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CLINICAL REPORT

Use of Soy Protein-Based Formulas in Infant Feeding

Guidance for the Clinician in Rendering Pediatric Care

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ABSTRACT

Soy protein-based formulas have been available for almost 100 years. Since the first use of soy formula as a milk substitute for an infant unable to tolerate a cow milk protein-based formula, the formulation has changed to the current soy protein isolate. Despite very limited indications for its use, soy protein-based formulas in the United States may account for nearly 25% of the formula market. This report reviews the limited indications and contraindications of soy formulas. It will also review the potential harmful effects of soy protein-based formulas and the phytoestrogens contained in these formulas.

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words
soy protein, infant formula, infant feeding, cow milk protein allergy, nutrition, galactosemia, vegetarian

Abbreviations
AAP—American Academy of Pediatrics
IgE—immunoglobulin E

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THE AMERICAN ACADEMY of Pediatrics (AAP) is committed to the use of human milk as the ideal source of nutrition for infant feeding. However, by 2 months of age, the majority of infants in North America are receiving at least some formula. Soy-based infant formulas have been available for almost 100 years.[1] Despite limited indications, soy protein-based formula accounts for approximately 20% of the formula market in the United States. Because an infant formula provides a source of nutrition for an extended interval, its nutritional adequacy must be proven, and the indications for its use must be substantiated and well understood. This statement updates the 1998 AAP review of soy protein-based formulas and addresses the ongoing concern of phytoestrogens in soy formulas.

COMPOSITION

Isolated soy protein-based formulas currently on the market are all free of cow milk protein and lactose and provide 67 kcal/dL. All are iron-fortified and meet the vitamin, mineral, and electrolyte specifications addressed in the 2004 guidelines from the AAP for feeding term infants[2] and established by the US Food and Drug Administration.[3] The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45 to 2.8 g per 100 kcal or 1.65 to 1.9 g/dL. The fat content of soy protein-based formulas is derived primarily from vegetable oils. The quantity of specific fats varies by manufacturer and is usually similar to those in the manufacturer's corresponding cow milk-based formula. The fat content ranges from 5.02 to 5.46 g per 100 kcal or 3.4 to 3.6 g/dL. The oils used include soy, palm, sunflower, olein, safflower, and coconut. Docosahexaenoic and arachidonic acids now are added routinely.

In formulas, carbohydrate sources are corn maltodextrin, corn syrup solids, and sucrose, with content ranging from 10.26 to 10.95 g per 100 kcal or 6.9 to 7.4 g/dL. Until 1980, mineral absorption from soy formulas was erratic because of poor stability of the suspensions and the presence of excessive soy phytates.[4] Because soy protein isolate formulas still contain 1.5% phytates, and up to 30% of the total phosphorus is phytate bound, they contain 20% more calcium and phosphorus than cow milk-based formulas and maintain the ratio of calcium to available phosphorus of 1.1 to 2.0:1. With the current formulations, bone mineralization, serum concentrations of calcium and phosphorus, and alkaline phosphatase concentrations in term infants through 12 months of age are equivalent to those observed in infants fed cow milk-based formulas.[5–7] Because soy phytates and fiber oligosaccharides also bind iron and zinc,[9] all soy-based formulas are fortified with iron and zinc.[8,9]

Phytoestrogens in Soy Protein-Based Formulas

Of the many heat-stable factors present in soy formulas, the phytoestrogens are of particular interest in human health. Phytoestrogens consist of several groups of nonsteroidal estrogens, including isoflavones. Isoflavones are commonly found in legumes, with the highest amount found in soybeans.[1,10] Concerns raised in relation to phytoestrogens/isoflavones include their potential negative effects on sexual development and reproduction, neurobehavioral development, immune function, and thyroid function. On the other hand, epidemiologic studies have

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suggested a protective effect of isoflavones against a number of adult chronic diseases, including coronary heart disease and breast, endometrial, and prostate cancers.[11,12]

