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VIEWPOINT ARTICLE

# When should we use partially hydrolysed formulae for frequent gastrointestinal symptoms and allergy prevention?

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## ABSTRACT

Experts reviewed the literature to determine whether partially whey hydrolysed formulas (HF) offer benefits in the dietary management of frequent gastrointestinal symptoms and allergy prevention. Compared with standard cow's milk-based formulas, partially whey HF confer a limited protective effect against allergic disease in high-risk infants, particularly atopic dermatitis, but not respiratory allergies. No randomised clinical trials have been published on partially whey HF in infants with colicky symptoms. The group did not find sufficient evidence to support the use of partially whey HF in regurgitation, although recent data suggest that a thickened partially whey HF may be more effective. Partially whey HF, fortified with prebiotics and/or probiotics, with high levels of sn-2 palmitate in the fat blend or without palm oil, provide some benefit in functional constipation.

**Conclusion:** Overall, partially whey HF may offer a useful alternative to intact protein in the dietary management of common functional gastrointestinal symptoms.

## INTRODUCTION

There is confusion about the role of partially hydrolysed formulas (HF) in the management of common functional gastrointestinal symptoms in infants, including persistent crying, gastro-oesophageal reflux and constipation. Several publications, including meta-analyses, have discussed the role of these formulas in allergy prevention. In many countries, these formulas are marketed as having the ability to improve digestibility and as being effective in the dietary management of common gastrointestinal symptoms, including constipation, fussiness, excessive crying, colic and spitting up. However, many of these symptoms can be considered as part of the normal developmental process during infancy and are often not the manifestation of underlying gastrointestinal diseases.

In infancy, food-allergic reactions can occur in breastfed and formula-fed infants. Cow's milk protein is one of the most common food allergens in infancy, although multiple food hypersensitivities may occur. In recent years, there has been an increased focus on the role of food allergens in the pathogenesis of gastro-oesophageal reflux disease, infantile colic and constipation in infancy (1). Therefore, an international group of experts decided to meet and design a review strategy to clarify the current understanding of the benefits and potential indications of partially HF. This review focuses on partially whey protein HF, as most publications and formulas on the market contain this type of protein. Several studies have shown that partially whey HF support adequate growth (2,3).

## METHOD

Most members of this panel met in London, UK, and discussed the need to review the available data on the efficacy of partially HF in preventing food allergy in patients at high risk and to clarify and identify the benefits, if any, of these formulas in patients with constipation, regurgitation, colic/fussiness, etc. The panel's first task was to properly

define partially HF. Then, four subgroups of experts were created to review four topics: allergy prevention, colic, regurgitation and constipation. Later, all members of the panel reviewed all the topics and provided comments and recommendations.

**Partially hydrolysed formulas: definition**

Hydrolysed formulas are manufactured using enzymatic processes that break native proteins into smaller pieces. The enzymatic digestion may be partially or extensive, resulting in larger or smaller peptide fragments. To produce the least allergenic formulas, cow's milk proteins can be modified by enzymatic hydrolysis with progressive destruction of sequential epitopes. Based on the degree of enzymatic hydrolysis, ultraheating and ultrafiltration, protein hydrolysates are categorised as partially HF or extensive HF (3).

There is no general agreement on the criteria to define partially and extensive HF, and protein size is generally used to identify each one. The degree of protein hydrolysis may be characterised by biochemical techniques, such as the spectrum of peptide molecular weights or the ratio of alpha-amino nitrogen to total nitrogen (4).

