

ORIGINAL ARTICLE

Allergic diseases among very preterm infants according to nutrition after hospital discharge

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To determine whether a cow's milk-based human milk fortifier (HMF) added to mother's milk while breastfeeding or a cow's milk-based preterm formula compared to exclusively mother's milk after hospital discharge, increases the incidence of developing allergic diseases among very preterm infants (VPI) during the first year of life.

Of a cohort of 324 VPI (gestational age 24–32 wk), the exclusively breastfed VPI were shortly before discharge randomized to breastfeeding without fortification or supplementing with a fortifier. Those not breastfed were fed a preterm formula. The intervention period was from discharge until 4 months corrected age (CA). Follow-up was performed at 4 and 12 months CA including specific IgE to a panel of allergens at 4 months CA.

The incidence during and prevalence at 12 months CA of recurrent wheezing (RW) was 39.2% and 32.7%, while atopic dermatitis (AD) was 18.0% and 12.1%, respectively. Predisposition to allergic disease increased the risk of developing AD ($p = 0.04$) [OR 2.6 (95% CI 1.0–6.4)] and the risk of developing RW ($p = 0.02$) [OR 2.7 (95% CI 1.2–6.3)]. Boys had an increased risk of developing RW ($p = 0.003$) [OR 3.1 (95% CI 1.5–6.5)]. No difference was found between nutrition groups. None developed food allergy.

Compared to exclusively breastfed, VPI supplemented with HMF or fed exclusively a preterm formula for 4 months did not have an increased risk of developing allergic diseases during the first year of life.

The expression of allergic diseases varies with age, and symptoms may disappear and be replaced by other symptoms. In infancy, the main atopic/allergic symptoms are atopic dermatitis (AD), gastrointestinal symptoms, and recurrent wheezing (RW), whereas bronchial asthma and allergic rhino-conjunctivitis are the main problems later in childhood. Adverse reactions to food, mainly cow's milk protein (CMP), are most common in the first year of life, whereas allergy to

inhalant allergens mostly occurs later. A variety of factors are known to influence the risk of allergic disease, such as atopic predisposition, exposure to allergens (e.g., cow's milk and egg), and environmental factors (1). It is also well known that the mode of early feeding influences the risk of food allergy and that breastfeeding is associated with a lower frequency of AD, RW, and cow's milk protein allergy (CMPA) compared with cow's milk formula feeding (1–3).

Human milk is the best nutrition also for preterm infants, but it may lead to insufficient intake of protein and energy. The use of fortified human milk produces adequate growth and satisfies the specific nutritional requirements of preterm infants (4). Cow's milk-based fortifiers have been used for years in most neonatal intensive care units for nutrient enrichment/fortification of human milk, e.g. Enfamil® human milk fortifier (HMF) was introduced in 1984 and was

Abbreviations:

HMF,; human milk fortifier; PF,; preterm formula; VPI,; very preterm infants; GA,; gestational age in weeks; BW,; birth weight; SGA,; small for gestational age; PMA,; post-menstrual age; CA,; corrected age; AD,; atopic dermatitis; RW,; recurrent wheezing; CMPA,; cow's milk protein allergy; CMP,; cow's milk protein; SPT,; skin prick test; ITT,; intension to treat; PP,; per protocol.

reformulated with a higher protein level in 2002 (5). Preterm infants are usually discharged from hospital care early and with a body weight below the usual birth weight (BW) of a healthy term [40-wk post-menstrual age (PMA)] infant. Close monitoring of growth is recommended, and supplementation should be considered if the preterm infant is discharged with subnormal weight for age (6, 7). Meanwhile, the optimal nutrition to meet the needs of a growing preterm infant after hospital discharge, and at the same time to avoid possible negative health effects such as developing e.g., allergic diseases, still needs to be evaluated. As a part of a randomized controlled trial (RCT) on nutrient enrichment of mother's milk while breastfeeding after hospital discharge, we investigated whether there was an increased incidence of allergic disease among VPI supplemented with a cow's milk-based HMF or a preterm formula compared to exclusively breastfeeding after hospital discharge.

Patients and methods

In a prospective RCT on nutrition and growth after hospital discharge, VPI with a gestational age (GA) ≤ 32.0 wk were recruited consecutively from four neonatal intensive care units in Denmark (Holbaek, Kolding, Hans Christian Andersen Children's Hospital, Odense and Skejby, Aarhus). Exclusion criteria were diseases or circumstances influencing eating- and feeding ability at discharge. In case of exclusion from the RCT because of CMPA or parent's refusal of participation because of predisposition to allergic diseases, these VPI were kept in this study for follow-up with parent's acceptance.

