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Review article

Cow's milk-based infant formula supplements in breastfed infants and primary prevention of cow's milk allergy: A commentary of the Committee on Nutrition of the French Society of Pediatrics

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ABSTRACT

The role of nutritional interventions for the primary prevention of cow's milk allergy (CMA) remains debated as well as the role of early introduction of allergenic foods, which is largely encouraged from the beginning of complementary feeding. Considering the introduction of cow's milk protein (CMP), current recommendations suggest avoidance of any cow's milk formula (CMF) supplements in breastfed infants in the maternity ward. By contrast, based on poor evidence, some authors support systematic supplements of CMP in breastfed children at risk of allergy from the first week of life. The Committee on Nutrition of the French Society of Pediatrics considers that such a proposal requires more clinical studies and mainly randomized and placebo-controlled clinical trials before becoming a recommendation.

Introduction

Knowledge of food allergy has dramatically increased over the past decade, but the role of nutritional interventions for the primary prevention of cow's milk allergy (CMA) remains debated [1]. A recent publication [2] addresses specifically this issue for breastfed infants. In good agreement with the literature, the authors suggest avoidance of any cow's milk formula (CMF) supplements in breastfed infants in the maternity ward [2].

In the same paper, the authors state that, "there seem[s] to be sufficient observational arguments to propose to children at risk of atopic disease, an early and regular introduction of CM [cow's milk], from the first days of life" and thus "if exclusive BF [breastfeeding] is desired [to]: Discuss with the family of infants at atopic risk the early introduction of CM." Briefly, this means daily supplementation of

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breastfed infants with small amounts of CM or CMF (i.e., 10 mL/day) from the first week of life onwards. Based on current evidence from the literature, the Committee on Nutrition of the French Society of Pediatrics (CNFSP) considers that the latter recommendation lacks sufficient scientific evidence.

We address the specific issue of the use versus the elimination of CMF for the primary prevention of CMA in breastfed infants and oppose the recommendation of systematic concurrent bottle-feeding in breastfed infants.

CMF consumption in breastfed infants in the maternity ward

Several papers suggest that exposure to CM protein in breastfed infants during the first few days of life in the maternity ward may considerably increase the risk of CMA. The initial observation was made by Host et al. [3] and led to the concept of "dangerous bottle" (of CMF).

In a prospective cohort of 6209 exclusively breastfed infants followed up from birth for CMA, Saarinen et al. [4] showed that one of the significant risk factors for the presence of CM-specific immunoglobulin E (IgE) was the exposure to CM protein in the maternity ward (odd ratio [OR]: 3.5; 95% confidence interval [CI]: 1.2–10.1).

Kelly et al. [5] compared the outcome of exclusively breastfed infants, CMF-fed infants, or breastfed infants with CMF supplementation (45.8% of neonates less than 24 h old). The latter were 7.03 time (95% CI: 1.82–27.25) more likely to exhibit CMA than those exclusively breastfed. By contrast, CMA did not differ in exclusively CMF-fed or breastfed infants (OR: 0.42; 95% CI: 0.16–1.07).

In the Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC) trial [6], an interventional non-blinded clinical trial, newborns were randomized immediately after birth to breastfeeding with or without the use of either an amino acid-based elemental formula for at least the first 3 days of life (breastfeeding / elemental formula group), or a CMF (5 mL/day) from the first day of life to 5 months of age (breastfeeding / CMF group). Sensitization to CM (IgE level >0.35 UA/mL) at the child's second birthday was found in 24 children (16.8%) in the breastfeeding / elemental formula group, significantly less commonly than in the 46 children (32.2%) in the breastfeeding / CMF group (relative risk [RR]: 0.52; 95% CI: 0.34–0.81).

In an interventional open randomized controlled trial in Japan, designed to support early CMF supplements during breastfeeding, described below [7], none of the 31 infants who avoided CMF in the first 3 days of life developed CMA, regardless of their diet afterwards (ingestion CMF group = 18; avoidance group = 13).

A systematic review in 2020 found that temporary supplementation with CMF in the first week of life may increase the risk of CMA [8].

Recently, Garcette et al. [9] published a French retrospective observational case–control non-randomized study involving 554 infants aged 6–9 months with a diagnosis of CMA and who were breastfed for at least 1 month. Additional CMF feeding in the maternity ward increased the risk for CMA (OR: 1.81; 95% CI: 1.27–2.59; $p<0.001$) compared to 211 age-matched controls.

To the best of our knowledge, there is no published evidence for a beneficial effect of the introduction of CMF during the first 3 days of life.