A wide range of base proteins, including cow's milk protein, soy and rice, are common ingredients of partially HF. When it comes to cow's milk, major protein fractions (i.e. whey, casein or both) may be used rather than whole cow's milk protein. Whole cow's milk-based formulas contain proteins in the range of 14 kD ($\alpha$-lactalbumin) to 67 kD (bovine serum albumin). Partially hydrolysed formulas contain reduced oligopeptides that have a molecular weight of generally <5 kD (ranges between 3 and 10 kD) and peptides in extensive HF have, in more than 90% of cases, a molecular weight of <3 kD (5). Both partially and extensive HF consist of a wide range of peptide sizes. In addition, commercially available (100%) partially whey HF contain 18% of peptides >6 kD, while extensive HF contain between 1% and 5% >3.5 kD. Peptides need to be in the range of 10–70 kD (predominantly 10–40 kD) to be able to act as an allergen (6). As a practical guideline for the industry, the appropriate cut-off for the absence of larger peptides has been determined to be approximately 1.5 kD (7).

**Partially hydrolysed formulas and primary allergy prevention**

The primary prevention of allergic diseases has become a public health priority in many developed regions with a high prevalence of atopic dermatitis, food allergy, asthma and allergic rhinitis. Tolerance development and allergy risk are influenced by a complex array of factors, including genetics, epigenetic regulation of gene expression, birth and feeding mode, microbial environment, exposure to environmental toxins or pollutants.

Exclusive breastfeeding for 6 months, and the introduction of a complementary diet from 4 to 6 months, is recommended. If breastfeeding is not possible, use of a partially HF has been suggested for infants with a family history of atopy. This recommendation follows the findings of a Cochrane review on the role of hydrolysed formulas in allergy prevention, as well as more recent meta-analyses (8,9). The German Infant Nutritional Intervention study (3), the largest trial to date that compares the effects of partially and extensive HF, and standard infant formula, provides the most convincing data of the protective effects of partially whey HF and casein-predominant extensive HF. However, the role of partially HF in primary allergy prevention is still debated. In addition, there are few studies assessing the effect of partially HF in not-at-risk infants. However, these infants represent an important percentage of the infants who will develop atopic manifestations (10). In high-risk infants, when breastfeeding is not possible, hydrolysates of documented safety and efficacy have an indication in infant feeding up to the age of 4–6 months (9).

*Atopic dermatitis*

Atopic dermatitis, or eczema, affects up to 20% of infants and young children in many developed countries. The German Infant Nutritional Intervention study showed a significant reduction in the incidence of atopic dermatitis using extensive casein HF (OR 0.42, 95% CI, 0.22–0.79) and partially whey HF (OR 0.56; 95% CI, 0.32–0.99), compared with standard infant formula (3). The per-protocol analysis of this study at 6 and 10 years suggests that this protective effect is sustained (3). The relative risk for the cumulative incidence of atopic dermatitis in the intention-to-treat analysis (n = 2,252) was 0.82 (95% CI, 0.68–1.00) for partially whey HF, 0.91 (95% CI, 0.76–1.10) for extensive whey HF and 0.72 (95% CI, 0.58–0.88) for extensive casein HF compared with standard infant formula. In the per-protocol analysis (n = 988), effects were stronger, with corresponding figures of 0.67 (95% CI, 0.51–0.88), 0.77 (95% CI, 0.59–1.02) and 0.58 (95% CI, 0.42–0.8), respectively (11).

Several meta-analyses have confirmed the benefits that HF play in preventing atopic dermatitis in high-risk infants. Health economic modelling found this approach to be cost-effective in a range of healthcare settings. In contrast, a randomised controlled trial evaluating the use of partially HF or soy formula compared with standard infant formula, after discontinuation of breastfeeding, showed no protection against the development of allergic manifestations at the age of 2 years and between the ages of 6 and 7 years.

Thus, exclusive breastfeeding should be encouraged as the primary means of preventing atopic risk. However, when infants are not exclusively breastfed, partially whey HF may be considered as a measure to potentially reduce the risk of developing atopic dermatitis (9).

