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# CAN WE PREVENT FOOD ALLERGIES BEFORE THEY START? THE EMERGING SCIENCE OF EARLY INTRODUCTION

## By Christopher M. Warren, PhD

Convergent data from a variety of sources clearly indicate that food allergy (FA) prevalence has markedly increased over recent decades.[1-4] IgE-mediated food allergy is now estimated to directly affect roughly 8% of U.S. children and 11% of U.S. adults, rendering it of major public health importance.[5,6] Of U.S. children and adults with FA, nearly half are estimated to have current allergies to multiple foods.[7] Both genetic and environmental factors are implicated in the development of food allergies. Research indicates moderate associations between family history of FA (and other allergic diseases like atopic dermatitis and asthma) and increased risk of pediatric FA.[8] However, most children with FA do not have a parent with a FA,[9] which highlights the importance of early life environmental exposures—the most important of which is arguably the infant diet.

Delay in introducing commonly allergenic solids (e.g. peanut protein, cow's milk, hen's egg) has been linked observationally to increased risk of developing allergic conditions, including not only FA, but also asthma and allergic rhinitis.[10-12] While the mechanisms for FA development are clearly multi-factorial, a prominent theory — the Dual Allergen Exposure Hypothesis — proposes that when infants are exposed to food proteins through the skin, particularly via an altered, inflamed skin barrier (as can occur in infants with severe eczema), it can promote pro-allergic immune pathways and lead to FA.[13] In contrast, according to this Dual Allergen Exposure Hypothesis, oral introduction of commonly allergenic solids—where the infant's immune system receives its first exposure to these food proteins via their gastrointestinal tract—helps establish an appropriate, (i.e. "tolerogenic") immune response.

The first rigorous test of this theory was the seminal Learning Early About Peanut (LEAP) study, which showed that introducing developmentally appropriate peanut-containing foods (e.g. Bamba® peanut puffs) between 4-11 months of age in "high-risk" infants (defined as those with eczema and/or egg allergy) resulted in an 81% reduced risk of peanut allergy development by 5 years of age.[14] Participants in the intervention group were instructed to feed the baby at least 6g of peanut protein per week, whereas the control group was instructed not to feed any peanut-containing foods. Adherence to the prescribed study protocol was very high among participants, and the very strong preventive effect of early introduction of peanut prompted the National Institute of Allergy and Infectious Diseases (NIAID) to sponsor the 2017 Addendum Guidelines for the Prevention of Peanut Allergy. These guidelines, which remain in effect today, recommend introducing peanut-containing foods at 4-6 months of age to high-risk infants, around 6 months to infants at moderate risk (i.e. those with mild-to-moderate eczema), and in accordance with family preference and cultural practices for the remaining infants deemed at low risk.[15]

However, while the LEAP study provided valuable data about the primary prevention of peanut allergy, peanut is only one of many commonly allergenic solids and accounts for only a small proportion of the total population-level burden of FA. The single center Enquiring About Tolerance (EAT) randomized controlled trial conducted in the United Kingdom, explored whether the early, deliberate introduction of multiple commonly allergenic solids—cow's milk, peanut, hen's egg, sesame, cod, and wheat—into the infant diet, beginning at 3 months of age, could prevent allergy to these foods.[16-18] In this study, 1,303 infants were randomized at 3 months of age to an early introduction group (EIG) with breastfeeding followed by sequential introduction (randomized order of introduction) of 6 allergenic foods or a control group that was exclusively breastfed. The standard introduction group (SIG) followed the UK infant feeding recommendations of exclusive breastfeeding for around 6 months with no introduction of allergenic foods before 6 months of age.

While the intention-to-treat analysis did not identify a statistically significant reduction in FA to ≥1 foods by 1-3 years of age (5.6% in the EIG vs. 7.1% in the exclusively breastfed group, p=0.32), the per protocol analysis found significantly lower prevalence of FA in the EIG group (2.4% vs. 7.3%, p=0.01). The observed difference in FA prevalence was driven by significantly lower prevalence of peanut (0% vs. 2.5%, p=0.003) and egg allergies (1.4% vs. 5.5%, p=0.009) among members of the early peanut introduction group who were adherent to the intervention, compared to the control participants who did not introduce these allergens according to the protocol. While a difference in peanut (1.2% vs. 2.5%, p=0.11) and egg (3.7% vs. 5.4%, p=0.17) allergy prevalence was still present among the EAT study's intent-to-treat population for both allergens, for neither allergen was this difference statistically significant. However, the failure to detect a significant intervention effect associated with early allergen introduction in the intent-to-treat population must be considered in the context of the low observed rates of adherence to the recommended early introduction protocol. Overall, only 42% of participants assigned to the EIG met the criteria for adherence (3g of allergen protein per week for at least 5 weeks between 3 and 6 months of age). However, it is notable that among infants with visible eczema at enrollment, those in the EIG were significantly less likely to develop any FA (SIG, 46.7%; EIG, 22.6%; P=0.048). Crucially, introduction of multiple allergenic foods during the first year of life in the EAT study did not affect the growth of the participants or the duration of breastfeeding and was safe.

