March 2009

PEDIATRIC NUTRITION
RESOURCE LINE

INTEGRATIVE MEDICINE REPORT®

Short-term benefits sufficient to promote breast-feeding for all newborns

Jackson K, Nazar A. Breast-feeding, the immune response and long-term health. J Am Osteopath Assoc *2006;106:203-7.*

There are enough short-term benefits from breast-feeding to continue to promote it for all newborn infants, even if it has no proven effect on the development of chronic disease later in life, as several authors concluded after reviewing the literature.

Kelly Jackson, PhD, and Andrea Nazar, DO, West Virginia School of Osteopathic Medicine, Lewisburg, summarized the reported effects of breast-feeding on the infant's immune system and possible consequences of discontinuing breast-feeding prematurely. "Human breast milk contains large quantities of secretory IgA," they confirmed. These antibodies—formed as a consequence of the mother's previous exposure to infectious agents—can bind to potential pathogens in the infant and prevent their attachment to cells. Leukocytes contained in early colostrum also help kill microbial pathogens through the process of phagocytosis. In addition, certain enzymes contribute to the antimicrobial effects of human breast milk, while nucleotides in human milk are known to enhance immune function in infants as well.

Whether or not the immunologic advantages of breast-feeding influence the development of chronic disease later in life is uncertain, but one group of researchers found that at 4 months of age, infants who were exclusively breast-fed had significantly larger thymus glands than partially breast-fed or formula-fed infants. Several studies have shown breast-fed infants develop higher levels of certain antivaccine antibodies compared with formula-fed infants. In contrast, the immunogenicity of a live viral vaccine such as the rotavirus vaccine may be inhibited by high levels of secretory IgA in human breast milk.

It is not clear if breast-feeding decreases an infant's susceptibility to develop autoimmune disorders later in life. However, one meta-analysis suggested that exclusive breast-feeding during the first three months of life did protect children against allergic rhinitis, although not significantly so. Other literature reviews have led researchers to conclude that breast-feeding probably protects infants from atopic allergies. Recent evidence also suggests that it may be protective against the development of insulin-dependent diabetes mellitus, although evidence supporting this association is not conclusive.

"Breast-feeding is well-known to provide immune protection and prevent various diseases in the perinatal period," review authors concluded. Thus, premature cessation of breast-feeding may result in fundamental changes in the immune system, they added, enhancing the risk of infants developing autoimmune disease or hypersensitivity reactions later in life.

Evidence supports the addition of nucleotides to infant formula

Gutiérrez-Castrellón et al. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. Br J Nutr *2007;98:S64-S67.*

There is sufficient evidence to support the addition of nucleotides to infant formula based on a systematic review and meta-analysis of the literature carried out by Mexican researchers.

Dr. Pedro Gutiérrez-Castrellón, Paediatric Health Evidence Analysis Centre, National Institute, Mexico, and colleagues analyzed available evidence to establish the safety, efficacy and dose-response effect of ribonucleotide-supplemented infant formula (RSIF) according to results from randomized clinical trials comparing RSIFs to formula that did not contain nucleotides or to breast milk. "Outcome measures were: antibody titres to common pediatric vaccinations; total lymphocytes, lymphocyte subclasses and NK-cells; and episodes of diarrhea and acute respiratory infection," the authors indicated. Fifteen studies were considered suitable for inclusion in their analysis.

Results of the meta-analysis showed that antibody responses to vaccination against *Haemophilus influenzae*, diphtheria toxin and oral polio vaccine were better when infants received nucleotide-fortified formula compared with infants receiving breast milk or control formula. Infants fed the nucleotide-fortified formula also had fewer episodes of diarrhea than infants fed either breast milk or control formula.

In contrast, there were no differences in rates of acute respiratory infections between infants fed nucleotide-enriched formula and those who received other sources of nutrition. As the authors noted, available evidence suggests that the health benefits of nucleotide-fortified formula begin when formulas are supplemented at a nucleotide dose 1.9 mg/418.4 kJ. Health benefits are maintained or potentially

increased when supplementation is increased to a dose of 10.78 mg/418.4 kJ.

Thus the researchers concluded that the evidence considered for the present analysis supports formulas supplemented with nucleotides at levels of at least 5 mg/418·4 kJ (33 mg/L) but that it was "important to note that 50% of the evidence from studies with formula supplemented with 10.78 mg/418.4 kJ (72 mg/ L) shows considerably greater effects on end point variables."

