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Is it time to reconsider the role of partially hydrolyzed infant formulas in the prevention of allergic diseases?

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Abstract

Allergic diseases are on the increase worldwide, incurring a high socioeconomic burden on patients, families, and healthcare systems. As a permanent cure for most allergies is still lacking, prevention is of paramount importance. So far, several strategies, including nutritional interventions, have been proposed to halt this phenomenon with inconclusive results. The use of partially hydrolyzed formulas (pHFs) for non-exclusively breastfed infants has been proposed by several scientific bodies; however, most have withdrawn this suggestion based on the concept of insufficient evidence. During the last few years, emerging evidence suggests that specific pHFs may reduce the risk of allergies in individuals at high risk for allergy development based on their heredity. In this article, we review the role of pHFs and propose that in non-exclusively breastfed infants at high-risk for allergy, the use of pHFs remains one of the most targeted interventions, as consistent data indicate a possible role in allergy prevention. © 2025 Codon Publications. Published by Codon Publications.

Introduction

A dramatic increase in allergic diseases has been observed in many countries over the last few decades,^{1,2} affecting not only the quality of life^{3,4} of patients and their families but also posing a high economic burden on healthcare systems.^{5,6} Allergic diseases may be mediated by different

immunologic mechanisms (Immunoglobulin E [IgE], non-IgE, or mixed)⁷ and present with a spectrum of clinical phenotypes, including life-threatening conditions such as severe asthma and anaphylaxis.⁸ Currently, as a permanent cure is lacking for many of these diseases, multidisciplinary management^{3,9} throughout life is often essential for several allergic patients. It is critically important to identify and

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apply effective strategies to prevent their development rather than struggle with their management.

Allergy prevention has been in the eye of the storm for many years while, at the same time, technological evolution, urbanization, environmental pollution, and dietary patterns have been changing radically.¹⁰⁻¹² Recommendations for nutritional interventions during infancy, especially the use of partially hydrolyzed formulas (pHFs) as means of prevention for allergic diseases, have diametrically changed within the last few years, despite the fact that the scientific evidence used to reach any conclusions are no different. Even though the effect of recent environmental and lifestyle changes on the human genome are unclear,¹³ it could be hypothesized that studies performed in previous generations should offer lower weight to contemporary meta-analyses.

Atopic dermatitis (AD), the most common inflammatory skin disease in early life, and cow's milk protein allergy (CMPA) are considered as the first steps in the "Atopic March," followed by other allergic phenotypes such as food allergy, asthma, and rhinitis.¹⁴ In an effort to halt this progress in allergic diseases, several prevention strategies have been proposed that include nutritional interventions,¹⁵⁻¹⁷ either in the maternal diet during pregnancy and breastfeeding or in the infant's diet. Examples of interventions in the maternal diet involve supplementation with vitamin D,¹⁸ avoidance of ultra-processed foods,¹⁹ and implementation of different diet indices such as the Mediterranean diet.²⁰ In infants, nutritional interventions include the use of hydrolyzed infant formulas, the timing of cow's milk and solid food introduction, use of probiotics,²¹ and increase in dietary diversity during the second semester of life.^{22,23} Furthermore, other non-nutritional factors such as the mode of delivery, application of skin emollients,²⁴⁻²⁷ excessive use of antibiotics, and exposure to pets and pollutants may contribute to the development of allergic diseases with as yet inconclusive results.²⁸

In this review, we revisited nutritional interventions for allergy prevention, emphasizing on the potential role of pHFs in light of recent scientific evidence.