Since publication of the EAT study, numerous randomized trials have explored the effectiveness of early introduction of commonly allergenic solids, namely milk and egg, for primary prevention of allergy to those foods. For example, the Japanese PETIT trial was terminated early due to the strong preventive effect of egg protein introduction (29.4% risk difference) between 4-6 months of age among a high-allergy risk population.19 More recent data from the Japanese SPADE study also indicate that even earlier introduction of cow's milk between 1-2 months can prevent cow's milk allergy in a general population sample while not competing with breastfeeding.[20] Finally, the Scandinavian PreventADALL study recently concluded that FA (measured at 3 years of age) can be prevented by the introduction of peanut, cow's milk, egg, and wheat in small quantities starting at 3 months of age.[21] Like the EAT study, this study found that early introduction of commonly allergenic solids is safe in a general population sample and that it did not interfere with breastfeeding.

Overall, the LEAP and EAT studies along with the more recent studies summarized above support the safety of deliberate introduction of peanut and other highly allergenic food proteins along with other complementary foods during infancy and demonstrate the potential of such approaches to reduce FA incidence early in life among all risk strata.[22] This emerging evidence was recently considered by an international work group comprised of experts from all major North American Allergy Societies, who issued a new "Consensus Approach to the Primary Prevention of Food Allergy through Nutrition." This work group concluded that there "is strong evidence supporting that peanut-containing foods should be introduced into the infant's diet starting around 6 months of life, but not before 4 months of life, and that cooked egg/egg-containing products (e.g. boiled, scrambled, or baked egg) should be introduced in a similar time frame."

With respect to other common food allergens, the work group recommended to "not deliberately delay the introduction of other potentially allergenic complementary foods (cow's milk, soy, wheat, tree nuts, sesame, fish, shellfish), once introduction

of complementary foods has commenced at around 6 months of life but not before 4 months."[23]

Taken together, these data provide strong support for the safety and effectiveness of early introduction of allergenic solids for the primary prevention of FA. Many questions remain regarding the optimal dose, timing, frequency, and format of how these foods should be introduced for maximum preventive benefit; however, given the population's growing burden of FA it is imperative that we find answers. One such effort is the CAN DO study, which is currently underway at Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University, and Rush University medical centers. This study is testing the effectiveness of early, frequent introduction of small amounts of commonly allergenic solids (including soy yogurt) starting around 4 months of age for prevention of allergic disease. The results of this study aim to inform the next generation of infant feeding guidelines and help pave the way to a healthier, less food-allergic future.

**ABOUT THE AUTHOR**

**Christopher M. Warren, PhD,** is a doctorally-trained epidemiologist and prevention scientist who serves as founding Director of Population Health Research at Northwestern University's Center for Food Allergy and Asthma Research. He has authored over 75 peer-reviewed manuscripts, including dozens of high-impact publications in the field of food allergy epidemiology and prevention.

# SOY CONSUMPTION DURING CHILDHOOD AND PREGNANCY

## By Mark Messina, PhD, MS

Soy is commonly consumed in Asian countries during pregnancy[1-4] and childhood[5-9] as it is during other stages of life. However, a comprehensive technical review published in 2021 highlighted the need to better understand the effects of soy, and especially soybean isoflavones, in children and pregnant women as only limited research involving these 2 groups has been conducted.[10] Research involving children is particularly important because young people may be especially sensitive to the influence of diet and because dietary habits established when young may track into adulthood. This sensitivity may also apply to pregnancy, with respect to both the mother and developing fetus. To help fill the research void, the Soy Nutrition Institute Global recently funded two 12-week intervention studies, one involving healthy children and the other involving children with fatty liver disease which will begin later in 2023.

A brief review of research relevant to children and pregnant women is presented below.

**Children**

Soy has been used for decades as a source of protein in U.S. government feeding programs targeting malnourished children throughout much of the developing world.[11-13] The U.S. Agency for International Development (AID) outlines the importance of corn-soy blends in a comprehensive fact sheet for those who want to learn about these products and how to use them.[14] The high quality of soy protein is one reason for its widespread use in these programs.[15] Soy protein has also been shown to directly lower blood cholesterol in children as it has in adults; although relatively few studies in the former have been conducted.[16-20] Arguably, the most intriguing proposed benefit of soy foods is that when consumed early in life, breast cancer risk is reduced. This hypothesis, which was proposed in 1995,[21,22] has gained support over the years from the results of animal[21,23,24] and observational[25-28] studies.