Feeding regimens were identical at the four pediatric departments and are described in details in (8). Fortification with HMF (cow's milk based) was initiated from day 10–14 from birth for all VPI and fortification of mother's own expressed milk was performed until discharge, but with decreasing amounts during the last week(s) while the infant was improving sucking directly from the breast.

Shortly before hospital discharge, the breastfed VPI in the RCT were randomized to either breastfeeding without supplementation (group A) or intervention with fortification (five packets Enfamil® Human Milk Fortifier (HMF); Mead Johnson Nutritional, Evansville IN, USA) of mother's milk daily until 4 months corrected age (CA) (group B). VPI who were bottlefed were fed a preterm formula (Enfalac® Preterm Formula; Mead Johnson Nutritional, Nijmegen, Netherlands) (group C) until 4 months CA. For all groups, parents were instructed to refrain from introducing any complementary food until 4 months CA.

BW, GA, single birth, or multiple births were recorded. Based on interviews and questionnaires at the time of randomization, information on mother's age, education, and occupation, smoking habits, atopic predisposition (at least one first-degree relative with reported allergic disease), and previous breastfeeding experience were obtained. Mother's social group was defined according to The Danish National Centre of Social Research based on education and occupation (9). Infants were examined at the outpatient clinics at

term, 2, 4, 6, and 12 months CA. At 4 and 12 months of age, a standardized questionnaire-based interview about possible allergic symptoms such as; urticaria, AD (areas of scaly, erythematous, and itchy eczematous rash revealed by physical examination), gastrointestinal symptoms (colic, diarrhea, or vomiting without known infection), episodes of RW (at least two episodes of wheezing, most often associated with respiratory infections, and diagnosed by a physician), and rhinitis/conjunctivitis, and treatment was performed by a pediatric nurse or doctor. CMPA was proven by controlled elimination/challenge test in a hospital setting. At 4 months CA, a blood sample was drawn for later analysis for specific IgE antibodies (egg white, milk, peanut, dust mites (Dermatophagoides Pteronyssinus and Farinae), dog, cat, grass pollen, and latex) by ImmunoCAP 250 (Pharmacia, detection limit 0.35 kU/l). All blood samples were analyzed at Odense University Hospital. Data on duration of breastfeeding and introduction of formula and/or complementary food were recorded.

Ethics

The study was approved by the Danish National Committee on Biomedical Research Ethics (J.nr. VF20030208) and the registrations were approved by the Danish Data Protection Agency (J.nr.2007-41-1349). Informed consent was obtained from the parents after written and oral information.

Statistics

Data were analyzed using STATA (version 11, Statacorp, College Station, TX, USA).

The incidence is the percentage of new cases of VPI with allergic symptoms from birth to 12 months CA. The prevalence is the percentage of VPI having allergic symptoms at 12 months CA. The prevalence is corrected for missing data at 12 months CA.

Multivariate logistic regression was used to determine which clinical relevant factors (GA, BW, gender, atopic predisposition, nutrition, time of introduction to complementary food, mother's age, social group, parents smoking at home) possibly influenced the development of AD and/or RW before 12 months CA. The preterm infants were defined as SGA if the BW was below the expected weight by more than 2 SD according to a reference (10). Analyses were performed by intention to treat (ITT) and treated per protocol (PP).

Results

The study cohort consisted of 324 (51%) VPI, as parents of 156 (25%) refused to participate and 153 (24%) were excluded of an initial cohort of 633 VPI (Fig. 1). In the refusal group, VPI had a significant higher GA, BW, and younger mothers compared to the study cohort ($p < 0.05$), and 50% were breastfed at discharge while 65% were breastfed in the study cohort ($p = 0.002$). Characteristics of the 324 participating infants and their parents are shown in Table 1.

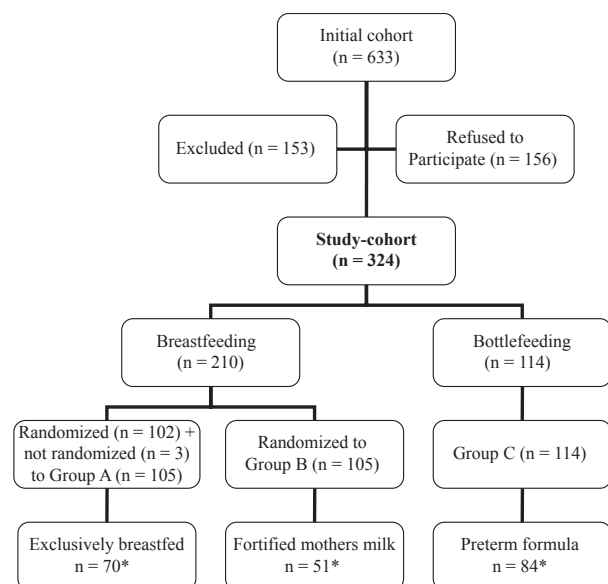


Figure 1 Participation flowchart. Treated per protocol (*) (n = 205). By ITT 283/324 remained in the study at 12 months corrected age.