Nutritional Interventions for Allergy Prevention

Breastfeeding

Exclusive breastfeeding is the optimal source of nutrition in early life with a multitude of established benefits²⁹ for both the mother and the child; this should be strongly encouraged and supported by all healthcare professionals. The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life, continuing at least up to the age of 2 years.³⁰ The duration of breastfeeding may affect the development of allergic diseases, although this is still unclear.^{31,32} Breastmilk composition varies, depending on the age of the breastfed infant, its nutritional needs, and health status at each time point.³³

Breastfeeding has gained interest in allergy prevention both as a complete source of nutrition and to the potential

effect of breast milk's specific components in inflammatory processes. Studies examining the role of human milk oligosaccharides (HMOs),³⁴ micro ribonucleic acids (miRNAs),^{35,36} and maternal allergen-specific immunoglobulin G (IgG)³⁷ have shown some beneficial effect on allergy prevention, although results remain indecisive and further studies are needed to clarify this. These components may also play an important role in the modification of intestinal microbiota, further affecting immunological responses of infants.^{38,39}

Maternal diet during breastfeeding, especially specific micronutrients and vitamins which could promote immunological regulation, has also been the focus of interest. Amongst others, the effects of zinc (Zn), iron (Fe), iodine, and vitamins A, C, and D have been explored, although none has shown favorable effects.²⁰ Scientific evidence remains insufficient to enable recommendations of intake or avoidance of specific foods, food groups, or nutrients to prevent the development of allergic disease in breastfed infants. A diverse diet, including all food groups, even those considered highly allergenic, is generally proposed for the breastfeeding mother. Avoiding any food or food group is not recommended as a means of allergy prevention due to lack of evidence and the risk of nutritional deficiencies.⁴⁰⁻⁴²

Breastmilk substitutes

In cases where exclusive breastfeeding is insufficient or when medically indicated (i.e., galactosemia)⁴³ or even when a mother does not wish to breastfeed her baby, infant formulas have long been used as breastmilk substitutes.

The role of standard formulas (SFs) in the development of allergic diseases has been examined from different perspectives. Regarding the timing of infant formula introduction (first days vs. later), data suggest that infant formula provision within the first 24 hours of life versus later may increase the risk of developing an allergic disease;⁴⁴ however, continued exposure to cow's milk proteins in early life (even in small amounts) appears to prevent CMPA compared to occasional exposure.^{45,46} Besides the timing and consistency in milk formula consumption, the role of HMOs, probiotics, and prebiotics as additional components in infant formulas have been studied with inconclusive findings.⁴⁷⁻⁴⁹

During the last three decades, attention has also been given to the role of special infant formulas other than SF for the prevention of allergic diseases. Extensively hydrolyzed formulas (eHFs), pHFs, and soy-based infant formulas represent the most studied types so far; pHFs and eHFs consist of the hydrolysate products of intact cow's milk protein hydrolysis (whey, casein, or both). The final molecular weight (MW) of the hydrolysate, as determined by the extent of hydrolysis, defines the final product as an eHF or a pHF (eHF has MW < 3 kDa [kilodalton] and pHF between 3 and 10 kDa).^{50,51} Currently, eHF and soy formulas are commonly used in the management of CMPA with insufficient evidence to support their effectiveness in allergy prevention.⁵² Although pHFs have been widely used for the prevention of allergies, their efficacy remains debatable and according to the European Food Safety Authority, it should be established by high-quality randomized controlled clinical trials for each pHF.⁵³

Partially hydrolyzed infant formulas

Compared to SFs, which consist of intact milk protein molecules presenting high allergenicity, pHFs contain smaller milk protein peptides with reduced allergenic properties.⁵⁴ Breaking down milk protein into smaller peptides was proposed in the early 90s as a potential nutritional intervention for allergy prevention, particularly in infants at high risk for allergy development.^{55,56} The process of infant formula hydrolyzation may include different stages and means to achieve several degrees and structures of the final product (hydrolysate).

Production of pHF

To produce hydrolysates, the protein fraction (whey or casein) should be selected. A potential heat treatment is applied to denature and conform the intact protein molecule, as this method affects the bonding structures. With increasing temperature, the disulfide and hydrophobic bonds break down, thus unfolding the protein molecules and exposing the polypeptide chain. Of note, each protein molecule has a distinct temperature point of denaturation, and therefore, temperature level can affect the exposure of bonds that are further broken down.⁵⁷ After heat treatment, a mixture of proteolytic enzymes (e.g., trypsin, papain, bromelain) are used to break down the bonds between amino acids, producing smaller molecules of proteins. The proteolytic reaction ends by denaturing the enzymes using the heat treatment. The final step to producing a hydrolysate is the filtration to collect only the required size of molecules, excluding larger ones.⁵⁸