*Cow's milk allergy*

Most studies on the effect of partially HF found no significant effect on the prevention of food allergy, in particular cow's milk allergy. The Cochrane review of 2006 stated that, in high-risk infants who are unable to be completely breastfed, there is limited evidence that prolonged feeding with a hydrolysed formula rather than a standard infant formula prevents cow's milk allergy (8). Only one randomised study found a preventive effect for

partially HF versus standard infant formula (15.6% versus 42.8%, p = 0.014) (12). The Melbourne Atopy Cohort Study was a trial of 620 infants, who were randomised to receive standard infant formula, soy formula or partially whey HF at the time of weaning from breastfeeding. Limiting the analysis to standard infant formula (n = 193) and partially whey HF (n = 191), there was no significant difference in clinical allergic reactions to cow's milk protein at 2 years of age [cow milk formula – six cases (1.6%) and partially whey HF – six cases (3.2%); $I^2 = 0.992$, p = 0.32, NS] (13). Given the small number of trials, the role of partially whey HF in the prevention of cow's milk allergy remains uncertain.

*Asthma and allergic rhinitis*

Several studies have assessed the preventive effect of partially HF on asthma and allergic rhinitis. Overall, there was no significant preventive effect on the incidence or prevalence of asthma or allergic rhinitis (9).

In summary, partially HF have been shown to confer a limited protective effect against atopic disease in high-risk infants, compared with standard infant formula. This preventive effect appears to be greatest for atopic dermatitis, whereas respiratory allergies (asthma, allergic rhinitis) were not prevented. One study also found that the risk of cow's milk allergy was reduced by partially HF, but no long-term data are available. Data on the additional preventive benefit of atopic disease, by adding probiotics and/or prebiotics to partially HF, are not available. Further large-scale, randomised clinical trials are required.

**Partially hydrolysed formulas and infants with fussiness, excessive crying and colicky symptoms**

Infantile colic affects between 16% and 26% of young children. It occurs equally in breastfed and formula-fed infants and in both sexes. Symptoms include excessive crying in otherwise thriving infants, which often occurs in the evenings. Crying episodes often start in the first weeks of life and then decrease before resolving at the age of 4–5 months. The Rome III criteria defined infantile colic as 'episodes of irritability, fussing, or crying that begin and end for no apparent reason and last at least 3 h a day, at least 3 days a week for at least 1 week'. Rome III modified the original Wessel criteria, which stated that the duration of symptoms had to be at least 3 weeks.

Despite its relatively benign nature, this condition can be extremely distressing for parents, especially when they are dealing with their first child. Mothers of infants that cry excessively often believe that their child is not healthy (14). Although the aetiology of infantile colic is not known, there is limited evidence linking persistent crying in the young infant to food allergy. Early studies have demonstrated a high prevalence of infantile colic in infants with cow's milk allergy. In fact, in a sequential cohort of 100 patients with challenge-proven cow's milk allergy, 44% of infants displayed irritability and colicky behaviour during the cow's milk challenge procedure (15). This led to the hypothesis that infantile colic may represent a subgroup of a clinical presentation of cow's milk allergy. However, there is no general agreement on what proportion of infants with infantile colic suffers from cow's milk allergy. Regarding the management of infantile colic in breastfed infants, clinicians should advise mothers to continue breastfeeding. Eliminating cow's milk from the maternal diet may also be recommended to assess for possible cow milk allergy. In formula-fed infants with colic, the elimination of cow's milk protein and use of extensive HF have been shown to be an effective treatment.

Young infants with long crying bouts, hard-to-soothe behaviour and fussiness that do not match the Rome III criteria are also frequently labelled as colicky babies. This kind of crying is different from the crying related to infantile colic defined previously. Reasons for these symptoms include hypersensitivity, reaction to food ingredients, inadequate feeding practices, normal neurodevelopmental changes and, in a small percentage, organic diseases. In fact, the colicky crying pattern that results from organic disease is not more than 5%.

