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Soy formula for prevention of allergy and food intolerance in infants (Review)

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[Intervention Review]

Soy formula for prevention of allergy and food intolerance in infants

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ABSTRACT

Background

Allergies and food reactions in infants and children are common and may be associated with a variety of foods including adapted cow's milk formula. Soy based formulas have been used to treat infants with allergy or food intolerance. However, it is unclear whether they can help prevent allergy and food intolerance in infants without clinical evidence of allergy or food intolerance.

Objectives

To determine the effect of feeding adapted soy formula compared to human milk, cow's milk formula or a hydrolysed protein formula on preventing allergy or food intolerance in infants without clinical evidence of allergy or food intolerance.

Search methods

The standard search strategy of the Cochrane Neonatal Review Group was used. Updated searches were performed of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE (1966 - March 2006), EMBASE (1980 - March 2006), CINAHL (1982 - March 2006) and previous reviews including cross references.

Selection criteria

Randomised and quasi-randomised trials that compare the use of an adapted soy formula to human milk, an adapted cow's milk or a hydrolysed protein formula for feeding infants without clinical allergy or food intolerance in the first six months of life. Only trials with > 80% follow up of participants and reported in group of assignment were eligible for inclusion.

Data collection and analysis

Eligibility of studies for inclusion, methodological quality and data extraction were assessed independently by each review author. Primary outcomes included clinical allergy, specific allergies and food intolerance. Where no heterogeneity of treatment effect was found, the fixed effect model was used for meta-analysis. Where significant or apparent heterogeneity was found, results were reported using the random effects model and potential causes of the heterogeneity were sought.

Main results

Three eligible studies enrolling high risk infants with a history of allergy in a first degree relative were included. No eligible study enrolled infants fed human milk. No study examined the effect of early, short term soy formula feeding. All compared prolonged soy formula to cow's milk formula feeding. One study was of adequate methodology and without unbalanced allergy preventing co-interventions in treatment groups. One study with unclear allocation concealment and 19.5% losses reported a significant reduction in infant allergy, asthma and allergic rhinitis. However, no other study reported any significant benefits from the use of a soy formula. Meta-analysis found no significant difference in childhood allergy incidence (2 studies; typical RR 0.73, 95% CI 0.37, 1.44). No significant difference was reported in one study

in infant asthma (RR 1.10, 95% CI 0.86, 1.40), infant eczema (RR 1.20, 95% CI 0.95, 1.52), childhood eczema prevalence (RR 1.10, 95% CI 0.73, 1.68), infant rhinitis (RR 0.94, 95% CI 0.76, 1.16) or childhood rhinitis prevalence (RR 1.20, 95% CI 0.73, 2.00). Meta-analysis found no significant difference in childhood asthma incidence (3 studies, 728 infants; typical RR 0.71, 95% CI 0.26, 1.92), childhood eczema incidence (2 studies, 283 infants; typical RR 1.57, 95% CI 0.90, 2.75) or childhood rhinitis incidence (2 studies, 283 infants; typical RR 0.69, 95% CI 0.06, 8.00). One study reported no significant difference in infant CMPI (RR 1.09, 95% CI 0.45, 2.62), infant CMA (RR 1.09, 95% CI 0.24, 4.86), childhood soy protein allergy incidence (RR 3.26, 95% CI 0.36, 29.17) and urticaria. No study compared soy formula to hydrolysed protein formula.

Authors' conclusions

Feeding with a soy formula cannot be recommended for prevention of allergy or food intolerance in infants at high risk of allergy or food intolerance. Further research may be warranted to determine the role of soy formulas for prevention of allergy or food intolerance in infants unable to be breast fed with a strong family history of allergy or cow's milk protein intolerance.

PLAIN LANGUAGE SUMMARY

Soy formula for prevention of allergy and food intolerance in infants

When babies are not exclusively breastfed, evidence suggests that using a soy formula instead of a cow's milk formula does not reduce allergies in infants and children. Infant formulas have been designed to try to lower the chances of developing allergy or food intolerance. These formulas include hydrolysed cow's milk and soy formulas. A review of trials found that in infants at high risk of allergy who are unable to completely breastfeed, there is no reduction in allergies in later infancy and childhood associated with feeding soy formula compared to a cow's milk formula. No eligible studies were found that compared a soy with a hydrolysed protein formula.