Rethinking palm olein-containing formulas

Koo WK, Hockman E, Dow M. Palm olein in the fat blend of infant formulas: Effect on the intestinal absorption of calcium and fat and bone mineralization. J Am Coll Nutr *2006;25(2):117-22.*

The use of palm olein (PO) in infant formulas to match human milk content of palmitic acid has unintended physiological consequences and formulas containing PO should be avoided or substituted with formulas containing synthetic triacylglyceride.

Dr. Winston Koo, Wayne State University, Detroit, Michigan, and colleagues evaluated published clinical data on the physiologic effects of using palm oil and its low melting fraction, PO, as a dominant lipid source in the fat blend of infant formulas. Nine publications were identified with non-PO and PO comparison groups. Post-natal ages of the infants included in the studies were from birth to 192 days at study onset.

"Within each published study, there was some variability in the effect size between non-PO and PO groups and standardized results were consistently significantly positive in favour of the feeding with non-PO formulas with respect to increased intestinal fractional absorption of fat, palmitic acid and calcium," the authors reported.

"The overall conclusion from the clinical studies analyzed in this report is that the use of PO to match the content of palmitic acid in infant formulas to that of human milk has unintended physiological consequences and its avoidance or substitution with synthetic triacylglyceride can prevent this detrimental effect," study authors concluded, who added that "understanding the physiological effects of nutrient sources is critical to advances in the development of infant formulas."

Whereas palm olein is a constituent in most infant formulas, it is important to note that Similac does not contain palm olein and thus ensures optimal absorption of fat, palmitic acid and calcium in infants requiring formula feeding.

Table 1. Comparison of Fractional Absorption of Fat, Palmitic Acid, Calcium, Total Body Bone Mineral Content (BMC) and Bone Mineral Density (BMD) Between Infants Fed Different Infant Formulas with Data Standardized to the Infants Fed Formulas with PO

A No PO vs. PO formulas

Reference	Parameter	Effect size
Am J Clin Nutr 1996;64:291-6.	Fat	2.88 (P<0.001)
	Palmitic acid	1.36 (P<0.001)
	Calcium	1.64 (P<0.01)
J Am Coll Nutr 1998;17:327-32.	Fat	1.33 (P<0.01)
	Palmitic acid	0.96 (P<0.05)
	Calcium	1.73 (P<0.01)
J Am Coll Nutr 2002;21:564-9. (Casein hydrolysate-based formulas with/without PO)	Fat	1.82 (P<0.01)
	Calcium	1.32 (P<0.01)
J Am Coll Nutr 2002;21:564-9.(Soy-based formulas with/without PO)	Fat	-0.56 (NS)
	Calcium	1.44 (P<0.05)
Pediatrics 1997;99:E12.	BMC	1.00 (P<0.01)
Pediatrics 2003;111:1017-23.	BMC	0.61 (P=0.003)
	BMD	0.48 (P=0.01)

B Synthetic triacylglyceride vs. PO formulas

Reference	Parameter	Effect size
Arch Dis Child 1997;77:F178-F184.	Palmitic acid	1.65 (P<0.01)
	Calcium	1.43 (NS)
Am J Clin Nutr 1995;61:1037-42.	Fat	0.48 (NS)
	Palmitic acid	1.06 (P<0.01)
	Calcium	0.71 (NS)
J Pediatr Gastroenterol Nutr 1996;23:553-60. (Synthetic triacylglyceride formula with PO formula)	Fat	1.53 (P<0.001)
	Palmitic acid	2.07 (P<0.001)
	Calcium	1.13 (P<0.05)
J Pediatr Gastroenterol Nutr 1996;23:553-60. (Synthetic triacyglyceride formula at 50% of above-mentiond formula with PO formula)	Fat	0.60 (NS)
	Palmitic acid	0.92 (P<0.05)
	Calcium	0.16 (NS)
Am J Clin Nutr 1999;70:920-7.	BMC	0.68 (P=0.02)
	BMD	0.67 (P=0.009)

Adapted from Koo et al. *J Am Coll Nutr* 2006.

Findings linking IDA and neurodevelopmental delay/stroke in infants supportive but not conclusive

85th Annual Meeting of the Canadian Paediatric Society. Victoria, British Columbia, June 24-28, 2008.

Evidence linking iron deficiency anemia (IDA) and neurodevelopmental delay as well as stroke in infants and children is supportive but not conclusive, according to a Toronto-based pediatrician.

