Soy Infant and Extensively Hydrolyzed Formula as Therapeutic Formula for Cow's Milk Protein Allergy

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ABSTRACT

Cow's milk protein allergy (CMPA) is a food allergy mostly suffered by children aged < 3 years that can be mediated by IgE or non-IgE or both. The prevalence of CMPA in children is heterogeneous between populations. Meta-analysis study showed that the prevalence was 2-3% in infants and < 1% in children aged < 6 years. Although the prevalence is quite small but proper management is very important because it affects the quality of life of children and to avoid the risk of anaphylactic reaction that threatens life. Therapy for CMPA is to avoid cow's milk protein and its derivatives; it is also recommended for breast-feeding mothers to do the same. Therapeutic milk formulas that can be given is extensively hydrolyzed formula (eHF) or soy infant formula (SIF). The selection of formula became adebate, especially about the safety, effectiveness and cost.

Keywords: *cow milk protein allergy, soy infant formula, extensively hydrolyzed formula*

ABSTRAK

Alergi susu sapi (ASS) merupakan alergi makanan yang paling banyak diderita oleh anak dibawah usia 3 tahun yang dapat diperantarai oleh IgE atau Non-IgE atau keduanya. Prevalensi ASS pada anak-anak bervariasi di berbagai populasi. Penelitian meta-analisis menunjukkan prevalensi sebesar 2-3% pada bayi dan < 1% pada anak dibawah usia 6 tahun. Meskipun memiliki prevalensi yang cukup kecil, tatalaksana yang tepat sangat penting karena mempengaruhi kualitas hidup anak dan menghindari resiko reaksi anafilaktik yang mengancam nyawa. Terapi untuk ASS adalah menghindari protein susu sapi dan semua produk turunannya. Ibu menyusui juga direkomendasikan untuk melakukan hal yang sama. Susu formula terapeutik yang dapat diberikan adalah susu soya dan susu terhidrolisis ekstensif. Pemilihan formula menjadi pembahasan terutama tentang keamanan, efektivitas dan biaya.

Kata kunci*: alergi susu sapi, susu soya, susu terhidrolisis ekstensif*

INTRODUCTION

Food allergy is defined as adverse effects on health because of the specific immune response induced by food.[1] Cow milk protein allergy is the most common food allergies suffered by children aged < 3 years.[2,3] Cow milk protein allergy in children can be mediated by IgE or non-IgE or both. One study reported 60% of cases mediated by IgE.[4]

Cow milk protein allergy (CMPA)in children have a heterogeneous prevalence between populations. Meta-analysis studies in Europe show a prevalence of 2-3% in infants and < 1% in children aged < 6 years.[2,3,5,6] Other studies showed that CMPA in infants were 0.3-7.5 % with 82% symptoms appeared in the first 4 months of life.[7-11] One cohort study reported CMPA prevalence was 2.2-2.8% in children aged 1 year and the same ratio was found in a larger study with 18-34

month follow up.[5,11,12] Study in Israel reported that the incidence of CMPA in infants were 0.5 % and 0.6% in children aged 3 years old, with higher prevalence found in boys compared to girls.[13,14]

Natural tolerance of CMPA can occur in children. Intolerance may occur by 15% in the first year, 22-28% in the second year, 51% in the third year, 55-67% in the fourth year and can reach 78% in sixth year.[9,15] Even in a study conducted in different populations, the tolerance rates were found to be higher.[16] CMPA has wide range of symptoms from gastrointestinal, skin to respiratory symptoms.[17] Symptoms that arise due to this allergy range from mild to severe and even life-threatening reactions, such as anaphylaxis reaction that might compromise respiratory and cardiovascular system.[17] Cow's milk is the third most common food that can cause anaphylactic reactions after peanuts and tree nuts; 10-19% of anaphylaxis cases which occur due to food are caused by cow's milk.[18] Despite the low prevalence and natural tolerance thatoccur concurrently with the increased age, the risk of severe life-threatening anaphylaxis arestillpresent.[17-21] There has been a lot of debate on therapeutic formula feeding recommendations in CMPA children that have been used as therapy. The debate are about the time of administration, safety issue, and cost.

