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Review Article

Soy-based infant nutrition: a review

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Dietary consumption of soy varies worldwide. In Asia, people traditionally consume large quantities of soy, while in Europe, soy is not part of the traditional or daily eating habits. The USA is a major soy producer. The mean intake of isoflavones by an adult is 8 - 50 mg/day in Asia but only 0.5 – 3.5 mg/day in the Western world.[1] The soy intake of a vegetarian is 3 – 12 mg/day and a vegan achieves an intake of 15-60 mg/day.[2]

In the early 1900s, soy-protein preparations were the only option for the treatment of cow's milk protein allergy (CMPA). The first report of the use of a soybean-based formula for infants dates from 1909.[3] Most soy drinks are not enriched with zinc, iron, calcium, phosphorous, methionine, or carnitine. Soy drinks also do not contain soy isolate. Soy products that do not fulfill the criteria to be an infant formula are not adapted for infant feeding.

Soy in infant nutrition

Since the 1960s, the composition of soy infant formula (SIF) has been improved to meet the nutritional needs of infants. Previously, SIF contained soy flour with a protein content of only 70%. Now, SIF contains soy isolate with a 95% protein content.[4] The anti-protease activity present in soy is more than 90% destroyed by heating.[5] The residual concentration of phytate in soy protein isolate is 1.5%. Phytate decreases the bioavailability of phosphorous, zinc and iron.[6] Amino acids and minerals such as methionine, carnitine, taurine, iron, zinc, calcium, and phosphorous are added to SIF in appropriate amounts. The American Academy of Pediatrics (AAP) concluded that aluminium in SIF is not a safety issue, except in preterm infants and infants with renal failure.[7] These infants should not use soy infant formula because of the aluminium content, as aluminium increases the risk for developing osteopenia and may have negative effects on growth.[8,9]

Soy contains stachyose and raffinose fibers, which may produce alpha-1,4-galactose, leading to flatulence and diarrhea in sensitive individuals due to hind-gut fermentation.[10] However, the amounts of these fibers present in SIF are low, so SIF is even considered to be safe in the treatment of galactosemia.

Phytoestrogens, mainly genistein and daidzein, are vegetable estrogens with a similar structure to

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human estrogen, but with strongly reduced activity. Soy isoflavones may function as estrogen agonists or selective estrogen receptor modulators.[2] The mean isoflavone intake in infants who are fed breast milk or cow's milk-based formula is 0.005 – 0.01 mg/day, while the intake of a SIF-fed infant is 6 – 47 mg/day.[2] The data published by Setchell *et al*. and Cao *et al*. showed that urine and plasma concentrations of genistein and daidzein were several hundred times higher in SIF-fed infants than in breastfed infants or infants fed cow's milk-based formula.[11,12] However, it cannot be concluded from these studies that genistein and daidzein are biologically active.[12]

Negative health effects by phytooestrogens were demonstrated more than 50 years ago in animals. Sheep that were fed clover with phytooestrogens became sterile.[12] Although this study clearly indicates that plant compounds can interact with the mammalian neuroendocrine system, the phytooestrogen responsible for these effects was coumestrol, a compound that is not present in high levels in SIF. Fertility problems were shown in rats, because of an abnormal secretion of luteinising hormone.[14] Other animal studies with pure phytoestrogens have shown conflicting information. While some studies suggest that phytoestrogens are safe, others suggest potentially harmful effects including carcinogenic properties if the exposure occurs during critical periods of development.[15] Tan *et al*. concluded that SIF feeding did not result in gross adverse reproductive effects in male marmosets, though testicular size was increased and testicular cell composition was altered in SIF-fed animals.[16] Consistent but indirect evidence was found for possible compensated Leydig cell failure.[15] But human studies did not show a risk for these side effects.[15-18] No statistically significant differences were observed in men and women exposed to SIF during infancy for self-reported pubertal maturation, menstrual and reproductive history, height and weight and current health.[17] Women who had been fed SIF reported slightly longer duration of menstrual bleeding with no difference in severity of menstrual flow.[17] The clinical implication of this finding is unclear.

Giampietro *et al*. did not find a negative effect of SIF on a number of plasma parameters (bone alkaline phosphatase, osteocalcin, 17-beta-estradial, or parathyroid hormone) or urinary levels of bone metabolism markers.[19] In boys, there was no increase in gynaecomastia, hypospadias or feminization.[4,20] Furthermore, girls did not show signs or symptoms of precocious puberty.[20] Breast tissue was more prevalent in the second year of life in infants who received SIF for at least 3 months versus those that were breastfed and those fed dairy-based formula (22.0% vs. 10.3%; P=0.02) with an odds ratio of 2.45 (95% CI 1.11 to 5.39).[21] No differences in breast bud prevalence were observed during the first year of life.[21] Unlike infants on dairy-based formula and/or breastfeeding, infants fed SIF did not demonstrate a decline in the prevalence of breast development during the second year of life.[21]

Phytoestrogens present in SIF impose a preserving effect on breast tissue that has evolved in early infancy, eventually leading to a slower waning of infantile breast tissue.[1] Hugget *et al*. reported that most of the phytoestrogens (mainly genistein and daidzein) present in the plasma of SIF-fed infants are in a conjugated form and, therefore, unable to cause hormonal effects.[22] However, these results are still under debate.

