Role of infant early cow's milk formula exposure

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ABSTRACT

It is now well accepted that early introduction of certain potentially allergenic foods as peanut and egg contribute to reduction of allergy to these foods. Studies on early introduction of cow's milk are confounded by potential effect on breast feeding, transient exposure in maternity wards and the need to distinct between IgE- and non-IgE-mediated allergy. Still, a growing body of evidence demonstrates that the concept of early introduction for the prevention of food allergy applies for milk protein as well. Introduction at age 4-6 months is too late and transient exposure in the first few days of life might lead to the reverse effect. Therefore, the concept in the case of milk should be: "introduce as early as possible, as long as it is persistent".

KEY WORDS

Milk allergy; Early introduction; Breast feeding; Oral food challenge; Milk supplementation

KEY POINTS

- Most available data demonstrates that early introduction of milk protein reduces the risk for milk allergy
- For early introduction to be effective in the case of milk it should be started much sooner than the 4-5-month recommendation for peanut and egg, and the sooner the better
- Transient, even if brief, early introduction shortly after birth could increase the risk for milk allergy
- Therefore, introduction shortly should be persistent to achieve maximal protection

INTRODCUTION

The first scientific description of cow's milk allergy (CMA) was published >100 years ago (27). Since that time it is apparent that CMA has become a global problem (31-32, 46,48,58,63,70). Recently the burden of food allergy on the US population was described (75). The increase in the prevalence of CMA paralleled the increase in the prevalence of other food allergies (i.e. peanut and tree nuts) and of other allergic conditions, such as respiratory allergies (reviewed in 52). The emergence of the food allergy epidemic, especially the increasing prevalence and associated morbidity and mortality of peanut allergy in the US, UK and Australia fueled efforts to reverse this trend. While the underlying causes for the increase in allergic diseases are likely multifactorial, in the case of food allergy, one "immediate suspect" was the timing of introduction of allergenic foods. During the first half of the 20th century it was noted that introduction of raw egg yolk (which is for all practical purposes egg white protein) to infants at the age of 3 months, as was customary to try to avoid rickets and anemia, resulted in the development of rashes or other evidence of intolerance. In contrast, administration of egg yolk at the age of 6-9 months was well tolerated (17,22). It was therefore believed that within the relatively short period of 3 to 6 months an infant can develop immunologic protection against potent allergens. This, together with the belief that cow's milk is nearly always identified as the cause of eczema in a very young infant, led to the thought that if an infant, with heredity predisposition to the development of allergic disease, could be started on some other food than the traditional cow's milk, the incidence of atopic dermatitis might be minimized. This was the state of mind that furnished the first international recommendations on timing of introduction of allergenic foods. In 1998, the British Committee on Toxicity of Chemicals (COT) in Foods published detailed dietary recommendations which stated that "pregnant women who are atopic, or for whom the father or any sibling of the unborn child has an atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy", and that "Breast-feeding mothers who are atopic, or those for whom the father or any sibling of the baby has an atopic disease, may wish to avoid eating peanuts and peanut products during lactation" (6). They also added that "during weaning of these infants, and until they are at least three years of age, peanuts and peanut products should be avoided". In 2000, the American Academy of Pediatrics (AAP) basically, adopted these recommendations (1). In 2004, The EAACI guidelines recommended that "A dietary regimen is unequivocally effective in the prevention of allergic diseases in high-risk children. In these patients, breast feeding combined with avoidance of solid foods and cow's milk for at least 4-6 months is the most effective preventive regimen. In the absence of breast milk, formulas with documented reduced allergenicity for at least 4-6 months should be used" (41). In 2005, the Australian Society of Clinical Immunology and Allergy published a position statement about allergy prevention in children, recommending avoidance of potentially allergenic foods such as egg and milk until 12 months of age, and peanuts, nuts and shellfish until after 2-4 years of age (53). While admitting the lack of evidence for these recommendations, they justified this policy in the following statement: "there is no evidence that avoiding peanuts, nuts and shellfish during early life is harmful for high risk children". In recommendations published in 2008, by an expert group set up by the Section on Pediatrics of the European Academy of Allergology and Clinical Immunology, the authors stated that the most effective dietary regimen for the prevention of allergic diseases in high-risk infants, particularly in early infancy, regarding food allergy and eczema, is exclusively breast feeding for at least 4–6 months combined with