Three breastfed VPI (a couple of twin-boys (GA 31.6) and a girl (GA 32.0)) were not randomized because of atopic predisposition and parent's request. None of them received HMF during their hospitalizations.

One boy (GA 29.4) with AD from 3 months CA was suspicious of CMPA after hospital discharge. He received HMF added to mother's own milk or donor milk during hospitalization and was bottlefed with preterm formula after hospital discharge. A skin prick test (SPT) was positive (4 mm), while specific IgE was <0.35 KIU/l to milk and egg, respectively. Controlled elimination/challenge procedure with milk was negative and thus the suspicion to CMPA was not confirmed. There was no clinical suspicion on allergy to egg.

Table 1 Characteristics of 324 preterm infants and their mothers

<i>Preterm infants</i>	
GA at birth (median) (min–max) (wk)	29 + 6 (24.1–32.0)
Birth weight (median) (min–max) (g)	1283 (535–2255 g)
SGA (weight z-score < 2 SD)	68/324
Boys	178/324
Multiple births	122/324
Predisposition to allergic disease	63/253
Introduction to complementary food ± SD (mean) (corrected age) (wk)	17.3 ± 4.0 wk
<i>Mothers</i>	
Mother's age ± SD (mean) (yr)	30.7 ± 4.9
Social group ± SD (mean) (1 = high, 2, 3, 4 and 5 = low)	3.14 ± 1.31
Very preterm infants with parents (one or two) smoking at home	116/319 (36%)
Mothers smoking	61/319 (19%)
Fathers smoking	94/294 (32%)

Information on allergic symptoms was obtained in 90% (290/324) VPI. Because of withdrawal of 7 VPI before 12 months CA, there was 283 VPI remaining at 12 months CA (ITT analysis). An overall incidence and prevalence (corrected for missing data from 4 VPI) of allergic symptoms at 12 months CA among those 283 VPI is shown in Table 2.

Information on atopic predisposition was obtained from 78% (253/324) with 25% (63/253) predisposed to allergic diseases. The number of VPI who completed in their assigned nutrition groups until 2 months CA was 205 (63%) with 199 (61%) remaining at 12 months CA (PP-group). Comparing nutrition groups (A, B, and C), no difference was found between nutrition groups as regards development of AD or RW during the first year of life.

Atopic predisposition was associated with the development of AD (ITT and PP), while gender (ITT and PP) and atopic predisposition (PP) were associated with RW using multiple regression models (Table 3). Analyzing only breastfed VPI (A plus B) early introduction to complementary feeding (16.0 ± 3.5 vs. 17.8 ± 3.7 wk) was associated with development of RW (p = 0.006) (OR 0.97 (95% CI 0.95–0.99)).

Specific IgE were analyzed in blood-samples from only 51% (163/320) VPI at 4 months CA. In 2 VPI, specific IgE to cow's milk was detected: In a girl (GA 31.0), specific IgE to milk was 0.38 KIU/l. She received HMF added to donor milk and mother's milk during hospitalization. She was exclusively breastfed at discharge and supplemented with mature formula and complementary food shortly before 4 months CA. She had two episodes with wheezing treated with bronchodilator at 9 and 11 months CA and no other allergic symptoms were reported. In a boy (GA 29.6), specific IgE to milk was 0.36 KIU/l. He also received HMF added to human milk during hospitalization. He was bottlefed with preterm formula from hospital discharge until 4 months CA. He did not show any allergic symptoms before 12 months CA.

Discussion

Allergic symptoms in this age group are often unspecific and only seldom represent a true allergic disease, and the most common allergic symptoms are AD and RW. When these conditions are caused by allergy, it will most often be a food allergy e.g., to milk or egg. We found an overall incidence of possible allergic symptoms among VPI within 12 months CA to be 56.2% (159/283), while the prevalence at 12 months CA was 41.8%, most of these being RW, probably because of viral infections and small airways.

Predisposition to allergic disease and being a boy increased the risk of developing AD and RW within the first 12 months CA. Nutrition with or without CMP after hospital discharge was not associated with development of any allergic symptoms.