BACKGROUND

Allergy, which affects over 20% of people, is a specific reaction to a normally harmless substance (allergen) characterised by a specific IgE response. Common allergies include allergic rhinitis or hay fever, asthma, eczema or atopic dermatitis and food allergies. Food allergies are less prevalent, with cow's milk allergy (CMA) documented in 1.8% of children compared with 0.5% of children allergic to soy protein (Halpern 1973). Allergy to multiple foods occurs, with 10 - 14% of children with CMA reported as allergic to soy (Bock 1990; Zeiger 1999). In contrast, food intolerance, which affects 2 - 3% of infants, does not imply a specific mechanism, but is a reproducible adverse reaction to a specific food or food ingredient (Host 1995). The manifestations of food intolerance are multiple, with gastrointestinal manifestations including enterocolitis being common. Cow's milk protein intolerance (CMPI) is the most common (Jakobsson 1979), but sensitisation to other foods including soy protein is also frequent (Burks 1994). Many infants with food intolerance become tolerant over time, with the risk of persisting intolerance increased with evidence of atopy (Host 1995; Carroccio 2000).

An increased duration of exclusive breast feeding has been associated with a reduced incidence of allergy (Gruskay 1982; Oddy 1999; Saarinen 1995; Saarinen 2000), although not all studies support this association (Wright 2001; Sears 2002). Despite this potential benefit, many infants are not exclusively breast fed (UNICEF 2001). Consequently, these infants receive either short or long term supplementary or sole feeding with an infant formula (usually adapted cow's milk or soy milk) or are weaned from the breast to a formula. Therefore, many infants are exposed to cow's milk or soy formula early in life resulting in an increased risk of allergy or food intolerance. Formulas prescribed to infants with the intention of preventing allergy and food intolerance include hydrolysed cow's milk, elemental formulas, and adapted soy or hydrolysed soy formulas. One rationale for using soy formulas is the assumption that soy protein is less antigenic than cow's milk protein (Cantani 1997). This rationale has been questioned (ACP 1998), as soy protein may also cause allergic disease and some infants with CMA are also allergic to soy protein (Hill 1984; Bock 1990; Host 1995; Zeiger 1999). Current soy formulas are thought to provide adequate nutrition and support adequate growth (AAP 1998; Cantani 1997; Churella 1994; Lasekan 1999).

A diagnosis of allergy and food intolerance may be made either by questionnaire or clinician assessment, and may be confirmed by specific skin or serological testing or by allergen elimination/challenge. The diagnostic criteria for different atopic conditions and food reactions are not uniform and the mode of ascertainment of atopy is variable. The aim of this review was to determine the role of adapted soy infant formulas for prevention of allergy and food intolerance in infants. A secondary aim was to determine if there are any other important benefits or harms in terms of infant growth and development from using adapted soy formulas. This review does not include treatment of infants with clinically recognised allergy or food intolerance.

OBJECTIVES

The objective of this review was to determine the effect of an adapted soy formula for infant feeding on allergy and food intolerance in infants and children. A secondary objective was to determine if there are any other important benefits or harms of

adapted soy formulas regarding infant growth and development. Individual comparisons will be made between infants fed adapted soy formulas versus infants fed with breast milk, adapted cow's milk formula or a hydrolysed protein formula. Planned subgroup analyses included:

- Infants who are term, or preterm
- Infants at low, or high risk of allergy or food intolerance

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised trials that compare the use of an adapted soy formula to human milk, an adapted cow's milk or a hydrolysed formula. Only trials with > 80% follow up of participants and reported in group of assignment (intention to treat) were eligible for inclusion. Cross-over trials were not eligible.

Types of participants

Infants in the first six months of life without clinical evidence of allergy or food intolerance.

Types of interventions

Adapted soy formula compared to a control group fed either:

- Breast milk;
- Adapted cow's milk formula;
- Hydrolysed infant formula.

Adapted soy formula may be used in infants for either:

- Early short term supplementation or sole feeding with an infant formula;
- Prolonged supplementation of breast fed infants, sole formula feeding in the first months of life, or weaning from the breast using infant formula.

The following separate comparisons were intended:

1. Soy formula versus human milk for:

- Early short term infant feeding;
- Prolonged sole or supplemental infant feeding.

2. Soy formula versus cow's milk formula for:

- Early short term infant feeding;
- Prolonged sole or supplemental infant feeding.

3. Soy formula versus hydrolysed formula for:

- Early short term infant feeding;
- Prolonged sole or supplemental infant feeding.

Within each of the above comparisons, the following subgroup analyses were prespecified:

1. According to infant risk of allergy or food intolerance:

- Low risk infants (no family history allergy or food intolerance in 1st degree relatives);

- High risk infants (family history allergy or food intolerance in 1st degree relatives or high cord IgE level).

2. According to method of ascertainment of allergy:

- Allergy / food intolerance confirmed by test;
- Blinded measurement for allergy or food intolerance.

3. According to extent of protein hydrolysis of hydrolysed formula:

- Soy formula versus extensively hydrolysed formula;
- Soy formula versus partially hydrolysed formula.

