

# Soy Allergy Following Early Soy Feeding in Neonates

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**ABSTRACT:** **Background:** Feeding neonates with humanized milk formula in maternity hospitals may increase the prevalence of milk allergy in infants. However, prospective studies of the possible allergenic effect of very early soy-based formula feeding are lacking.

**Objectives:** To assess the prevalence of soy allergy in infants fed soy-based formula in the first 3 days of life.

**Methods:** The study group included 982 healthy full-term infants born within a 7 month period at a hospital that routinely uses soy-based formula to supplement breastfeeding. In-hospital feeding was recorded and the parents were interviewed once monthly over the next 6 months regarding feeding practices and clinical symptoms suggesting soy allergy in the infant.

**Results:** Ninety-nine percent of the infants received soy-based formula supplement in hospital, and 33%–42% at home. No cases of immediate allergic reaction to soy or soy-induced enterocolitis were reported.

**Conclusions:** The use of soy-based formula in the early neonatal period does not apparently increase the prevalence of soy allergy in infants followed for the next 6 months.

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**KEY WORDS:** food allergy, neonates, soy, oral tolerance

Soy-based formula is indicated for use in infants with galactosemia and hereditary lactase deficiency or when parents prefer a special diet for religious or ethical considerations [1,2]. It may be given to infants with immunoglobulin E-mediated cow's milk allergy [3]. Its popularity has grown in recent decades; in Israel, one study showed that 31.5% of infants aged 12 months were fed SBF, most of them (70.6%) for more than 6 months, often without clinical indication [4].

Allergic reactions to soy in infants and small children have been documented mainly in those with atopic dermatitis and manifested mainly by gastrointestinal symptoms (vomiting, enterocolitis, enteropathy) [5,6]. The rate of adverse reac-

tions to soy in the general pediatric population is < 1%. Anaphylaxis is rare [2].

Exposure of neonates to an allergenic food might increase the prevalence of this food allergy due to the skewed TH2 neonatal immune response [7]. A prospective clinical study conducted in maternity hospitals reported that feeding neonates humanized milk formula led to a higher risk of cow's milk allergy at age 18–24 months than feeding human milk or whey hydrolysate formula [8]. However, our search of the literature did not yield any prospective studies on the risk of soy allergy in soy-fed neonates.

The present study was prompted by our earlier findings that five of seven infants who presented with soy-induced enterocolitis had been born at the Maayanei Hayeshua Hospital in central Israel, which serves the ultra-Orthodox Jewish community and because of religious considerations routinely uses SBF to supplement breastfeeding in newborns [9]. This practice provided us with a unique population to assess the impact of early soy feeding on subsequent development of soy allergy.

## SUBJECTS AND METHODS

The study group included full-term infants without perinatal complications who were born at Maayanei Hayeshua Hospital, Bnei Brak, Israel, from September 2002 to March 2003. Newborns at this hospital who require breast milk supplement are fed SBF (Materna Tsimchit<sup>®</sup>, Maabarot, Israel).

After parental consent was obtained, the feeding of each newborn during his/her 3 day stay in the neonatal department was recorded by the study nurse. After discharge, the same nurse interviewed the parents by telephone once monthly for 6 months using a structured questionnaire that covered current feeding of the infant, signs and symptoms of allergy, time between soy ingestion and symptoms, if any, and treatment, including elimination of dietary soy.

Soy allergy was defined as reported symptoms of rash, urticaria and angioedema, vomiting, diarrhea, or wheezing appearing immediately after ingestion of SBF, or recurrent vomiting and/or diarrhea developing up to 4 hours after ingestion of SBF.

SBF = soy-based formula

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The study was approved by the Institutional Review Board of Schneider Children’s Medical Center of Israel and Rabin Medical Center.

