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Soy-based infant formulas: A review of developmental and nutritional considerations

Abstract

Soy-based infant formulas are widely used as a source of nutrition for children in the first year of life, but research is still lacking on how soy formulas affect infant nutrition and development short-term and long-term. This review article examines research spanning nearly four decades and discusses implications for infant nutrition, development (with particular emphasis on the role of phytoestrogens), and other physical effects correlated to the use of soy-based infant formula. Proposals for future research are also presented.

Keywords: soy-based infant formula, soy formula, infant formula, infant development

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Abbreviations: CM, cow's milk; HPLC, high performance liquid chromatography; GC/MS, gas chromatography – mass spectrometry; TPO, thyroid peroxidase; LC/MS, liquid chromatography – mass spectrometry; UV-VIS, ultraviolet-visible

Introduction

Many brands of soy-based infant formulas are commercially available in any supermarket. Soy-based infant formulas have been in use for more than 100 years[1] and continue to be very popular as a nutritional supplement for growing infants. Recent findings in soy research even suggest that the phytoestrogens in soy may contribute to a lowered risk of cardiovascular disease, cancer, and a lessening of the effects of menopause—all of which could be added bonuses to consuming a soy diet early in life.[2] However, as researchers investigate the effects of soy on infants, some concerns are arising about both the hormonal (phytoestrogen) and nutritional impacts that soy has on the infant physiology. Inquiries into the amount of phytoestrogens contained in soy formulas compared to cow's milk and breast milk, how these foods function differently on the infant metabolism, as well as research on the effects of dosage and timing of soy feedings have produced interesting results. Yet there still remain some unanswered questions about how soy exposure in youth affects the later years of an individual.

The nutritional aspects of soy are also a concern to researchers, especially since soy is the sole source of nourishment for many infants for at least several months of their development. Studies have been done on how the nutrition of soy formulas compares to breast feeding and cow-milk formulas; how infant growth and development responds to each of these feeding methods; how soy formulas may be a wise alternative to cow milk because of food allergies; and how soy interacts with the immune system. These studies will be presented along with the current attitudes and recommendations about using soy as a primary source of nutrition for growing children.

Discussion

Hormonal effects of soy

Analysis methods: Traditional methods for analyzing the amount of isoflavones in soy included gas chromatography and mass spectrometry (GS/MS). Recently, it was found that High Performance Liquid Chromatography (HPLC) was faster, demanded less technician time, less preparation time and less expensive equipment.[3] Consequently, most of the studies regarding the amount of phytoestrogens in soy formulas have used HPLC.

Numerous studies have been done extracting phytoestrogens from soy formulas and comparing these amounts to the amount of phytoestrogens in breast-milk collected after maternal soy consumption. Franke et al.[4] used HPLC and diode-array ultraviolet scanning in their study, and found that the total isoflavones in four popular soy formulas varied from 155 mg/g to 281mg/g.[4] The researchers noted that this variation is probably due to the environmental conditions of the soybean growth and the genetic disposition of the particular breeds of plants. Breast-milk, they found, contains anywhere from 0.2 mMol to 1.5 mMol/L.[3] The lower concentration of isoflavones may provide the benefits of phytoestrogens without as many of the risks of high exposure from soy formulas.

Irvine et al..[5] also used HPLC to study the amount of isoflavones in five popular soy formulas and six other soy infant foods. They concluded that, if the manufacturer's instructions were followed, an 0-4month-old infant would receive 3mg/kg body weight of isoflavones, and after 4 months of age supplementing an infant's diet with soy foods may increase the isoflavone intake by 25%.[5]. Using GC/MS, Dwyer et al.[6] analyzed 3 popular soy formulas[*First Alternative*, *Enrich*, and *Glucerna*]and found that when following the manufacturer's instructions of preparation, a single serving of infant soy formula may contain over 1000 mg of isoflavones.[6] These levels are higher than levels that have been shown to alter reproductive hormones in premenopausal women,[7] and it is not certain what effect these high levels of isoflavones have on infant development.