According to the type of intact protein and proteolytic enzyme mixture used, the temperature applied, and the time each procedure was performed, the degree of hydrolysis and the final hydrolysates produced are unique.⁵⁹ Hence, the allergenic and immunogenic properties of each distinct hydrolysate are different; however, not all hydrolysates with the same MW have the same effect in immunological response as a result of the distinct final epitopes formed.^{59,60}

Biological mechanisms and evidence from animal studies

The biological mechanisms of how pHFs could prevent the development of allergies remain unclear. It has been suggested that breaking down intact cow's milk proteins into smaller pieces—thus producing partially hydrolyzed proteins—result in reduced allergenicity and promotes immunogenicity through T-cell reactivity and proinflammatory cytokine secretion.^{61,62}

Based on the hypothesis that sensitization to food allergens occurs through inflamed or damaged skin,^{14,63–65} studies in animal models tried to demonstrate any preventive effect of pHFs in cutaneous damage.^{66,67} It was pointed out by Holvoet et al. (2021) that pHFs have a role in preventing transepidermal water loss (TEWL) through reduction of total IgE levels and stimulation in the expression of genes that are related to skin barrier function.⁶⁶ Additionally, Iwamoto et al. (2020)⁶⁷ suggested that for skin which is already damaged, pHFs reduce the epicutaneous immunogenicity by suppressing inflammatory cytokines (e.g., interleukin [IL]-2, IL-4, IL-5, and IL-13).

Other experiments indicate that pHFs may have a preventive role in CMPA development⁶⁸ via expressing regulatory B and T cells, preventing immunoglobulin M-immunoglobulin A (IgM-IgA) class switching in the mesenteric lymph nodes.^{69,70} Moreover, pHFs may have a role in promoting eubiosis balance in the intestinal microbiota by producing short chain fatty acids that stimulate anti-inflammatory cytokines.³⁸

Human prospective studies on the role of pHFs in allergy prevention before 2018

The German Infant Nutritional Intervention (GINI), the Melbourne Atopic Cohort Study (MACS), and the large French cohort study Étude Longitudinale Française depuis l'Enfance (ELFE) are among the largest prospective studies that examined the role of pHFs in allergy prevention, and still publishing interesting though controversial results.

The GINI study was the oldest birth cohort with follow-ups, until recently. The initial results at the age of 12 months showed that feeding with a specific whey-based pHF can reduce the risk of AD in high-risk for allergy infants (based on family history of allergy) compared to SF. Importantly, this effect persisted at 3, 6, 10, 15, and 20 years of age.^{71–76} Regarding asthma development, a risk reduction effect was observed in the pHF group compared to the SF group between the ages of 11 and 15 and between 16 and 20 years.^{75,76} Any allergic manifestation as outcome was analyzed up to the age of 10 years did not show any statistically significant difference, although it is noteworthy that the prevalence was lower in all age groups fed with the pHF.^{71–74} In the GINI study, mothers were encouraged to exclusively breastfeed; the study formulas were introduced at any time point within the first 6 months of life if the infant could not be exclusively breastfed. Although no dietary restrictions were given to the breastfeeding mothers, nutritional restrictions were applied during the solid food introduction period.^{75–77}

In 2002, a randomized controlled trial (RCT) conducted in Singapore, which included 153 infants at high risk for allergy due to their heredity and who were exclusively formula fed with either a pHF or a SF, showed a significantly lower cumulative incidence of eczema up to the age of 24 months in the group of infants fed with the pHF compared to the SF group. Moreover, a difference in wheezing was also observed, although it was not statistically significant.⁷⁸ In this study, no dietary restrictions were applied after the age of 4 months and vaccinations were performed according to the local immunization scheme. The infants were closely followed-up and data were cumulatively analyzed at 3, 6, 12, 18, 24, and 30 months of life.