COW'S MILK PROTEIN ALLERGY: DIAGNOSIS AND MANAGEMENT

Management of cow's milk protein allergy (CMPA) consists of diagnosis and therapy in children with CMPA. Diagnosis can be performed in children by dietary elimination of cow's milk protein, standardized oral challenge test, IgE specific test, skin test, and patch test. The gold standard for diagnosing CMPA is standardized oral challenge test. Although gold standard is available, it is still difficult to diagnose CMPA. Many clinicians diagnose CMPA based on the signs and symptoms[17, 21]

Therapy in children with CMPA is to avoid the allergens which is cow's milk protein. In breastfed children it is recommended that the mothers also avoid the consumption of cow's milk protein and its derivatives. In children with milk formula we can give therapeutic formula which are extensively hydrolyzed formula (eHF), amino acid formula (AAF), or soya infant formula (SIF) with isolated soy-based protein.[17,21] Each formula has its own indications, advantages and disadvantages.[17,21] There are much debate going on about the administration of SIF and eHF in children with CMPA. The debate are about safety of SIF, cost and palatability of eHF, and the effectiveness comparability between the two of them.[12,21-23]

FORMULA RECOMMENDATION ON CHILDREN WITH CMPA

Soy allergies in children are less common than CMPA.[24] Although more rare, 10-14% of children with CMPA arealso allergic to soy.[21,25,26] Studies by Klemola et al showed that adverse reactions to soy was more often to be found in children with cow milk allergy on age less than 6 months but after followed for 2 years soy sensitization was not higher than children with eHF.[25]

Prospective study in healthy infants comparing breastmilk, cow's milk formula and SIF by Halpern reported allergic response 0.5 % to soy and 1.8% to cow's milk.[27] This study was also consistent with study by Fomon who found < 1% of adverse effects in infants given SIF.[28] National survey in the US reported that the incidence of CMPA is 3.4% and soy allergies are 1.1%.[29] There are two double-blind studies with placebo controls reported soy allergy by 5% and 4%.[30,31] Even recent study showed that 64/66 children with IgE-mediated CMPA could tolerate soy. A double-blind clinical study with placebo control by Zeigler was also consistent with the finding; 86% of infants with IgE-mediated CMPA weretolerant to soy.[13,26]

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guideline considering the transition to SIF in infants after the age of 6 months due to an allergic reaction in children with CMPA to soy is more often to be found in children aged < 6 month.[17,21] American Academy of Pediatrics (AAP) states SIF administration can be given to children with CMPA and mature infants.[17,21] SIF administration are proven not beneficial in the prevention of atopic disease in healthy infants or high risk infants.[17,21-23] AAP does not recommend SIF in CMPA children with enteropathy or cow's milk protein-induced enterocolitis because 30-64% infants with cow's milk protein-induced enterocolitis also experienced enterocolitis induced by soy.[17,21,32-34] Enterocolitis cases induced by cow's milk and SIF reported from a preliminary study conducted on 76 subjects were 58% and 47% respectively. This condition may become tolerance by 60% in cow's milk and 20% in SIF with the majority of patients tolerant in age 3-4 years.[35] AAP also recommends that amino acids formula can be considered as the first line in the

case of severe signs and symptoms such as enterocolitis with hypoproteinemia and failure to thrive or severe anaphylatic cases.[17,21]