There is interest not just in the amount of isoflavones in infant formula, but also in the amount of isoflavones in breast milk after the nursing mother consumes soy products. Franke et al.[8] tested the isoflavone content in human milk after the subjects consumed 5, 10, or 20g of roasted soybeans. Milk was collected from 2 postpartum women 12 hours before consuming soy, then at 0, 24 and 72 hours after consuming 5, 10, or 20g soy. The concentration of isoflavones in the breast milk reached a maximum concentration of only about 70 nmol/L.[8] A normal feeding of breast milk at this concentration would provide about a thousandth the amount of isoflavones than are contained in a typical serving of soy formula.

***In Vitro* Research:** Divi et al.[9] studied the effects of two isoflavones, genistein and daidzein, on thyroid peroxidase (TPO), a catalyst essential in the synthesis of thyroid hormone.[9] They studied soybean extract using HPLC, UV-VIS spectrophotometry, and liquid chromatography / mass spectrometry (LC/MS) to identify genistein and daidzein. Incubation of either of the isoflavones (50mM of each, separately) with TPO in the presence of hydrogen peroxide (200 mM) caused the enzyme to be inactivated; however, in the presence of iodine (0.15 to 5.0 mM) prevented this inactivation. This suggests that in iodine-deficient individuals who are exposed to high levels of phytoestrogens may develop thyroid problems. Several cases of alleged soy-related thyroid disorders have been documented,[10-12] but additional controlled, double-blind clinical experimentation is needed that would clarify whether continual isoflavone replenishment through feeding would interfere with TPO activity even in the presence of iodine.

Human Research: One of the most important questions in this area of research is how much of the abundant isoflavones in infant soy formulas are actually absorbed into the infant's body. Setchell et al.[13] used reverse-phase HPLC to determine the isoflavone content in five samples of each of the five major soy infant formulas: Nursoy powdered formula, Isomil powdered and liquid formula, Prosobee liquid formula concentrate and Alsoy liquid formula concentrate. The phytoestrogen content varied from 316 ± 28 mg/g to 64 ± 9 mg/g. Twenty-one 4-year-old Caucasian males were fed exclusively on a diet of soy formula (Isomil) or cow-milk formula or breast milk (n=7 on each diet), and their plasma concentrations of isoflavones was measured. The plasma concentration of genistein and daidzein in soy-fed infants was significantly higher than in the other groups—in some cases up to 1000 ng isoflavones per mL of plasma.[13]

Irvine et al.[14] studied infant urine to determine how much of the isoflavones being consumed were absorbed and excreted. After using HPLC to determine the isoflavone content of the study soy formulas, the researchers discovered that a combined 51 ± 7% of the isoflavones consumed were recovered in the urine.[14] A significant amount of isoflavones are apparently being absorbed by the infant digestive system.

Summary: HPLC is a good method for determining the amount of isoflavones in soy-based infant formula. Although the amount of isoflavones varies among the different soy formulas, in a regular serving most formulas provide a dose of phytoestrogens that is at least as high or much higher than the amount of isoflavones that demonstrates effects on the menstrual cycle of women. Breast milk, while still containing some isoflavones, contains a much lower concentration than soy formula. Since isoflavones have been shown to interfere *in vitro* with an important thyroid enzyme, a constant diet of soy formula may modulate thyroid development of an infant. Several studies have shown that infants do absorb and excrete up to 50% of the isoflavones they ingest, so it is important that researchers focus on the effects that isoflavones have on the infant physiology in the concentrations at which they are ingested. Long-term studies are necessary.

Nutritional effects of soy

Human research: Although soy formulas have been used for decades, until recently there was a lack of rigorous studies showing whether a soy diet provides for the nutritional needs of a growing infant. In a randomized controlled clinical trial, Churella et al.[15] studied the effects of different amounts of soy protein on growing infants. At two days of age, 32 males and 32 females were randomly assigned to a commercial soy formula (2.91 g protein/100 Kcal) or a soy formula containing less protein (2.45 g protein/100 Kcal) and fed that diet until 112 days of age. The only statistically significant difference was a lower plasma urea nitrogen concentration in the low protein group. The study concluded that a commercial soy formula provides enough protein to meet the needs of a normal, term infant from 2 to 112 days of age.[15] However, in this study the growth in soy-protein-fed infants was not compared to breast-fed or cow-milk-formula infants. Jung et al.[16] addressed the question of nutritional differences between soy isolate formula and milk-based formula, and their effects of growth on 40 healthy, full-term newborn white or Spanish infants until 112 days of age. They showed that body weights, lengths and head circumference did not significantly differ between the two groups. Neither group showed retarded development or general rejection of either formula.[16]