avoidance of solid food and cow's milk for the first 4 months (23). All these recommendations were based on "expert opinion" rather than on solid evidence-based research. The experts in the various panels postulated that the infant immature immune system is "not ready" to handle successfully potentially allergenic proteins (1). However, these recommendations did not lead to the expected outcome and the food allergy epidemic continued to inflate. In a sequential cohort from the same geographical location in the UK, peanut allergy increased from 0.5% in a cohort of 3-4 –year-old children born in 1989 to 1.4% in a cohort of children at a similar age range born between 1994 and 1996 (20). Similarly, a 2-fold increase in the prevalence of peanut allergy among children in the USA (0.4% vs 0.8%) was observed over a five-year period (1997-2002) using random-digit telephone surveys (64). The "Bamba" study which compared the rate of peanut allergy in Jewish children in Israel and the UK, associated for the first time a lower prevalence of allergy to a specific food (peanut) with early introduction (10). The LEAP study that followed swinged the pendulum, of how to reduce the peanut allergy "epidemic", from late to early introduction of peanuts (11). As a result, numerous professional societies issued consensus communications recommending early introduction of peanut to the diet of high-risk infants (14). Several studies examined the possibility that early introduction of Egg may prevent egg allergy. The PETIT study demonstrated the most convincing results to justify early introduction of egg to high-risk infants (atopic dermatitis) to prevent egg allergy (43). However, the evidence in the case of milk was less conclusive. While in several studies the effect of early introduction of cow's milk protein (CMP) showed promising results (29), a systematic review published in 2014 on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group considered that the findings about the preventive benefits of breast feeding against milk allergy for infants at high or normal risk are mixed (9). A meta- analysis published in 2016 found the results for milk didn't reach a degree of significance compared to peanut and egg (36). In addition, the timing of CMP introduction is further complicated by the role of exposure to CMP during pregnancy, the impact on breast feeding, which promotion is of paramount importance, and the use of alternative infant formulas such as extensively hydrolyzed formula (3,34), partially hydrolyzed formula (PHF) (5,36,37,39,47,71-74) and soy-based formula (2,42) in infants who cannot be exclusively breastfed. Furthermore, the diagnosis of non-IgE mediated food allergy is much more frequent in the case of milk than in the case of solid foods such as egg or peanut, and the effect of early introduction on IgE vs. non-IgE mediated food allergy is likely different. An editorial published in 2016 in the Journal of allergy and clinical immunology argued for the need for a convincing well designed study to answer the question of early introduction of milk (19). Since then, several well designed randomized controlled studies were performed, shedding more light on the optimal timing for CMP introduction to prevent CMA. In this chapter we intend to critically analyzes the early and most recent data in order to answer the question of what is the role of early cow's milk formula introduction in infants.

THE EFFECT OF EARLY INTRODUCTION ON THE RATE OF CMA

We identified 18 studies examining this questions. We subdivided these studies according to their design (observational vs interventional), the population size (small cohorts vs. population based), and nature (healthy vs. high-risk infants), the comparison groups (CMA vs. control or IgE-mediated vs. non-IgE mediated) and the

timing and persistency of CMP introduction and relevance of the methods to the question on stake, any allergy vs. food allergy vs. CMA.

Observational case-control studies (Table 1A)

