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FPIN's Clinical Inquiries

Effects of Soy Protein-Based Formula in Full-Term Infants

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Clinical Question

Are there long-term detrimental effects of soy protein-based formula in full-term infants?

Evidence-Based Answer

There are no significant long-term detrimental effects associated with the use of currently available, commercially produced, isolated soy protein-based formula in full-term infants. (Strength of Recommendation: B, based primarily on cohort studies). The number of well-controlled, long-term studies is limited.

Evidence Summary

Isolated soy protein-based formulas represent approximately 25 percent of the market share of infant formulas sold in the United States. They are approved by the U.S. Food and Drug Administration (FDA) to give to full-term infants. Since the first modern use of soy protein-based formula in 1909, changes have been made to improve safety and nutritional effectiveness. In 1976, the American Academy of Pediatrics (AAP) Committee on Nutrition established content specifications for soy protein-based formulas; those on the market today meet current requirements for vitamins, minerals, and electrolyte content.¹

No large randomized controlled trials were found that evaluated potential long-term detrimental effects of soy protein-based formula. Current recommendations are based on extrapolation from limited data and observational studies. A search found studies with samples ranging in size from five to 811 participants. Several potential adverse effects have been evaluated (Table 1).²⁻⁸

Table 1. Adverse Effects of Soy Protein-Based Formula

| Outcome studied | Findings | Study design |
|---|-------------------------------|--|
| Bone mineralization ² | No detrimental effects | Prospective cohort |
| Calcium phosphate deficiency ^{2,3} | No detrimental effects | Structured review; prospective cohort |
| Cognitive development ³ | No detrimental effects | Structured review |
| Dysmenorrhea ⁴ | Slight increase in pain score | Historical cohort |
| Growth ³ | No detrimental effects | Structured review |
| Immune cell populations ⁵ | No detrimental effects | RCT |
| Menstrual duration ⁴ | Slight increase in duration | Historical cohort |
| Nutritional status ^{3,6} | No detrimental effects | Structured review; systematic review of RCTs |
| Protein metabolism ³ | No detrimental effects | Structured review |
| Response to vaccines ⁷ | No detrimental effects | RCT |
| Sensitization allergy ^{6,8} | No detrimental effects | RCT; systematic review of RCTs |
| Thyroid effects ³ | No detrimental effects | Structured review |
| Visual acuity ³ | No detrimental effects | Structured review |

RCT = randomized controlled trial.

Information from references 2 through 8.

The Center for the Evaluation of Risks to Human Reproduction selected soy protein-based formula for further evaluation because of public concern about possible health effects.⁹ This joint program of the Centers for Disease Control and Prevention, the FDA, and the National Institutes of Health evaluates agents of public health concern by developing and applying tools of modern toxicology and molecular biology. For this evaluation, a 14-member panel of government and nongovernment scientists from diverse disciplines (including family medicine, pediatrics, neonatology, toxicology, and other basic sciences) were selected to evaluate the data. The panel reviewed 229 studies, including 38 studies on the effects of soy protein-based formulas on human health, provided by an unspecified search methodology. Using a consensus approach, the expert panel concluded that the human studies were of limited utility in evaluating possible adverse effects of soy formula on reproduction and development because of poor study design, lack of experimental detail, or small sample size. Although no long-term detrimental effects to growth or sexual maturation were identified, the panel failed to issue a conclusive recommendation because of the lack of quality data.⁹

We identified only one study that specifically addressed the long-term effects of soy protein-based formula. It was a historical cohort study of adults who were 20 to 34 years of age and had previously participated in a controlled feeding study from 1965 to 1978 (248 participants received soy protein-based formula, and 563 received cow's milk). There was no association between exposure to soy protein-based formula and general health or reproductive outcomes. There was a correlation between receiving soy protein-based formula as an infant and an

increased duration of menstrual bleeding later in life (adjusted mean difference, 0.37 days; 95% confidence interval [CI], 0.06 to 0.68; P = .02). Greater menstrual discomfort (unadjusted relative risk for extreme discomfort versus no or mild pain, 1.77; 95% CI, 1.04 to 3.00; P = .04) was also reported.⁴ Several confounding variables were not controlled for in the original feeding study, including the use of older soy protein-based formulations, which limits the applicability of the findings to current formulas.⁴

Recommendations from Others

The American Academy of Family Physicians (AAFP) and the AAP recommend the use of breast milk exclusively for at least the first six months of life.^{1,10} The AAP recommends that, for full-term infants whose nutritional needs are not being met from maternal breast milk or cow milk-based formulas, soy protein-based formula is a safe and effective alternative.¹ The AAFP has no current policy recommendation regarding the use of soy protein-based formula.

Clinical Commentary

Parents often consult physicians regarding how best to feed their infants. These decisions can be complicated by many factors, including nutritional information, bonding, convenience, and advice from others. Although it is helpful to know that no detrimental effects were associated with soy protein-based formula compared with cow milk-based formula, no information comparing it with breast milk was included. Because breastfeeding is the preferred infant feeding method for the first six months of life and because it has shown clear benefits over any type of formula feeding, this comparison is vital when counseling parents.

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Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).

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