Does soy formula provide enough of other nutrients needed for healthy growth and development? A randomized clinical trial by Kulkarni et al.[17] looked at 46 very-low-birth-weight infants and their growth on one of three formulas: Isomil (soy isolate), Similac with iron (cow's milk formula), or Similac 24 LBW (hypercaloric milk-based formula). Clinical diagnosis of rickets was made in 60% of the infants fed Isomil, and significantly low levels of serum phosphorus and high levels of serum alkaline phosphatase were also observed. The researchers suggest that the low solubility of minerals and bioavailability of nutrients in the soy formula contributed to the high frequency of rickets. They suggest that prolonged soy formula feeding should be avoided in very-low-birth-weight infants in order to promote health and proper development.[17]

Another measure of infant growth and development is bone mineral content and how diet affects this formation. Venkataraman et al.[18] studied fifty-six full term infants in a randomized controlled trial, assigning the infants to a diet of either human milk, cow milk-based formula and soy milk-based formula. After 6 months (measurements taken on the distal third left radius site every other month), researchers found that final bone mineral content and bone width were significantly greater in the soy formula-fed group than in the human milk group. Researchers suggest that improved mineral suspendability in the formula allowed for the increase in bone mineralization in the formula-fed group.[18]

Hillman also studied bone mineral content in a similar experimental design—she used only 31 infants, but took measurements over the first year of life. Her results showed that all groups of infants mineralized in the same fashion, when adequate vitamin D was provided and the soy formula had improved mineral suspendability.[19] Other studies with very similar experimental design[20] found that there was no statistical difference in bone mineral content between soy formula-fed infants and infants fed cow milk-formula or human milk.

An important question when considering the nutritional value of soy is how well it is how well it is tolerated in the digestive tract. In a randomized clinical trial, Brown et al.[21] fed 34 male infants either soy protein isolate, lactose-free formula with added soy polysaccharide, and lactose-free formula without additives. All infants had chronic diarrhea and were offered a maximum of 187.5 mL/kg body weight of formula per day. Results indicate that there was no significance among the different formulas in retention of nitrogen, change in diarrheal severity or absorption of macronutrients. However, the soy-fiber formula group had a statistically significant decrease in the duration of diarrhea.[21] This suggests that soy-polysaccharide formulas may be useful in management of young patients with acute diarrhea.

In a multi-center study, Nadasi showed that while 287 infants and children (>8yr) were fed soy-protein formula for a minimum of one month, the frequency of undesirable feeding-related symptoms (abdominal cramps, gas, bloating, colic, diarrhea, fussiness, spitting up, vomiting, etc.) was significantly decreased.[22] Nadasi concluded that these infants and children on a soy formula diet continued to thrive normally and that the soy formula was generally well tolerated.

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Several researchers have looked into the use of soy protein formulas as a replacement for cow milk formulas in infants with cow's milk (CM) hypersensitivity. Cantani et al.[23] report that 20 of 21 infants with atopic dermatitis due to CM hypersensitivity had improved skin lesions and regular growth on a soy protein formula diet.[23] In another study on CM hypersensitivity, Iyngkaran et al.[24] studied 22 infants recovering from diarrheal disease associated with CM protein intolerance. The infants were maintained on hypo-allergenic formula for 4-6 weeks, then challenged successively: first with soy protein formula, then 24 hours later with CM protein, and again with soy protein 24 hours after CM protein challenge. Results show that in all but three infants, development of clinical histological reactions and mucosal injury occurred. The researchers conclude that in some intolerant individuals, soy protein may evoke the same reactions as CM protein causes. They suggest that infants recovering from diarrhea might reduce the risk of damaging the mucosa membrane by avoiding foods containing either CM protein or soy protein.[24] Vandenplas reiterated in a review of current literature that 10-15 percent of infants allergic to cow's milk will also react to soy, so although soy may be a good alternative in many cases of cow's milk allergy or hypersensitivity, it is not always warranted.[25]