The structural similarity of phytoestrogens with 17-estradiol has prompted studies on the possible effects of soy isoflavones on reproductive function and growth. Numerous toxicity studies in rats have demonstrated some effects on estrogen-related tissues, but overall maternal reproductive function and fetal development were unaffected.[13–15] A recent study of the isoflavone genistein demonstrated adverse consequences of neonatal exposure in mice[16]; however, feeding of soy formula (and not individual components) has not demonstrated these adverse effects in animals.[17]

The possible effects of soy isoflavones on various forms of carcinogen-induced and estrogen-induced tumorigenesis have been investigated in animal models, but no clear conclusion can be drawn.[18,19] Soy diets were reported to stimulate growth of estrogen-dependent mammary tumors in mice in a dose-dependent manner.[20,21] Contrary to these results, phytoestrogens in typical dietary quantities were reported not to have estrogen-like activity in female ovariectomized macaque monkeys, but they antagonized estrogen-induced cellular proliferation in the breast.[22]

In humans, very limited data to date suggest that soy phytoestrogens have a low affinity for human postnatal estrogen receptors and low potency in bioassays.[23] The absorption, distribution, metabolism, and excretion of soy isoflavones vary, depending on age and gender and among cultural groups; interindividual variability has been documented in several studies.[24,25] However, differences in gender have been inconclusive.[26–28] Analysis of maternal and cord plasma and amniotic fluid indicates placental transfer of these compounds after soy consumption; no deleterious effects were discerned in the fetuses of Japanese mothers with relatively high soy consumption.[29]

Isoflavones are excreted in human milk, although the concentration is very low. The concentration of isoflavones in human milk reflects maternal diet, with omnivores demonstrating considerably lower concentrations of isoflavones compared with vegans.[30,31] Setchell and Cassidy[32] estimated that the amount of isoflavones ingested by infants fed soy-based formulas on a body weight basis exceeded those reported to increase the length of the menstrual cycle in adult women. However, an increased incidence of feminization in male infants[33] or an increased incidence of hypospadias in high soy-consuming populations[34] have not been observed. Even in infants fed soy-based formulas exclusively, the sulfate and glucuronide conjugates of phytoestrogens are identified in plasma, although both of these are rapidly excreted.[27] Data on reproductive health in young adults 20 to 34 years of age who had previously participated in a controlled feeding study of soy formula as infants demonstrated a longer duration of menstrual bleeding and greater discomfort in women exposed to soy as infants.[35] We cautioned against overinterpretation of their data, however, because there was no increase in menstrual blood flow in the women exposed to soy formula as infants and no statistically significant differences in >30 other outcome variables measured.[35]

Consumption of soy products by infants with congenital hypothyroidism complicates their management, as evidenced by a prolonged increase in thyroid-stimulating hormone when compared with infants not fed soy formula; the authors of 2 studies suggested closer monitoring and a possible need for an increased dose of levothyroxine.[36,37] In infants receiving replacement hormone, the phytates may interfere with the uptake of exogenous thyroid hormone by binding the thyroxine within the lumen, increasing fecal loss, and reducing the efficacy of oral thyroid hormone.[36,38] In an extensive review of the effects of soy protein and soybean isoflavones, little evidence was found that soy foods or isoflavones adversely affect thyroid function in iodine-replete individuals with euthyroidism.[39] This review also found that, similar to infants, adults with hypothyroidism may need additional doses of thyroid hormone with the concomitant use of soy foods because of the effects on absorption. Trials with dietary soy isoflavones have not reported adverse effects on thyroid function in rats.[40] These data suggest that there is a lack of sufficient evidence suggesting short-term or long-term adverse effects of soy consumption on endocrine function.

In summary, although studied by numerous investigators in various species, there is no conclusive evidence from animal, adult human, or infant populations that dietary soy isoflavones may adversely affect human development, reproduction, or endocrine function.