Adverse reactions of SIF administration are enteropathy, enterocolitis, proctitis, injury to the small intestine villi, malabsorption, hypoalbuminemia and failure to thrive. These adverse reactions have been found in at least 4 studies.[36-39] Signs of enterocolitis can be found in the form of bloody diarrhea, ulceration, histology feature of inflammatory bowel disease (IBD) acute or chronic. This is expected because theinjured intestinal mucosa due to cow's milk increases the uptake of soy protein in the gut, thus enhancing the immunological response to soy antigen. Eosinophilic proctitismay also befound in children who receive SIF.[33,40-43]

Soya infant formula is a rational choice for mature infants if breastfeeding is not possible and intolerance to cow's milk is present. Another indications of SIF are galactosemia, hereditary lactase deficiency and conditions that require vegetarian diet.[17,21] Education and good communication can convince caregivers that colic usually disappears spontaneously at the age of 4-6 months. Colic is not an indication of SIF administration although some reports stated that it may reduce colic complaints.[44-46]

In children with age less than 12 months, eHF with casein and whey base are well tolerated.[17,21,47]eHF is defined as formula containing peptide with a molecular weight < 3000 Da, which does not trigger allergic reactions in 90% of cases of children with CMPA.[21,47] However, there are some children who need amino acid formula (10%) because theycannot tolerate eHF.[48] Formula feeding in children with CMPA should consider several things, such as the potential for allergies, formula composition, cost, children tolerance, and clinical data that show the effectiveness of formula.[17] In case of CMPA with severe signs and symptoms, AAF can be considered as the first line, while in mild to moderate CMPA, eHF is preferable than SIF. In case the children cannot tolerate eHF, SIF is a rational and safe choice.

SOY INFANT FORMULA: INDICATION AND SAFETY ISSUES

Soy infants formula (SIF) administration is often debated because although it does not contain cow's milk protein, 10-14% children allergy to cow's milk are also allergic to soy, and enterocolitis due to soy also occur in 30-64% CMPA children with cow's milk protein-induced enterocolitis.[21,25,26,32-34] This condition often become clinician's consideration when giving SIF because despite the low prevalence of soy allergy, there remains a possibility of severe anaphylaxis risk that can be life threatening. Recommendation from the AAP and EPSGHAN state that SIF is a rational choice and can be justified in CMPA children.[17,21]

Current SIF is based on isolated soy protein and is different from 100 years ago soy formula with soy flour as based protein. Currently SIF contains different fiber, phytate, digestibility, protease inhibitors and proteins than the old one. SIF is easily digestible and contain high amino acid content fortified with L-methionine, L-carnitine and taurine. High content of phytate is overcome with zinc and iron fortification as well as increased levels of calcium and phosphor; phytate may cause impaired absorption of minerals. The content of protease inhibitors have also been reduced up to 90%. Existing deficiencies in the old soy formula is improved in modern SIF.[22]

SIF showed no significant difference when compared to cow's milk formula and breast milk with parameters such as body length, weight and head circumference.[22,49] However, children with breast milk have cognitive development that isslightly better than those with formula milk.[49]Another study also found no differences in bone mineralization between breast milk and SIF with cow's milk formula.[21,50-53]It is also stated that SIF correlation with sexual development, thyroid disease, immune function, as well as high levels of aluminum is not a safety issue.[21]Current study cannot prove that SIF cause hypothyroidism in children with euthyroid conditions, disorders of sexual development also has not been proven, aluminum levels in infant formula though high but still within the limits allowed by Food and Agriculture Organization of the United Nation (FAO) and World Health Organization (WHO). U.S. Food and Drug Agency (FDA) also stated that SIF is safe.Soya infants formula should not be given to premature infants or infants with impaired renal function.[21,22]

The correlation between SIF and hypothyroidism was studied by Messina et al. The study analyzed many other studies that examined the relationship between the effects of soy or isoflavones on thyroid function of healthy subjects. This study found no effect or only a very limited effect. This study examined 8 studies with women as sample, 4 studies with men as sample and 2 studies with both as sample.[54] AAP states that in children with congenital hypothyroidism, they require levothyroxine dose enhancement due to phytate that

inhibit the absorption of thyroxine.[55,56] Nevertheless, in the case of euthyroid the thyroid hormone deficiency was not found in subjects who consumed soy.[21,54]