A randomized, double-blind controlled study by Chandra looked at the effect of using whey hydrolysate formula, conventional CM formula, or a soy protein formula on 216 infants who were at high risk for atopic diseases and food allergies because of family history. A control of 72 infants who were breast-fed during the study were also evaluated. Each group followed their regimen for 4-6 months. The infants were followed up 5 years later to assess the incidence of atopic disease development. Results showed a lowering in the cumulative incidence of atopic disease, eczema and asthma in the breast-fed group (odds ratio of about.422) and the whey hydrolysate group (odds ratio of about.322). The soy formula was not effective (odds ratio of about.759). Later double-blind placebo-controlled food challenges showed a lower prevalence of food allergy in the whey hydrolysate group than in the soy formula group or the CM formula group.[26]

Another consideration of researchers is how soy formulas affect the infants' immune system. May et al.[27] studied infants who were fed either CM formula from birth to 112 days of age, then exposed to various CM proteins. Immunologic reactions were highest in infants fed conventional CM formulas from birth, and somewhat lower in infants fed with heat-treated cow's milk or milk-base formula of lower protein. Using a soy formula from birth to 112 days of age did not prevent an antibody response to the CM protein, with the response being at least as high or higher than in infants fed cow's milk from birth.[27]. In a similar immunologic study, Zoppi et al.[28] fed 41 normal full-term infants either cow's milk formula or a soy protein formula of equal calorie content but with two levels of protein in each type of formula (2.0 or 4.0 g/kg/day cow's milk protein, and 2.0 or 5.0 g/kg/day soy protein). Results indicate that the infants who received soy formula had less gammaglobulin, immunoglobulin and other immunity factors, as well as impaired T lymphocyte markers and reactivity when compared with the infants on cow's milk diets. Morbidity (especially upper respiratory tract infections) was increased in the soy protein group, but also in any infant who received lesser amounts of protein.[28]

Kjellman and Johansson performed a randomized controlled trial on 48 children with a strong history of atopic disease in order to assess the effect that cow's milk formula and soy formula had on the development of atopic disease and immunoglobulins. From weaning to 9 months, the children were fed with either a cow's milk formula or a soy milk formula. Results show that two-thirds of the children developed symptoms of atopic disease, and withholding cow's milk for the first 9 months of life (i.e. using a soy formula) did not significantly reduce the incidence of cow's milk-intolerance symptoms. No difference in the serum immunoglobulins was found among the groups during the observational period.[29] A similar randomized study done by Zoppi et al.[30] studied 39 normal full-term infants fed with soy formula of three levels of protein: 2.5, 4.0, or 5.5 g/kg/day. Results show that after four months, growth in the low-protein group was slightly lower than the other two, and serum gammaglobulin and immunoglobulin levels increased with increasing protein levels of the formulas. The high-protein formula-fed infants had highest gammaglobulin and immunoglobulin levels, and lowest morbidity.[30]

A study by Zoppi et al.[31] studies the response to the oral rotavirus vaccination in infants fed different formulas. In a randomized, controlled clinical trial, 28 full term infants were breast-fed during the first month of life, and thereafter for the next five months were randomly assigned to breast-feeding (n=8), adapted milk-formula (n=13) or soy formula (n=7). Weight gain was similar in all groups. After the oral dose of RIT 4237 rotavirus vaccine was given, the IgM/IgG antibody growth against the virus was lowest in the soy-fed group (only 2 of 7 infants developed proper immune response to the vaccination). This suggests that a soy-protein formula diet may interfere with immunization procedures.[31] The authors note that their results align with other studies showing altered antibody responses in soy-formula-fed infants receiving diphtheria, tetanus, pertussis, and poliovirus vaccines.[32]

Summary: The results of studies regarding the nutritional quality of soy as an infant diet show mixed results. While most soy formulas seem to be high enough in protein to provide for a growing infant's needs, the formula also needs to have high solubility and bioavailability of nutrients and minerals in order to prevent malnutrition and related diseases. Soy protein formulas may provide a feeding option for infants who are cow's milk intolerant, but this depends on the amount of protein in the formula and on the infant's history of food protein allergy. Immunologic responses to soy protein are often not as pronounced as responses to cow's milk protein, but this can also be a disadvantage if it proves to lessen the effectiveness of various immunization processes. More studies in all areas would validate the results presented here.