Paediatricians should confirm that red flags related to organic conditions are not present. In very fussy babies with excessive gas and soft stools, with or without the presence of diaper rash, the crying and gassiness are sometimes associated with low lactase activity or secondary lactose maladsorption (16). A thorough medical history and physical exam are critical for a correct diagnosis. Concerning the management of excessively fussy babies, it is important to reassure parents that excessive crying at an early age is often not a manifestation of a disease. It is beneficial to empower parents and ask them to consider the first 3 months of life as a test that they can overcome, with positive consequences for the baby and family (17). Lactose-free infant feeding does not adversely affect growth in term infants. The presence or absence of lactose in infant feeding is an area of debate: while the advantage of lactose-reduced or lactose-free infant feeding is not evidence based, doing so is also not related to any negative effect.

Regarding feeding these babies, there is no justification to discontinue breastfeeding. In formula-fed infants, when low lactase activity is suspected and the child has gassiness, diarrhoea and, in some cases, diaper rash due to the evacuation of acidic stools, lactose may be withdrawn temporarily from the diet (18). Lactose maladsorption or intolerance is mainly a load phenomenon. There is no scientific support for the use of soy formula in these patients. However, in a study of 1803 infants with common digestive symptoms, 19.8% of parents reported colicky symptoms and the baby received a soy-based infant formula recommended by medical personnel (19). Unfortunately, this study provides no data on the effect of soy. A meta-analysis of various treatments for infantile colic showed that substituting soy infant formula for cow's milk-based infant formula was effective, but this benefit disappeared when the analysis was limited to studies of good methodological quality (20).

Two recent studies showed a beneficial effect of *Lactobacillus reuteri* DSM 17938 on crying time in breastfed infants without demonstrated cow's milk allergy. Savino

 

et al. (21) showed that *L. reuteri* in early breastfed infants improved symptoms of infantile colic and was well tolerated and safe. Szajewska et al. (22) also demonstrated that infants with infantile colic, who were exclusively or predominantly breastfed, benefited from the administration of *L. reuteri*, compared with a *placebo*. However, data on the additional benefit of probiotics and/or prebiotics in infants presenting with colicky symptoms added to a partially HF are limited.

No randomised clinical trials have been published demonstrating the efficacy of partially whey HF in infantile colic. Experience has shown that partially hydrolysed formulas can be a useful option when cow's milk protein allergy is not a potential cause of the colic or when the extensive hydrolysate would be too expensive. In fact, various randomised controlled trials have been published demonstrating the efficacy of whey-based partially hydrolysed formulas. In some cases, these formulas are lactose-reduced or lactose-free and have added prebiotics showing, with varying levels of evidence, a reduction in the number of crying episodes per week and total crying time. However, the role of lactose can be questioned, as soy formula was not associated with a benefit.

There are insufficient data to recommend a partially HF as single dietary intervention in colicky infants as most studies included other dietary changes as well. However, there seems to be a trend that partially HF may be better tolerated. Given the fact that partially HF are nutritionally adequate and safe, its use can be debated given the nonsignificant trend of improvement in the absence of adverse effects. In breastfed babies, there is no reason to suspend breastfeeding.

**Partially hydrolysed formulas and regurgitation**

Gastro-oesophageal reflux presents as regurgitation in more than two-thirds of otherwise healthy infants and represents a topic of discussion with paediatricians at one-quarter to one-fifth of all routine 6-month infant visits (23). Gastro-oesophageal reflux is defined as the passage of gastric contents into the oesophagus. In most cases, it is considered a normal physiologic process that occurs several times a day in healthy infants, children and adults and must be distinguished from gastro-oesophageal reflux disease, which includes troublesome symptoms or complications associated with gastro-oesophageal reflux (23). Differentiating between gastro-oesophageal reflux and gastro-oesophageal reflux disease involves the identification of other clinical signs or conditions (red flags), which usually indicate the possible presence of underlying pathological processes. Poor weight gain, failure to thrive, dysphagia, abdominal or substernal/retrosternal pain, cough, laryngitis, sinusitis and wheezing in infancy may raise the suspicion of gastro-oesophageal reflux disease and suggest the need to conduct further diagnostic or therapeutic interventions. From the diagnostic point of view, for most paediatric patients, a thorough history and a careful physical examination in the absence of warning signs are sufficient to reliably diagnose uncomplicated gastro-oesophageal reflux (23).

