants had the outcome when not exposed to supplements of CMF (relative risk 0.52 [0.34; 0.81]). These results suggested that sensitisation could occur in the first 3 days of life. Kelly et al.¹⁴ explored the impact of formula supplementation on the likelihood of developing CMA in a case-control study. They compared 55 CMA-diagnosed children to 55 milk-tolerant age- and sex-matched controls. Breastfed infants who had been given formula supplements with CMP were 7.03 times more likely to develop CMA than those who were exclusively breastfed and 16 times more likely to exhibit CMA than those who were exclusively bottle fed.

Our results do not suggest that contact with CMP should be avoided during early infancy in exclusively breastfed infants (apart from the stay at maternity hospital) but we could not clearly differentiate the specific roles of occasional or repeated contacts. Both prolonged breastfeeding and no or infrequent contacts with small amounts of CMP in the first months have been reported as risk factors for CMA suggesting that regular contacts with CMP may induce immune tolerance.^{7, 15} In a case-control study comparing 51 patients with IgE-mediated CMA with 102 age- and sex-matched controls, the adjusted odds ratio of delayed (started more than 1 month after birth) or no regular cow's milk formula (less than once daily) was 23.74 with a very large confidence interval (95% CI, 5.39–104.52).¹⁵

As a practical consequence, Kelly et al. recommended avoiding unnecessary formula supplementation at maternity hospital in infants who will be exclusively breastfed to reduce risk of development of CMA.¹⁴ Urashima et al.⁶ concluded that sensitisation to CMP but also clinical CMA were primarily preventable by avoiding CMF supplementation at birth. Our results are in line with these opinions.

We found that avoiding dairy products during pregnancy and/or breastfeeding was strongly associated with a later risk of CMA. There is no evidence to recommend that pregnant women should avoid allergenic foods through pregnancy and while breastfeeding.^{2, 16} In fact, such a measure may even be counterproductive. A Cochrane review found a slight but significant reduction in gestational weight gain in women respecting an allergen elimination diet during pregnancy, lactation or both for prevention of atopic disease in childhood.¹⁷ Some data suggested that elimination of allergens during pregnancy could enhance the risk of allergy in infants,¹⁸ but subsequent studies contested this beneficial effect.¹⁹ Data issued from the Danish National Birth Cohort examined the risk of allergic disease in infants during the 18 first months according to consumption or not of peanuts and tree nuts during pregnancy. Such intake tended to decrease the risk of allergic disease development in

children such as asthma and allergic rhinitis, but not food allergy.¹⁸ These results were not confirmed by most of following studies.¹⁹ Finally, the recent report of the American Academy of Pediatrics did not recommend increasing consumption of allergenic foods during pregnancy in order to prevent allergy in offspring.²⁰ Our results suggesting that avoiding dairy products during pregnancy or breastfeeding could enhance a later risk of CMA in infants needs to be, therefore, confirmed.

This study bears important limitations. Expected sample size could not be fully reached (27% of expected sample were lacking), leading to a decrease in expected power. Of note, missing values regarding risk factors were limited and 95% of the analysed subjects were retained in the multivariate analyses. Lack of power did not prevent the complementary bottles at maternity hospital to be strongly associated with a later risk of CMA in our population. The diagnosis of CMA was based on the physician's opinion. If the diagnosis of CMA seemed likely for IgE-mediated forms with either positive skin prick tests or CMA-specific IgE testing and when a challenge test was performed, it could be more questionable when the symptoms evocative of CMA disappeared after the elimination diet since many of them could resolve spontaneously, independently of CMP exclusion. Overestimation of CMA could, therefore, not be excluded. We performed sensitivity analyses using 3 definitions of cases: infants with positive allergic tests; infants with positive allergic test or symptoms improvement during the elimination diet; and infants with positive allergic tests or positive challenge test after symptoms improvement during the elimination diet. For these analyses, the group of controls remained unchanged. The risk of CMA associated with complementary bottles at maternity hospital was only marginally affected (Table [S1](#)). The mechanism of CMA was classified according to the investigator's opinion. We cannot rule out that some mechanisms may have been misclassified. Nevertheless, 42.4% of patients with suspected IgE-mediated CMA had a history of immediate cutaneous symptoms. Data collection was retrospective, and a recall bias cannot be ruled out, especially in controls. However only very young infants were included in the study and we can assume that the mothers had reliable memories of their stay in maternity hospital. Type of bottle at maternity hospital was unknown for 28.4% of infants, but it is very likely that a large majority of them received a formula containing nonhydrolysed CMP. The number of physicians who recruited the data was very high, each of them reporting only a few patients. We made this choice because the sample size we wanted to reach was important and to ensure a good recruitment we decided to limit the number of patients enrolled by each physician.

Our study confirms that bottles given at maternity hospital to newborns who will be exclusively breastfed is associated with a later risk of CMA. Therefore, when mothers decide to exclusively breastfeed their children, complementary bottles at maternity hospital should be avoided or, when they are indicated for medical reasons, extensively hydrolysed proteins formulas should be preferred. Our study did not differentiate extensively and partially hydrolysed formulas. Partially hydrolysed formulas, however, have not proven their efficacy to prevent CMA later in life.¹² Similarly, elimination of dairy products during pregnancy and

breastfeeding should be banished, especially in infants at risk of developing allergy.

