Modified Proteins in Allergy Prevention

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Abstract
Around 2.5% of neonates experience hypersensitivity reactions to cow's milk protein during the first year of life, which is highly associated with early exposure to cow's milk. To prevent early allergy development, cow's milk proteins in infant formulas were modified by hydrolyzation processes for use in children at high atopic risk who need milk supplementation in the first months of life. Dependent on the degree of modification, hydrolyzed cow's milk formulas are differentiated into extensively and partially hydrolyzed whey or casein hydrolysates (pHF, eHF). However, their allergy-preventive potential seems not only to depend on the degree but also on the process of hydrolysis. pHF and eHF can be used for primary prevention of allergy in infants at high atopic risk, while only eHFs are indicated for secondary prevention in patients with manifest cow's milk allergy. In clinical trials a consistent trend to a reduction in atopy, mainly atopic eczema and food allergy, by certain pHFs and eHFs could be demonstrated in children with a familial risk of atopy until the age of 6 years. Because more than 50% of allergic children do not have a family history of atopy, it would be worthwhile to consider primary allergy prevention with hydrolysates for all children who need supplementation to breastfeeding.

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Introduction

Allergic diseases are complex multifactorial disorders involving a combination of genetic and environment interactions. One of the most important environmental risk factors for later development of food allergy and other allergic diseases in the postnatal period is the early exposure to food allergens.

The prevalence of food allergy in infants and young children in the general population is estimated at 5–6% [1]. It is often associated with allergic manifestations in the gastrointestinal tract, on the skin and in the respiratory tract, and sometimes even causes life-threatening anaphylactic reactions.
Around 2.5% of neonates experience hypersensitivity reactions to cow's milk protein during the first year of life [2], which in turn is highly associated with early exposure to cow's milk. Milk proteins constitute the most common food allergens provided to children in the first months of life. Children who are not exclusively breastfed but instead fed a regular cow's milk formula, receive a 106 times higher oral antigen load than fully breastfed children.

Interest has therefore focused on possibilities to reduce the early allergen load to not fully breastfed children by altering infant formula as the most important modifiable environmental factor in early life, especially in children at high atopic risk.

**Oral Tolerance**

Food proteins are per se immunogen, characterized by the capacity to either initiate the production of specific IgE antibodies and/or T-cell immune responses, or to induce oral tolerance. Whether an immunogen will be allergenic or tolerogenic is influenced by the genetic disposition of an individual, by the dose, the nature and time point of the first introduction of an antigen, and by environmental factors like passive smoke exposure, infections, microbial gut composition and others which can either promote or protect against the development of allergy [3].

In contrast to sensitization, which is the process that leads to an immunologic hypersensitivity after exposure to an allergen, oral tolerance is defined as the induction of an antigen-specific immunologic hypo- or non-reactivity after oral ingestion [4]. Normally, lower molecular weight proteins processed by gut-associated lymphoid tissue induce oral tolerance without sensitization. The best means to induce oral tolerance is breast milk, even if it can contain food proteins which may lead to sensitization of the baby [5]. Consequently, because intact proteins in regular cow's milk formula may increase the risk of sensitization, hydrolyzed formulas with lower molecular weight proteins similar to those in breast milk have been developed to avoid early sensitization.

**Hydrolyzed Infant Formulas**

Hydrolyzed cow's milk-based infant formulas have in common that the proteins have been modified in order to reduce their allergenic potential. Dependent on whether they are intended for primary or secondary prevention (in cow's milk-sensitive infants) the degree and kind of modification are different.

Several physicochemical procedures for protein modification have been used, mainly ultra-heating and enzymatic cleavage. While heating at more than 80°C destroys the conformity of the molecule, but not the structural
epitopes, enzymatic hydrolysis modifies both and thus is by far the most effective mode to reduce the allergenicity of a protein. The most commonly used enzymes for the production of infant formulas are pig-derived trypsin or chymotrypsin, but proteases from bacteria and moulds can also be used.

The process of enzymatic cleavage and the duration of heating are responsible for the different lengths and allergenicities of the peptides and thus for the allergy-preventive effect.

Accordingly, dependent on the degree of modification of the proteins, hydrolyzed cow's milk formulas are differentiated into extensively and partially hydrolyzed whey (W) or casein (C) hydrolysates.