The MACS failed to show any protective effect of a nutritional intervention with a whey-based pHF in allergy prevention. In this study, infants at high-risk for allergy were recruited and followed-up by telephone calls. Skin prick tests were performed at the age of 6, 12, and 24 months and clinical examinations took place annually from 3 to 7, 12, and 18 years old.⁷⁹ Regarding allocation procedures, subjects were pooled initially to the standard cow's milk and soy formulas, while allocation to the pHF started later. The timing of study formulas' introduction was broad (0–6 months of life) and restrictions were applied to the order of solid food introduction.^{79,80}

In the ELFE study, no interventions were applied, but researchers collected data retrospectively on participants' infant feeding regimen based on parental report. This study did not manage to show any protective effect of pHF with the label "hypoallergenic" in the development of allergic diseases in early childhood.⁸¹ Note that infants who reported CMPA or use of eHF or AAF at the age of 2 months were removed from the analysis; thus subjects with this important outcome during the first 6 months of life were excluded, probably affecting the results. Follow-ups were performed by telephone calls and email communication with additional home visits made by researchers at the age of 3.5 years.⁸² Diagnoses for allergic diseases were recorded using parental report of doctor diagnosis.⁸³ Furthermore, only the type of feeding at the age of 2 months was accounted for the analysis, which excludes the role of any changes in the feeding regimen after the second month of life that may have affected the infants' sensitization status, thus probably affecting the final results. Table 1 presents birth cohort studies which investigated the potential preventive role of the pHF in allergy compared to the SF. A detailed table on RCT studies regarding the role of hydrolyzed formulas in allergy prevention has been recently published by Li et al.⁸⁴

Recommendations for the use of pHF in allergy prevention before and after 2018

As shown in Table 2, the use of pHFs has been widely suggested for allergy prevention by many scientific committees⁸⁹⁻⁹⁹ for about 20 years, particularly for those infants at high risk for developing allergies based on their family history of allergic disease. Despite favorable results in many studies, the preventive role of pHFs has been questioned after doubts were raised in a systematic review¹⁰⁰ and supported by a meta-analysis.¹⁰¹ These articles highlighted biases at several levels in the original studies that reduced the strength of the evidence in favor of a preventive role. Literature on this hot topic remains contentious while most of the available studies are difficult to be compared due to differences in the methodological designs applied and the specific pHF assessed.

As a result of this debate, many scientific bodies have revised their recommendations on the use of pHF in allergy prevention (Table 2).^{4,40,41,102-105} In 2021, the European Academy of Allergy and Clinical Immunology (EAACI)⁴⁰ recommended that the use of hydrolyzed formulas could be an option among others when exclusive breastfeeding is not feasible, but also stating that available studies were difficult to be compared due to their heterogeneity. The British Society of Allergy and Clinical Immunology (BSACI) and the Food Allergy Specialist Group of the British Dietetic Association (BDA) propose a SF as complementary feeding if needed instead of a hydrolyzed infant formula.¹⁰⁵ The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN),⁴ the Australasian Society of Clinical Immunology and Allergy (ASCIA),¹⁰⁴ the American Academy of Asthma Allergy and Immunology (AAAAI),⁴¹ and the Canadian Paediatric Society Allergy Section (CPSAS)¹⁰³ agree that there is no sufficient evidence to confirm the use of pHF in the prevention of allergic disease; however, the German recommendations for allergy prevention suggest that if breastfeeding is not possible (or

insufficient) for infants at high risk of allergies, a formula with proven effectiveness, demonstrated in allergy prevention studies, could be given until complementary food is introduced.¹⁰⁶

Interestingly, the Canadian Society of Allergy and Clinical Immunology (CSACI) does not make any reference to the use of pHFs for the prevention of allergy in their guidelines, but instead highlights the need for systematic regular ingestion of intact cow's milk protein.⁴⁶

The future of studies investigating interventions for allergy prevention

The relationship between healthcare professionals and milk formula manufacturers has long been placed under scrutiny. It may be reasonable that some authors express their anxiety about the threat to breastfeeding posed by the availability and recommendation of using infant formulas.¹⁰⁷ At the same time, it is of paramount importance to distinguish between manipulated recommendations or "fabricated results" in studies and the results of independent, dedicated scientists from well-designed randomized trials. Furthermore, to examine the effect of any commercially available product, especially when it affects infants, the product should be of the highest quality at its source. Therefore, industry collaboration and/or funding is unavoidable in such studies, particularly in blind randomized clinical trials in which infant formulas must be unidentified. These trials should be conducted under appropriate supervision⁴³ and without doubt, researchers should be objective and unbiased when analyzing and interpreting their data.