Aluminum in Soy Protein-Based Formulas

In 1996, the AAP issued a statement (since retired) on aluminum toxicity in infants and children and discussed the relatively high content of aluminum in soy-based formulas.[41] Although the aluminum content of human milk is 4 to 65 ng/mL, that of soy protein-based formula is 600 to 1300 ng/mL.[42,43] Mineral salts used in formula production are the source of the aluminum. Aluminum, which makes up 8% of the earth's crust as the third most common element, has no known biological function in humans.[43] The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal function in preterm infants and children with renal failure. Because aluminum competes with calcium for absorption, increased amounts of dietary aluminum from isolated soy protein-based formula may contribute to the reduced skeletal mineralization (osteopenia) observed in preterm infants and infants with intrauterine growth retardation.[44] Term infants with normal renal function do not seem to be at substantial risk of developing aluminum toxicity from soy protein-based formulas.[42]

USE IN TERM AND PRETERM INFANTS

Numerous studies have documented normal growth and development in term neonates fed methionine-supplemented isolated soy protein-based formulas.[42,45–48] Average energy intakes in infants receiving soy protein-based

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formulas are equivalent to those achieved with cow milk formulas.[42] In infants fed soy protein-based formulas, the serum albumin concentration, as a marker of nutritional adequacy, is normal,[46,49–51] and bone mineralization is equivalent to that documented with cow milk-based formulas in term infants.[5–7] Literature reviews and clinical studies of infants fed soy protein-based infant formulas raise no clinical concerns with respect to nutritional adequacy, sexual development, thyroid disease, immune function, or neurodevelopment.[1] Additional studies confirm that soy protein-based formulas do not interfere with normal immune responses to oral immunization with poliovirus vaccine.[52,53] The US Food and Drug Administration has approved these formulas as safe for use with infants.

On the other hand, soy protein-based formulas are not recommended for preterm infants. Serum phosphorus concentrations are lower, and alkaline phosphatase concentrations are higher in preterm infants fed soy protein-based formula than they are in preterm infants fed cow milk-based formula.[54,55] As anticipated from these observations, the degree of osteopenia is increased in infants with low birth weight receiving soy protein-based formulas.[50,56] Even with supplemental calcium and vitamin D, radiographic evidence of significant osteopenia was present in 32% of 125 preterm infants fed soy protein-based formula.[56] The cow milk protein-based formulas designed for preterm infants are clearly superior to soy protein-based formula for preterm infants.

USE IN DISORDERS OF CARBOHYDRATE METABOLISM

When strict dietary lactose elimination is required in the management of infants with galactosemia or primary lactase deficiency (extremely rare), soy protein-based formulas are safe and cost-effective. In addition, soy protein-based formulas can be a dietetic alternative for families wishing to avoid feeding their infants formulas containing animal products. Soy protein-based formulas with sucrose as the carbohydrate are contraindicated in sucrase-isomaltase deficiency and in hereditary fructose intolerance.

USE IN ACUTE DIARRHEA AND SECONDARY LACTASE DEFICIENCY

A number of studies have addressed the role of these formulas in the recovery from acute infantile diarrhea complicated by secondary or transient lactase deficiency. However, after immediate rehydration, most infants can be managed successfully with continued breastfeeding or standard cow milk or soy formula.[57,58] In an extensive review, Brown[57] noted that the dietary failure rate of lactose-containing formulas was 22%, whereas that of lactose-free formulas was 12%. In a study comparing human milk, cow milk-based formula, and soy protein-based formula, no difference was found in the rate of recovery from rotavirus or nonrotavirus diarrhea on the basis of nutritional therapy.[49] However, the duration of diarrhea has been reported to be shorter in infants receiving soy protein-based formula,[51,59] and the duration of liquid stools may also be reduced by adding additional soy polysaccharide fiber[60] or by resuming a mixed-staple diet.[61]

Lactose free and reduced lactose-containing cow milk formulas are now available and could be used for circumstances in which elimination or a reduction in lactose in the diet, respectively, is required. Because primary or congenital lactase deficiency is rare, very few individuals would require a total restriction of lactose. Lactose intolerance is more likely to be dose dependent. Thus, the use of soy protein-based lactose-free formulas for this indication should be restricted.