Extensively hydrolyzed formulas (eHFs) contain more than 95% peptides with molecular weights of <3,000 Da. More than 60 years ago they were primarily intended as formulas for secondary prevention to treat children with cow's milk allergy (CMA). They meet the definition of the American Academy of Pediatrics (AAP) for a hypoallergenic formula to treat CMA [6], which states that 90% of children with proven CMA tolerate the formula in a double-blind, placebo-controlled food challenge (DBPCFC) and during a 7-day open treatment follow-up with only occasional reports of hypersensitivity reactions (<5%).

The molecular weight profile of partially hydrolyzed formulas (pHFs) shows a much lower percentage of peptides with molecular weights of <3,000 Da and a higher percentage of peptides with molecular weights in the range of 3,000–10,000 Da. They were primarily developed for use in children with non-IgE-mediated formula intolerance and were later recognized by the American and European Societies for Pediatric Allergy and Clinical Immunology as potential formulas for primary allergy prevention [6, 7].

Like the first pHF that was developed in 1985, most pHFs today are whey hydrolysates, while eHFs are either whey or casein hydrolysates.

**Oral Tolerance Induction: Differences between pHF and eHF in Animal Models**

In an animal model the capacity of regular and hypoallergenic infant formulas to produce specific antibodies has been investigated. It could be shown that partially and extensively hydrolyzed cow's milk-based infant formulas result in a 100 to 10,000 times lower production of specific antibodies compared with standard cow's milk formula [8].

Oral ingestion of a food protein normally leads to induction of specific immune tolerance to the respective antigen. Already back in 1984 Strobel and Ferguson [9] were able to show in an animal model that oral tolerance induction with intact proteins is possible and dependent on the age of the individual as well as on the amount and kind of antigen. Early studies by Mowat et al. [10] suggested that oral tolerance induction plays a role in allergy prevention.
In contrast to the well-accepted oral tolerance induction with intact food proteins, only little experience has been made with modified food antigens such as hydrolyzed infant cow’s milk-based formulas.

Fritsché et al. [11] observed a significant antibody suppression of IgE anti-β-lactoglobulin (BLG), but not IgE anti-ovalbumin in rats following exposure to cow’s milk, when they were pre-fed a regular cow’s milk formula or pHF-W, but not when they were pre-fed eHF-W or water.

It was also shown that a pHF-W but not an eHF-W can induce oral tolerance to intact whey protein [11]. This was later confirmed and further differentiated by Peng et al. [12] in naïve mice. They demonstrated that unsensitized mice fed a cow’s milk formula (Nan) for only 1 week or a pHF-W (Nan-HA) for 4 weeks developed oral tolerance to the whey allergens BLG, BSA and α-lactalbumin. In contrast, mice fed eHF-Ws (Alfare and Pepti junior) or an eHF-C (Pregestimil) for 1–4 weeks failed to develop oral tolerance [12]. This group has also shown that, in already sensitized mice, ongoing antibody responses to BLG can be suppressed after 12 weeks feeding of standard formula, but not after feeding hydrolyzed formulas [12].

From these experiments it is suggested that, pHFs like Beba-HA and Nan-HA can induce oral tolerance only in naïve mice after 4 weeks feeding. As opposed to the previous experiments by Fritsché et al. [11], who suggested that the same doses of intact cow’s milk formula and the pHF induce the same level of oral tolerance in the same time, in the studies by Peng et al. [12] a time-dependent difference between the two formulas is assumed, suggesting that the tolerogenity of intact protein in Nan is stronger than the modified polypeptide in Nan-HA or Beba-HA, probably due to the smaller molecular weight of the polypeptides. While most immunogenic allergens are proteins with a molecular weight of 10,000–100,000 Da, polypeptides smaller than 5,000 are no longer immunogenic.

**pHF and eHF for Primary Allergy Prevention**

Cow’s milk-based hydrolysates are generally recommended for primary allergy prevention by the Committees of Nutrition of the European Society for Paediatric Allergy and Clinical Immunology (ESPACI) together with the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the AAP for infants at high risk of developing atopic diseases, if breastfeeding is not possible or insufficient in the first months of life [6, 7, 13]. An infant is considered to be at high atopic risk if at least one parent or biological sibling is allergic [14, 15].