Studies describing allergic symptoms and studies on dietary prevention among preterm infants are very few. By the age of 18 months CA, Lucas et al. found an overall incidence of one or more allergic symptoms among 777 preterm infants (BW < 1850 g) to be 44% (wheezing 22.5% and eczema/AD

Table 2 The incidence [rate of occurrence of new cases from birth to 12 months corrected age (CA)], the median age of onset of allergic symptoms, and the prevalence (rate of cases at 12 months CA) among 283 very preterm infants (VPI)

Allergic symptoms	No of cases	Incidence (%) (birth to 12 months CA)	Median corrected age of onset of symptoms (months) (min–max)	Prevalence (%) (cases at 12 months CA)¶
Urticaria	7	2.5	7.2 (0.8 to 9.3)	0.0
Atopic dermatitis Total	51	18.0	6.1 (–2.6 to 11.9)	12.1
Treated with steroids	8	2.8	6.7 (0.2 to 11.9)	–
Treatment unknown	43	15.2	6.1 (–2.6 to 11.9)	–
Gastrointestinal symptoms	38	13.4	1.0 (–3.3 to 6.8)	1.4
Recurrent wheezing Total	111	39.2	7.1 (–0.4 to 12.0)	32.7
Treated with bronchodilators (*)	7 (oral) 23 (inh.)	10.6	8.0 (1.9 to 11.9)	–
Treated with inhaled glucocorticosteroids‡	31	11.0	6.1 (–0.4 to 11.1)	–
Treatment unknown	50	17.7	7.3 (–0.2 to 12.0)	–
Rhinitis§	27	9.5	2.1 (–2.7 to 11.8)	3.7
Conjunctivitis§	10	3.5	5.8 (–0.2 to 11.1)	1.8
One or more of the above symptoms	159	56.2	–	41.8

Treatment with; *beta-2-agonist oral or inhaled, †inhaled glucocorticosteroids, ‡2 VPI were also treated with leukotriene receptor antagonists. §One child was treated with oral antihistamine (Claritin®). ¶corrected for missing data from 4 VPI at 12 months CA.

Table 3 Variables associated with development of atopic dermatitis and recurrent wheezing

			By multiple regression model	
			p-value	Odds Ratio (95% CI)
<i>By intension to treat (n = 219)</i>				
Atopic dermatitis (AD)	+AD	–AD		
Atopic predisposition	16/41	37/182	0.03	2.3 (1.1–5.0)
Recurrent wheezing (RW)	+RW	–RW		
Boys	76/111	80/172	0.000	3.3 (1.8–6.1)
<i>Treated per protocol (n = 155)</i>				
Atopic dermatitis (AD)	+AD	–AD		
Atopic predisposition	12/30	28/129	0.04	2.6 (1.0–6.4)
Recurrent wheezing (RW)	+RW	–RW		
Atopic predisposition	19/55	21/104	0.02	2.7 (1.2–6.3)
Boys	49/72	61/127	0.003	3.1 (1.5–6.5)

19.4%). They found atopic predisposition, maternal smoking, vaginal delivery and duration of ventilation to be associated with wheezing, and multiple births to be associated with AD (11). The same study-population was used for two randomized trials (A: banked donor milk vs. preterm formula and B: term vs. preterm formula) and found that CMP intake was not associated with an overall risk of developing allergic disease, but in the subgroup with atopic predisposition, early exposure to CMP increased the risk of developing allergic diseases – especially AD and CMPA (12).

Chronic respiratory morbidity has been described as common following preterm birth, particular if complicated by bronchopulmonary dysplasia (BPD) (13, 14). In our study,

VPI with BPD have been excluded from the RCT. A recent but solely register- and population-based study on ‘administrative claims data’ found that preterm infants (born ≤ 32 wk) had a higher prevalence of persisting asthma later in childhood (11.7%) compared with term births (8%) [OR 1.51 (95% CI 1.40–1.63)] (15). A study from New Zealand based on parental reports at 12 months of age found an incidence of RW among very preterm infants (VPI) (< 33 wk) to be 14.5% and among term infants to be 3%. They found significant risk factors to be parental history of asthma, maternal smoking, siblings at home, neonatal oxygen supplementation at 28, 36, and 40 wk of gestation (16). A Swedish birth cohort (on preterm and term infants) study found a cumulative incidence on RW (doctors diagnosed and any wheezing) to be 27% up to 2 yr of age (17). The incidence and prevalence of RW up to 1 yr of age among ‘healthy VPI’ were 39.2% and 32.7%, respectively, in our study, indicating that preterm birth might increase the risk of RW even though preterm infants with BPD were excluded from our study.