Sexual development and hormonal disorders often become safety issues on SIF administration that cause many studies trying to prove the correlation between high isoflavone in SIF and its active metabolite in blood.[21,22] Isofavone is phytoestrogens that hypothetically may cause disruption of sexual development and disorders of hormonal development in infant. Isoflavones are found in the umbilical blood of infants in a study that proved isoflavones could pass through the placental barrier. Further study also found that isoflavone levels in infants who receive soy were hundreds of times higher than children who did not. This study also suggested that high levels of soy could not be linked to whether the activity of the isoflavones in the body of the infant were also high. This is because high levels and bioactivity are two different things.[57-60]

Many studies in animals and mice claimed that soy was significantly proven to affect sexual development in mice. Study reported that the metabolism of isoflavones in the blood in the form of genistein, daidzein and glycitein in animals, especially rodents were very different compared to metabolism in humans.[61] The active metabolite in humans or non-conjugated isoflavones in adults and infants is < 1% in a stable condition and < 2% at peaks.[61] This is incontrast to mice that were proven to be 20-150 higher than that of human adults and infants. The study concluded that the metabolism of isoflavones in humans and animals did not show any correlation and thus, it was concluded that soy interference with sexual development and hormonal should not be drawn from the study in animal especially rodent.[61] Although at 2010 one study reported a possible association between uterine fibroids and SIF with a risk ratio of 1.25 but when calculated with a confidence interval, the risk ratio were 0.97-1.61 so the risk ratio was not significant.[62]

There were two randomized controlled clinical studies and one cohort study that examined the correlations between immune function, the risk of respiratory infections and gastrointestinal tract to SIF administration. These studies stated that SIF, breast milk and cow's milk formula did not differ significantly with parameter such as B lymphocytes, T lymphocytes, IgA, IgG and IgM from poliovirus, diphtheria or Haemophilus influenzae. Episodes of respiratory tract infections and acute diarrhea were also similar.[63-66] This study was also supported by the AAP, SIF does not interfere with oral immunization of polio vaccine.[21] Current study has not or cannot prove SIF associated immune system disorders in children.[21,22] Recent years study found that modern SIF administration was not significantly different to the other milk with parameter such as growth, calcium levels, hemoglobin levels and protein concentration.[21,22]

EXTENSIVELY HYDROLYZED FORMULA: INDICATION AND SAFETY ISSUES

Extensively hydrolyzed formula (eHF) is defined as formula containing peptides with a molecular weight < 3000 Da. There are 2 eHF bases: whey protein and casein protein. These protein are proved to be safe and tolerable in 90% of CMPA children with 95% confidence interval.[21,47] Studies in 2013 stated that eHF was beneficial to prevent atopy diseases and CMPA in children aged 4-6 months who did not get exclusive breastfeeding.[23]

Administration of eHF is only slightly better than partial hydrolyed formula, however no conclusive result on this matter.[23] Study by Vandenplas et al found that eHF meaningfully and significantly reduce the symptoms of CMPA.[67] This study examined eHF in children suspected with CMPA that test positive or negative from standardized oral challenge. Symptom score reduction was found in both groups with the largest score decline in CMPA confirmed children.[67]

Hydrolyzed formula are proven to prevent atopy diseases and CMPA in children,but further studies are still needed.[23,68-70] It is also shown to reduce symptoms and the largest score declines is in CMPA confirmed children.[67] This shows that eHF is also a rational choice for CMPA children.[17,21-23] The cost of eHF is also an important problem as it is not cost effective when compared with other formula milk.[17,21] Cost is a problem, particularly in developing countries so the sustainability could not be achieved.