**RESULTS**

Full feeding data were available for 982 of the 1002 healthy full-term infants (525 females, 477 males; birth weight 2045–5320 g, median 3430 g) born at Maayanei Hayeshua Hospital during the study period. Almost all infants (n=972, 98.9%) received SBF supplement during their 3 day in-hospital stay; the remainder were breast-fed exclusively (n=7, 0.7%) or given humanized milk formula supplement (n=3, 0.3%). Telephone follow-up revealed that 33% (at age 1 month) to 42% (at age 6 months) were fed SBF at home, either exclusively or in addition to breastfeeding and/or solid foods [Table 1].

During the 6 month follow-up, 28 events of wheezing, 30 of rash and 55 of vomiting/diarrhea (total 113 events) were reported for 109 infants. None of the events was attributed to a specific food, including SBF, by the parents, and none necessitated elimination of SBF. There were no reported cases of immediate soy-induced systemic allergic reaction or enterocolitis.

Owing to the very small number of neonates who were breast-fed only or received humanized milk formula in the neonatal department, a comparison with the SBF-fed neonates was impossible.

**DISCUSSION**

The main finding of this study was the absence of self-reported soy allergy in a cohort of 982 infants of whom 99% were fed SBF in the neonatal department. During the next 6 months, the rate of SBF use in the study population ranged from 33% at age 1 month to 42% at age 6 months, either exclusively or in addition to breastfeeding and/or solid foods. Our rate at age 6 months was much higher than the 23% reported for the same age group by Berger-Achituv et al. [4]. We attribute this difference to the specific nutritional habits of the ultra-Orthodox Jewish community who account for the large majority of patients at Maayanei Hayeshua Hospital.

Ours is the first prospective population-based study of soy allergy in infants fed SBF during the neonatal period. The lack of self-reported soy-induced allergic reactions is surprising, even in view of the overall low prevalence of soy allergy in children [2]. Our findings might be explained by the induction of oral tolerance to soy by early and persistent feeding. Animal studies have shown that oral tolerance can be induced after administration of either a single high dose of antigen or repeated lower doses [10]. Accordingly, Du Toit et al. [11] recently found that Jewish children in Israel have a significantly lower prevalence of peanut allergy than Jewish

**Table 1.** Rate of soy-based formula use during a 6 month follow-up period in 982 Infants

Month	Exclusive SBF	Breastfeeding + SBF	Breastfeeding + SBF + solid foods	SBF + solid foods	Total
1	163 (16.6)	158 (16)	2 (0.2)	5 (0.56)	328 (33)
2	191 (19.45)	146 (14.86)	–	5 (0.56)	342 (34.8)
3	192 (19.55)	158 (16)	3 (0.3)	26 (2.64)	379 (38.49)
4	189 (19.24)	149 (15.17)	14 (1.42)	58 (5.9)	410 (41.73)
5	194 (19.75)	103 (10.48)	20 (2.03)	99 (10.08)	416 (42.34)
6	165 (16.80)	82 (8.35)	24 (2.4)	145 (14.76)	416 (42.35)

Values presented are the number and percent of infants  
Solid foods were defined as at least one of the following: cereals, corn flour, rice, chicken, vegetables, fruits

children in Britain despite their earlier and higher consumption of peanut snacks during the first year of life [11].

It is also possible that soy allergy differs between infancy and childhood/adulthood. In a multicenter study in Germany, the prevalence of specific IgE to soy increased from 2% at age 2 years to 7% at age 10 years [12]. Specific IgE to birch pollen was observed in 86% of the children aged 10 years who were sensitized to soy. These findings may suggest that in infants, the primary sensitization to soy through the gastrointestinal tract manifests clinically as soy-induced enterocolitis, as described in our earlier study [9]. In older children and adults, however, soy allergy occurs secondary to birch sensitization due to cross-reacting pollen antigens and might lead to a systemic reaction [12,13].

We did not extend the follow-up beyond 6 months because if any infant was susceptible to soy allergy (by primary sensitization through the gut) it would have developed by then. In addition, we did not screen the whole study population for soy-specific IgE antibodies because the positive predictive value of soy-specific serum IgE is low and the purpose of our study was to document soy-induced hypersensitivity reactions and not sensitization [14].