From the therapeutic point of view, for noncomplicated reflux, no intervention is required for most infants. Effective parental reassurance and educating parents regarding regurgitation and lifestyle changes, adjusting feeding regimens, positioning and avoidance of environmental smoke exposure are usually sufficient to manage infantile reflux (23).

Staelens et al. published a double-blind, randomised, cross-over study comparing the gastric emptying in 20 healthy newborns fed standard infant formula, a partially HF and an extensive HF containing 50 mL 13C-octanoic acid. The extensive HF emptied significantly faster than standard infant formula and partially HF (medians 46 versus 55 and 53 min, respectively) (24). However, the gastric emptying in infants fed either partially HF or standard infant formula did not show any statistically significant difference between both the study groups (24).

In another study, 70% of infants with regurgitation were fed a partially HF fortified with prebiotics and low levels of lactose and demonstrated a reduction of 1.87 in the number of regurgitation episodes between day 1 and day 7 (95% CI: 1.57–2.16; $p < 0.05$) and of 0.18 (95% CI: 0.06–0.31; $p < 0.05$) between day seven and day 14 (25).

A recent prospective, double-blind, randomised cross-over trial was performed for a 1-month period in 115 formula-fed infants, aged 2 weeks to 5 months, comparing two antiregurgitation formulas: first, a nonhydrolysed protein and locust bean gum and second, a partially whey hydrolysate, locust bean gum and specially treated starch. The primary endpoint was the frequency of regurgitation. The study showed that the number and volume of regurgitation episodes decreased significantly in both the groups, but the reduction was statistically greater in the hydrolysate group (26).

In summary, thickened formulas reduce regurgitation. Recent studies indicate that thickened partially HF may have an additional benefit, although the data are too limited to result in a recommendation.

**Partially hydrolysed formulas and constipation**

Constipation is a common problem in childhood with an estimated prevalence of 3% in the Western world (27). In 17–40% of children, constipation starts in the first year of life. Constipation is a debilitating condition characterised by infrequent or painful defecation, faecal incontinence and abdominal pain. It may cause distress to the child and family and can result in emotional disturbances and family discord (27).

Hard stools are found only in 1.1% of exclusively breastfed infants versus 9.2% of standard formula-fed infants, and firm or hard stools are often seen with the change from breast milk to infant formula or after the introduction of solids (27).

Most infants who present with constipation have functional constipation, and rarely does constipation have an organic aetiology. Cow's milk allergy has been shown to be a possible cause of constipation in some young children. However, there is still a strong debate on this relationship,

 

in part due to the fact that allergy testing is often negative in these patients.

Regarding management of functional constipation, the first step is parental education. Paediatricians should discuss the myths and worries about functional constipation and point out that it is one of the most frequent, nondangerous conditions in paediatrics and that it usually has a relatively benign long-term outcome. Infants who have constipation and have not yet begun solid foods can be treated with the addition of indigestible, osmotic active carbohydrates to the formula, titrating the dose to induce a daily bowel movement. Glycerine suppositories or rectal stimulation with a lubricated rectal thermometer can be used occasionally if there is a need for urgent, rapid relief, such as when there is a very hard stool in the rectum, but should not be used frequently. Mineral oil, which poses the risk of lipoid pneumonia if aspirated, or enemas such as phosphate are not indicated and may be harmful in infants.

Regarding dietary management, if an infant with functional constipation is receiving breast milk, is growing and feeding normally and has no signs or symptoms of obstruction or enterocolitis, then reassurance and close follow-up should be sufficient. It is well known that infants fed standard formula are more prone to have hard stools due to differences in fat digestion and absorption and in carbohydrate and protein composition compared with breast milk. If the infant is receiving a standard infant formula, it is recommended to verify that formula preparation is correct. However, in practice, a change of formula is often suggested.