An epidemiologic survey found that the incidence of early fibroid (uterine leiomyomata) diagnosis was associated with factors such as maternal prepregnancy diabetes, low childhood socioeconomic status and high gestational age at birth, but also with SIF consumption.[23] A high intake of soy products by three women was shown to cause reversible effects on reproductive health (infertility, dysmenorrhea, abnormal uterine bleeding, and uterine leiomyomata).[24] One may speculate that such adverse effects may have a more permanent impact in infants because of the critical window of opportunity in reproductive organ development.

Yellayi *et al*. reported that injections of pure genistein in adult mice were associated with reduced immune function.[25] Strom *et al*. showed that there was a higher use of drugs for asthma and allergy in women who were fed soy compared to women who were fed cow's milk formula (P=0.047), but not in men (P=0.08).[17] However, these data should be regarded with caution as they were collected retrospectively after 20 to 34 years. Businco *et al*. showed that the response to polio vaccination in SIF-fed infants was normal.[26] Immune development is considered to be similar in infants fed cow's milk or SIF.[8] Genistein reduces intestinal cell proliferation in vitro and in vivo

in piglets without affecting intestinal enzyme activity or nutrient transport.[27] Soy isoflavones are bioactive within the neonatal intestine and could reduce the severity of rotavirus infections.[28] Isoflavones at concentrations present in SIF were shown to inhibit rotavirus infection in vitro.[28]

After initial reports suggesting a relationship between goiter and soy consumption, an intervention study in young men did not confirm this.[29] Fort *et al.* concluded that the use of SIF was significantly higher in children with autoimmune thyroid disease (prevalence 31%) in comparison to siblings who were not SIF-fed (prevalence 12%; chi-square = 7.22; $P < 0.01$) and healthy, unrelated control children (prevalence 13%, chi-square = 5.03; $P < 0.02$).[30] Soy infant formula was reported to alter thyroid hormone levels and was associated with autoimmune thyroid disease.[30,31] In the absence of iodine, soy isoflavones may have an inhibitory effect on thyroxin synthesis,[32] but modern SIF formulations are iodine-fortified. Nevertheless, infants with congenital hypothyroidism are more difficult to treat if they are fed SIF than if they are fed standard formula.[33] SIF-fed infants with congenital hypothyroidism may need increased levothyroxine doses to achieve normal thyroid function tests.[33]

Modern SIF meets all the nutritional requirements and safety standards of infant formula.[15] Since 2000, SIF fulfilled the European directives and legislation for infant feeding. In a review comparing SIF to cow's milk formula, there was no difference in growth on the infants.[17] Giampietro *et al.* showed that infants who were fed SIF for at least 6 months and subsequently followed up to the age of 8 years had normal bone development.[19]

Indications of soy infant formula

The major differences between SIF and standard infant formula are the protein origin and carbohydrate content. Therefore, indications for the use of SIF are generally related to digestive intolerance to lactose or cow's milk protein. Strict medical indications for SIF are limited to rare conditions, such as galactosemia and hereditary lactase deficiency.

According to the AAP and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), extensively hydrolysed cow's milk-based infant formulas (eHF) are the preferred infant food for the treatment of CMPA.[7,34] The ESPGHAN guideline suggests that soy can be used after the age of 6 months if tolerance has been demonstrated; the AAP guideline does not consider age in its recommendation. Soy is better tolerated in IgE-mediated CMPA.[7,34,35] Anaphylactic reaction to soy in SIF are rare. There are more reports from the literature with regards to severe reactions to soy in adults. Pubmed mentions only one case report of an anaphylactic reaction to SIF in a CMPA CHILD, but the SIF turned out to be contaminated with cow's milk.[36] Soy infant formula is an alternative for treating CMPA, because extensive hydrolysates have a low acceptability due to their bitter taste and are expensive. They are also not widely available.

In infants, lactose malabsorption may be either transient because of slow lactase maturation, or secondary to another disease causing (partial) atrophy of the small bowel villi. The infant formula industry is able to make lactose-free cow's milk-based formulas. The use of SIF after failure of realimentation following infectious gastroenteritis is controversial. The ESPGHAN and AAP guidelines recommend standard, lactose-containing, infant formula for realimentation. However, some literature suggests that lactose-free feeding during realimentation after acute gastroenteritis is better tolerated than lactose-containing formula. Therefore, lactose-free formula is recommended after failure of lactose-containing formula.[7] Although SIF is used in some infants who present with crying, fussiness and increased intestinal gas production, there is limited evidence to support such practice. Nor are there any indications to recommend SIF for the prevention CMPA, to treat colic, or to supplement breastfeeding. The incidence of allergy to soy or cow's milk proteins is comparable, affecting 2 - 5% of infants.

Conclusions

Soy-based infant formula has been adapted to the nutritional needs of infants and soy formula-fed infants have normal growth and development. Reproductive and developmental toxicities of isoflavones have been reported in animals, and some effects on the development of sexual organs in infants have been

reported, as well. The medical indications for soy are very limited, but SIF is also used for economic and philosophical reasons. Opinions differ regarding the use of SIF in the treatment of infants with CMPA. Allergy to soy occurs in roughly 10% of infants with CMPA. To date, epidemiological findings on SIF are insufficient to provide evidence-based data on the occurrence and/or incidence of adverse events. Soy infant formula remains an option in the feeding of full term infants if breastfeeding is not possible and if cow's milk formula is not tolerated.

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