Commentary

Should we continue to counsel families to use hydrolyzed formulas as a means of allergy prevention in high-risk infants?

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Abstract

The prevalence of food allergy in North America is high, and has increased over time. As a result, focus has shifted from treatment to allergy prevention. Previous studies have suggested that hydrolyzed formula may prevent atopic dermatitis in high-risk infants. As a result, multiple international guidelines including the Canadian Paediatric Society (CPS) position statement on allergy prevention recommend the use of hydrolyzed formula as a means of allergy prevention in mothers who are not breastfeeding or using donor breastmilk. However, a recent systematic review has not supported an association between use of hydrolyzed formula and allergy prevention. In addition, studies are emerging supporting the use of early and regular cow's milk formula as a means of cow's milk allergy prevention.

WHY GUIDELINES SUCH AS THE 2013 CPS POSITION STATEMENT RECOMMEND USE OF HYDROLYZED FORMULAS AS A MEANS OF ALLERGY PREVENTION

The prevalence of food allergy in Canada is approximately 7.5% based on self-reported data in a cross-Canada survey (1). The CPS position statement on allergy prevention in high-risk infants from 2013 recommends that there is evidence to support the use of hydrolyzed formula compared to intact cow's milk formula to protect against atopic dermatitis in childhood (2). High-risk infants in this position statement are defined as having a first-degree relative with an allergic condition such as atopic dermatitis, food allergy, asthma, or allergic rhinitis (2).

The CPS recommendation is largely based on results of a large randomized controlled trial on infant feeding, the German Infant Nutritional Intervention (GINI) study, and a Cochrane review (3,4). The GINI study randomized 2,252 newborn infants at high risk for atopic disease at birth to receive one of four formulas as a substitute for breastmilk if necessary: partially hydrolyzed whey formula (pHF-W),

extensively hydrolyzed whey formula (eHF-W), extensively hydrolyzed casein formula (eHF-C), or cow's milk formula. The primary outcome was allergic disease (3). At the 10-year follow-up, GINI found a reduction in the cumulative incidence of allergic disease with hydrolyzed formula with a relative risk of 0.87 (95% confidence interval [CI] 0.77 to 0.99) for pHF-W, 0.94 (95% CI 0.83 to 1.07) for eHF-W and 0.83 (95% CI 0.72 to 0.95) for eHF-C compared with intact cow's milk formula. The relative risk of atopic dermatitis at 10-year follow-up was 0.82 (95% CI 0.68 to 1.00) for pHF-W, 0.91 (95% CI 0.76 to 1.10) for eHF-W and 0.72 (95% CI 0.58 to 0.88) for eHF-C compared with cow's milk formula. The conclusion of the 10-year follow-up GINI study was that both pHF-W and eHF-C have long-term preventative effects on the incidence of atopic dermatitis.

In addition, a Cochrane review on hydrolyzed formulas and allergy prevention published in 2006 concluded that there was 'limited evidence' to support the use of hydrolyzed formulas compared to cow's milk formula in high-risk infants for prevention of both infant/childhood allergy and infant cow's milk allergy (4).

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WHY GUIDELINES ARE BEING CHANGED

In 2016, a systematic review and meta-analysis conducted in the UK on the use of hydrolyzed formula and risk of allergic disease based on 37 intervention trials including 28 randomized controlled trials (over 19,000 participants) was published (5). This meta-analysis found no consistent evidence that partially or extensively hydrolyzed formulas reduced the risk of allergic conditions in high risk infants. The authors explicitly state 'These findings do not support current guidelines that recommend the use of hydrolyzed formula to prevent allergic disease in high risk infants'. In addition, this meta-analysis noted a high degree of publication bias with many of the studies having 'high or unclear risk of bias and evidence of conflict of interest'.