None of the hydrolysates meets all the definition criteria as a formula for prevention, which include that it has to be tested in a prospective controlled clinical trial in children with a positive family history for atopy, it should be given exclusively for the first 6 months of life, followed by at least another 12
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months of observation, and verification of symptoms by a DBPCFC. Finally, it must be documented that at the age of 18 months children fed the hydrolyzed formula had significantly less allergic symptoms compared to the control group fed a regular cow’s milk formula [6].

The most difficult criteria to fulfill is exclusive formula feeding for the first 6 months and verification of symptoms by DBPCFC. Studies with exclusive formula feeding can only be performed in the rather rare cases where mothers are either unable or unwilling to breastfeed. Therefore, only one study compared pHF with CMF in non-breastfed high-risk children [16]. In all other studies the formulas were fed as supplements to breastfeeding. Although DBPCFC is the gold standard to prove the association between the accused allergen and symptoms, many mothers in real life refuse to agree to it.

The allergy-preventive potential of eHF and pHF in high-risk infants has been evaluated in several meta-analyses [17, 18].

Hydrolyzed formulas were compared with breastfeeding, cow’s milk formula, soy formula and combinations of them. Taking the reports together, a consistent trend to a reduction in atopy, mainly atopic eczema and food allergy (especially CMA), can be demonstrated. Most of the studies had a follow-up of 12–24 months, and only a few studies followed children until the age of 5 and 7 years [16, 19].

Studies that investigated the effect of a partial hydrolysate mainly used the whey-based pHF by Nestlé (Beba-HA, Nan-HA), most of the studies with eHF used the casein-based eHF by Mead Johnson (Nutramigen).

The study designs are different in many methodological aspects, including the definition of high atopic risk (single or biparental family history), randomization (yes, no, when and how), blinding (no, yes, single or double blinding), and finally, but most important, the outcome definition. A direct comparison of the studies may therefore not be appropriate.

Taking all studies which were selected for the meta-analyses together regardless of the differences, a preventive effect on the prevalence and cumulative incidence of allergic manifestations with eHF and also pHF can be demonstrated, which is mainly driven by the reductions in atopic dermatitis and food allergy.

pHF versus eHF in Allergy Prevention

The American and European Pediatric Societies for Allergy and Clinical Immunology and Gastroenterology (AAP/ESPACI/ESPGHAN) preferably recommend eHF for allergy prevention, but also recognize that pHFs have preventive potential [6, 7, 13].

The argument to recommend eHFs is the extremely reduced antigenicity to avoid an immunologic response. On the other hand those who prefer the pHFs argue that a certain residual antigenicity is necessary to induce oral
tolerance, as shown in animal models [11, 12]. The question arises whether results from the animal models can be translated for infants in general and especially for infants considered at high atopic risk. The few studies that investigated eHF and pHF in one study showed no significant difference between the two with regard to reduction in atopic dermatitis [17, 20–24], but a better effect on reduction in food and CMA with eHF-C [17, 20, 21].

The German Infant Nutritional Intervention Study (GINI), which is the largest study ever performed in the field of allergy prevention with hydrolysates (n = 2,252), compared the effect of a pHF-W (Beba-HA), an eHF-W (Nutrilon Pepti), and an eHF-C (Nutramigen) with the effect of a standard cow’s milk formula in children at high atopic risk, until the age of 6 years [22–24].

The 3-year results have clearly demonstrated several important findings in the field of allergy prevention with hydrolysates. First, pHF-W and eHF-C have a significant allergy-preventive effect driven mainly by the reduction in atopic eczema, while the eHF-W used in this study has not [23]. This is in contrast to the study by Halken and Høst [21] who used a different eHF-W but the same eHF-C as in the GINI study. Their eHF-W (Profylac) showed a similar effect as eHF-C, suggesting that obviously not only the residual antigenicity or the protein source but also the process of hydrolysis may be responsible for the effect. This has further clinical relevance as it underlines the necessity to use only formulas for prevention which have proven preventive potential in controlled studies.

Second, none of the formulas has any effect on asthma.

Third, the effects of the hydrolysates are modified by the specific allergic phenotype in the family. After post hoc stratification for the presence or absence of atopic eczema in the family history, the incidence of atopic eczema in children from families without atopic dermatitis can be reduced to different degrees with all three hydrolysates, but significantly only with pHF-W. In contrast, in children with atopic eczema in the family, only eHF-C significantly reduced atopic eczema in the offspring. This result on the modifying effect of the genetic background was first shown in the GINI study.