Types of outcome measures

Primary outcomes:

- All allergy including asthma, atopic dermatitis, allergic rhinitis or food allergy
- Food intolerance

Individual analyses were performed to determine what type of food intolerance or allergy is prevented including:

- Asthma
- Atopic dermatitis
- Allergic rhinitis
- Cow's milk or soy protein intolerance
- Food allergy
- Urticaria
- Anaphylaxis

Allergy and food intolerance was sought at the latest time it was documented with adequate follow up in each trial. This included disease that was documented in infants, later childhood and adulthood where available.

The following definitions of age of allergy were used:

- Infant allergy cumulative incidence: allergy occurring from birth up to two years of age
- Childhood allergy cumulative incidence: allergy occurring from birth up to 10 years of age (or up to age of latest report between two and 10 years)
- Childhood allergy period prevalence: allergy reported that was present between two and 10 years of age
- Adolescent allergy: allergy present from 10 to 18 years of age
- Adult allergy: allergy present after 18 years age of age.

Secondary outcomes:

- Growth parameters including head circumference and weight gain as defined by author. This included growth and nutritional status whilst receiving formula, and long term effects
- Cost, including incremental cost analysis or cost effectiveness analysis of using a soy formula versus breast or use of a cow's milk formula for prevention of food intolerance and allergy

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. The initial electronic search included searches of the The Cochrane Central Register of Controlled Trials (CENTRAL,

The Cochrane Library, Issue 4, 2003), MEDLINE (1966 - January 2004), EMBASE (1980 - January 2004) and CINAHL (1982 - December 2003). Additionally, references in studies identified as potentially relevant and references in previous reviews and guidelines were searched.

The search was updated March 2006 with additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE (1966 - March 2006), EMBASE (1980 - March 2006) and CINAHL (1982 - March 2006) and previous reviews including cross references (all articles referenced), previous reviews including cross references, abstracts, conferences (Pediatric Academic Societies 2003-2005 and Perinatal Society of Australia and New Zealand 2004-2005).

The search strategy involved the following keywords, using the search fields of abstract, MeSH subject heading, exploded subject heading, publication type, subject heading word, text word, and title. A search on all fields for [infan* OR newborn* OR neonat* OR pediatric* OR paediatric*] AND [feed* OR food OR formula* OR soy* OR allergies OR diet* OR protein OR milk*] was conducted, limited by the following terms: [random* OR trial* OR comparative study OR controlled study]. No language restrictions were used.

Data collection and analysis

This review updates a previous version ([Osborn 2004](#)).

Eligibility of studies for inclusion were assessed independently by each review author. The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the trials included were evaluated in terms of allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised individuals. Each review author extracted the data separately, data were then compared and differences resolved by consensus. The standard methods of the Neonatal Review Group were used to synthesise the data. Effects were expressed as relative risk (RR), risk difference (RD) and number needed to treat (NNT), with 95% confidence intervals (CI) for categorical data, mean difference (MD) or weighted mean difference (WMD) and 95% CI for continuous data where appropriate. The heterogeneity test was used to help guide advisability about pooling data from different trials. Where no heterogeneity of treatment effect was found the fixed effect model was used for meta-analysis. Where significant or apparent heterogeneity was found, results were reported using the random effects model and potential causes of the heterogeneity sought in terms of methodological quality, types of infants enrolled, use of co-interventions or treatment comparison made. As this review examined the use of a soy formula for long term prevention of food intolerance and atopy, crossover trials where all infants receive both treatments were not eligible for inclusion. Studies with other allergy prevention co-interventions were included in the initial analyses. Where these allergy preventing co-interventions were unbalanced (i.e. applied to the treatment but not the control group), then the studies were excluded from subsequent analyses.

Subgroup analyses were intended according to:

1. Infant risk of allergy or food intolerance: low risk infants (no family history allergy or food intolerance in 1st degree relatives); high risk infants (family history allergy or food intolerance in 1st degree relatives or high cord blood IgE level).

2. Method of ascertainment of allergy or food intolerance: allergy / food intolerance confirmed by test = clinical allergy confirmed by challenge testing or testing for atopy (e.g. skin testing or serological testing for specific IgE, asthma confirmed by testing for presence of bronchial hyperresponsiveness and food intolerance confirmed by elimination/challenge). Included in this definition is clinical allergy in a patient where atopy has been confirmed by testing (e.g. asthma where atopy has been confirmed by skin prick testing or RAST for specific IgE); blinded measurement for allergy or food intolerance - where measurement of outcome blinded to treatment allocation (this analysis was not prespecified).

3. Extent of protein hydrolysis: Soy formula versus extensively hydrolysed formula; and Soy formula versus partially hydrolysed formula. An extensively hydrolysed formula should meet the definition provided by the AAP Committee on Nutrition (AAP 2000) - the extensively hydrolysed proteins derived from cow's milk in which most of the nitrogen is in the form of free amino acids and peptides ≤ 1500 kDaltons, and should, at a minimum, ensure with 95% confidence that 90% of infants with documented CMA will not react with defined symptoms to the formula under double-blind, placebo-controlled conditions.