The isoflavones in soy are thought to change cells in the developing breast in a manner that makes them permanently less likely to be transformed into cancer cells. More specifically, mechanisms for the protective effect of early isoflavone exposure include increasing cell differentiation,[29,30] BRCA1 gene expression,[31] and estrogen receptor-β

levels.[32] However, although isoflavones are the soybean components thought to be responsible for this proposed benefit, they have also led to concerns about childhood soy consumption. Most concerns relate to the possibility that soy could advance the age of puberty onset, especially in girls. It is noteworthy that children may absorb isoflavones more efficiently than adults.[33,34]

Over the last several decades, there has been a secular trend among girls to enter puberty, as judged by age of menses onset (AOM), earlier in life. However, this trend has occurred in soy food-consuming and non-consuming countries alike.[35-45] Furthermore, a retrospective observational study found no relationship between AOM and soy intake among U.S. Seventh-day Adventist girls, a high-soy-consuming population.[46] Clinical studies have also found no effects of soy on hormone levels including thyroid hormone (boys and girls),[47] estrogen (girls),[48,49] and testosterone (boys),[49] but these studies involved very small numbers of participants. A reasonable intake recommendation for children is up to 2 servings of soy daily; although age, body weight, and dietary habits may dictate what is best for any individual child.

**Pregnancy: Maternal Effects**

Recent evidence suggests that soy intake during pregnancy may reduce risk of gestational diabetes mellitus (GDM). Although the data are limited, all 3 prospective epidemiologic studies (2 from China50,51 and 1 from Japan)[3] that examined this relationship found statistically significant protective effects even after adjustment for a variety of potentially confounding variables. In addition to the observational data, a small randomized controlled trial of Iranian women found that the addition of soy to the diet of women with GDM significantly improved glucose homeostasis parameters, triglycerides, and biomarkers of oxidative stress, as well as reduced the incidence of new-born hyperbilirubinemia and hospitalization.[52] Also, consumption of a soy protein rich diet reduced the need for insulin therapy in Indian women with GDM while having no effect on maternal and neonatal thyroid function.[53]

GDM is defined as the type of hyperglycemia diagnosed for the first time during pregnancy.[54] It is the most common metabolic disorder of pregnancy[55] and is associated with an increased risk of adverse perinatal outcomes[56] and possibly an increased risk of long-term ill-health outcomes in the mother[57] and her child(ren).[58]

**Pregnancy: In Utero Effects**

Despite the common practice among Asian women of consuming soy while pregnant, concern has been raised that the resulting in utero isoflavone exposure could adversely impact the fetus.[59,60] It has been known for decades that maternal isoflavone exposure leads to quantifiable amounts of isoflavones in amniotic fluid.[61] Nevertheless, concern arose after a British observational study reported that soy consumption was associated with an increased risk of hypospadias, a common genitourinary anomaly in which the opening of the urethra is on the underside of the penis.[62] The authors speculated that isoflavones were responsible for this association. However, in this study, the consumption of dried peas, beans, lentils, and chickpeas was associated with a 7-fold increased risk of hypospadias, despite non-soy legumes containing negligible amounts of isoflavones.[63,64]

More importantly, subsequently published observational research shows maternal soy consumption is not associated with an increased risk of hypospadias.[65,66] In fact, in a large Japanese study involving 41,578 mothers who delivered singleton live male births, compared with mothers in the reference group (genistein intake 11th-89th percentiles), those in the low intake group (≤10th percentile) had an elevated risk of their sons having hypospadias. Neither adverse nor beneficial effects of genistein, which is the primary soybean isoflavone, on hypospadias were observed in the high intake group (≥90th percentile). The authors concluded that low maternal isoflavone intake in early pregnancy was associated with an elevated risk of hypospadias. Low natto and tofu intake were each associated with about a two-fold increased risk.

Finally, although only conjecture, there is a school of thought that maintains isoflavones are unlikely to exert in utero effects because of the much larger amounts of endogenously produced estrogen to which the fetus is exposed.[67,68] With respect to intake, there is no reason to differentiate soy food consumption recommendations between pregnant and non-pregnant women.

**ABOUT THE AUTHOR**

**Mark Messina, PhD, MS,** is chairperson of the Soy Connection editorial board and director of nutrition science and research for Soy Nutrition Institute (SNI) Global. He is also the co-owner of Nutrition Matters, Inc., a nutrition consulting company, and is an adjunct professor at Loma Linda University. His research focuses on the health effects of soy foods and soybean components.