CONCLUSION

The debate about the safety issue on SIF ranging from levels of aluminium, phytate, corellation of isoflavone and sexual development disorders, bone mineralization, immune system, endocrine and infection. Many studies showing contradictory results in this regard, but recent studies showed that all of these were not proven and inconclusive. In regard to this, the administration of SIF is safe and cost effective for mature CMPA children if the children cannot tolerate eHF. However giving therapeutic formula

without indication cannot be easily justified. In the end, therapeutic formula feeding in children should take the tolerance of child, potential allergies and costs into account.

REFERENCES

1. NIAD-Sponsored Expert Panel Report, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID sponsored expert panel. J Allergy Clin Immunol 2010;126:S1–58.
2. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol 2011;127:594–602.
3. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007;120:638–46.
4. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. J Allergy Clin Immunol 1999; 103(5 Pt 1):717–28.
5. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. Allergy 1990;45:587–96.
6. Host A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/ intolerance and atopic diseases in childhood. Pediatr Allergy Immunol 2002;13(suppl 15):23–8.
7. ESPGAN Working Group. Diagnostic criteria for food allergy with predominantly intestinal symptoms. J Pediatr Gastroenterol Nutr 1992;14:108–12.
8. Bock SA. Prospective appraisal of complaints of adverse reaction to foods in children during the first 3 years of life. Pediatrics 1987;79:683–8.
9. Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. J Pediatr 1990;116:862–7.
10. Gerrard JW, McKenzie JW, Golubott N, Garzon JZ, Maningan CS. Cow's milk allergy: prevalence and manifestations in an unselected series of newborns. Acta Paediatr Scand 1973;234:1.
11. Schrander JJ, van den Bogart JP, Forget PP, Schrander-Stumpel CT, Kuijten RH, Kester AD, et al. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. Eur J Pediatr 1993;152:640–4.
12. Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, Kuitunen P, Lope L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. J Allergy Clin Immunol 1999;104:457–61.
13. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol 2010;126:77–82.e1.
14. Iacono G, Carroccio A, Montalto G, Cavataio F, Bragion E, Lorello D, et al. Severe infantile colic and food intolerance: a long-term prospective study. J Pediatr Gastroenterol Nutr 1991;12:332–5.
15. Host A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. Pediatr Allergy Immunol 1994;5(suppl 5):1–36.
16. Schrander JJ, Oudsen S, Forget PP. Follow up study of cow's milk protein intolerant infants. Eur J Pediatr 1992;151:783–5.
17. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr 2012;55: 221–9.
18. Colver AF, Nevantaus H, Macdougall CF, Cant AJ. Severe food-allergic reactions in children across the UK and Ireland, 1998–2000. Acta Paediatr 2005;94:689–95.
19. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. J Allergy Clin Immunol 2007;119:1016–8.
20. Uguz A, Lack G, Pumphrey R, Ewan P, Warner J, Dick J, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. Clin Exp Allergy 2005;35:746–50.
21. Bhatia J, Greer F. Use of soy protein-based formulae in infant feeding. Pediatrics 2008;121:1062–8.
22. Vandenplas Y, Castrellon PG, Rivas R, Gutierrez CJ, Garcia LD, Jimenez JE, et al. Systematic review with meta-analysis: safety of soya-based infant formulas in children. Br J Nutr 2014;111:1340-60.
23. Fleischer DM, Spergel JM, Assaad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol 2013;1:29-36.
24. Bruno G, Giampietro PG, Del Guercio MJ, Gallia P, Giovannini L, Lovati C, et al. Soy allergy is not common in atopic children: a multicenter study. Pediatr Allergy Immunol 1997; 8:190–3.
25. Klemola T, Vanto T, Juntunen-Backman K, Kalimo K, Korpela R, Varjonen E. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. J Pediatr 2002; 140:219–24.
26. Zeiger RS, Sampson HA, Bock SA, Burks AW Jr, Harden K, Noone S, et al. Soy allergy in infant and children with IgE-associated cow's milk allergy. J Pediatr 1999;134:614–22.
27. Halpern SR, Sellars WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of childhood allergy in infants fed breast, soy, or cow milk. J Allergy Clin Immunol1973;51:139–51.
28. Fomon SJ. Introduction to section IV.. Food intolerance in infancy: allergology, immunology, and gastroenterology. In: Hamburger RN, eds. Carnation Nutrition Education Series. 1st ed. New York: Raven Press 1989:I.p.201
29. Johnstone DE, Roghmann KJ. Recommendations for soy infant ormula: a review of the literature and a survey of pediatric allergists. Pediatr Asthma Allergy Immunol 1993;7:77–88.
30. Sampson HA. Jerome Glaser lectureship. The role of food allergy and mediator release in atopic dermatitis. J Allergy Clin Immunol 1988;81:635–45.
31. Businco L, Bruno G, Giampietro PG, Cantani A. Allergenicity and nutritional adequacy of soy protein formulas. J Pediatr1992;121(5 pt 2):S21–S28.
32. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. Pediatrics 2003;111(4 pt 1):829–35.
33. Powell GK. Milk- and soy-induced enterocolitis of infancy: clinical features and standardization of challenge. J Pediatr 1978;93:553–60.

34. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features o food protein-induced enterocolitis syndrome. J Pediatr 1998;133: 214–9.
35. Jarvinen KM, Sickles L, Nowak-Wegrzyn A. Clinical characteristics of children with food protein-induced Enterocolitis (FPIES). J Allergy Clin Immunol 2010;125:AB85.
36. Ament ME, Rubin CE. Soy protein: another cause of the flat intestinal lesion. Gastroenterology 1972;62:227–34.
37. Perkkio M, Savilahti E, Kuitunen P. Morphometric and immunohistochemical study of jejunal biopsies from children with intestinal soy allergy. Eur J Pediatr 1981;137:63–9.
38. Poley JR, Kein AW. Scanning electron microscopy of soy protein-induced damage of small bowel mucosa in infants. J Pediatr Gastroenterol Nutr 1983;2:271–87.
39. Iyngkaran N, Yadov M, Looi LM, Boey CG, Lam KL, Balabaskaran S, et al. Effect of soy protein on the small bowel mucosa of young infants recovering fromacute gastroenteritis. J Pediatr Gastroenterol Nutr 1988;7:68–75
40. Cook CD. Probable gastrointestinal reaction to soybean. N Engl J Med 1960;263:1076–7.
41. Halpin TC, Byrne WJ, Ament ME. Colitis, persistent diarrhea, and soy protein intolerance. J Pediatr 1977;91:404–7.
42. McDonald PJ, Goldblum RM, Van Sickle GJ, Powell GK. Food protein-induced enterocolitis: altered antibody response to ingested antigen. Pediatr Res 1984;18:751–5.
43. Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. Arch Dis Child 1984;59:326–9.
44. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. Pediatrics 1982;70:7–10.
45. Thomas DW, McGilligan K, Eisenberg LD, Lieberman HM, Rissman EM. Infantile colic and type of milk feeding. Am J Dis Child 1987;141:451–3.
46. Taubman B. Parental counseling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomized trail. Pediatrics 1988;81:756–61.
47. Greer F, Sicherer S , Burks A. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183.
48. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulae. Pediatrics 2000;106:346–9.
49. Andres A, Cleves MA, Bellando J, Pivik R, Casey P, Badger T. Developmental status of 1-year-old infants fed breast milk, cow's milk formula, or soy formula. Pediatrics 2012;129;1134-40.
50. Hillman LS, Chow W, Salmons SS, Weaver E, Erickson M, Hansen J. Vitamin D metabolism, mineral homeostasis, and bone mineralization in term infants fed human milk, cow milk-based formula, or soy-based formula. J Pediatr 1988;112:864–74.
51. Mimouni F, Campaigne B, Neylan M, Tsang RC. Bone mineralization in the first year of life in infants fed human milk, cow-milk formula or soy-based formula. J Pediatr 1993;122:348–54
52. Venkataraman PS, Luhar H, Neylan MJ. Bone mineral metabolism in full-term infants fed human milk, cow milk-based, and soy-based formulas. Am J Dis Child 1992;146:1302–5.
53. Andres A, Casey PH, Cleves MA, Badger TM. Body fat and bone mineral content of infants fed breast milk, cow's milk formula or soy formula during the first year of life. J Pediatr 2013;163:49–54.
54. Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid 2006;16:249–58.