For the outcome of atopic dermatitis in the meta-analysis, although several low-quality studies showed more positive outcomes, results of several randomized controlled trials did not support use of hydrolyzed formula in prevention of atopic dermatitis. There was no significant difference in risk of eczema between extensively hydrolyzed formula and intact cow's milk formula at age 0 to 4 years (odds ratio [OR] 0.84; 95% CI 0.67 to 10.7).

Results of the meta-analysis showed no significant difference in risk of other food allergies with partially or extensively hydrolyzed formula compared to standard cow's milk formula at age 0 to 4 years or extensively hydrolyzed formula at ages 5 to 14 years. There was no significant difference in food allergy to cow's milk, egg, or peanut with standard formula or hydrolyzed formulas (5). There was no significant difference between partially hydrolyzed formula and standard cow's milk formula for recurrent wheeze, or long-term risk of allergic rhinitis (5).

As a result of this meta-analysis, international guidelines about the use of hydrolyzed formula as a means of allergy prevention are changing. For example, the 2017 guideline on infant feeding and allergy prevention by the Australasian Society of Clinical Immunology and Asthma (ASCIA) notes 'no convincing evidence to support a protective role' for hydrolyzed formula in the prevention of atopic conditions in childhood (6).

There are also emerging observational studies suggesting that in fact early regular cow's milk formula ingestion may have a protective role against cow's milk allergy especially in the first few months of life (7–9). A 2010 prospective feeding study of 13,019 infants in Israel noted that early introduction of intact cow's milk formula in the first 14 days of life, and given regularly at least once a day, significantly reduced the risk of oral challenge-confirmed cow's milk allergy (OR of 19.3 for introduction after 14 days of life; $P < 0.001$) (7). A retrospective case-control study in Japan of 51 children with IgE-mediated cow's milk allergy compared to 102 controls and to 32 children with egg allergy noted that delayed (started >1 month after birth) or irregular (<1 /day) exposure to cow's milk formula

was associated with a significantly increased risk of cow's milk allergy with an adjusted odds ratio of 23.74 (95% CI 5.39 to 104.52) (8). A recent analysis of an Australian longitudinal, population-based study of 5276 infants noted that early exposure to cow's milk within the first 3 months of life was associated with a reduced risk of cow's milk allergy (adjusted odds ratio 0.31; 95% CI: 0.10 to 0.91) at a year of age (9). As highlighted in the 2013 CPS statement recommendations, in order to achieve tolerance to highly allergenic foods, they should be consumed several times per week (2).

There have been no randomized trials examining early cow's milk introduction as a means of allergy prevention. It is not clear why cow's milk ingestion is protective so much earlier in life than other allergenic foods such as egg or peanut but cow's milk is the only allergenic solid that could be ingested in early infancy (in the form of formula). In addition, the potential implications of early and regular cow's milk formula introduction on benefits of exclusive breastfeeding require serious consideration except in families who choose not to, or cannot, breastfeed exclusively. A recent review on the impact of earlier solid introduction on the benefits of exclusive breastfeeding found no evidence thus far that earlier solid introduction (between 4 and 6 months of age) would impact the benefits of ongoing breastfeeding during that time, or total breastfeeding duration (10).

CONCLUSION

In summary, a recent large systematic review and meta-analysis conducted in the UK does not support a role for hydrolyzed formula in allergy prevention and noted strong bias in studies supporting this benefit. As a result, guidance is changing to no longer recommend hydrolyzed (partially or extensively) infant formula for the prevention of allergy.

In addition, three recent observational studies suggest that early and regular cow's milk formula introduction may have a role in cow's milk allergy prevention. Based on this evidence, families placing a high value on cow's milk allergy prevention (e.g., due to their infant being at high risk of development of food allergy) may choose to supplement breastfeeding with regular intact cow's milk formula starting in the first few weeks of life. For most infants, however, the CPS position statement recommends exclusive breastfeeding over formula feeding in early infancy due to the numerous other beneficial health effects for mother and infant associated with breastfeeding.

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