USE IN COLIC AND "FORMULA INTOLERANCE"

Perhaps the most common reason for use of soy formulas by infant care providers is for relief of perceived formula intolerance (spitting, vomiting, fussiness) or symptoms of colic. Colicky discomfort is described by the parents of 10% to 20% of infants during the first 3 months of age.[62] Although many factors have been implicated, parents frequently seek relief by changing infant formulas. Although some calming benefit can be attributed to the sucrose[63,64] and fiber content,[65] controlled trials of cow milk and soy protein-based formulas have not demonstrated a significant benefit from soy.[66,67] The value of parental counseling as to the cause and duration of colic seems greater than the value of switching to soy formula.[68] Because most colicky behavior diminishes spontaneously between 4 and 6 months of age, any intervention at that time can be credited anecdotally.

SEVERE GASTROINTESTINAL REACTIONS TO SOY FORMULA

As with cow milk protein-based formula, severe gastrointestinal reactions to soy protein-based formula have been described for >40 years[69] and encompass the full gamut of disease: enteropathy, enterocolitis, and proctitis. Small-bowel injury, a reversible celiac-like villus injury that produces an enteropathy with malabsorption, hypoalbuminemia, and failure to thrive, has been documented in at least 4 studies.[70–73] In case series of infantile food protein-induced enterocolitis caused by cow milk protein, 30% to 64% of infants had concomitant soy-induced enterocolitis,[74–77] with enterocolitis manifested by bloody diarrhea, ulcerations, and histologic features of acute and chronic inflammatory bowel disease.[69,75,78–80] Afflicted infants have responded to replacing the soy protein-based formula with a hydrolyzed protein formula. It is theorized that the intestinal mucosa damaged by cow milk allows increased uptake and, therefore, increased immunologic response to the subsequent soy antigen. Eosinophilic proctocolitis, a more benign variant of enterocolitis, also has been reported in infants receiving soy protein-based formula.[81,82]

These dietary protein-induced syndromes of enteropathy and enterocolitis, although clearly immunologic in origin, are not immunoglobulin E (IgE)-mediated, reflecting instead an age-dependent transient soy protein hypersensitivity. Because of the reported high frequency of sensitivity to both cow milk and soy antigens in infants, soy protein-based formulas are not indicated in

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the management of documented cow milk protein-induced enteropathy or enterocolitis. Hydrolyzed protein formulas should be used for these infants. Most, but not all children, can resume soy protein consumption safely after 5 years of age.

SOY PROTEIN-BASED FORMULAS AND PREVENTION OF ATOPIC DISEASE

Any ingested large molecular weight protein is a potential antigen to the intestinal immune system, including soy protein. In soy protein isolate, 90% of the pulp-derived protein resides in 2 major heat-stable globulins: β-conglycin, with a molecular weight of 180 000; and glycinin, with a molecular weight of 320 000.[83] After enteric digestion, the number of potential antigens generated at the mucosal surface is enormous.[84] As a result, the in vitro demonstration of antigen-specific antibody can be difficult. The antigenicity of soy protein, suspected since 1934,[85] was documented in low-risk infants by Eastham et al in 1982.[86] Intrauterine sensitization has been documented by demonstrating antigen-specific antibody in human amniotic fluid.[87]

Recognizing that soy protein is antigenic does not mean that soy protein is highly allergenic. In a prospective study of healthy infants fed human milk, cow milk formula, or soy protein-based formula, Halpern et al[88] documented true allergic responses in 0.5% and 1.8% of infants to soy formula and cow milk formula, respectively. This frequency is consistent with the summary by Fomon[89] that in 3 decades of study of soy protein-based formulas, <1% of soy formula-fed infants had adverse reactions. In a national survey of pediatric allergists, the occurrence of allergy to cow milk was reported at 3.4%, whereas allergy to soy protein was reported to be 1.1%.[90] Two large studies of infants with atopic dermatitis addressed the frequency with which a double-blind, placebo-controlled challenge with soy protein was positive. Sampson[91] documented a positive soy allergy in 5% of 204 patients, whereas Businco et al[92] implicated soy in 4% of 143 children.