Starting in 1975 Saarinen et al followed infants whose parents volunteered to participate. Of the 236 enrolled infants, 150 were followed from infancy to age 17 years to examine the effect of breast feeding as prophylaxis against atopic disease. The results were published in 1995 (55). The prevalence of food allergy in general was highest at 1-3 years, in infants who had short (<1 month) or no breast feeding, but was comparable to infants who were breastfed, at older ages. No details were provided about the specific foods causing the allergy. Of note, food allergy was diagnosed by history alone, and there was no mention of skin testing or sIgE measurements for foods throughout the study. This likely accounts for the higher than expected prevalence of food allergy, peaking at 24% at age 3 years and decreasing to 7% at adolescence. Another study, published in 2009 by Sanchez-Valverde et al, supported these previous descriptions, showing that a shorter duration of exclusive breast feeding and the use of artificial formula together with breast feeding, are associated with increased risk for IgE-CMA (62). The findings of this study as well, should be interpreted cautiously. First, the authors compared patients with IgE-CMA to those with non-IgE CMA while a comparison to non-allergic controls was not performed. In addition, the diagnosis was made clinically, and was based on symptoms that are not considered typical of IgE-CMA (bloody stools, frequent regurgitation, rejection of food, or atopic dermatitis**)**. Tests for sensitization and oral food challenges (OFCs) were performed only following an elimination diet of unspecified duration, and no normalization was done for the possibility that sensitization and IgE-CMA developed during the elimination period. A Taiwanese prospective birth cohort study by Liao et al, published in 2014, followed 258 infants from birth and examined the association between exclusive breast feeding for <4 months or ≥4 months and between milk sIgE at ages 6, 12, 18, 24, and 36 months (35). A decreased risk of CMP sensitization was found, in those breastfed for ≥4 months, at age 12 months 0.2 (95% CI, 0.07–0.5), 18 months 0.2 (95% CI, 0.07–0.5), and 24 months 0.2 (95% CI, 0.04–0.7) but not at 36 month of age. No data on actual CMA was provided. In a retrospective case-controlled Japanese study (2016), Onizawa et al compared 51 patients with IgE-CMA with 102 controls (1:2 matching) and 32 unmatched patients with IgE-egg allergy (40). While cow's milk formula (CMF) supplementation in maternity wards was comparable in all 3 groups, the rate of early (within the first month of life) and early continuous (continued until at least age 6 months) CMF feeding was significantly lower (11.8% and 3.9%, respectively) in CMA patients compared to controls (58.8% and 51%, respectively) and to egg-allergic infants (43.8% and 34.4%, respectively) (45). They concluded that early continuous exposure to CMP was protective against development of CMA. In another population-based study from Boston, published 2022, Switkowsky et al examined the effect of CMP introduction at age <2 weeks, 2 weeks-<6 months, ≥6 months, using questionnaires administered in infancy, on parent-reported CM adverse reaction (CMAR) via annual questionnaires at age 2-13 years (n=1298), and on milk sensitization (n=505) and IgE-mediated milk allergy (milk sensitization +epinephrine auto injector carriage, n=491) at age ~8 years (66). 32% of the infants were introduced to CMP at <2 weeks, 38% at 2 weeks-<6 months, and 30% at ≥6 months. Children introduced to CMP at ≥6 months had over twice the risk of CMAR reported at any time between 2-13 years as children introduced at <2 weeks (OR: 2.1, 95% CI:

1.2, 3.7). However, the predicted probability of CMAR in early childhood among those with CMP introduction at age <2wks, who did not receive a formula supplementation at delivery, was four times that of children with CMP introduction at age <2wks who did receive a formula supplement, with a fully adjusted OR of 5.1 (95% CI: 1.6, 16.2).

Observational population-based studies (Table 1B)

These limited relatively small studies were followed by larger population based prospective studies. In a series of studies beginning in 1988, Host published his findings on a cohort of 1749 Danish infants followed prospectively for the development of cow's milk allergy (CMA) or cow's milk intolerance (CMI) during their first year of life (24-26). A total of 39 infants (2.2%) developed CMA/CMI. The higher rate of CMA/CMI (4.5%) in infants who were solely or mainly cow's milk formula (CMF) fed during the first month of life compared to those who were exclusively breastfed (1.7%) *(p* < .001) led the author to conclude that early neonatal intake of CMP is probably a condition of sensitization and later adverse reactions to CMP. However, the symptoms used to diagnose CMA/CMI (recurrent wheezing, eczema, vomiting and/or diarrhea not due to coincidental infection or other demonstrable cause, infantile colic, and failure to thrive) are not characteristics of food allergy, and in 9 infants the symptoms developed during exclusive breast feeding (24-25). Moreover, while CMF feeding during the first month was significantly more frequent than exclusive breast feeding in infants with CMI (3.9% vs. 0.7%, p < .001), it was as frequent (1%) in infants solely breastfed as in CMF fed infants (0.6%) among those with CMA. In the largest to date prospective cohort study from Israel, published in 2010, Katz et al found that among 13,019 infants followed from birth, the introduction of CMP was significantly earlier among 66 infants diagnosed with IgE-CMA (61.6 ± 92.5 days) compared to healthy infants (116.1 ± 64.9 days) (P < 0.001) (29). Importantly, only 0.05% of the infants who were started on regular CMF within the first 14 days versus 1.75% of those who were started on formula between the ages of 105 and 194 days had IgE-mediated CMA (P < 0.001). While the nature of this study, observational rather than interventional, makes a selection bias possible, the size of the group studied and the very high (>90%) rate of retained patients makes it unlikely. The HealthNuts study was another large population-based observational study of 5,276 infants investigating modifiable risk factors for pediatric food allergy. An initial analysis derived from this data, by Goldsmith et al in 2016, found no evidence of an association between duration of breast feeding or type of infant formula used, and cow's milk allergy at 1 year of age after adjusting for confounding variables (18). However, there was no data on age of diagnosis of CMA and on the timing and quantity of CMP introduction. The Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study, from 2017, prospectively collected nutrition questionnaire data at age 3, 6, 12, 18, and 24 months to determine timing of introduction of cow's milk products, egg, and peanut (68). At age 1 year, infants underwent skin prick testing to cow's milk, egg white, and peanut. Among 2124 children with sufficient data, delaying introduction of cow's milk products beyond the first year of life significantly increased the odds of sensitization to that food (cow's milk aOR 3.69, 95% CI 1.37-9.08). There was no data on food allergy. A later analysis derived from the HealthNuts cohort was published in 2019 by Peters et al. (51). The authors examined specifically the effect of early exposure to CMP (within the first 3 months of life) on the development of milk allergy at age twelve-months.