Studies have shown that the type of macronutrients in formulas plays a role in the stool pattern, such as stool consistency and frequency. For example, harder stools are frequent in infants fed formulas containing palm olein oil or palm oil as the main source of fat. Palm oil has a reduced content of fatty acids esterified to glycerol in the sn-2 position and an increase in those esterified in the sn-1 and sn-3 positions. Fatty acid in positions sn-1 and sn-3 undergoes hydrolysis in the intestine, releasing palmitic acid, which is poorly absorbed and forms calcium soaps responsible for firmer stools (28,29). Thus, a formula rich in fatty acids in position sn-2 is likely to soften the stools.

Regarding carbohydrates, a recent study compared a lactose-free milk protein formula to a standard lactose-containing milk-based formula in healthy full-term infants and found that the lactose-free group had a significantly higher percentage of softer stools and lower percentage of hard stools compared with lactose group at 14 and 28 days of age (30). However, the authors did not explain the mechanism underlying these findings. These findings are relevant as many of the partially HF brands do have a reduced lactose content.

Concerning the type of proteins present in infant formulas and their impact on infants' stool patterns, it is recognised that constipation is more frequent in casein than in whey-predominant formulas (27). Hydrolysed formulas produce more frequent and softer stools. Mihatsch et al. found that the gastrointestinal transit time was shorter when a partially HF, containing an ultra-filtrated mixture of hydrolysed whey and hydrolysed casein, with a molecular weight 75% <1.5 kD, 15% free amino acids, is used compared with standard preterm formula. In fact, the partially whey HF had a markedly shorter gastrointestinal transit time (9.8 h) than standard infant formula (19 h) (31). A study compared several formulas and breastfeeding to define expected ranges of stooling. Significantly more stools were passed by breastfed and extensive HF-fed infants versus standard infant formula or soy-based formulas. In fact, infants receiving breast milk or an extensive HF had twice as many stools as other formula groups (27).

Partially whey HF, fortified with prebiotics and/or probiotics, with high sn-2 palmitate in the fat blend or without palm oil as the main source of fat in the oil blend, have been tested lately and seem to offer a good alternative for managing functional constipation in infancy (27). There are no studies evaluating the efficacy of a partially whey HF as single intervention in constipated infants. There is some evidence that partially whey HF induce softer stools than standard infant formula in nonconstipated infants.

## DISCUSSION

Gastrointestinal symptoms such as constipation, fussiness, colic or spitting up are very common at an early age. Nevo et al. reported that 47% of infants underwent changes in their formula in the first 6 months of life, usually without consultation with a health professional, and often for a perceived gastrointestinal problem (18,23,27). Both exclusively breastfed and formula-fed infants can suffer from these symptoms. However, the incidence of general symptoms of gastrointestinal intolerance is lower in babies fed mother's milk, as compared to formula-fed infants (18,23,27).

Evaluation of feeding technique, effective reassurance of the caregivers, and careful education is all that is needed to alleviate parental anxiety in most cases. When the child is formula-fed, these mild digestive feeding issues generally cause parents and healthcare practitioners to switch to a different infant formula based on the belief that the symptoms may be a reflection of a formula intolerance.

In the last few years, new formulas, intended to help these children, have been launched worldwide. One of the main characteristics of these formulas is that the proteins are partially hydrolysed. Many of these formulas also contain other bioactive ingredients such as prebiotics, probiotics or special types of fats in their oil blends and, in general, contain low levels of lactose or are lactose-free.