# PRACTICAL TIPS FOR INTRODUCING SOY IN THE FIRST YEAR

## By Jill Castle, MS, RDN

In the first year of life, babies move from drinking breastmilk or infant formula as their only source of nutrition to eating a variety of foods from the family diet. There are a lot of important food transitions happening at this time.

Which soy foods are appropriate for the growing infant?

**During the First 6 Months**

During the first half of an infant's life, babies need breastmilk or infant formula to meet their nutritional requirements for growth and development. A 2018 review study found no abnormalities in human development when babies consumed soy infant formula.[1] Additionally, another large study of babies from South Korea found no differences in neuro-development when they were fed soymilk formula versus cow's milk formula.[2]

Soy infant formula appears to be a safe, nutritionally complete option for babies in the first year of life, and it's the only plant-based, non-dairy infant formula option available. A soy infant formula is an option for infants who have a milk allergy or intolerance (although babies have a higher chance of also being allergic to soy), or if a family wants to follow a plant-based eating pattern.[3]

**Starting Solids at 6 Months**

No matter the dietary pattern a family follows, and with ongoing breastfeeding, several soy foods can be introduced when babies begin complementary foods around 6 months of age, whether they're using a spoon or a baby-led weaning approach. It's desirable to introduce soy at this time as it may help prevent the development of a soy allergy.

**Feeding by Spoon**

Start with a thin puree and build up the consistency as the baby adapts and learns to eat. You can always change the texture by adding more (or less) breast milk or infant formula. Try:

- Silken or soft calcium-set tofu pureed with vegetables or fruit, or mixed with fortified infant cereal
- Steamed and mashed shelled edamame pureed with fortified infant cereal or pureed vegetables
- Soy yogurt mixed with pureed fruit

**Feeding with Baby-Led Weaning**

When using baby-led weaning, make sure foods are well-cooked, soft, and cut into shapes that babies can easily grasp in their palms or hand. Introduce flavors by adding aromatics, herbs, and spices. Avoid salt and seasonings with sodium like soy sauce. Try:

- Firm tofu cut into long rectangular shapes, or "fingers"
- Steamed edamame crushed with a finger or fork-mashed

### Finger Foods at 8 Months and Beyond

When baby demonstrates a pincer grasp (using the thumb and pointer finger to pick up small bits of food), self-feeding takes off. Sit with baby while they eat to monitor for choking and experiment with the following:

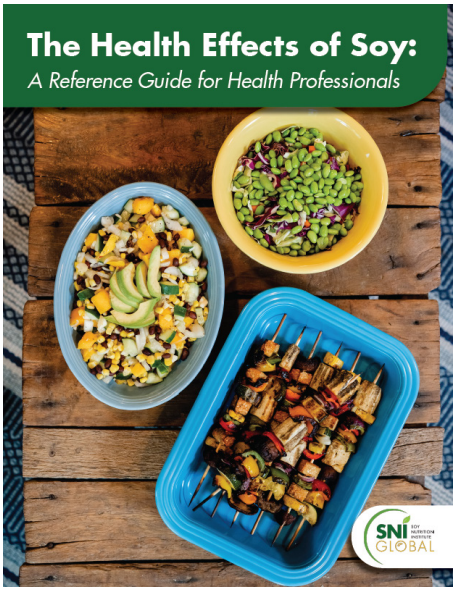
- Small, diced pieces of soft calcium-set tofu
- Steamed and mashed soybeans (you may flatten them with your finger)
- Small, diced pieces of tempeh
- Soy yogurt served in a bowl with a baby spoon (let baby self-feed)

### After Baby Turns 1

As a baby grows and self-feeds, try steamed edamame, seasoned or marinated tofu stir-fried with vegetables, or a smoothie made with soy yogurt and fruit. Unflavored soymilk is appropriate to offer after a baby turns one.

### ABOUT THE AUTHOR

**Jill Castle, MS, RDN,** is a pediatric dietitian with deep expertise and experience in childhood nutrition. She is the founder and CEO of The Nourished Child, a website and podcast for parents, and is expecting the release of her next book, Size Wise (Workman), in early 2024.

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This guide is packed with topics ranging from a multitude of health outcomes to discussion of the different types of soy foods. This resource can help your clients and patients understand the health benefits soy protein, isoflavones and oil can offer.

To view, go to: *sniglobal.org/health-professional-guide*

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**PRACTICAL TIPS FOR INTRODUCING SOY IN THE FIRST YEAR**

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