In 2022, the Allergy Reduction Trial (ART), a multi-center double-blinded randomized controlled study, was carried out in Bulgaria, Cyprus, and Greece.⁸⁸ The study examined the effect of a nutritional intervention with a specific whey-based pHF compared to a SF on allergy prevention in 551 infants at high risk for allergy, and its results were analyzed by an independent third party. ART is one of the most updated randomized controlled birth cohort trials in the field of allergy prevention, which included not only non-exclusively breastfed infants but also exclusively breastfed infants as a parallel observational group. Moreover, it accommodated the needs of modern lifestyle, which obligates mothers in many countries to combine breastfeeding with an infant formula in order to return to their work, allowing the switch to mixed-feeding groups up to the age of 10 weeks, if needed, but still supporting the continuation of breastfeeding for as long as possible. The primary study outcomes at the age of 6 months included AD and CMPA. Results showed that in non-exclusively breastfed infants, supplementation with this specific pHF significantly reduced the risk of developing AD compared to those who consumed the SF during the first 6 months of life. The preventive effect was particularly strong in those infants having a family history of AD. In addition, a nonstatistically significant trend toward prevention of CMPA was observed for those who consumed the pHF in combination with breastfeeding. Interestingly, the prevalence of CMPA was similar in both the SF and the exclusively breastfeeding groups.¹⁰⁸ In ART, study participants were recruited before or right after delivery from both public and private sector maternity clinics. During the first 6 months of life, infants

Table 1 Selected birth cohort studies investigating the potential role of pHF in allergy prevention compared to SF.