Sensitivity analysis was performed for studies of adequate methodology defined as adequate randomisation and allocation concealment, and $< 10\%$ losses to follow up.

RESULTS

Description of studies

Three studies (Johnstone 1966; Kjellman 1979; Miskelly 1988) met criteria for inclusion in the review (see 'characteristics of included studies'). Twenty-five studies or reports were excluded (see 'characteristics of excluded studies'). The size of the included studies was generally small with Johnstone 1966 enrolling 292 infants, Kjellman 1979 50 infants and Miskelly 1988 533 infants.

Types of infants: all included studies enrolled newborn infants who were at 'high risk' of allergy on the basis of a family history of allergy in a first degree relative. One study enrolled infants whose mothers elected not to breast feed (Johnstone 1966). Kjellman 1979 enrolled breast fed infants who were allocated to formula when weaned and Miskelly 1988 randomised infants to breast feeding with supplemental formula if required or to a 'normal' diet.

Types of interventions: All studies compared use of an adapted soy formula to an adapted cow's milk formula. Co-interventions: Kjellman 1979 reported dietary and environmental co-interventions in both soy formula and cow's milk formula groups. Two studies reported differential co-interventions in the soy formula group including additional maternal dietary (Miskelly 1988) and infant dietary allergen avoidance advice (Johnstone 1966; Miskelly 1988). Individual studies: Johnstone 1966 randomised infants to a soy formula or a control group fed an evaporated cow's milk formula for the first nine months. The infants fed soy milk had dietary advice to avoid cow's milk, egg and wheat containing foods for at least nine months. Kjellman 1979 randomised infants being weaned from breast feeding to a soy milk or cow's milk formula till nine months of age. Co-interventions were reported in both groups including dietary allergen and environmental allergen avoidance measures. Miskelly 1988 randomised infants to breast feeding with supplemental

formula when required or to a 'normal' diet. Co-interventions in the supplemental soy formula group included mothers limiting cow's milk intake when pregnant and lactating and infants avoiding cow's milk containing foods for at least four months. Rates of soy formula feeding were not reported. By six months, 61% of the intervention group and 99% of the control group had been exposed to cow's milk.

Types of outcomes: Johnstone 1966 reported allergic disease at the latest time seen ranging from 3 - 10 years age. Infants had unblinded physician assessment for hay fever, asthma and allergic rhinitis. Kjellman 1979 reported allergic disease determined by repeated physician assessment up to four years of age, including asthma, eczema, allergic rhinitis urticaria and gastrointestinal allergy. RAST tests were performed for cow's milk and soy IgE. Miskelly 1988 reported allergy determined by blinded physician assessment and use of diary and questionnaires up to 7 years age including asthma, eczema and allergic rhinitis. Skin prick tests and peak expiratory flow rates also performed.

Commercial sponsorship: Two studies (Kjellman 1979; Miskelly 1988) reported direct or indirect support from companies manufacturing infant formulas.

Risk of bias in included studies

All studies reported a random method of patient allocation, although two studies did not report method of randomisation (Johnstone 1966; Kjellman 1979). The allocation sequence was adequate for two studies (Kjellman 1979; Miskelly 1988) but unclear for one study (Johnstone 1966). Blinding of intervention only was not reported by any study. Blinding of measurement was reported by Miskelly 1988. Johnstone 1966 reported 19.5% losses at the end of the follow up period, Kjellman 1979 reported 4% losses at four years and Miskelly 1988 reported 9% losses at one year and 16% at seven years. Two studies included differential (unbalanced) co-interventions (Johnstone 1966; Miskelly 1988) and were not considered for subsequent analyses. One study did not have differential co-interventions and was considered of adequate methodology with random method of patient allocation, adequate allocation concealment and $< 10\%$ losses to follow up (Kjellman 1979).

Effects of interventions

COMPARISONS 1-2: SOY FORMULA VERSUS HUMAN MILK

No eligible studies were found that compared use of a soy formula with human milk feeding, either for early short term or prolonged infant feeding.

COMPARISON 3: EARLY SHORT TERM FEEDING: SOY FORMULA VERSUS COW'S MILK FORMULA

No eligible studies were found that compared early short term feeding with a soy formula compared to a cow's milk formula.