In addition, partially HF have been extensively tested in patients at risk of developing allergy. Our panel reviewed all available data regarding the role of these formulas in these patients. We conclude that results of clinical trials have shown that partially HF offer some protective effects against allergic disease in high-risk infants, compared with standard cow's milk-based formulas. This preventive effect appears to be more relevant for atopic dermatitis and has not been demonstrated for respiratory allergies such as asthma or

 

rhinitis. A single trial has shown that partially whey HF were able to reduce the risk of developing cow's milk allergy. However, more studies and long-term data are required to provide any recommendation on the prevention of this entity. Not enough data are available on the role of partially whey HF fortified with probiotics and/or prebiotics in allergy prevention. Although the number of non-at-risk infants developing allergy later in life is substantial, no studies have been performed in an unselected population.

Infants with excessive crying or hard-to-soothe behaviour, that does not match the Rome III definition of infantile colic, are often labelled as colicky babies. Some trials have demonstrated the efficacy of partially whey HF in the community when cow's milk allergy was not considered to be the cause of the infant's colic symptoms. Several partially whey HF brands are lactose-reduced or lactose-free and have added prebiotics or probiotics and have shown certain benefits in the management of common functional gastrointestinal manifestations such as fussiness and colicky symptoms (18).

Although not enough studies evaluate the role of thickened partially whey HF in patients with regurgitation, some studies have showed potential favourable effects (26).

The type of proteins in infant formula plays a critical role in defining the infant's stool characteristics. Constipation is seen more frequently in casein than in whey-predominant formulas (27). Some studies have shown that the transit time and gastric emptying are faster when infants are fed formulas with hydrolysed protein formulas compared with standard formulas (whole proteins). Also, other trials have shown that infants who receive breast milk or a hydrolysed formula have twice as many stools as babies fed with either standard formulas or soy-based formulas. In addition, well-conducted clinical trials have demonstrated that partially whey HF, supplemented with prebiotics and/or probiotics without palm olein as the main source of fat in the oil blend or high in sn-2 palmitate in the fat blend, appeared to offer a good alternative for managing functional constipation in infants.

In conclusions, partially whey HF may offer an acceptable alternative to standard infant formula for primary allergy prevention, mainly for atopic dermatitis, in high-risk infants who are not exclusively breastfed. More studies are needed to determine their real benefit in the prevention of cow's milk allergy. Infants with constipation may also benefit by switching to these types of formulas, mainly if they are fortified with pre- or probiotics, and if they have an oil blend known not to produce hard stools. In colicky babies with excessive crying, the available information shows that these formulas might be of some help, when cow's milk allergy is not suspected. Overall, partially hydrolysate may offer some promise over native protein in the dietary management of common functional gastrointestinal symptoms.

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## References

1. Sicherer SH. Clinical aspects of gastrointestinal food allergy in childhood. *Pediatrics* 2003; 111: 1609–16.
2. Betoko A, Charles MA, Hankard R, Forhan A, Bonet M, Regnault N, et al. Determinants of infant formula use and relation with growth in the first 4 months. *Matern Child Nutr* 2014; 10: 267–79.
3. von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, et al. Allergies in high-risk school children after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 2013; 131: 1565–73.
4. Jost R, Fritsche R, Pahud JJ. Reduction of milk protein allergenicity through processing. *Bibl Nutr Dieta* 1991; 48: 127–37.
5. Lowe AJ, Dharmage SC, Allen KJ, Tang ML, Hill DJ. The role of partially hydrolyzed whey formula for the prevention of allergic disease: evidence and gaps. *Expert Rev Clin Immunol* 2013; 9: 31–41.
6. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; 121: 183–91.
7. Aas K. What makes an allergen an allergen? *Allergy* 1978; 33: 3–14.
8. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006; CD003664.
9. Vandenplas Y, Bhatia J, Shamir R, Agostoni C, Turck D, Staiano A, et al. Hydrolysed formulas for allergy prevention. *J Pediatr Gastroenterol Nutr* 2014. (in press).
10. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. *J Allergy Clin Immunol Pract* 2013; 1: 29–36.
11. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr Med Res Opin* 2010; 26: 423–37.
12. Vandenplas Y, Hauser B, Van den Borre C, Sacre L, Dab I. Effect of a whey hydrolysate prophylaxis of atopic disease. *Ann Allergy* 1992; 68: 419–24.
13. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128: 360–5. e4.
14. Forsyth BW, McCarthy PL, Leventhal JM. Problems of early infancy, formula changes, and mothers' beliefs about their infants. *J Pediatr* 1985; 106: 1012–7.
15. Hill DJ, Hosking CS. Infantile colic and food hypersensitivity. *J Pediatr Gastroenterol Nutr* 2000; 30(Suppl.): S67–76.
16. Gormally S. Clinical clues to organic etiologies in infants with colic: In Barr R, St James-Roberts I, Keefe M, editors. *New evidence on unexplained early infant crying: its origins, nature and management*. Skillman, NJ: Johnson & Johnson Pediatric Institute, 2001: 133–49.