In a recent meta-analysis of 5 randomized or quasi-randomized studies, the authors concluded that feeding with soy formula should not be recommended for the prevention of atopy in infants at high risk of developing allergy.[93] Furthermore, the use of soy protein-based formula during the first 3 months of age does not reduce the frequency of positive antibody responses to cow milk formula introduced later in infancy.[93] When human milk feeding is supplemented with soy formula in infants at high risk, the anticipated frequency of eczema by 2 years of age is not significantly reduced.[94,95] Interpretation of these data are obscured by multiple alterations in the maternal diet and by environmental stimuli. However, isolated soy protein-based formula has no advantage over cow milk-based formula for supplementing the diet of a breastfed infant.

Regarding soy proteins and other food allergies, in 1 partly prospective, partly retrospective study of the risk factors for the development of peanut allergy, feeding of soy milk or soy protein-based formula was associated with the development of peanut allergy (odds ratio: 2.6; 95% confidence interval: 1.3–5.2).[96] However, in a randomized trial of soy formula feeding in infants with cow milk allergy, there was no association between soy formula ingestion with the development of peanut allergy.[97] Thus, the evidence that soy formula feeding increases the risk of developing peanut allergy is contradictory, and additional study is warranted.

Sensitization to soy has been reported in 10% to 14% of infants with cow milk allergy.[98,99] One study documented similar adverse reactions to soy in IgE-associated and non-IgE-associated cow milk allergy (11% vs 9%).[99] A second study evaluated infants and children with IgE-associated cow milk allergy (ages 3–41 months), and 14% (95% confidence interval: 7.7–22.7) were determined to have soy allergy.[98] Thus, although most infants with IgE-mediated cow milk allergy will tolerate soy formula, because of the 10% to 14% crossover rate, the use of an extensively hydrolyzed protein formula rather than a soy formula may be considered in infants allergic to cow milk formula. Although reported in the literature, severe anaphylaxis after soy protein exposure is uncommon, especially in infants.[100,101]

SUMMARY

1. In term infants, although isolated soy protein-based formulas may be used to provide nutrition for normal growth and development, there are few indications for their use in place of cow milk-based formula. These indications include (*a*) for infants with galactosemia and hereditary lactase deficiency (rare) and (*b*) in situations in which a vegetarian diet is preferred.
2. For infants with documented cow milk protein allergy, extensively hydrolyzed protein formula should be considered, because 10% to 14% of these infants will also have a soy protein allergy.
3. Most previously well infants with acute gastroenteritis can be managed after rehydration with continued use of human milk or standard dilutions of cow milk-based formulas. Isolated soy protein-based formulas may be indicated when secondary lactose intolerance occurs.
4. Isolated soy protein-based formula has no advantage over cow milk protein-based formula as a supplement for the breastfed infant, unless the infant has 1 of the indications noted previously.
5. Soy protein-based formulas are not designed for or recommended for preterm infants.
6. The routine use of isolated soy protein-based formula has no proven value in the prevention or management of infantile colic or fussiness.
7. Infants with documented cow milk protein-induced enteropathy or enterocolitis frequently are as sensitive to soy protein and should not be given isolated soy protein-based formula. They should be provided formula derived from hydrolyzed protein or synthetic amino acids.

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8. The routine use of isolated soy protein-based formula has no proven value in the prevention of atopic disease in healthy or high-risk infants.

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