Skin prick testing to cow's milk was conducted on the second half of the cohort (n=2,715). Early exposure to CMP was associated with a reduced risk of cow's milk sensitization (wheal ≥2 mm) (adjusted odds ratio [aOR] 0.44, 95% CI 0.23-0.83), parent-reported reactions to cow's milk (aOR 0.44, 95% CI 0.29-0.67), and CMA (aOR 0.31, 95% CI 0.10-0.91) at age 12 months (51). Another Israeli population-based study published in 2021 in an abstract form prospectively recruited newborns shortly before birth and divided them to groups according to parents' preference: exclusive breastfeeding; breastfeeding with at least one daily meal of CMF, and feeding with CMF only (33). Infants were followed monthly until the age of 12 months. Five hundred and seven infants (51.4%) were exclusively breastfed until 12 months of age, 318 (32.2%) combined breastfeeding and CMF, and 162 (16.4%) ate only CMF. An immediate reaction to CMP, proven by skin test, developed in 9 infants (0.91%), all were exclusively breastfed. Within the group of exclusively breastfed infants, the prevalence of CMA was 1.77% compared to zero in the other groups (RR=1.96, CI 95% 1.23-1.96, p=0.004). of note, this study was not peer-reviewed and was published only as an abstract. Tezuka et al reported in 2021 the results of data derived from the Japan Environment and Children's (JECS) birth cohort prospective study which included more than 100,000 children across Japan (67). The main exposure factor was the regular consumption of infant formula milk divided into 3 age time frames (<3 months, 3-6 months, 6-12 months) and the outcome was physician-diagnosed milk allergy prior to age 6 or 12 months. Multivariable regression analyses revealed that introducing regular consumption of formula within the first 3 months of age was associated with a lower risk of CMA at 12 months. According to our opinion, the most important information derived from that study was that this protective effect was lost if infants discontinued regular CMP consumption at 3-6 months, suggesting that the effect of very early CM exposure on CMA may disappear if the exposure is brief.

Interventional studies (Table 2)

In 2016, the EAT study, one of the most famous and influential studies in food allergy prevention, was published. This study, published by Perkin et al, was the first prospective randomized controlled study evaluating the effect of early introduction of 6 different foods simultaneously on the development of food allergy (49). EAT was a single center study on singleton 3 month-old exclusively breastfed infants who were recruited from the general population in England and Wales. Participants were randomly assigned to a standard-introduction group (SIG) who was to be exclusively breastfed to approximately 6 months of age followed by consumption of allergenic foods according to parental discretion, or an early-introduction group (EIG) who was to have 2 grams twice weekly of each of six allergenic foods (cow's milk, peanut, boiled hen's egg, sesame, whitefish and wheat) introduced at the age of 3 months. Participants had scheduled assessments at 1 year of age and 3 years of age. In this study the investigators found protective effects for early introduction of peanut and egg, but not a significant protective effect for early introduction of CMF. Although patient adherence in this study was overall low (in the case of milk, 85.2%% of the participants in the EIG adhered to the protocol and 85.6% of the participants in the SIG avoided CMF until 6 months of age), there was a tendency for protective effect in the EIG, but the rates of CMA were not significantly different between the two groups (P = 0.63) even in the per-protocol analysis. There are several possible explanations for this finding. The first one is that the size of the group, at least in the case of milk, was too small. In the per-protocol analysis 3/525 of the SIG and 1/415 of the EIG