Other effects of soy

Methylation: Although fairly preliminary, an interesting study by Harlid et al..[33] looked at possible differences in DNA methylation between soy formula-fed and cow formula-fed infants. Vaginal epithelial cells were collected from 50 infant girls and evaluated for epigenome-wide DNA methylation. Soy-fed infants showed increased DNA methylation at the proline rich 5 like gene (PRR5L) compared to the cow formula-fed infants, with the effects becoming more pronounced after 126 days. The researchers postulate that suppression of PRR5L may promote TNF-alpha associated autoimmune diseases due to its downstream effects on TTP and TNF-alpha, although additional confirmation is needed.[33] This study did not compare the results to a cohort of breastmilk-fed infants, which would have been helpful.

Female Development: Studies of cohorts suggest correlation between soy formula feeding early in life and development of endometriosis.[34] Additionally, in women diagnosed with fibroids, exposure in early life to soy formula was correlated with larger fibroid growth.[35] Other studies suggest that soy formula feeding early in life may be associated with very early menarche (<10 years) or late menarche (14-15 years)[36] as well as heavy menstrual bleeding following menarche.[37] Because these studies partially rely on retrospective data about soy formula feeding in infancy, their conclusions are not fully confirmed.

Cognitive Development: A study by Andres looked at 391 breastfed, soy formula-fed, and cow's milk formula-fed infants at 1 year of life and compared using Bayley Scales of Infant Development and Preschool Language Scale-3. No significant differences were found between development of the formula-fed infants, although breastfed infants showed a slight cognitive advantage at that age.[38]

Gut Microbiome: Piacentini et al.[39] investigated whether a change to soy formula would significantly impact gut microflora in healthy infants. Twelve infants had their cow's milk formula replaced with soy formula and the researchers studied microbial composition before and after the change. No significant alteration of intestinal flora was detected.[39] However, additional studies in neonatal pigs indicate that gastrointestinal morphology, biochemistry, and microbial abundance may be influenced by soy formula,[40,41] so additional human studies are needed to confirm.

Summary: Soy formula in infancy may have wide effects on development, particularly female development, although these effects require further research for validation. Epigenetic studies in particular may provide molecular-level mechanisms through which the effects of soy on humans can be understood.

Conclusion

Despite its long history of use, relatively little is known about how the hormonal and nutritional components of soy affect the infant and child physiology. Studies show that commercially-available soy products vary greatly in their content of isoflavones, protein and other nutrients. Different formulas even react differently in an infant's system depending on the infant's history of food allergy, tolerance of soy protein, age and stage of development, weight, previous feeding history, the dosage of soy received, the timing of soy received, and the duration of soy feeding. There are many variables that remain to be explored by controlled, randomized clinical testing.

The National Toxicology Program concluded in 2009 that infant exposure to isoflavones in soy formula was of "minimal concern." However, on related pages in the National Institutes of Health information database, it also states that infants are likely more susceptible to the estrogenic effects of soy formula, and these effects may not be evident for many years after exposure.[42] Continuing research is certainly warranted.

A general recommendation based on all the data is to breast-feed infants whenever possible, since this generally results in a lower ingestion of phytoestrogens and of proteins that may illicit unfavorable reactions. However, if breast-feeding is not possible, soy formulas may provide a good alternative to conventional cow's milk formulas, especially in the case of individuals with a history or risk of cow's milk protein or lactose intolerance. Before feeding a soy formula to an infant, the levels of nutrients, protein and phytoestrogens contained in the formula should be considered. The infant should be monitored carefully for symptoms of intolerance or other adverse reactions that may develop.

Sheehan suggests that future studies should look at the soy-formula consuming population as a whole: infants consuming soy products currently, as well as older children, adolescents, adults and the elderly previously exposed to soy during developmental years should be included. Some specific questions to address should include estrogenic and thyroid hormone-related effects of soy, as well as a wide variety of toxicity considerations.[43]. Transgenic soy products should also be evaluated, since it is estimated that 93% of soybean crops in the United States are genetically modified and concomitantly subjected to high levels of toxic pesticides and herbicides.[1]. The long-term effects this may have on infant development is unknown.

Soy formulas will undoubtedly be used for years to come, and additional research will continue to elucidate the possible benefits as well as potential risks of a soy-based diet for infants. This growing body of evidence can provide healthcare professionals and parents the information necessary to make the best feeding choice for their infant.

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Conflicts of interest

The author declares no financial interest or conflict of interest in this manuscript.

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