 

17. Barr RG, St James-Roberts I, Keefe M, editors. *New evidence on unexplained early infant crying: its origins, nature and management. Johnson & Johnson Pediatric Round Table Series*. Skillman, NJ: Johnson & Johnson Pediatric Institute, 2001: 183–245.
18. Vandenplas Y, Gutierrez-Castrellon P, Velasco-Benitez C, Palacios J, Jaen D, Ribeiro H, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. *Nutrition* 2013; 29: 184–94.
19. Berger-Achituv S, Shohat T, Romano-Zelekha O, Ophir E, Rachmani S, Malovizky D, et al. Widespread use of soy-based formula without clinical indications. *J Pediatr Gastroenterol Nutr* 2005; 41: 660–6.
20. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review. *BMJ* 1998; 316: 1563–9.
21. Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, et al. *Lactobacillus reuteri* DSM 17938 in infantile colic: a randomized, double-blind, *placebo*-controlled trial. *Pediatrics* 2010; 126: e526–33.
22. Szajewska H, Gyrczuk E, Horvath A. *Lactobacillus reuteri* DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, *placebo*-controlled trial. *J Pediatr* 2013; 162: 257–62.
23. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009; 49: 498–547.
24. Staelens S, Van den Driessche M, Barclay D, Carrié-Faessler AL, Haschke F, Verbeke K, et al. Gastric emptying in healthy newborns fed an intact protein formula, a partially and an extensively hydrolysed formula. *Clin Nutr* 2008; 27: 264–8.
25. Savino F, Cresi F, Maccario S, Cavallo F, Dalmasso P, Fanaro S, et al. "Minor" feeding problems during the first months of life: effect of a partially hydrolysed milk formula containing fructo- and galactooligosaccharides. *Acta Paediatr Suppl* 2003; 441: 86–90.
26. Vandenplas Y, Leluyer B, Cazaubiel M, Housez B, Bocquet A. Double-blind comparative trial with two antiregurgitation formulae. *J Pediatr Gastroenterol Nutr* 2013; 57: 389–93.
27. Tabbers MM, Di Lorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014; 58: 265–81.
28. Alarcon PA, Tressler RL, Mulvaney A, Lam W, Comer GM. Gastrointestinal tolerance of a new infant milk formula in healthy babies: an international study conducted in 17 countries. *Nutrition* 2002; 18: 484–9.
29. Fewtrell MS, Kennedy K, Murgatroyd PR, Williams JE, Chomtho S, Lucas A. Breast-feeding and formula feeding in healthy term infants and bone health at age 10 years. *Br J Nutr* 2013; 7: 1–7.
30. Lasekan JB, Jacobs J, Reisinger KS, Montalto MB, Frantz MP, Blatter MM. Lactose-free milk protein-based infant formula: impact on growth and gastrointestinal tolerance in infants. *Clin Pediatr (Phila)* 2011; 50: 330–7.
31. Mihatsch WA, Högel J, Pohlandt F. Hydrolysed protein accelerates the gastrointestinal transport of formula in preterm infants. *Acta Paediatr* 2001; 90: 196–8.

 