developed CMA. Second, all participants completely avoided CMP for the first 3 months of life. According to numerous population based prospective studies (29,31-32,46,48,58,63,70) including the Europrevell study (63) the expected prevalence of CMA in that age is 0.5% or less, suggesting that for early introduction to be effective it might need to be started sooner, at least in the case of milk protein. Third, the definition of CMP avoidance in the SIG was a daily formula intake of less than 300 ml (9 grams of milk protein). This dose significantly surpasses the dose of 2-gram protein weekly, thought to be sufficient to prevent CMA (40). Of the SIG, 8.8% were introducing milk formula, in amounts less than 300 ml per day at a median age of 22 weeks, and were potentially consuming sufficient CMP to reduce their expected prevalence of CMA. In a per-protocol analysis from the EAT study, the relative risk of a positive result on skin-prick testing to milk at age 36 months was 88% lower in the EIG than in the SIG (P = 0.02) (49). Another interventional RCT trial by Sakihara et al, published in 2021, recruited newborns from 4 hospitals in Japan. Participants ingested CMF as required to supplement breast feeding before 1 month of age and were then randomly allocated to supplemental breast feeding with at least 10 mL of CMF daily (ingestion group, n=242) or breast feeding +/- soy supplementation and avoidance of CMF (avoidance group, n=249) between 1 and 2 months of age (60). Oral food challenge was performed at 6 months of age. In the intention-to-treat analysis, there were 2 CMA cases (0.8%) among the ingestion group and 17 CMA cases (6.8%) among the avoidance group (risk ratio=0.12; 95% CI 5 0.01-0.50; P < .001). Of note, the 2 patients in the ingestion group who developed CMA ingested only small amounts of CMF. In the per-protocol analysis, none of the 204 ingestion group participants had OFC-confirmed CMA compared with 17 (8.7%) of the 195 avoidance group participants (P<0.001). Importantly, breast feeding was not impaired as approximately 70% of the participants in both groups were still being breastfed at age 6 months (59). A pilot study from Stanford evaluated the safety of early introduction of single foods, including milk vs. two foods (milk/egg, milk/peanut) vs. a mixture of 10 foods including milk at low (total 300 mg), medium (total 900 mg), or high (total 3000 mg protein) doses vs. no early introduction in 180 infants between 4–6 months of age (55). None of the infants in the consumption groups, including those in the low mixture group who consumed only 30 mg of milk protein daily, developed milk allergy. In a cluster-randomized trial (PreventADALL), published in 2022, Skjerven et al randomized 2397 newborn infants, from the general population in Norway and Sweden, to the following groups: (1) no intervention; (2) skin intervention (skin emollients; bath additives and facial cream; from age 2 weeks to <9 months, both at least four times per week); (3) food intervention (early complementary feeding of peanut, cow's milk, wheat, and egg from age 3 months); or (4) combined intervention (skin and food interventions) (65). Parents were instructed to let the infant taste each of the foods from the finger of a parent or from a teaspoon at least 4 days per week, complementary to regular feeding, and to continue to include the food in the infant's diet until at least 6 months of age without any dose restrictions. Full protocol adherence was low in the food intervention group (35%) but the vast majority of infants were exposed to the interventional foods before 6 months of age. Interestingly, the exposure rates from 6 to 12 months of age in both intervention and non-intervention groups were similar. The prevalence of food allergy to any of the interventional foods at age 36 month was reduced in the food intervention group compared with the no food intervention group (risk difference –1·6% [95% CI –2·7 to –0·5]; OR 0·4 [95% CI 0·2 to 0·8]). This finding was driven by a reduction in peanut allergy in infants consuming a small dose of peanut, on

average between 1 and 3 times a week, up to 6 months of age. The number of patients with CMA was too small to find statistical significance. An accompanying Editorial argued that any studies to attempt to resolve the issues of dose and duration of consumption required to induce tolerance would have to be prohibitively large, but such studies are unnecessary, with PreventADALL providing robust evidence to support early allergenic food introduction among all infants, including infants not at high risk of food allergy in whom the majority of food allergies occur (50).