COMPARISON 4: PROLONGED FEEDING: SOY FORMULA VERSUS COW'S MILK FORMULA - ALL STUDIES

Outcome 04.01: All allergy

Three studies (Johnstone 1966; Kjellman 1979; Miskelly 1988) compared prolonged infant feeding with a soy formula compared to a cow's milk formula in the first months of life. No study reported infant allergy. Two studies (Johnstone 1966; Kjellman 1979) enrolling a total of 283 infants reported childhood allergy cumulative incidence. Johnstone 1966 reported a significant

reduction in childhood allergy cumulative incidence diagnosed between 3-10 years of age (RR 0.37, 95% CI 0.24, 0.56). The chi-square test for heterogeneity found significant ($p < 0.00001$) and substantial ($I^2 = 94.9\%$) heterogeneity between the studies. Meta-analysis of the two studies found no significant difference in childhood allergy cumulative incidence (typical RR 0.67, 95% CI 0.18, 2.46). Potential explanations for heterogeneity include differences in intensity of exposure to study formula, allergy preventing co-interventions in some studies and substantial methodological differences between studies.

Outcome 04.02: Asthma

Miskelly 1988 reported no significant difference in infant asthma cumulative incidence (one study: RR 1.10, 95% CI 0.86, 1.40). Johnstone 1966 reported a significant reduction in childhood asthma cumulative incidence (RR 0.34, 95% CI 0.17, 0.68). Meta-analysis (three studies, 728 infants) found no significant difference in childhood asthma cumulative incidence (typical RR 0.71, 95% CI 0.26, 1.92), with significant ($p = 0.02$) and substantial ($I^2 = 73.3\%$) heterogeneity found between the studies (Johnstone 1966; Kjellman 1979; Miskelly 1988).

Outcome 04.03: Eczema

Miskelly 1988 reported no significant difference in infant eczema cumulative incidence (RR 1.20, 95% CI 0.95, 1.52) and childhood eczema period prevalence (RR 1.10, 95% CI 0.73, 1.68). Meta-analysis (two studies, 283 infants) found no significant difference in childhood eczema cumulative incidence (typical RR 1.57, 95% CI 0.90, 2.75).

Outcome 04.04: Allergic rhinitis

Miskelly 1988 reported no significant difference in infant rhinitis cumulative incidence (RR 0.94, 95% CI 0.76, 1.16) or childhood rhinitis cumulative incidence (RR 1.20, 95% CI 0.73, 2.00). Johnstone 1966 reported a significant reduction in childhood allergic rhinitis cumulative incidence (RR 0.21, 95% CI 0.10, 0.43). Meta-analysis (two studies, 283 infants) found no significant difference in childhood rhinitis cumulative incidence (typical RR 0.69, 95% CI 0.06, 8.00), with significant ($p = 0.006$) and substantial ($I^2 = 91.6\%$) heterogeneity found.

Outcome 04.05: CMPI

Kjellman 1979 reported no significant difference in infant CMPI cumulative incidence (RR 1.09, 95% CI 0.45, 2.62).

Outcome 04.06: CMA

Kjellman 1979 reported no significant difference in infant CMA cumulative incidence (RR 1.09, 95% CI 0.24, 4.86).

Outcome 04.07: Soy protein allergy

Kjellman 1979 reported no significant difference in childhood soy protein allergy cumulative incidence (RR 3.26, 95% CI 0.36, 29.17).

Outcome 04.08: Urticaria

Kjellman 1979 reported no significant difference in childhood urticaria cumulative incidence (RR 0.36, 95% CI 0.11, 1.18).

COMPARISON 5: PROLONGED FEEDING: SOY FORMULA VERSUS COW'S MILK FORMULA - STUDIES WITH NO UNBALANCED CO-INTERVENTIONS, ADEQUATE METHODOLOGY

Only Kjellman 1979 compared prolonged soy formula to cow's milk formula feeding with no differential (unbalanced) allergy preventing co-interventions and with adequate methodology.

Outcome 05.01: All allergy

Kjellman 1979 reported no significant difference in childhood allergy cumulative incidence (RR 1.23, 95% CI 0.82, 1.84).

Outcome 05.02: Asthma

Kjellman 1979 reported no significant difference in childhood asthma cumulative incidence (RR 7.58, 95% CI 0.41, 139.32).

Outcome 05.03: Eczema

Kjellman 1979 reported no significant difference in childhood eczema cumulative incidence (RR 1.28, 95% CI 0.73, 2.27).

Outcome 05.04: Allergic rhinitis

Kjellman 1979 reported no significant difference in childhood rhinitis cumulative incidence (RR 2.54, 95% CI 0.74, 8.66).

Outcome 05.05: CMPI

Kjellman 1979 reported no significant difference in infant CMPI cumulative incidence (RR 1.09, 95% CI 0.45, 2.62).

Outcome 05.06: CMA

Kjellman 1979 reported no significant difference in infant CMA cumulative incidence (RR 1.09, 95% CI 0.24, 4.86).

Outcome 05.07: Soy protein allergy

Kjellman 1979 reported no significant difference in childhood soy protein allergy cumulative incidence (RR 3.26, 95% CI 0.36, 29.17).

Outcome 05.08: Urticaria

Kjellman 1979 reported no significant difference in childhood urticaria cumulative incidence (RR 0.36, 95% CI 0.11, 1.18).