CM or CMF consumption in breastfed infants after discharge from the maternity ward

Pros

Some observational studies suggest that CMF supplementation during the first few months of life may be associated with a reduced rate of CMA.

In a questionnaire survey carried out with 13,019 Israeli infants [10], the mean age of CM protein introduction in healthy infants was significantly lower than in those with IgE-mediated CMA, i.e., 61.6 ± 92.5 days vs. 116.1 ± 64.9 days, $p<0.001$. Only 0.05% of the infants who were started on a regular CMF within 2 weeks of age had IgE-mediated CMA, vs. 1.75% of those who were started on CMF between 105 and 194 days of age ($p<0.001$). This retrospective survey had limitations (see below).

In a questionnaire survey of 374 egg-allergic children in Japan [11], 171 had IgE-mediated CMA between 3 and 24 months of age. The risk for CMA was 61.3% in exclusively breastfed infants and 14.7% in those breastfed with daily CMF supplementation.

In the Australian Health Nuts longitudinal population-based food allergy survey, the questionnaire administered at 1 year of age [12] found that 42% of the 5276 12-month-old infants were exposed to CM protein in the first 3 months of life, of whom 87% were also breastfed. Early exposure to CM protein was associated with a reduced risk of CM skin prick test wheal of >2 mm (adjusted OR: 0.44; 95% CI: 0.23–0.83), parent-reported reactions to CM (OR: 0.44; 95% CI: 0.29–0.67), and CMA (OR: 0.31; 95% CI: 0.10–0.9), at the age of 12 months.

In the interventional Japanese open randomized controlled trial mentioned above [7], breastfed infants were randomly allocated to either ingest at least 10 mL of CMF daily (ingestion group) or avoid CMF (avoidance group) between 1 and 3 months of age. There were two CMA cases in the ingestion group (0.8% of 242) and 17 CMA cases in the avoidance group: (6.8% of 249): RR: 0.12; 95% CI: 0.01–0.50 (p <0.001).

Cons

Several studies argue against CMF supplementation during the first few months of life in breastfed infants.

In the aforementioned Saarinen study [4], significant risk factors for the presence of CM-specific IgE in allergic infants were, in addition to the exposure to CM in the maternity ward, breastfeeding during the first 2 months, either exclusively (OR: 5.1; 95% CI: 1.6–16.4) or combined with infrequent exposure to small amounts of CM (OR: 5.7; 95% CI: 1.5–21.6).

The aforementioned questionnaire survey carried out with 13,019 Israeli infants [10] supporting early introduction of CMF is fraught with several biases, precisely described by Koletzko et al. [13]. Briefly, the authors rely on the self-reporting of the parents, and provide neither the number of patients with each symptom, e.g., their CM skin prick test positivity, nor how they chose the time intervals used for analysis, etc. Also, the authors did not report the family history: parents with atopic disease in the family may consider later introduction of CMP, so that reverse causality cannot be excluded.

Following criticism of this questionnaire survey [10], Koletzko et al. [13] performed a post hoc analysis of the German Infant Nutritional Intervention (GINI) study in high-risk infants carefully followed up with weekly diaries, regular visits to the study center, and systematic measurement of CMP-specific IgE. The data did not confirm the conclusion by Katz et al. [10] that introduction of CM protein during the first 2 weeks reduces the risk for specific IgE-positive CMA. Koletzko et al. [13] therefore advised not to deviate from the recommendation to breastfeed exclusively for the first 4 months of life.

In the aforementioned ABC trial [6], post hoc analysis of the results at 24 months of age showed a trend toward an association between earlier start of supplementation with CMF and higher levels of CM-IgE subsequently.

In the Japan Environment and Children's Study [14], a nationwide birth cohort involving over 100,000 mother–child pairs, regular consumption at 3–6 months of age was strongly associated with a reduction in 12-month CMA (aRR: 0.22; 95% CI: 0.12–0.35; $p<0.001$),

whereas no association was observed at 0–3 months (aRR: 1.07; 0.90 –1.27).

Also, as underlined in the correspondence [15] following the Sakihara et al. study [7], more than 90% of infants enrolled in this randomized clinical trial received CMF within 3 days of birth, in contradiction to the suggested "rule" of avoiding CMF supplements in the first 3 days of life. Moreover, the same authors showed that in the case of early introduction of CMF, a subsequent discontinuation of CMF ingestion, particularly in the first month of life, may be associated with an increased risk of CMA (RR: 65.7; 95% CI: 14.7–292.5) [16]. Therefore, there are doubts about the effective adherence of mothers to the continuation of these supplements over the duration of the study.

Of note, these studies only address the use of formula supplements in breastfed infants. They involve neither the comparison of breastfed infants with formula-fed infants in the prevention of CMA, nor the potential role of raw milk in the prevention of allergy and asthma [17].