55. Conrad SC, Chiu H, Silverman BL. Soy formula complicates management of congenital hypothyroidism. Arch Dis Child 2004;89:37–40.
56. Chorazy PA, Himelhoch S, Hopwood NJ, Greger NG, Postellon DC. Persistent hypothyroidism in an infant receiving a soy formula: case report and review of the literature. Pediatrics 1995;96(1 pt 1):148–50.
57. Adlercreutz H, Yamada T, Wahala K, Watanabe K. Maternal and neonatal phytoestrogens in Japanese women during birth. Am J Obstet Gynecol 1999;180(3 pt 1):737–43.
58. Cao Y, Calafat AM, Doerge DR, Umbach DM, Bernbaum DC, Twaddle NC, et al. Isoflavones in urine, saliva and blood of infants: data from a pilot study on the estrogenic activity of soy formula. J Expo Sci Environ Epidemiol 2009;19:223–34.
59. Son HY, Nishikawa A, Ikeda T, Imazawa T, Kimura S, Hirose M. Lack of effect of soy isoflavone on thyroid hyperplasia in rats receiving an iodine-deficient diet. Jpn J Cancer Res 2001;92:103–8.
60. Dinsdale E, Ward W. Early exposure to soy isoflavones and effects on reproductive health: a review of human and animal studies. Nutrients 2010;2:1156-87.
61. Setchell K, Brown N, Zhao X, Lindley S, Heubi J, King E, et al. Soy isoflavone phase II metabolism differs between rodents and humans: implications for the effect on breast cancer risk. Am J Clin Nutr 2011;94:1284–94.
62. D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the sister study. Environ Health Perspect 2010;118:375–81.
63. Zoppi G, Gasparini R, Mantovanelli F, Gobio-Casali L, Astolfi R, Crovari P. Diet and antibody response to vaccinations in healthy infants. Lancet 1983;2:11–4.
64. Businco L, Bruno G, Grandolfo ME, Nofello F, Fiore L, Amato C, et al. Response to poliovirus immunization and type of feeding in babies of atopic families. Pediatr Allergy Immunol 1990;1:60–3.
65. Ostrom KM, Cordle CT, Schaller JP, Winship TR, Thomas DJ, Jacobs JR, et al. Immune status of infants fed soy-based formulas with or without added nucleotides for 1 year: part 1: vaccine responses and morbidity. J Pediatr Gastroenterol Nutr 2002;34:137–44.
66. Cordle CT, Winship TR, Schaller JP, Thomas DJ, Buck RH, Ostrom KM, et al. Immune status of infants fed soy-based formulas with or without added nucleotides for one year: part 2: immune cell populations. J Pediatr Gastroenterol Nutr 2002;34:145–53.
67. Vandenplas Y, Greef E, ALLAR study group. Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy. Acta Paediatr 2014;103:e243-50.
68. von Berg A, Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533-40.
69. von Berg A, Koletzko S, Filipiak-Pittroff B, Laubereau B, Grubl A, Wichmann HE, et al. Certain hydrolyzed formulas

reduce the incidence of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. J Allergy Clin Immunol 2007;119:718-25.

70. von Berg A, Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I, et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). J Allergy Clin Immunol 2008;121:1442-7.

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