A population-based birth cohort study among term infants in Denmark found an incidence of AD to be 11% (18) and the cumulative 1-yr prevalence to be 8.2% (19). An association between AD and being a boy and predisposed to atopy (maternal) was found (18). In a large Norwegian prospective cohort study, based on clinical examinations if parents reported allergic symptoms, they found a prevalence of AD at 1 yr of life to be 13% among preterm infants (GA 28–35 wk) and 10% among term infants. There was no significant difference between preterm and term infants (20). A much higher prevalence of AD at 12 months post-term of 35.8% was found in a British prospective study among preterm infants (GA ≤ 37 wk) based on questionnaires and home-visits by midwives (21). Our study is also a population-based birth cohort of preterm infants, and the incidence and

prevalence of AD in our study were 18% and 12.1%, respectively, and seem to correlate very well with the results of the Norwegian study.

The main allergic symptoms reported in our study are RW and AD. Our results are based on standardized questionnaire-based interviews performed by the doctors and/or nurses when the VPI attended the out-patient clinics for follow-up examination at 4 and 12 months CA. Allergic gastrointestinal symptoms have been reported with an incidence of 13.4% but a prevalence of 1.4% at 1 yr of age. Symptoms from the gastrointestinal tract are unspecific and are difficult to interpret among preterm infants. A Norwegian study (22) including preterm and term infants diagnosed 27 (9 preterm) of 555 with adverse reactions to cow's milk such as pain behavior, gastrointestinal symptoms (excessive vomiting or diarrhea), respiratory symptoms, and AD. Twenty-six of these infants were diagnosed by elimination/challenge tests (all but one were exclusively breastfed). Non-IgE-mediated reactions were the most frequent and just one child with AD as the presenting symptom, had a positive SPT as well as elevated IgE level to cow's milk. No difference was found between preterm and term infants. In our study, 38 of 283 reported gastrointestinal symptoms but none had food allergy.

The allergic symptoms urticaria, rhinitis, and conjunctivitis are also difficult to interpret among preterm infants. Two children suspicious of these allergic diseases showed no sensitization at SPT and the specific IgE analysis.

In our study, 24% VPI were excluded and parents of 25% VPI refused to participate. Other studies dealing with VPI have shown similar problems with exclusion and refusals (23). The parents have often experienced their VPI critically ill and they do not have resources for participation in a study also. At 4 months CA, only 51% VPI had blood drawn for specific IgE analysis, because many parents did not want their infant to experience a *veno-puncture*. A Norwegian study found one child with elevated IgE levels to both egg and milk and one child with only elevated IgE levels to egg (22). In our study, one child was suspicious of CMPA because of AD and a positive SPT, but CMPA was not confirmed by elimination/challenge test, and further two VPI (2/163) had positive IgE reactions to cow's milk but none of them had CMPA.

Breastfeeding possibly influences the occurrence of asthma and allergic disease through different mechanisms. The infant gut is immature and may poorly exclude multiple allergens or large quantities of allergens that can react with the immune system. Human milk contains substances that may influence the micro flora in the gut and possibly protect the intestinal mucosa. Cytokines/growth factors in human milk also may promote the maturation of gastrointestinal mucosa restricting the penetration of antigenic material and contribute to the anti-inflammatory effect of human milk (24). Especially preterm infants with an even more immature intestine might have an increased risk of absorption to food allergens and development of food allergy (such as CMPA). Cases of three preterm infants, who presented signs suggestive of sensitization to CMP after supplementation of their mother's milk with a HMF, have been reported. The diagnoses were based on clinical response to elimination of the allergen from the diet only (25). In our study, 321 VPI received a cow's milk-based HMF during hospitalization, and only one was suspected but not confirmed to have food allergy after hospital discharge while he was fed a cow's milk-based preterm formula. Multicomponent fortification of human milk for preterm infants is associated with improvements in growth, and support the use of fortification as a common practice in neonatal intensive care units (26, 27). In our study, fortification was used also after hospital discharge and did not increase the risk of developing allergic diseases among VPI during the first year of life.

Conclusion

Cow's milk-based fortification of mother's milk or preterm formula for preterm infants after hospital discharge was not associated with an increased risk of developing allergic diseases until 1 yr of age among VPI. Predisposition to allergic disease and being a boy increased the risk of developing both AD and RW. No one was diagnosed with CMPA. Compared to other studies of preterm infants, wheezing was reported with a high incidence and prevalence, while AD was reported with an incidence and prevalence comparable with other studies. The infants in our study will be followed according to allergic symptoms until 6 yr of age.

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