Discussion

In the maternity ward: consensus against CMF supplements in breastfed infants

Data in the literature provide the basis for a large consensus against the use of CMF supplements in infants in maternity ward [18,19].

In breastfed infants, additional evidence argues against CMF supplements

Interference with breastfeeding

Reviews from scientific societies show that breastfeeding is the optimal method of infant feeding and that interfering with breastfeeding may be hazardous for numerous reasons (see in [20,21]). Interfering with breastfeeding from the first week of life onward using daily CMF supplements seems disputable. Recommending early additional feeds of CMF may result in wrongful discontinuation by mothers who may view breastfeeding as insufficiently "nutritious" [22]. Factors resulting in a shorter duration of exclusive breastfeeding are not very well known [23]. In a 2016 Cochrane review, providing breastfeeding infants with CMF, compared to exclusive breastfeeding, did not affect rates of breastfeeding at hospital discharge or at 3 months, but did so at 4 and 5 months [24]. More recently, an Australian study showed that the use of formula for >7 days in the first 2 months in breastfed infants was one of the factors associated with subsequent breastfeeding cessation [25]. A Mexican study showed that women were less likely to breastfeed for more than 1 month if they gave infants other liquids during their hospital stay [26].

Wrong goal in allergy prevention?

A review published in 2019 concluded there was insufficient evidence to determine the relationship between shorter versus longer duration of exclusive human milk feeding prior to the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span [27]. However, several reviews (see reviews in [28,29]), and a recent study [30], published after the Cochrane review indicate that any duration of exclusive breastfeeding for ≥3–4 months is protective against wheezing in the first 2 years of life, and that longer duration of any breastfeeding protects against asthma even after 5 years of age.

Therefore, an attempt to reduce CMA through an early start of formula feeding might result in an increase in the asthma epidemic. This would be even more worrisome given the fact that CMA is usually self-limited, which is not the case for asthma.

Lack of scientific evidence

As underlined in the Australian publication by Peters [12], "[their] findings are from an observational study and clinical trials are warranted to further assess this association [between early introduction and CMA prevention] before any recommendations to infant feeding guidelines can be made."

Most studies supporting early introduction of CMF in breastfed infants are observational, based on questionnaires, which are associated with a high level of uncertainty as to the exact mode of feeding received by enrolled children in the first few months of life. The only intervention study was from Sakihara et al., [7], which was randomized but open.

Over the last few decades, there have been several examples in nutrition of opinions based on surveys that did not sustain rigorous scrutiny in appropriately designed, randomized controlled trials (RCTs). The "gluten at 6 months" rule, deeply rooted in many developed countries, and supported by observational studies, was challenged by two RCTs published in the *NEJM* in 2014. The Lionetti [31] RCT showed that the later introduction of gluten was associated with a delayed onset of disease, and the Vriezinga [32] RCT showed that in a group of high-risk infants the introduction of small quantities of gluten at 16–24 weeks of age did not reduce the risk of celiac disease by 3 years of age.

Today, CMA is a public health concern despite its self-limited outcome, and proactive measures are needed. However, owing to the level of evidence currently available, the health risks of nonexclusive breastfeeding may outweigh any favorable effect on CMA and may even increase the incidence of such allergy [15].

To avoid misguidance, guidelines should rely on studies made according to the gold standard, i.e., RCTs [33]: Observational studies, e.g., case-control studies and cohort studies raise reasonable hypotheses about the determinants of disease, whereas well-designed RCTs can demonstrate a consistent causal relationship.

Conflict regarding starting age for CMF supplementation

In the design of Sakihara's trial [7], the comparison was made based on a CMF supplement between 1 and 3 months of age, with or without such a supplement during the first month. The recommendation made by Sabouraud-Leclerc et al. [2] to start CMF supplements as soon as possible is in conflict with the "no CMF supplement" rule in maternity wards by the same authors. There are no data relating to the age at which CM protein introduction might be beneficial for prevention of CMA in breastfed infants.

In conclusion, most studies supporting CMF supplementation to prevent CMA are observational, conducted with questionnaires of low scientific value, with only one interventional study, randomized but open, with low evidence and conflicting results. Potential detrimental effects of such a policy have not been searched for. Well-designed RCTs are needed before any recommendations can be made on CMF supplements during breastfeeding.

Recommendations

In breastfed infants, the CNFSP does not recommend the use of systematic CMF or CM supplements either in the maternity ward or after discharge form the maternity ward when exclusive breastfeeding is desired and possible.

Declaration of Competing Interest

The authors have no conflict of interest with this work.

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