Outcome 05.09: Growth

Kjellman 1979 compared soy formula versus cow's milk formula feeding. Weight gain was stated to be normal in both groups with no significant differences between groups, but no data were reported and duration of follow up of weight gain not reported. No other study reported growth parameters.

COMPARISON 06: EARLY SHORT TERM FEEDING: SOY FORMULA VS HYDROLYSED FORMULA

No eligible studies were found that compared early short term feeding with a soy formula compared to a hydrolysed formula.

COMPARISON 07: PROLONGED FEEDING: SOY FORMULA VERSUS HYDROLYSED FORMULA

No eligible studies were found that compared early short term feeding with a soy formula compared to a hydrolysed formula.

COMPARISON 08: PROLONGED FEEDING: SOY FORMULA VERSUS PARTIALLY HYDROLYSED FORMULA

No eligible studies were found that compared prolonged feeding of soy formula with partially hydrolysed formula.

COMPARISON 09: PROLONGED FEEDING: SOY FORMULA VERSUS EXTENSIVELY HYDROLYSED FORMULA

No eligible studies were found that compared prolonged feeding of soy formula versus extensively hydrolysed formula.

SENSITIVITY ANALYSIS

Sensitivity analysis according to methodological quality is documented above.

DISCUSSION

No eligible studies were found comparing soy formula with human milk feeding, or for the early short term use of a soy formula compared to a cow's milk or a hydrolysed formula. In high risk infants receiving prolonged formula feeding, this review found no evidence of benefit from use of a soy formula compared to a cow's milk formula for prevention of allergy or food intolerance. Evidence from one trial of a reduction in childhood cumulative incidence of allergy, asthma and allergic rhinitis was not supported by other trials or the overall meta-analyses. In addition, there are methodological concerns with this trial regarding concealment. This review found no eligible studies comparing use of a soy formula to a hydrolysed protein formula in high risk infants. Studies to date suggest that soy formula cannot be recommended for feeding of high risk infants for the prevention of allergy or food intolerance. This review found no eligible studies that enrolled low risk infants, although this population is even less likely to benefit. No studies reported outcomes beyond 10 years, so no conclusion can be made about the effect of soy formula on adolescent or adult allergy. This review should be viewed in conjunction with the review 'Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants' ([Osborn 2003](#)), which found limited evidence of benefit from use of a hydrolysed protein formula compared to a cow's milk formula for preventing allergy in high risk infants.

Caution should be taken in interpreting the conclusions of this review. In the analysis of soy formula compared to cow's milk formula that included only studies of adequate methodology with no unbalanced co-interventions, only one relatively small study was eligible. All studies reported commercial sponsorship. A beneficial effect from use of soy formula for prevention of allergy or food intolerance cannot be excluded due to the limited power of the included studies, particularly for the prevention of CMPI or CMA. A trend to increased soy protein allergy was reported by one study suggesting a possible mechanism for the development of allergy in infants receiving a soy formula. Given the limited size of included studies, the conclusions of this review may be sensitive to the findings of unpublished studies. Given the limitations to the evidence, where soy formulas are commonly used, further studies of soy formula may be warranted.

AUTHORS' CONCLUSIONS

Implications for practice

Feeding with a soy formula cannot be recommended for prevention of allergy or food intolerance in infants at high risk of allergy or food intolerance.

Implications for research

Further research may still be warranted to determine the role of soy formula for prevention of allergy or food intolerance in infants unable to be breast fed with a strong family history of allergy or cow's milk protein intolerance.

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References to studies included in this review

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Johnstone 1966

Methods	Adequate randomisation: yes, method not reported. Allocation concealment: unclear. Blinding of intervention: no. Blinding of measurement: no. Losses to follow up: yes, 57/292 (19.5%) post allocation losses.
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Johnstone 1966 (Continued)

Participants	Newborn infants with parent or sibling with asthma, eczema or hayfever.
Interventions	1. (n = 115 after losses) Soy formula (brand not reported). 2. (n = 120 after losses) Evaporated cow's milk formula (brand not reported). Permitted whole cow's milk after 5 months. Co-interventions: soy formula group advised to avoid all cow's milk products, egg and wheat containing foods for 1st 9 months. Cow's milk group advised to introduce oats, barley, rice, beef and lamb products as 1st solids. Only 5 infants fed egg or chicken.
Outcomes	Primary outcome(s): allergic diseases in later childhood. Other outcomes: hayfever, asthma and allergic rhinitis up to 10 years (childhood allergy cumulative incidence). Diagnosed by unblinded paediatrician. Definitions: hayfever - seasonal rhinorrhoea and sneezing confirmed by physical examination and scratch or intradermal skin tests. Bronchial asthma - wheezing confirmed by clinical examination and relieved by epinephrine bronchodilator. Perennial allergic rhinitis - nasal congestion outside pollen season with typical symptoms and signs and eosinophils in nasal mucus. Atopic eczema - definition not reported.
Notes	Results as latest time of follow up (up to 10 years) reported as childhood allergy cumulative incidence. Differential co-interventions. Hay fever (seasonal allergic rhinitis) reported separately to perennial allergic rhinitis. No commercial sponsorship reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kjellman 1979