Speaking at the 2008 annual meeting of the Canadian Paediatric Society, Dr. Patricia Parkin, Associate Professor of Paediatrics, University of Toronto, Ontario, reviewed research on the neurodevelopmental consequences of IDA as synthesized in two systematic reviews (*J Nutr* 2001;649S, *Cochrane Database of Systematic Reviews* 2001). Seven studies of children under the age of 2 collectively showed that children with IDA at study entry were at a developmental disadvantage at follow-up at ages 4 through to 14. However, socioeconomic variables may not have been adequately controlled in these studies, as Dr. Parkin indicated, which could have influenced their findings.

Five randomized controlled trials evaluated whether short-term iron supplementation benefit children. None demonstrated any treatment benefit, but again, the trials may have been too short to have affected neurodevelopment, as one longer-term randomized trial did show a benefit in children who received iron supplementation.

Some literature has also demonstrated that anemic children do less well on cognition and school achievement and that with treatment, they tended to catch up in cognition but not in school achievement. Several other randomized comparisons between healthy children who were supplemented with iron for six to 18 months and those who were not suggested that supplemented infants enjoyed small but transient benefits, as Dr. Parkin reported.

There is, however, no question that IDA is much less likely to occur in iron-supplemented children compared to those who receive no iron. For example, Lozoff (*Pediatrics* 2003;112:846-54) reported that IDA was seen in only about 3% of healthy infants at 12 months who did not have IDA at six months but who received iron supplementation vs. approximately 22% of infants who did not. No differences were seen in global test scores in this study population but infants who did not receive iron supplementation processed information more slowly, were less likely to interact socially or check their caregivers' reactions than children who received iron.

Dr. Parkin and colleagues also compared 15 children between the ages of 12 and 38 months who had suffered a stroke to 143 children who had not. After controlling for mitigating risk factors, Dr. Parkin and colleagues found that previously healthy children who had had a stroke were 10 times more likely to have IDA than healthy children who had no stroke.

Intrauterine growth restriction, premature birth and early cord clamping, all of which may contribute to low initial stores of iron, can compromise iron status in an infant. Iron stores may also be depleted from prolonged exclusive breast-feeding beyond six months and from use of whole cow's milk, as mammalian milk generally has low concentrations of iron.

Recommendations are for mothers to continue to breast-feed exclusively for the first six months of life, but if mothers are not breast-feeding, pediatricians recommend the use of an iron-fortified formula until 9 to 12 months of age.

"Picky eaters" have lower dietary variety/diversity scores

Carruth et al. The phenomenon of "picky eater": A behavioral marker in eating patterns of toddlers. J Am Coll Nutr *1998;17:180-6.*

Toddlers whose mothers feel they are "picky eaters" have significantly lower dietary variety and diversity scores than toddlers who are not picky eaters. Somewhat surprisingly, however, nutrient intake among picky eaters was not significantly different from that of non-picky eaters.

Registered dietitian Betty Ruth Carruth, PhD, University of Tennessee, Knoxville, and colleagues interviewed 74 Caucasian mothers of upper socioeconomic status and 44 mothers of lower socioeconomic status. "Using trained interviewers, six days of food intake, two administrations of a questionnaire about toddler's eating behaviour, and one administration of the Family Environment Scale (FES) were collected in the home," researchers reported. The questionnaire used was modified to assess whether mothers considered their child to be a picky eater, based largely on behaviour-type questions, and the dietary variety and diversity scores for each interview were calculated from reported food intake.

Each mother was interviewed twice during a 24- to 36-month study interval. At both interviews, the dietary variety and diversity scores were lower among picky eaters compared with non-picky eaters (Table 2).

Table 2. Dietary Variety (No. of Recommended Servings/Food Groups Consumed/Day) and Diversity (Total No. of Foods Consumed Over 3 Days) Scores for Toddlers 24 to 36 Months of Age

Dietary scores	Picky eater	Non-picky eater	Univariate ANOVA for mean differences
Interview I			
Variety	0.78	0.83	*P*=0.03
Diversity	30.3	32.2	*P*=0.08
Interview II			
Variety	0.75	0.81	*P*=0.009
Diversity	29.9	33.9	*P*=0.03

"For interviews 1 and 2, the dietary Variety Index for Toddlers score was significantly different for picky eaters compared to non-picky eaters," the authors noted, "while the Diversity Index score was significantly different at interview 2."