Study Name	First author(s)	Design	Country	Population	Participants	Intervention duration	Follow-up visits	Age at outcomes report	Outcome measures	Outcomes	Main findings
N/A	Marini et al., 1996 ⁸	RCT	Italy	High risk for allergy term infants	pHF: 48; SF: 47	First 5 or 6 months of life	3, 6, 12, 24, and 36 months of age	1 year; 2 years; 3 years	Physical examination;	AD; recurrent wheezing; gastrointestinal symptoms; allergic conjunctivitis	Infants fed with the pHF had less incidence of AD and recurrent wheezing at all time points.
N/A	Oldaeus et al., 1997 ⁸	RCT	Sweden	High risk for allergy term infants	pHF: 51; SF: 49	First 9 months of life	3, 6, 9, 12, and 18 months of age	3 months; 6 months; 9 months; 12 months; 18 months	Symptom diary completed by parents; AD scoring based on a 20-body area assessment system; DBPCFC; SPT	AD; asthma; gastrointestinal allergy; allergic rhinoconjunctivitis	The cumulative incidence of eczema was lower in the group of pHF compared to the SF group though not statistically significant, and this result disappeared after 12 months of life.
N/A	Chan et al., 2002 ⁷	RCT	Singapore	High risk for allergy term infants, exclusively formula fed	pHF: 53; SF: 57	First 4 months of life	1, 3, 4, 5, 9, 12, 18, and 24 months to 30 months of age	3 months; 6 months; 12 months; 18 months; 24 months; 30 months	Physical examination	Eczema; wheezing; urticaria	Exclusive feeding with a pHF during the first 4 months of life reduces the risk of eczema. This effect persisted up to 24 months of life.
GINI	von Berg et al., 2003; 2007; 2008; 2013; 2016 ^{7,75} Gappa et al., 2021 ⁷⁶	RCT	Germany	High risk for allergy term infants	pHF: 557; SF: 556	First 6 months of life (no specific duration for formula feeding)	1, 4, 8, and 12 months	1 year; 3 years; 6 years; 10 years; 15 years	Physical examination; SCORAD; SPT; IgE;	AM; AD; Urticaria; FA-GIT; asthma; AR	The use of pHF-HA reduced the incidence of AD, particularly in those with family history of AD, at the age of 12 months, compared to those fed with the SF. This effect was cumulatively persistent at the ages of 3, 6, 10, 15 and 20 yrs. Incidence of asthma was lower between the ages 11-15 and 16-20 in the pHF compared to the SF group.
MACS	Lowe et al., 2011 ⁸⁰ Peters et al., 2017 ⁸	RCT	Australia	High risk for allergy term infants	pHF: 206; SF: 206	First 6 months of life	6, 12, and 24 months (for SPT) every 4 weeks until 64 weeks, 18 months, 2, 3-7 years, 18 years	2 years; 6 years; 7 years;	Medical history; physical examination; SPT;	AM; eczema; food reactions; asthma; AR; SPT reactivity	No evidence that a partially hydrolyzed whey formula reduced the incidence of allergic manifestations up to 2 years of age nor the prevalence of allergic sensitization up to the age of 7 yrs.
ELFE	Davisse-Paturet et al., 2019 ⁸¹	Non-interventional birth cohort study	France	General population	pHF (non-HA): 239; pHF (HA): 251; SF: 7149	No intervention/ the type of infant formula used at the age of 2 months was recorded	No follow-up visits	2 months; 1 year; 2 years;	Parental report of medical diagnoses (CMPA, eczema, wheezing, asthma attack, other FA); questionnaire to physicians (FA diagnosis and method used to confirm; IgE or SPT)	CMPA; FA; eczema; wheezing; asthma attack	The use of pHF-HA at 2 months was not associated with a lower risk of any of the outcomes up to 2 years, it was associated with a higher risk of wheezing, FA, and, to a lesser extent, eczema.
ART	Nicolaou and Pancheva et al., 2022 ⁸⁸	RCT	Bulgaria; Cyprus; Greece	High risk for allergy term infants	pHF: 160; SF: 171	First 6 months of life	2, 4, and 6 months of age	6 months	Physical examination; SCORAD; CoMiss; OFC; SPT	AD and CMPA	AD incidence was statistically significantly lower in the group fed with the pHF compared to those fed with the SF. CMPA incidence was lower in those fed with the pHF; however, this difference was not statistically significant.

pHF: partially hydrolyzed infant formula; SF: standard formula; HA: hypoallergenic; non-HA: non-hypoallergenic; AM: allergic manifestations; AD: atopic dermatitis; CMPA: cow's milk protein allergy; AR: allergic rhinitis; FA-GIT: food allergy with manifestation in the gastrointestinal tract; RCT: randomized controlled trial; N/A: not applicable; GINI: German Infant Nutritional Intervention study; MACS: Melbourne Atopy Cohort Study; ELFE: Étude Longitudinale Française depuis l'Enfance; ART: Allergy Reduction Trial.

Table 2 Recommendations by the International Scientific Bodies on the use of partially hydrolyzed infant formulas and standard cow's milk infant formulas in allergy prevention.

Before 2018						After 2018					
Year	Authors	Scientific Body	Recommendation	For or against pHF (+/-)	Year	Authors	Scientific Body	Recommendation	For or against pHF (+/-)		
1999	Host et al.	ESPACI and ESPGHAN	In bottle-fed infants with a first-degree relative with a documented allergy, infant formula with confirmed reduced allergenicity is recommended while more studies are needed.	+/-	2024	Vandenplas et al.	ESPGAN	In bottle-fed infants with a first degree relative with a documented allergy, there is insufficient evidence to recommend the routine use of pHF for preventing CMPA.	-		
2014	Muraro et al.	EAACI	In non-exclusively breastfed infants at high-risk for allergy, a hypoallergenic formula with documented preventive effect should be provided until the age of 4 months; afterwards, a standard formula is recommended.	+	2021	Halken et al.	EAACI	There is no recommendation for or against using partially or extensively hydrolyzed formula to prevent food allergy in infants and young children.	+/-		
2006	Chapman et al.	AAAAI and ACAAI	Suggest the use of hypoallergenic or of reduced allergenicity infant formula.	+	2020	Fleischer et al.	AAAAI and CSACI	Do not routinely prescribe or recommend the use of any hydrolyzed formula for the specific prevention of food allergy or development of food sensitization.	+/-		
2008	Greer et al.	AAP	There is modest evidence that the use of pHF or eHF cannot be recommended in allergy prevention.	+/-	2019	Greer et al.	AAP	There is lack of evidence that partially hydrolyzed formula prevents atopic disease in infants and children, even in those at high risk for allergic disease.	-		
2008	N/A	ASCIA	There is some evidence that hydrolyzed formulas may reduce the risk of allergic disease in high-risk infants.	+	2019	Joshi et al.	ASCIA	Hydrolyzed formula is no longer recommended for the prevention of allergic disease.	-		