Again, this finding may have clinical relevance. The pHF-W is much cheaper and better tasting than the eHF-C. The eHF-C should thus be reserved as an allergy-preventive formula for children who have the highest risk for atopic eczema due to their genetic background with a positive family history for eczema.

The latest analysis at 6 years confirms the persistent allergy-preventive effect of eHF-C and pHF-W on atopic eczema, but still not on asthma, and it also shows for the first time a significant reduction in atopic eczema with eHF-W. This ‘late-onset’ effect is difficult to understand, and should be interpreted with caution [24].

At 6 years, the short- and long-term effects of pHF-W, eHF-W, eHF-C and cow’s milk formula on growth were also evaluated [25]. Altogether no
long-term consequences of the different formulas on body mass index were observed. However, feeding with eHF-C lead to a transientsly lower weight gain restricted to the first year of life. This may be caused by the composition of the formula or by a higher protein fraction in eHF-C. It has previously been shown that the intake of protein in excess of the protein requirements from casein-based formulas may have high serum nitrogen concentrations and may result in lower body mass index development. In the eHF-C group also significantly more children dropped out in the first year [22]. The possible reasons may have been the bitter taste, but also the lower weight gain that prompted the parents to withdraw.

**Primary Prevention – Visions for Future Use of pHF**

Today, primary prevention applies only for children considered to be at increased risk of developing allergy. Thus, the identification of high-risk children is a prerequisite. Several approaches to identify a child at risk have been studied, including different levels of cord blood IgE, eosinophil count or cytokine levels [15, 26], but none of these was superior to the identification through family history.

Genetic inheritance accounts for 20–40% dependent on the number of immediate family members affected with an allergic disease, and rises up to 80% if both parents suffer from the same manifestation [15]. However, for several reasons the family history is not always available, and more than 50% of allergic children come from families without allergy in an immediate family member [27]. Therefore most children are not identified as being at risk. It seems therefore worthwhile to consider primary prevention for all children.

In the GINI study the number needed to treat was calculated to avoid 1 case of atopic eczema until 3 and 6 years. The difference between eHF-C and pHF-W at 3 years was 1 (6 vs. 7 children), and at 6 years 3 (6 vs. 9 children). This underlines the high potential of hydrolyzed formulas for primary allergy prevention, and they could possibly be utilized for primary prevention in the general population.

**Conclusions**

Modification of cow’s milk proteins for primary prevention in infants at high risk of developing allergic disorders has been shown efficacious in several controlled clinical trials. Data, especially from the GINI study, confirm a consistent long-term preventive effect of certain hydrolyzed infant formulas (pHF-W and eHF-C) on allergic manifestations in high-risk children until the age of 6 years. The overall effect is mainly driven by the effect on atopic eczema.
A program for primary prevention, not only for children with a genetic predisposition for allergy but also for the general population of children, should be considered because more than 50% of allergic children originate from families which are either non-allergic or where the allergic predisposition is not evaluable.

References

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Discussion

Dr. Björkstén: You even convinced an old skeptic who always was critical of the claims related to partial hydrolysates. You say allergy but you are talking about eczema, and just to make it absolutely clear to me, is this eczema or is it allergic eczema you are talking about? Is it verified by skin prick test or is it clinical?

Dr. von Berg: It is both; it is eczema without sensitization and it is eczema with sensitization verified by specific IgE in serum. But I also showed ‘any allergic manifestation’ which is clinical because that was one of the primary outcomes of the study. However, an analysis of ‘any allergy’ excluding eczema showed no difference between the groups, which means that the significant effect on ‘any allergy’ is driven by the effect on eczema.

Dr. Björkstén: What is the price difference between regular formula, hydrolyzed formula, and hydrolyzed whey formula? It’s clear that there is an effect and you showed this beautifully. So the question of cost-efficacy in the intention to treat arises. For the parents the question would be at what cost is there an effect?

Dr. von Berg: The cost of partial hydrolyzed whey formula is roughly 30% more than regular cow’s milk formula, and about twice to three times higher for the extensively hydrolyzed casein formula. The price of the extensively hydrolyzed whey formula is somewhere in between. We are presently analyzing the cost-effectiveness of the formulas.