Investigators also calculated both groups' nutrient intake as a per cent of the RDA. Based on achieving 100% of the RDA, "both groups had less than recommended amounts of

calcium, zinc, vitamin D and vitamin E," they observed, but no significant difference in nutrient intake was observed by picky-eater status. Regarding family environment status, investigators also saw no difference in mean FES scores between upper and lower socioeconomic mothers, nor did functional characteristics of the family differ significantly by picky eater status.

"A toddler's limited food acceptance may lead to parents becoming frustrated as they try to cope with these behaviours," investigators remarked. "Parents need suggestions about age-appropriate experience that [may] help the toddler to accept a wide variety of foods, and to consume adequate amounts of foods that consistently meet energy and nutrient allowances over time."

Parents who consider their infants "picky eaters" may consider a liquid nutrition supplement to ensure their infant receives optimal nutrition.

Extensively hydrolyzed/free amino acid-based formulas meet strict labelling criteria for hypoallergenicity

Hypoallergenic formulas are intended for infants with allergic symptoms and both extensively hydrolyzed and free amino acid-based formulas meet the strict labelling criteria for hypoallergenicity, according to the Committee on Nutrition of the American Academy of Pediatrics (AAP) (Table 3).

Symptoms of food protein allergy—most notably cow's milk protein allergy in infants—include both IgE-associated reactions and those that are non-IgE mediated. Angioedema, urticaria, wheezing, rhinitis, vomiting, eczema and anaphylaxis are associated with the former, while non-IgE-mediated conditions include malabsorption with villous atrophy, eosinophilic proctocolitis, enterocolitis and esophagitis. "Some infants may experience extreme irritability or colic as the only symptom of food protein allergy," committee members indicated.

Lactose intolerance and phenylketonuria can also provoke adverse reactions to cow's milk protein, they added. All of these conditions may be alleviated by the use of alternative formulas. As nutrition committee members have observed, milk from goats and other animals, or formulas containing large amounts of intact animal protein, are not good substitutes for either breast milk or cow's milk-based infant formulas in infants allergic to cow's milk.

In contrast, "soy formulas have a long history as alternative formulas in infants who are allergic," the committee noted, "and although soy formulas are not hypoallergenic, they can be fed to infants with IgE-associated symptoms of milk allergy, particularly after the age of 6 months." The same cannot be said for infants with non-Ige-mediated symptoms such as enterocolitis where rates of cross reactivity to soy proteins is high among those made symptomatic from cow's milk and therefore should be fed hypoallergenic formulas from the onset.

Formulas based on partially hydrolyzed cow's milk proteins have been known to provoke significant reactions in many infants with cow's milk allergies and are not intended to be used to treat cow's milk allergy either. "At least 90% of infants [allergic to cow's milk] tolerate extensively hydrolyzed formulas as well as the more recently introduced free amino-acid-based infant formulas," the authors stated, "…while [infants] with severe colic may benefit from a one- to two-week trial of a hypoallergenic formula [as well]."

Other recommendations from the APP Committee on Nutrition on breast-feeding infants who develop symptoms of food allergy include:

Table 3. AAP 2008 Committee on Nutrition Recommendations

Exclusive breastfeeding for at least 4 months compared with feeding infants intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy in the first 2 years of life. Exclusive breastfeeding for at least 3 months protects against wheezing in early life but evidence that exclusive breastfeeding protects against allergic asthma occurring beyond 6 years is not convincing. There are insufficient data to support a protective effect of any dietary intervention against atopic disease after 4-6 months of age.
There is a lack of evidence that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants. Antigen avoidance during lactation does not prevent atopic disease either, with the possible exception of atopic eczema (although more data are needed to substantiate this).
For infants who are not breastfed exclusively for 4-6 months or who are formula-fed, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas compared with cow milk formula in early childhood.
Extensively hydrolyzed formulas may be more effective than partially hydrolyzed formulas in the prevention of atopic disease.
Solid foods should not be introduced before 4-6 months of age but there is no convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease. This includes foods considered to be highly allergic, including fish, eggs and foods containing peanut protein.
For a child who has developed an atopic disease that may be precipitated or exacerbated by ingested proteins via human milk, infant formula or specific complementary foods, treatment may require specific identification and restriction of cause food proteins.

This publication has been prepared by the editorial team of Medical Education Network Canada Inc.

To view the electronic version of this publication, please visit www.mednet.ca/2009/ho09-003e