Methods	Adequate randomisation: yes, method not reported. Allocation concealment: yes. Blinding of intervention: no. Blinding of measurement: not reported. Losses to follow up: yes, 2/50 (4%).
Participants	Infants with history on questionnaire of biparental allergy.
Interventions	Breast fed infants weaned to formula. 1. (n = 24) Soy milk formula till 9 months (Sojasemp, Semper, Sweden). 2. (n = 26) Cow's milk formula (brand not reported). Co-interventions in both groups: general advice to avoid fish, egg and strawberries to 9 months; avoid animal material in bedding, thorough vacuum cleaning and no new pets. Mean duration sole breast feeding 1.5 months.
Outcomes	Primary outcome(s): atopic disease and immunoglobulins. Other outcomes: repeated single paediatrician examination up to 4 years (childhood allergy cumulative incidence). Serum IgE and RAST for cow's milk and soy bean IgE. Obvious atopic disease: atopic dermatitis, bronchial asthma, allergic rhinitis, urticaria and gastrointestinal allergy (observed by paediatrician or occurred repeatedly to same food). Probable atopic disease: recurrent or persistent typical symptoms not observed by paediatrician. Possible atopic disease: symptoms or signs in which atopic mechanism cannot be excluded.

Kjellman 1979 (Continued)

Notes Clinical allergy taken as obvious and probable atopic disease.
Financial support form Forerafe Liv, Stockholm, Semper Fund for Nutritional Research.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Miskelly 1988

Methods	Adequate randomisation: antenatally allocated using sealed envelopes randomly assigned by computer. Allocation concealment: yes. Blinding of intervention: no. Blinding of measurement: yes. Losses to follow up: yes, 1 year 46/533 (9%) and 7 years 87/533 (16%) post randomisation exclusions. Unclear as to which group the 46 infants lost before 1 year were initially allocated to.
Participants	Infants with family history of asthma, eczema or hayfever in 1st degree relative.
Interventions	1. (n = 238) Intervention group (cow's milk avoidance): breast fed with supplemental soy formula if required till 6 months (brand not reported). Co-interventions: mothers limited cow's milk intake during pregnancy and lactation. Infants avoided cow's milk foods for at least 4 months. 2. (n = 249) Normal diet. No co-interventions. At 6 months - 99% controls and 61% of intervention group exposed to cow's milk. Incidence of exposure to soy milk not reported but only 33% in intervention group ever breast fed.
Outcomes	Primary outcome(s): allergic disease. Other outcomes: asthma, eczema and allergic rhinitis at 1 year (infant allergy cumulative incidence) and 7 years (childhood allergy cumulative incidence). Skin prick tests at 6 and 12 months. Specific and total IgE on cord blood and at 3 and 12 months. Blinded physician examination for eczema and history taken of any symptoms of allergy. No definitions given. Diary maintained by parents to 6 months. Yearly questionnaire sent from 2-6 years. Blinded physician assessment at 7 years. Skin prick tests and PEFr at 7 years. Definitions of allergy at 7 years: Asthma (diagnosed) - ever had asthma by blinded physician "opinion" (childhood cumulative incidence). Eczema (diagnosed): current eczema and history of eczema in past year (childhood period prevalence). Allergic rhinitis (diagnosis): in previous 12 months (childhood period prevalence).
Notes	Trial of breast feeding with supplemental soy formula (cow's milk avoidance) versus normal diet. Differential co-interventions. Commercial sponsorship: financial support and milk for Wyeth Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arshad 1992a	Used a hydrolysed soy formula (Aptamil HA).
Bellioni 1999	Enrolled infants with proven Ig-E mediated cow's milk allergy. Used goat's milk formula.
Burks 2001	Enrolled infants with diarrhoea.
Businco 1983	Cohort study.
Campbell 1989	Enrolled infants with infantile colic.
Carroccio 1997	Enrolled infants with cow's milk allergy.
Chandra 1989a	Data unable to be verified.
Chandra 1989b	Data unable to be verified.
Cordle 2002	Randomised to soy formulas with and without added nucleotides. Allergy not assessed as outcome.
Giovannini 1994	Excess post allocation losses (56 / 138) and not analysed in group of assignment (solely breast fed infants reported separately).
Gruskay 1982	Excess losses.
Hill 1999	Enrolled infants with multiple food protein intolerance.
Iacono 1998	Enrolled infants (age 11 to 72 months) with chronic constipation.
Klemola 2002	Enrolled infants with cow's milk allergy.
Koo 2003	Randomised to 2 formulas both containing soy oils. Allergy not assessed as outcome.
Lasekan 1999	Randomised to soy formulas with or without added nucleotides of mixed feedings. Allergy not assessed as outcome.
Lilja 1989	Trial of maternal allergen avoidance in pregnancy. Supplemental soy formula given non-randomly to infants as required.
Lothe 1982	Enrolled infants admitted with 'colic'.
Nadasdi 1992	Observational study.
Oggero 1994	Enrolled infants with colic and compared non-allergenic diet (soy or hydrolysed formula) with dicyclomine.
Ostrom 2002	Crossover study. Allergy not assessed as outcome.
Porch 1998	Excess losses.
Rigo 1994a	Method of treatment allocation unclear. Allergy not assessed as outcome.
Taubman 1988	Enrolled infants with excessive crying ('colic').

