Soy-Based Formulae and Infant Growth and Development: A Review

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ABSTRACT Soy-based infant formulae, initially developed for infants who were lactose intolerant or allergic to cow's milk–based formulae, now account for >25% of the infant formulae sold in the United States. Formulations have changed over the years to improve digestibility, the stability and availability of minerals, and protein quality. Recent concerns have been raised regarding the phytoestrogenic isoflavone content of soy-based formulae. A systematic review of the literature was conducted to evaluate various measures of infant health and development in clinical studies comparing modern soy-based formulae with other diets and to document areas in which further research seems warranted. Results suggest that modern soy-based formulae support normal growth and nutritional status in healthy term infants in y 1 of life. However, there are very limited data on sexual and reproductive development or outcomes such as immune function, visual acuity/cognitive development and thyroid function. Available data do not provide evidence of meaningful differences in timing of maturation, sexual development or fertility in adolescents or adults. Nonetheless, given evidence suggesting that early exposure to soy and/or isoflavones might have long-term effects, further research following infants fed soy-based formulae into adulthood is warranted.


KEY WORDS: infant nutrition, child development, soy, isoflavones, phytoestrogens

Soy-based infant formulae (SBF) have been used for >60 y (1,2). Initially developed for infants unable to tolerate the proteins in cow's milk–based formulae (CMF), SBF are now used more widely and account for ~25% of infant formulae sold in the United States (2,3). In this review, we evaluate human studies on the adequacy of modern SBF for supporting healthy growth and development of term infants, in comparison to more traditional CMF. Because the high concentration of phytoestrogenic isoflavones in soy formulae has led to speculation about possible endocrine effects in recent scientific literature (4,5), we also examine literature on sexual/reproductive outcomes.

In evaluating SBF, it is important to take into account the modifications that occurred over the years. During the 1970s, soy flours were replaced with highly refined soy protein isolates (SPI), and methionine fortification became standard (6,7). Levels of phytoestrogens in SPI are lower than those in soy flours (8). In the late 1980s, phytate content was reduced, and the stability of mineral suspension improved, resulting in substantially enhanced absorption of important micronutrients (1,9,10). Modern SBF continue to be fortified with concentrations of minerals higher than those in most CMF (1,3). This review focuses on studies comparing “modern” SBF with CMF and human milk (HM). However, in viewing longer-term endocrine effects for which data on modern SBF are lacking, findings from studies based on early formulations are presented.

MATERIALS AND METHODS

MEDLINE and ISI searches were conducted using the terms soy, soybean, soy-based formula and soy protein. The terms phytoestrogen, isoflavone, daidzein and genistein were used to find references on possible endocrine effects. These terms were combined with the following: infant, child, growth, development, puberty, thelarche, reproductive, sexual and immune. Citations were scanned to identify additional papers. For short-term outcomes, we present results of studies using modern SBF only. With the exception of bone mineral content (BMC), however, studies using early SBF had similar results. Before reformulation of the suspension, lower BMC was reported in SBF- vs. CMF-fed infants (11). Generalization of results to preterm, small-for-gestational-age and low-birth-weight infants is not possible because early studies (e.g., 12,13) used the old formulation and studies using modern SBF have been conducted exclusively with healthy term infants. Because long-term follow-up of modern SBF is not yet possible, studies of early SBF were reviewed to assess adolescent and adult outcomes. Follow-up studies on chloride-deficient soy formulas were excluded because of this known and subsequently replenished deficiency.

RESULTS

Nutritional status. Tables 1 and 2 summarize published studies evaluating modern SBF on growth and nutritional status (9,10,14–17). The majority were clinical trials (n = 5) in which formula type, but not HM feeding, was randomized. Studies were generally ≥1 y in duration, with exclusive SBF feeding from 0 to 4 mo. Sample sizes were generally small, but in most studies, the results were supported by comparisons of means and tests of significant difference.

Each of these studies reported comparable growth among infants fed SBF vs. CMF or HM. Infants fed SBF had energy or fluid intake volumes similar to those fed CMF. Markers such as serum albumin and blood urea nitrogen suggested no differences in protein metabolism in children fed SBF vs. CMF (9,14,16).
**TABLE 1**

Design of studies on soy-based infant formula (SBF) and infant growth and nutrition: 1988–present