Dr. Motala: Just a comment for information purposes. the enzyme that is used for the hydrolysis of extensively hydrolyzed formula and some of the partial hydrolyzed formula is porcine derived. Theoretically this doesn’t make it kosher nor does it make it halal, and in our country we have resistance from some of the very strictly religious Muslim and Jewish groups to use these formulas. People need to be aware of this and be able to deal with it. If parents ask about this, then we need to be honest and inform them. It is then up to the parents whether they want to use it or not, and it certainly will create a problem for parents who cannot afford amino acid formula; what do you then use? You may well be forced just to prescribe soy in that situation.

Dr. von Berg: As far as I know there is also an enzyme that is kosher but I don’t know for sure. I must ask somebody who is better informed.
**Dr. Motala:** There is just one for the partially hydrolyzed formula, but for the extensively hydrolyzed formula there is nothing.

**Dr. Haschke:** I would like to clarify two aspects: first, the cost of formula. There are differences between countries, but in general a partially hydrolyzed formula is 20% more expensive than a premium infant formula, whereas an extensively hydrolyzed formula is approximately 100–200% more expensive. Amino acid-based formulas are 400–500% more expensive than regular formulas. As long as they are reimbursed and prescribed it doesn't matter, but if parents have to buy these formulas it can be a substantial financial burden.

My second comment is related to halal and kosher infant formulas. The partially hydrolyzed formulas for prevention of allergy from the company where I work are accepted in Muslim countries and in Israel because we use an enzyme for hydrolysis which has the halal and kosher status. When it comes to the treatment of allergy with high-degree hydrolyzed formulas, it is the decision of the doctor who must inform the parents about the kind of formula he prescribes. High-degree hydrolyzed formulas are like medications to treat disease. A lot of drugs used in Moslem countries and Israel do not have the halal or kosher status, but there is a general rule to use them when they are lifesaving or as protection from a severe disease.

**Dr. von Berg:** I don't know how it is in other countries, but in Germany formulas for prevention are not reimbursed. Reimbursement is only made for therapy of a disease.

**Dr. Kneepkens:** You realize of course that you are actually making things more difficult with the 6-year results you show now. Because you showed before that extensively hydrolyzed whey formula performed worse than the other two formulas. So we decided not to use that one for prevention. But now you show that in the long run hay fever seems to be better prevented with the extensively hydrolyzed whey formula.

**Dr. von Berg:** We too are very puzzled by this finding. I think it's very difficult to explain, but there are some studies looking at the influence of exposure or avoidance of house dust mite allergen. Results from the MAS study in Germany [1] and the MAAS study in Manchester [2] showed that in the first years of life avoidance of exposure to house dust mite had no effect at all, but later on, at 7 years, lung function in those children who had strict avoidance was better than in those who were more exposed. So perhaps it is a late onset effect, but I have no idea what the mechanism could be. I think we should wait until the 10-year results of the GINI study come out, hopefully by the end of the year, to see whether the trend which we now observe will remain.

**Dr. Kneepkens:** You have followed a group of almost 900 children who were breast-fed for a prolonged period. I am sure you have their results also. I am interested in the results of these children in terms of atopic disease, especially as we are discussing costs of prevention.

**Dr. von Berg:** I did not show the data because it was not the intention of the study to compare hydrolysates with breast milk. However, when we look at the incidence of atopic eczema, breast milk is preventive compared to cow's milk formula, but not when compared with hydrolyzed formulas. We will show those results soon.

**Dr. Conway:** My question is related to the incidence of allergy in the parents. Clearly that is retrospective and perhaps dependent on their memory of it or altered diagnosis with time. So is it possible that your low incidence of allergic conditions in the parents may be an underestimation of the reality?

**Dr. von Berg:** For inclusion of the children we used a questionnaire before or just after birth in which the parents reported present or anamnestic allergic diseases in immediate family members. We performed neither a skin prick test nor a RAST, but the questionnaire was validated in the MAS study before, with good agreement between proven allergic diseases in the parents and the parental report. As we used a
very similar questionnaire, we think that the numbers are probably correct. The only thing is that we and others have realized that fathers don’t like to remember skin problems, and sometimes of course the wives don’t know about former diseases of their husbands. But we know who actually answered the questionnaires and mostly it was both the mother and father. We would have liked to do skin prick tests or RAST, but with this number of patients it was not possible.

**Dr. Mack:** In the GINI study the number of children with intestinal cow’s milk allergy seems to be quite low. Is this an unusual condition in Germany, or with the difficulty of diagnosing a non-IgE-mediated cow’s milk allergy, could some of those just not have been picked up?