Study	Reason for exclusion
Zeiger 1999	Observational study of soy formula in infants with cow's milk allergy.

DATA AND ANALYSES

Comparison 4. Prolonged feeding: Soy formula vs cow's milk formula - All studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All allergy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Infant cumulative incidence	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Childhood cumulative incidence	2	283	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.46]
2 Asthma	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Infant cumulative incidence	1	474	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.86, 1.40]
2.2 Childhood period prevalence	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Childhood cumulative incidence	3	729	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.26, 1.92]
3 Eczema	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infant cumulative incidence	1	461	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.95, 1.52]
3.2 Childhood period prevalence	1	446	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.73, 1.68]
3.3 Childhood cumulative incidence	2	283	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.90, 2.75]
4 Allergic rhinitis	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Infant cumulative incidence	1	460	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.16]
4.2 Childhood period prevalence	1	446	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.73, 2.00]
4.3 Childhood cumulative incidence	2	283	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.06, 8.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Cow's milk protein intolerance	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infant cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.45, 2.62]
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infant cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.24, 4.86]
6.2 Childhood period prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Soy protein allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Infant cumulative incidence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Childhood period prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [0.36, 29.17]
8 Urticaria	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.11, 1.18]

Analysis 4.1. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 1 All allergy.

Analysis 4.2. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 2 Asthma.

Analysis 4.3. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 3 Eczema.

Analysis 4.4. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 4 Allergic rhinitis.

Analysis 4.5. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 5 Cow's milk protein intolerance.

Analysis 4.6. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 6 Cow's milk allergy.

Analysis 4.7. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 7 Soy protein allergy.

Analysis 4.8. Comparison 4 Prolonged feeding: Soy formula vs cow's milk formula - All studies, Outcome 8 Urticaria.

Comparison 5. Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methodology

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infant cumulative incidence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.82, 1.84]
2 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Childhood period prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	7.58 [0.41, 139.32]
3 Eczema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infant cumulative incidence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Childhood period prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.73, 2.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Allergic rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [0.74, 8.66]
5 Cow's milk protein intolerance	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infant cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.45, 2.62]
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infant cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.24, 4.86]
6.2 Childhood period prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Soy protein allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Infant cumulative incidence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Childhood period prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [0.36, 29.17]
8 Urticaria	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Childhood cumulative incidence	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.11, 1.18]

Analysis 5.1. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methodology, Outcome 1 All allergy.

Analysis 5.2. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methododology, Outcome 2 Asthma.

Analysis 5.3. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methododology, Outcome 3 Eczema.

Analysis 5.4. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methododology, Outcome 4 Allergic rhinitis.

Analysis 5.5. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methododology, Outcome 5 Cow's milk protein intolerance.

Analysis 5.6. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methododology, Outcome 6 Cow's milk allergy.

Analysis 5.7. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methodology, Outcome 7 Soy protein allergy.

Analysis 5.8. Comparison 5 Prolonged feeding: Soy formula vs cow's milk formula - No-interventions - Adequate methodology, Outcome 8 Urticaria.

WHAT'S NEW

Date	Event	Description
11 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 3, 2004

Date	Event	Description
27 July 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DO wrote the protocol and review and entered data. Both authors independently searched for studies, assessed studies for eligibility, critically appraised studies and extracted the data. In the update, DO entered new or altered data and text. Both reviewers independently updated searches for studies, assessed studies for eligibility, critically appraised studies and extracted the data.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- RPA Newborn Care, Royal Prince Alfred Hospital, Sydney, Australia.

External sources

- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.

NOTES

This is a substantive update of the previously withdrawn version of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula; Food Hypersensitivity [*prevention & control]; Milk Hypersensitivity [etiology]; Randomized Controlled Trials as Topic; Soy Milk [*administration & dosage]

MeSH check words

Humans; Infant