<table>
<thead>
<tr>
<th>Reference/location year</th>
<th>Type of feeding</th>
<th>Duration SBF only SBF supplemented</th>
<th>Time of measurement</th>
<th>Attrition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(17)/U.S. 1994</td>
<td>SBF: Isomil</td>
<td>0–4 mo</td>
<td>mo 4</td>
<td>15%</td>
<td>OTH: SBF + cholesterol.</td>
</tr>
<tr>
<td></td>
<td>CMF: Pronutra</td>
<td>0–4 mo</td>
<td>mo 3</td>
<td>41%</td>
<td>SBF: Isomil.</td>
</tr>
<tr>
<td>(14)/Italy 1994</td>
<td>SBF: Isomil</td>
<td>5–6 mo</td>
<td>mo 6</td>
<td></td>
<td>Sample: infants with family history of IgE-mediated disease.</td>
</tr>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(16)/U.S. 1999</td>
<td>i) SBF</td>
<td>0–3 mo</td>
<td>mo 1, 2</td>
<td>20%</td>
<td>SBF: Isomil; ii) Multisoy; iii) MF.</td>
</tr>
<tr>
<td></td>
<td>ii) CMF</td>
<td>4–12 mo</td>
<td>mo 4, 6, 7, 12</td>
<td></td>
<td>Sample: private practice.</td>
</tr>
<tr>
<td>(15)/U.S. 1993</td>
<td>SBF: Isomil</td>
<td>0–13 mo</td>
<td>mo 2, 4, 6, 13</td>
<td>33%</td>
<td>SBF: Isomil; ii) MF.</td>
</tr>
<tr>
<td>(10)/U.S. 1992</td>
<td>SBF: Isomil</td>
<td>0–3 mo</td>
<td>mo 2</td>
<td>Not reported</td>
<td>SBF: Isomil.</td>
</tr>
<tr>
<td>(8)/U.S. 1988</td>
<td>SBF: Prosobee</td>
<td>4–12 mo</td>
<td>mo 2</td>
<td></td>
<td>HM: supplemented with vitamin D.</td>
</tr>
</tbody>
</table>

# Other outcomes

Data concerning other outcomes are limited, but largely suggest that modern SBF support healthy development. Two recent studies reported that SBF were not associated with poor visual acuity in infancy (20,21), despite lower levels of docosahexaenoic acid than breast-fed infants. Early studies (not shown) also reported that SBF-fed infants had normal or advanced cognitive development compared with CMF-fed infants. Supplementation of SBF with iodide in the 1960s is thought to have eliminated the risk of hypothyroidism (22). Two trials of modern formulae (9,10) reported similar levels of parathyroid hormone in infants fed SBF compared with other diets.

Limited evidence suggests that immune function in infancy is normal in SBF-fed infants. Impaired antibody responses to standard immunizations in infants consuming SBF diets has not been seen (23). However, young adults fed early SBF or CMF as infants tended to be more frequent users of asthma or allergy drugs than those fed CMF (18). A recent 5-year follow-up to a trial in infants with a family history of atopy found both conventional SBF and CMF to be associated with a higher incidence of asthma and eczema than in those fed HM or a modified CMF (24).

**DISCUSSION**

As detailed in Table 1, a substantial literature suggests that modern SBF adequately support a wide range of growth and...
nutritional status outcomes in healthy term infants. Data come primarily from clinical trials with randomized assignment of formulae and exclusive formula feeding for 3–4 mo; all have reported comparable nutritional outcomes in SBF- and CMF-fed infants through y 1 of life. Additionally, one recent long-term study found comparable growth in adults who followed these feeding regimens in infancy (18). Previous reviews of SBF adequacy reached similar conclusions (1), but did not present data to facilitate systematic comparisons across studies.

The evidence available on sexual/reproductive outcomes associated with SBF-feeding in humans is extremely limited. At this time, there are only two published reports (18,19), and it is not possible to draw strong conclusions. The absence of reports describing abnormal developments such as breast buds or menstrual cycle length (27,28). It has been shown that infants absorb and excrete soy isoflavones, but it is not known to what extent they are able to metabolize and deconjugate these compounds to biologically active forms (2,25,29,30). Interestingly, although concentrations of daidzein and genistein, the major isoflavones in soy, were higher in SBF-fed than in CMF-fed infants, researchers have reported relatively higher levels of endogenous estradiol in the first months of life, it is unknown whether the net hormonal effect of soy isoflavone exposure in infants might be estrogenic, antiestrogenic or neutral (2).

Earlier reviews on possible sexual/reproductive effects of SBF isoflavones have described high circulating levels of isoflavone metabolites in infants [e.g., (25)]. Infants exclusively fed soy-based diets are exposed to high concentrations of isoflavones relative to their body weight (25,26). Although human metabolism of soy isoflavones is not well understood, there is evidence that these compounds are biologically active in adult women, and may influence reproductive hormone levels and menstrual cycle length (27,28). It has been shown that infants absorb and excrete soy isoflavones, but it is not known to what extent they are able to metabolize and deconjugate these compounds to biologically active forms (2,25,29,30). Interestingly, although concentrations of daidzein and genistein, the major isoflavones in soy, were higher in SBF-fed than in CMF-fed infants, researchers have reported relatively higher levels of endogenous estradiol in the first months of life, it is unknown whether the net hormonal effect of soy isoflavone exposure in infants might be estrogenic, antiestrogenic or neutral (2).