The effect of early CMP introduction on CMA in high risk patients (Table 3)

Sakihara et al (2016) studied the relationship between the duration and frequency of CMF ingestion during the first 3 months of life and the development of CMA at 3-24 months by medical records of 374 patients with egg allergy aged ≤6 years (59). The diagnosis of CMA was highest (46/75, 61.3%) in infants exclusively breastfed up to 3 months, followed by those who were fed CMF but discontinued before age 3 months (95/177, 53.6%), those fed CMF, but not daily, until age 3 months (19/47, 40.4%), and was lowest (11/75, 14.7%) in those who were daily fed CMF until age 3 months. Most of the infants in the latter group who developed CMA were predominantly breast-fed and added small amount of CMF. In another recent (2022) multi-center RCT from Japan, Nishimura et al randomly allocated 163 Infants 3-4 months old with atopic dermatitis to either a mixed allergenic food powder (MP) containing egg, milk, wheat, soybean, buckwheat, and peanuts (n=83), or placebo powder (PP) (n=80) (44). The amount of powder was increased in a stepwise manner but was very low throughout the study. On week 2 the powder contained only 2.5 mg of CMP, at week 4, 7.5 mg, and at week 12, 20 mg. The occurrence of food allergy was assessed at 18 months old. While the incidence of food allergy episodes by 18 months was significantly different between the MP and PP groups (7/83 vs. 19/80, respectively; risk ratio 0.301 [95% CI 0.116 - 0.784]; P = 0.0066), the difference was not statistically significant for milk (2 infants in the MP group vs. 6 in the PP group) (44).

TRANSIENT CMP INTRODUCTION IN THE FIRST FEW DAYS OF LIFE **(Table 4)**

Studies on early introduction of CMP are confounded by the nature of milk supplementation in the first days of life. As mentioned above, in the 2010 study by Katz et al, only 0.05% of the infants who were started on regular CMP formula within the first 14 days versus 1.75% who were started on formula between the ages of 105 and 194 days had IgE-mediated CMA (P <0.001) (29). However, this study did not address milk supplementation in the nursery. Infants who are still in the nursery often receive intermittent milk supplementation, either with or without maternal awareness (13). This transient exposure might have an effect on future development of milk allergy. The issue of transient exposure to milk early after delivery, on the development of CMA is critical to our understanding the effect of early CMP on future allergy development. In 1988, Lindfors et al studied prospectively the incidence of atopic disease in healthy term infants with a birth weight between -1 and -2 SD who were fed cow milk formula (n=112) or "normal feeding" with breastmilk *(n* = 104), during the first few days of life (37). Until the age of 18 months, the rate of "allergic diseases" (atopic eczema, asthma or wheezing, allergic urticaria, recurrent gastrointestinal reactions to the same food) was higher among breastfed (33%) compared to formula fed infants (18%) (p<0.05) (30). In a follow-up study performed