2012	Seah et al.	MPA and MSAI	When breastfeeding is not possible, consider a hydrolyzed formula.	+				
2014	Vandenplas et al.	Middle East Consensus	All non-exclusively breastfed infants should receive a pHF for prevention of allergy until their risk has been assessed by a healthcare provider.	+				
2014	Schäfer et al.	DGAKI and DGKJ	Non-exclusively breastfed at-risk infants should receive hydrolyzed infant formula up to the age of 4 months.	+	2022	Kopp et al.	DGAKI	For non-exclusively breastfed infants, an infant formula with proven effectiveness in allergy prevention studies should be given until complementary food is introduced.
2017	Recto et al.	PSAAI and PSPHAN	Non-exclusively breastfed at high risk for allergy infants should receive a partially hydrolyzed whey formula or extensively hydrolyzed casein formula for at least 6 months to prevent allergic diseases.	+	2024	Casis-Hao et al.	PSAAI and PSPHAN	For non-exclusively breastfed infants, we cannot recommend for or against the use of partially hydrolyzed milk formula for the prevention of allergic disease.
					2018	N/A	BSACI and BDA (Food Allergy Specialists Group)	If breastmilk is not available, use a standard cow's milk formula rather than a "low allergy" (hypoallergenic) formula.
					2020	Ebisawa et al.	JSA	There is insufficient evidence on the usefulness of hydrolyzed milk in preventing the onset of food allergies.
					2021	Abrams et al.	CPS and CSACI	For non-exclusively breastfed infants, using a specific formula (i.e., hydrolyzed formula) is not recommended to prevent food allergies.

CMPA: cow's milk protein allergy; eHF: extensively hydrolyzed formula; pHF: partially hydrolyzed formula; SF: standard formula.

were allowed only the allocated study formula, while solid foods were permitted after the age of 4 months with no restrictions. Close follow-ups were performed at 2, 4, and 6 months of life by well-trained researchers. Diagnoses for AD and CMPA were objectively performed after clinical examination by an experienced physician and an oral food challenge, respectively. Data were cumulatively analyzed at the age of 6 months while further follow-up data are expected to inform whether the preventive effect of this specific pHF persists over time and if it applies to other allergic diseases.

Considerations and Future Perspectives on Allergy Prevention

Nutritional means for allergy prevention are not only restricted to the type of infant feeding regimen.¹⁰⁹ The timing of complementary feeding (including infant formula and consistency in formula intake,¹¹⁰ the use of probiotics, and HMOs which may act as prebiotics)^{111,112} has also been studied with promising results. Furthermore, regular ingestion, even of small amounts of the allergen, may have a preventive effect on food allergy rather than occasional early feeding, according to the CSACI's recent guidelines,⁴⁶ following the families' nutritional traditions. However, further data are required to confirm the role of other nutritional interventions in allergy prevention.

Breastfeeding is undoubtedly the optimal source of infant feeding and should be strongly encouraged by all healthcare professionals. It plays a crucial role on an infant's immune development, even though recent studies failed to show any protective effect against allergy prevention.^{32,113,114} A possible reason for this is the diversity in type and quantity of the allergens passing in each mother's breastmilk which may be affected by the quantity and type of milk and dairy products consumed by the mother and/or the mother's ability to break down the consumed proteins before passing into breastmilk.¹¹³ This ability may be affected by nonexplored genes coding the amount or specific enzymes that break down allergenic proteins; however, there is no scientific evidence to support this theory.