CONFLICT OF INTEREST

K. Garcette and P. Tounian perceived honoraria from NHS for the study coordination. P. Clerson who is an employee of the Contract Research Organization Soladis Clinical Studies perceived an honorarium from NHS. V. Hospital and P. Maigret are employed by MENARINI France, for NHS.

Supporting Information



Filename	Description
apa16195-sup-0001-Supinfo.docx Word document, 23.7 KB	Supplementary Material

Please note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing content) should be directed to the corresponding author for the article.

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Supplementary Table 1

Factors increasing the risk of IgE-mediated cow's milk allergy in breastfed infants: multivariate analysis taking into account the matching between infants recruited by a same physician

	CMA	IgE-mediated CMA
	Multivariate analysis	Multivariate analysis
	Odds ratio [95%CI]	Odds ratio [95%CI]
	p-value	p-value
At least one feeding bottle at maternity hospital	2.00 [1.21 ; 3.30] p=0.0068	2.68 [1.18 ; 6.08] p=0.0185
Elimination of dairy products during pregnancy and/or breastfeeding	5.19 [1.67 ; 16.17] p=0.0045	3.53 [1.05 ; 11.91] p=0.0419
History of allergy in at least one parent	4.05 [2.52 ; 6.51] p<0.0001	3.63 [1.87 ; 7.04] p=0.0001

Multivariate analysis was performed using conditional logistic regression model matching for the physician who included the infants and using the factors specified in the table as independent predictors. Multivariate analysis for CMA was based on 759 observations out of the total population (N=765, composed of 554 cases and 211 controls). The one for IgE-mediated CMA was based on 404 observations out of the IgE-mediated CMA subpopulation (N=416, composed of 205 cases and 211 controls). CMA: cow's milk allergy.

Supplementary Table 2

Factors increasing the risk of cow's milk allergy in breastfed infants (depending on the criteria retained by the physician for defining CMA cases)

	Subgroup 1		Subgroup 2		Subgroup 3	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Odds ratio [95%CI] p-value	Odds ratio [95%CI] p-value	Odds ratio [95%CI] p-value	Odds ratio [95%CI] p-value	Odds ratio [95%CI] p-value	Odds ratio [95%CI] p-value
At least one feeding bottle at maternity hospital	1.83 [1.23 ; 2.72] p=0.0029	1.90 [1.24 ; 2.90] p=0.0031	1.80 [1.27 ; 2.55] p=0.0009	1.80 [1.25 ; 2.58] p=0.0014	1.77 [1.22 ; 2.56] p=0.0027	1.79 [1.21 ; 2.65] p=0.0038
Elimination of dairy products during pregnancy and/or breastfeeding	5.50 [1.86 ; 16.23] p=0.0020	5.75 [1.87 ; 17.64] p=0.0022	6.21 [2.22 ; 17.37] p=0.0005	5.76 [2.02 ; 16.36] p=0.0010	6.13 [2.14 ; 17.54] p=0.0007	6.31 [2.15 ; 18.58] p=0.0008
History of allergy in at least one parent	3.77 [2.54 ; 5.60] p<.0001	3.67 [2.44 ; 5.50] p<.0001	3.20 [2.28 ; 4.49] p<.0001	3.03 [2.12 ; 4.29] p<.0001	3.52 [2.44 ; 5.08] p<.0001	3.39 [2.33 ; 4.95] p<.0001

Subgroup1: cases with positive allergic tests (N=229); Subgroup2: cases with positive allergic tests or symptom improvement following elimination diet (N=504);

Subgroup 3: cases with positive allergic tests or positive challenge test following symptom improvement during elimination diet) (N=321)

Univariate analysis was performed using logistic regression model for the risk of CMA using the factor specified in the row as independent predictor. Multivariate analysis was based on multivariate logistic regression model with the three factors forced in the model.

Supplementary Table 3

Factors increasing the risk of cow's milk allergy in breastfed infants (depending on the nature of the complementary bottle at maternity hospital)

			Cases N=554	Controls N=211	Univariate OR [95% CI] p-value	Multivariate OR [95% CI] p-value
Complementary bottle at maternity hospital	hydrolyzed/amino-acid formulas, or human bank milk or none	N (%)	348 (70.9%)	152 (80.0%)	-	-
	Routine's cow milk based	N (%)	143 (29.1%)	38 (20.0%)	1.64 [1.10 ; 2.46] P=0.0163	1.64 [1.07 ; 2.49] p=0.0218
History of allergy in at least one parent			326 (58.8%)	68 (32.2%)	3.00 [2.15 ; 4.20] p<0.0001	3.11 [2.17 ; 4.46] p<.0001
Elimination of dairy products during pregnancy and/or breastfeeding			59 (10.7%)	4 (1.9%)	6.17 [2.21 ; 17.24] p=0.0005	4.72 [1.66 ; 13.48] p=0.0037

Univariate analysis was performed using logistic regression model for the risk of CMA using the factor specified in the row as independent predictor. Multivariate analysis was based on multivariate logistic regression model with the three factors forced in the model.

Supplementary Figure 1: Cow's milk protein allergy (CMPA) diagnosis workflow reported for cases.