when children were at the age of 5 years, 3 children fed milk formula, compared to none among those who were breastfed during the first week, were sensitized to milk. Importantly, the duration of exclusive breast feeding following the first week was comparable (38). In another study, performed in Sweden in 1996 by Juvonen et al, a group of 129 infants was randomly assigned at birth to one of three feeding regimens: human milk (HM), cow's milk formula (CMF) or a casein hydrolysate formula (CHF) during the first 3 days of life. Infants were exclusively breastfed after the first week and were followed until the age of 3 years (28). One infant from the CHF-fed group compared to none in the CMP-fed infants was sensitized to CM during the study. Another study, performed in 1998 by De Jong et al examined 1533 neonates whose mothers intended to breast feed for at least six weeks and who were randomly assigned to receive CMP (n = 758) or a protein free placebo (n = 775) for at least 3 times during the first 3 days of life (7). There was no significant difference between the 2 groups in the levels of milk sIgE at age 1 and at age 5 years. However, ~50% of participants were not exclusively breastfed despite their intention (8). In a 1999 study from Finland, by Saarinen et al, 5385 unselected healthy full-term infants who required supplementary milk while in the hospital were randomly assigned to receive CMF (1789 infants), pasteurized human milk (1859 infants), or whey hydrolysate formula (1737 infants) and were compared to a group of 824 infants who were exclusively breastfed (56). The mothers were also asked to record the infant-feeding regimen daily during the first 8 weeks. The infants were followed for 18 to 34 months for symptoms suggestive of CMA. The primary endpoint was a challenge-proven adverse reaction to CM after a successful CM elimination diet. Exposure to CMP during the first 2 days after birth was associated with increased risk of CMA on multivariate analysis (54). Another study investigating the effect of CMP introduction during the first few days of life was published by Urashima et al in 2019 (69). Immediately after birth, 312 newborns were randomized to BF with or without amino acid–based elemental formula (EF) for at least the first 3 days of life (BF/EF group) or BF supplemented with CMF (≥5 mL/d) from the first day of life to 1 month and ≥40 ml/day after 1 month until weaning (5 months of age or starting solid food (BF+CMF group). Mothers allocated to the BF/EF group were allowed to add amino acid–based EF when they believed that amounts of BF were not enough. If the mother added more than 150 mL/d of EF to BF for 3 consecutive days, EF was switched to CMF after the fourth day. Thus, offspring allocated to BF/EF could avoid CMF for at least the first 3 days of life. Of note, some mothers in the BF+CMF group could ignore the protocol to skip feeding CMF for a while, e.g., 2 weeks, because of enough amounts of BF (personal communication). The primary outcome, sensitization to cow's milk (IgE level, ≥0.35 UA/mL) at the infant's second birthday, occurred in significantly fewer infants (16.8%) in the BF/EF group compared to infants in the BF+CMF group (32.2%), (RR, 0.52; 95%CI, 0.34-0.81). The prevalence of food allergy at the second birthday was significantly lower in the BF/EF than in the BF+CMF groups for immediate (4 [2.6%] vs 20 [13.2%]; RR, 0.20; 95%CI, 0.07-0.57) and for anaphylactic (1 [0.7%] vs 13 [8.6%]; RR, 0.08; 95%CI, 0.01-0.58) types. In a post-hoc analysis performed on the BF/EF group comparing 115 infants who were switched from BF/EF to BF+CMF within 14 days (n=73) or after 14 days of life (n=42) to a residual 39 infants who continued to receive BF/EF until 5 months of age, no difference was observed in the rate of milk allergy although there was a trend for earlier start of supplementation with CMF to be associated with higher levels of CM-IgE at 24 months of age (69). Importantly, there were 2 patterns among infants in the BF+CMF group who developed CMA. pattern 1 was rejecting CMF and

preferred drinking BF only before solid food or before reaching 5 months, and pattern 2 was stopping CMF and feeding BF only after starting solid food for a few months, e.g., 5 to 7 months and then using CMF or dairy products after a 1 to 3-month blank period. Pattern 2 seemed to be a major pattern (personal communication). An accompanying editorial concluded that these data may suggest that for early (before 3 months of age) introduction of CMF to be potentially protective against CMA, it should be sustained. Intermittent exposure may paradoxically increase the risk of CMA (12). Updated EAACI guidelines on preventing the development of food allergy in infants and young children, published in 2020, suggested avoiding supplementation with cow's milk formula in breastfed infants in the first week of life to prevent CMA in infants and young children (54). This update relied solely on the study by Urashima. While it was not specified in the guideline itself, in an accompanying editorial, Marques-Mejias et al stated that this recommendation relates only to temporary supplementation while there is no clear evidence that prolonged supplementation with CMF whilst breastfeeding increases the risk of CMA (21). As for regular consumption of cow's milk–based infant formula after the first week of life to prevent food allergy, this review concluded that introducing conventional cow's milk–based formula after the first week of life did not have a consistent impact on the development of CMA in infancy or early childhood. Another study from Ireland, by Kelly et al, recruited 55 CMA-diagnosed children who were breastfed only, formula fed only or breastfed with formula supplementation at <24 hours of age and compared them to 55 milk tolerant age- and sex-matched controls who were identified retrospectively (30). Breastfed infants given formula supplements were 7.03 (95% CI, 1.82-27.25) times more likely to exhibit CMA than those who were exclusively breastfed and 16 times more likely to exhibit CMA than those who were exclusively bottle-fed, while exclusively formula-fed infants were not significantly more likely to exhibit CMA than those who were exclusively breastfed (30). This study did not provide data on the type of feeding beyond the first 24 hours of life. Furthermore, it is clear from the univariate analysis of this study that exclusively breastfed infants had a significantly higher rate of CMA compared to the other 2 groups, and the rationale for performing the multivariate analysis, and for the variables included in it, were not entirely clear. A French case control study, by Garcette et al, compared medical and postnatal feeding history in 6-9 month old children with 554 CMA and 211 controls (16). The diagnosis of CMA was based on an evocative clinical history of CMA associated with at least 1 of the following: positive skin prick tests, positive milk-sIgE, history of anaphylactic reaction, improvement of symptoms under elimination diet or positive oral challenge test. 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 breast feeding (OR = 5.62 [1.99; 15.87]) were independent risk factors of CMA (59). Another study, performed by Saarinen et al in 2000, followed 6209 healthy newborn infants from 4 maternity hospitals in Finland (57). The diagnosis of CMA was based on the resolution of symptoms following elimination diet and on symptoms during re-introduction on an OFC. A total of 118 infants fulfilled the diagnostic criteria, giving a cumulative incidence of 1.9% for CMA in the whole cohort. Infants were divided into those with IgE-negative (n=43) and IgE-positive (n=75) CMA based on SPT/sIgE and the two groups were compared. The risk for the development of an IgE-positive reaction to cow's milk in infants with CMA was increased by exposure to cow's milk at hospital, and by no exposure or exposure to only small amounts of cow's milk at home during the first 8 weeks of life suggesting that both quantity and regularity of