In vitro and animal data, including studies of nonsoy phytoestrogens such as coumestans, have led to speculation that isoflavones may adversely affect developmental processes influenced by sex steroids, with potential consequences perhaps manifested only in puberty or adulthood (4). However, extrapolation across species may be inappropriate because of known

TABLE 2

Results of studies on soy-based infant formula (SBF) and infant growth and nutrition: 1988—present1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Growth length</th>
<th>Weight</th>
<th>Head</th>
<th>Other</th>
<th>Total intakes energy</th>
<th>Vol.</th>
<th>BMC status2</th>
<th>Nutrient</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials (17)</td>
<td>&lt;=</td>
<td>&lt;=</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;=</td>
<td>—</td>
<td>TC, LDL, HDL</td>
<td>Size at birth: groups similar. Growth: attained at mo 4. Lipids: LDL lower in SBF; HDL similar all groups.</td>
</tr>
<tr>
<td>(14)</td>
<td>&lt;=</td>
<td>&lt;=</td>
<td>&lt;=</td>
<td>BMI</td>
<td>—</td>
<td>—</td>
<td>&lt;=</td>
<td>Hb, EAA, Glu, transferrin, blood urea nitrogen, Ca, P, AP, TC</td>
<td>Size at birth: groups similar. Growth: rates similar, but SBF Z-scores slightly ↓. Lipids: TG lower in SBF. Protein: measures higher in formula-fed vs. HM.</td>
</tr>
<tr>
<td>(16)</td>
<td>&lt;=</td>
<td>&lt;=</td>
<td>&lt;=</td>
<td>—</td>
<td>—</td>
<td>&lt;=</td>
<td>—</td>
<td>albumin, Hb</td>
<td>Size at birth: groups similar. Tolerance: better in SBF (based on vomiting, stools).</td>
</tr>
<tr>
<td>(15)</td>
<td>&lt;=3</td>
<td>&lt;=3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;=</td>
<td>—</td>
<td>Serum Ca, P, Mg, AP, ↑ 1,25(OH)2D</td>
<td>Size at birth: groups similar. Growth: rates similar. SBF ↑ length through 26 wk, but similar at 52 wk. Ca: Elevated 1,25(OH)2D in SBF suggests Ca less bioavailable vs. HM.</td>
</tr>
<tr>
<td>(10)</td>
<td>&lt;=</td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>—</td>
<td>Ca, Mg, P, AP, PTH</td>
<td>Size at birth: groups similar. Tolerance: similar all groups.</td>
</tr>
<tr>
<td>Observational (9)</td>
<td>↑ 3</td>
<td>↑ 3</td>
<td>↑ 3</td>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>—</td>
<td>Albumin, vitamin D, PTH and Mg; urine Ca, P, 1,25(OH)2D</td>
<td>Size at birth: groups similar. Growth: rates similar. Ca: elevated 1,25(OH)2D in SBF suggests Ca less bioavailable vs. HM. P: AP low vs. HM but does not suggest deficiency.</td>
</tr>
</tbody>
</table>

1 Abbreviations: EAA, essential amino acids; AP, alkaline phosphatase; BMC, bone mineral content; BMI, body mass index; Ca, calcium; CMF, cow’s milk based formula; Glu, glucose; Hb, hemoglobin; HM, human milk; Mg, magnesium; 1,25(OH)2D, 1,25 dihydroxy vitamin D (calcitriol); P, phosphorus; PTH, parathyroid hormone; TC, total cholesterol; TG, triglycerides.

2 Blood chemistry unless otherwise noted.

3 Data not shown in paper; descriptions abstracted from text.
differences in metabolism, as well as in developmental norms (2). Furthermore, results of animal studies on possible sexual/reproductive effects of soy isoflavones have been inconsistent, indicating substantial variation within and across species, and differing also by dose and timing of exposure (2).

The possibility of beneficial effects of early-life consumption of soy foods for long-term outcomes such as breast cancer requires further study. Favorable effects have been suggested by experiments in rats (31–32) and by observational data from one study (33) that showed a protective relative risk of 0.5 (P < 0.05) for the highest vs. lowest quintile of soy food intake during adolescence.

Retrospective studies of younger cohorts fed modern formulae may be the only practical approach for further investigating long-term reproductive/sexual development. Careful measurement of potential confounders such as exposure to soy foods in childhood, adolescence and fetal development is critical because these exposures may be correlated with formula choice. Additionally, future studies should control for factors such as maternal age, education and family history of breast cancer, which may have influenced feeding choices and may be related to breast cancer risk (34).

Modern SBF appear to be adequate for normal growth and measures of nutritional status in early life. Although the data from the more rigorously controlled study (18) suggested no adverse effects of SBF on reproductive development and function in young adults, this area deserves further research. Studies of neurological development in individuals who consumed modern SBF are lacking, but a limited number of studies with early SBF suggested normal development. Studies of thyroid function after consumption of modern SBF are very limited, but also suggest no adverse effects. The data concerning immune function in SBF-fed infants are mixed. However, because SBF are often used for infants with allergies to cow's milk, further studies in this area should be randomized clinical trials. Although modern SBF have only been in use since the mid- to late 1980s, early SBF have been rather commonly used since the 1960s, without clinically obvious adverse effects.

The data concerning immune function, thyroid function and neurological development are very limited and should be confirmed in clinical trials. Given the evidence that soy isoflavones are biologically active in women, additional research in the area of reproductive development and function is warranted and observational studies seem appropriate.

LITERATURE CITED