**Dr. von Berg:** Actually when we designed the study the definitions of outcomes were very strict. The diagnosis of allergy in the gastrointestinal (GI) tract included a positive double-blind placebo-controlled food challenge. You may have realized that I didn’t talk about proven cow’s milk allergy. The reason is that although we had a rather high percentage of parentally reported food allergy, many of the parents refused the provocation test after a successful elimination period. So there is a huge gap between parentally reported and actually proven cow’s milk allergy. Thus our numbers on food allergy are probably underestimated.

**Dr. Björkstén:** When was the study unblinded?

**Dr. von Berg:** At the age of 3 years.

**Dr. Stanley:** I always found the diagnosis of hay fever in preschoolers very difficult. Were you surprised that the prevalence of hay fever was the same as the prevalence of wheeze or asthma?

**Dr. von Berg:** It was actually higher, and yes, it did surprise me. We were surprised that asthma was really very low, but again this is perhaps because of the strict definition of asthma. Symptoms of wheezing were much more frequent.

**Dr. Makrides:** In terms of thinking about the conclusion to consider the partially hydrolyzed formula for the whole population, would you care to speculate on what sort of other information you would need to further convince you of that, and whether there is any information in the non-intervention part of the GINI study that may help with that decision.

**Dr. von Berg:** I actually would like to see a large controlled study. However, from this background that more than 50% of allergic children don’t have a family history, it would make sense to consider the partial hydrolyzed formula for the whole population, but without such a study I wouldn’t recommend it.

**Dr. Exl-Preysch:** There are a number of studies showing that those partial hydrolysates, and we are not talking about allergies in this case, are in many respects better than a normal infant formula in terms of gastric emptying, gastric passage time, better digestion, and so on. So there are a lot of factors showing that such a formula is better. The other point I wanted to make is, as you said, that one would need a large study. I conducted a large study in Switzerland years ago with normal population of more than 1,000 children, and compared regular formula against partially hydrolyzed formula. If those infants with allergic risk were excluded, those without any risk had less atopic eczema until 2 years of age.

**Dr. von Berg:** I am sorry that I didn’t mention it, but I think your outcome was not really allergy, it was skin conditions in general, including atopic eczema.

**Dr. S. Koletzko:** In fact I think the GI manifestations are underestimated and one reason is because our epidemiologist, and we have had a lot of discussion about this, said a case is a case. So if a child had atopic dermatitis he was considered a case in this group regardless of whether this child vomited in addition or whether the child had diarrhea. So the case was not lost, but it was lost for manifestations within the GI tract. I also want to mention that in none of all the other studies performed do we have
clear data on food allergy because that would mean that a child with atopic eczema would have to undergo double-blind food challenges with all the food stuffs which the child has seen so far. This was not done in any of the studies, not even children with atopic eczema were challenged with cow’s milk. I think it is also impossible because, as Dr. von Berg said, the parents just refuse to have their child in for a double-blind challenge if they have mild or moderate eczema. I think we will never have the figures on prevention of food allergy because it’s just not possible.

_Dr. von Berg_: As I said, we probably underestimated the incidence because the percentage of parentally reported food allergy is much, much higher.

_Dr. Sinn_: The postnatal ward of a lot of hospitals now only stock partially hydrolyzed formula which is given to babies with or without a family history of allergy. It is used as a supplementary formula with only one or two feeds given before the baby is discharged home on breast milk. Is this practice justified when the evidence for partially hydrolyzed formula is based on long-term use and there is limited evidence on the benefits in supplementary feeds with partially hydrolyzed formula [3]?

_Dr. von Berg_: I think there are several reasons for it. One reason, and probably the first reason, was the study by Høst et al. [4] many years ago showing that only those children who were accidentally fed intact cow’s milk formula in the ward developed cow’s milk allergy. Another reason is that in the ward the newborn’s possible risk of atopy is not always known. Therefore, with regard to allergy prevention, it is safer to offer partial hydrolysate also to children without allergic risk than to feed a child at risk cow’s milk formula. And thirdly, as already said by Dr. Exl-Preysch, partially hydrolyzed formulas are much closer to breast milk, much more digestible, and the emptying of the stomach is much faster than with normal cow’s milk formula. So I think there really are advantages of the partially hydrolyzed formula in maternity wards.

References