milk consumption might be important (57). In this study, symptoms suggestive of CMA, even in those diagnosed with IgE-positive CMA, included symptoms not necessarily reflecting an IgE-mediated reaction, such as atopic dermatitis and continuous regurgitation which appeared up to 5 days after an OFC, and in many cases the reaction on OFC developed several hours after the challenge. In the Sakihara study from 2021, participants ingested CMF as required to supplement breast-feeding before 1 month of age when they were randomized. In that study, 30 ～ 40 % of participants in both groups ingested > 200mL of CMF per day in the neonatal period. The authors also performed a subgroup analysis of participants who ingested CMF in the first 3 days of life and were then randomly allocated to consume at least 10 mL of CMF daily or avoiding CMF between 1 and 2 months of age (61). The proportions of participants who developed CMA at age 6 months in those who discontinued CMF ingestion before age 1 month (n = 7 of 17, 41.2%; RR, 65.7; 95% CI, 14.7-292.5; P < 0.001), those who discontinued CMF ingestion during age 1 to 2 months (n = 3 of 26, 11.5%; RR, 18.4; 95% CI, 3.2-105.3; P =0.003), and those who discontinued during age 3 to 5 months (n = 7 of 69, 10.1%; RR, 16.2; 95% CI, 3.4-76.2; P <0.001) was significantly higher compared to those who continued CMF ingestion until age 6 months (n = 2 of 319, 0.6%) (61).

SUMMARY

The vast majority of the studies support the concept that early introduction of CMP has a protective effect on the development of CMA in non-selected as well as high risk atopic (egg allergic and atopic dermatitis) infants. Recent international guidelines, either did not distinguish between temporary (3 days) and continuous neonatal exposure to CMP, or suggested avoiding supplementation with cow's milk formula, in breastfed infants in the first week of life, to prevent CMA (54,59). However, we believe that there is convincing evidence that the deleterious effect of CMF introduction within the first days of life is dependent on subsequent elimination and, that in order to achieve a reduction in the expected rate of CMA, the exposure to CMP has not only to be early but also continuous. There is insufficient data to draw firm recommendation on the exact quantity and frequency of exposure required to achieve this protection. Also, the exact timing of exposure to CMP that would be effective in achieving this goal remains an open question, but in our opinion the earlier the better (50), especially considering the fact that supplementation with limited amounts of CMP was not shown to lead to discontinuation of breastfeeding (60). This concept is likely true not only in the case milk protein but also for other foods (54). For some reason, international committees find it difficult to abandon “old thoughts”. For example, a consensus document of the AAAAI, ACAAI and CSACI stated on 2021 that “to prevent peanut allergy and/or egg allergy, both peanut and egg should be introduced around 6 months of life, but not before 4 months” (15). We are not aware of any study that suggests that the introduction of egg or peanuts, earlier than 6 months, is harmful.

The observation that prevention of CMA requires continuous, rather than temporary, supplementation of CMP is similar to reports in oral immunotherapy (OIT), where continuous consumption of the treated allergen, in quantities and rates that are not yet fully known, is required to maintain the effect of successful desensitization (4). Primary (early introduction) and secondary (OIT) prevention of food allergy might comprise a spectrum of treatments with a similar mechanism. In fact, it is possible that early introduction represents a form of OIT, where significant adverse reactions are minimal due the fact that allergic adverse reactions are very mild in the first weeks or months of life. These last thoughts are not supported (yet) by research data but represent topics for further study.

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