Unconfirmed telephone survey data may be subject to misclassification bias [15]. However, people are more likely to answer questions about their child’s nutrition and intercurrent illnesses than any other personal questions. In addition, the clinical manifestations of soy-induced anaphylaxis, albeit rare, and soy-induced enterocolitis are dramatic and always prompt parents to seek emergency medical attention. Given that none of the reported manifestations (wheezing, diarrhea, rash) led the parents to eliminate SBF from the infants’ diet, we assume they were, indeed, unrelated to soy consumption. At the same time, the data from the neonatal department were recorded by the study nurse and were not dependent on parental recall.

Ig = immunoglobulin

The seven infants with soy-induced enterocolitis described by us in a previous study presented over a period of 5 years [9]. Thus, a prospective study of several annual birth cohorts may be needed to assess the true prevalence of soy allergy in soy-fed neonates. Furthermore, our findings may not be generalizable because the study population was very homogeneous.

It is noteworthy that our study was performed prior to October 2003, when several cases of infant encephalopathy caused by thiamine-deficient SBF occurred, leading to a general decline in the use of SBF in Israel [16]. However, none of the infants in our study received the defective brand of SBF (Remedia Super Soya 1). At present, physicians in Israel restrict recommendations for SBF to infants who have medical indications of IgE-mediated milk allergy or gastroenteritis with secondary lactose intolerance (Y. Levy, personal communication).

In conclusion, feeding with SBF during the first 3 days of life is not apparently associated with allergic reactions on subsequent exposure to SBF during the next 6 months of life. Nevertheless, the indications for SBF administration should be restricted to specific medical conditions. Further population-based studies of older children are needed.

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#### References

1. ESPGHAN Committee on Nutrition, Agostoni C, Axelsson I, Goulet O, et al. Soy protein formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2006; 42: 352-61.
2. Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008; 121: 1062-8.
3. Kemp AS, Hill DJ, Allen KJ, et al. Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion. *Med J Aust* 2008; 188: 109-12.
4. Berger-Achituv S, Shohat T, Romano-Zelekha O, et al. Widespread use of soy-based formula without clinical indications. *J Pediatr Gastroenterol Nutr* 2005; 41: 660-6.
5. Sicherer SH, Morrow EH, Sampson HA. Dose response in double-blind placebo controlled oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2000; 105: 582-6.
6. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. *Pediatrics* 2009; 123: e456-64.
7. Prescott SL, Taylor A, King B, et al. Neonatal interleukin 12 capacity is associated with variations in allergen-specific immune responses in neonatal and postnatal periods. *Clin Exp Allergy* 2003; 33: 566-72.
8. Saarinen KM, Juntunen-Backman K, Järvenpää AL, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. *J Allergy Clin Immunol* 1999; 104 (2 pt 1): 457-61.
9. Levy Y, Kornbrot B, Danon YL. Soybean allergy in cow milk intolerant infants. *Pediatr Asthma Allergy Immunol* 1998; 12: 253-8.
10. Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* 2005; 115: 3-12.
11. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; 122: 984-91.
12. Matricardi PM, Bockelbrink A, Beyer K, et al. Primary versus secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. *Clin Exp Allergy* 2008; 38: 493-500.
13. Ballmer-Weber BK, Holzhauser T, Scibilia J, et al. Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 2007; 119: 1489-96.
14. Östblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE antibodies and reported food hypersensitivity in 4-year-old children. *Allergy* 2008; 63: 418-24.
15. Greenland S. Statistical uncertainty due to misclassifications. *J Clin Epidemiol* 1988; 41: 1167-74.
16. Fattal-Valevski A, Kesler A, Sela BA, et al. Outbreak of life-threatening thiamine deficiency in infants in Israel caused by defective soy-based formulas. *Pediatrics* 2005; 115: e233-8.