Regarding the potential role of pHFs in allergy prevention, it is difficult to summarize and conclude for or against their use, despite the wide availability of publications. This is not only because of the differences in the methodological design of each study but also due to the distinct infant formula used and its immunological response *in vivo* as well as the genetic background of the examined population in each study.⁶¹ A recent review²¹ noted that a standard cow's milk formula (SF) should be suggested to mothers who choose not to breastfeed their infants, since recommendations on the preventive role of hydrolyzed formulas are questioned. Nevertheless, the results of available studies should be interpreted with caution, since most of them do not meet the requirements of double-blinded RCTs with rigorous methodological design and the employment of objective outcome measures such as the performance of oral food challenge for the diagnosis of CMPA. Moreover, the timing of formula introduction and recruitment procedures varied, while follow-up evaluation was performed at a wide range of time points, thus making comparison

of the results unreliable. Consequently, the existing concerns about the usefulness of pHFs in allergy prevention are expected and justified.

As already mentioned, not all hydrolyzed formulas are the same, since their allergenicity and immunogenicity differ as a result of the type and extent of hydrolysis applied,⁶⁰ leading to the formation of different epitopes. The characterization of each hydrolysate produced as partially hydrolysate or extensively hydrolysate can be used as a general indicator of the extent of hydrolysis, but it does not reflect their efficacy in allergy prevention or treatment. A recent study shows that the degree of hydrolysis is a poor predictor of the sensitizing capacity of the infant formulas, while the specific peptide sequences formed after hydrolysis uniquely affect the immunogenicity and allergenicity of the hydrolysates.⁵⁹ Interestingly, Bourdeau et al.¹¹⁵ explored the differences in allergenicity between different pHFs, showing that infant formulas produced by different manufacturers (even by the same manufacturer at a different batch) with similar MW are diverse in terms of allergenicity. This could explain the differences observed between the various RCTs even when the same brands and labels were used.

It is worth noting that the pHF examined in ART was not included in any of the previous randomized controlled studies nor in meta-analyses. A systematic review and meta-analysis of clinical trials published in 2024, which, amongst others, included data from the ART study, concluded that feeding an infant with pHF has a preventive effect on allergic disease compared to SF, especially on AD.⁸⁴ Therefore, further well-designed randomized controlled clinical studies are needed to shed light on the potential vital role of pHFs in allergy prevention. However, considering the recent data from the ART study, albeit the limitations, allergy prevention may be possible when targeting specific populations (i.e., infants at high-risk for allergy with family history of AD).

In our opinion, it would be extremely useful to compare the effect of different infant pHFs on allergy prevention produced by different manufacturers in one large prospective double-blinded randomized controlled birth cohort study, including infants from both the general population and those at high risk for allergies, from different parts of the world.

Conclusion

Allergic diseases constitute an increasing healthcare problem worldwide and prevention strategies are urgently needed. Several nutritional interventions have been examined with controversial findings. Whilst breastfeeding is undoubtedly the optimal source of nutrition during the first months of life, its role on allergy prevention appears inconclusive. Considering data from earlier studies and also recent findings showing a definite preventive role of specific pHFs particularly on AD, it is worth reconsidering the role of pHFs in the prevention of allergic diseases when exclusive breastfeeding is not possible. This is of paramount importance, given that the role of other nutritional interventions in allergy prevention is still unclear based on current scientific evidence. Further studies are needed to clarify this hot topic and inform evidence-based clinical practice recommendations.

Authors Contributions

MS and NN were involved in the conceptualization, drafting, and review of the manuscript. EP and PKY reviewed the manuscript. All authors accepted the final version of the manuscript.

Conflicts of Interest

MS is a research assistant and NN the Principal Investigator of the birth cohort RCT Allergy Reduction Trial (ART) in Cyprus: The cow's milk protein allergy risk-reducing effect of Frisolac Gold preventive HA: Multicenter, Placebo-Controlled trial, sponsored by Friesland Campina and conducted at the N Asthma and Allergy Centre. EP and PKY declare no conflict of interest.

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