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For fussiness & gas when sensitive to lactose on Sensitivity Premium milk-based infant formula with reduced lactose (S89)

Cow milk-based infant formulas containing a reduced content of lactose and/or no added lactose formulas are intended to be easier to digest and therefore gentle on the digestive system for infants experiencing transient lactase deficiencies resulting in lactose malabsorption. Lactose malabsorption may be an etiology for colic (excessive crying) during early development and following gastrointestinal upset due to deficiencies in the lactase enzyme.

During the first months after birth, the gastrointestinal (GI) system adapts to the various nutrients in order to develop digestive, absorptive and immunological functions. During this period, infants can suffer from many gastrointestinal disturbances.

Infantile colic is a common problem in infancy. Although the precise cause of colic is unclear, there are numerous hypotheses in the mainstream medical literature that can be grouped under two broad headings:

- physiological factors, ranging from lactose malabsorption, cow's milk intolerance and immaturity of the GI system to immaturity of the nervous system
- non-physiological factors, such as difficult infant temperament, inappropriate maternal response and deficiencies in parenting.

Colic is frequently reported, and despite over 40 years of research, its treatment is often ineffective and difficult. In recent decades, lactose malabsorption has been identified as one possible causative factor in infant colic. Lactose malabsorption syndrome is the physiologic problem that manifests as lactose intolerance and is attributable to an imbalance between the amount of ingested lactose and the capacity for lactase to hydrolyze the disaccharide. Undigested lactose cannot be absorbed. Thus, it is passed on to the colonic bacteria, which metabolize the lactose, producing gas and metabolic products that enhance colonic motility. The resulting failure to break down all the lactose in the food allows significant amounts to enter the large bowel, where it becomes a substrate for *Lactobacilli* and *Bifidobacteria* in the colon (Savino et al., 2005). Fermentation of lactose by these bacteria leads to production of lactic acid and hydrogen. The rapid production of hydrogen in the lower bowel distends the colon, sometimes causing pain, whereas the osmotic pressure generated by the lactose and lactic acid in the colon causes an influx of water, leading to further distension of the bowel.

Secondary lactase deficiency implies that an underlying pathophysiologic condition is responsible for the lactase deficiency and subsequent lactose malabsorption. Etiologies include

acute infection (e.g., rotavirus) causing small intestinal injury with loss of the epithelial cells containing lactose from the tips of the villi. The immature epithelial cells that replace these cells are often lactase deficient, leading to lactose malabsorption. Other causes of lactose malabsorption in infants include the following:

- infectious disease
- celiac spruce
- some antibiotics
- cow's milk protein intolerance
- malnutrition
- prematurity
- physiological insufficiency of GI enzyme systems

Developmentally, intestinal lactase is detected very late in the fetus. It is estimated that at 35-38 weeks of gestation, lactase concentrations are ~70% of full-term level, and full-term lactase levels are 2 to 4 times those found in infants 2-11 months of age (reviewed in Rosado, 1997). Despite these higher lactase levels in the newborn, transient lactase deficiencies may also occur due to varying stages of gastrointestinal (GI) maturity. In fact, most term infants are unable to absorb fully the lactose that is present in formula or breast milk in the first four months of life, in spite of having adult levels of mucosal lactase activity (Mobassaleh et al., 1985; Lim 2006; reviewed in Rosado, 1997). Interestingly, the incomplete digestion of lactose in the newborn allows for growth of hetero -fermenting species of *Lactobacilli* and *Bifidobacteria* (Savino et al., 2005). Growth of these bacteria can lead to gastrointestinal discomfort.

Lactase deficiencies during development and after intestinal injury occur during infancy. During these times, providing the infant with a formula containing a reduced amount of lactose may alleviate their discomfort, lessening the lactase activity needed for complete digestion of lactose.

As stated, deficiencies in GI enzyme systems may be one reason for the development of colic. Breath hydrogen levels indicate bacterial lactose fermentation in the colon. Although increases in breath hydrogen have been reported, results have been inconsistent.

In 1998, the hypothesis that colic symptoms could be relieved by reducing the lactose content of the infant's feed was tested in a small, double-blind study in which the feed of colicky babies was pre-incubated with lactase (Kearney et al., 1998). In this study, infants were randomized to add either lactase or placebo to their cow-milk based formula for 1 week, followed by a 2 day wash-out period. The addition was changed for the second week, so that subjects served as their own control. Thirteen infants meeting Wessel's definition of colic (3 hours of crying, 3

times per week for 3 weeks), demonstrated a mean reduction of crying time in excess of 1 hour and a 45% reduction in breath hydrogen (Kearney et al., 1998). This study was well conducted and the resulting reductions were significant, although the limited trial size has prevented any formal proof of effect.

In another larger study 53 infants were recruited, with information on 46 for cry time analysis and hydrogen breath tests on 34. The predetermined criteria for treatment success (>45% reduction in crying time and breath hydrogen) was achieved by 26% of infants overall (95% confidence interval) and by 38% of compliers (Kanabar et al., 2001).

Earlier studies with lactase are criticized because the lactase was given orally after feeding, a strategy which would have made dosage difficult, potentially reducing the lactase activity. In addition, the case definitions did not include duration measurements (reviewed in Garrison and Christakis 2000).

In both the Kearney and Kanabar studies, the infants feed was pre-incubated with the enzyme thereby reducing the lactose load on the infant. The study infants did respond to lactase and displayed a clinically significant reduction in crying time and breath hydrogen. These studies support the idea that symptoms can be relieved by reducing the lactose content of formula for an infant experiencing lactase deficiency, and that lactose malabsorption is a cause of gastrointestinal upset in infancy. Reduced lactose formulas offer an alternative to incubating formula with commercial lactase preparations and are easier to digest due to the reduction in lactose load.

In review of these studies it becomes clear that colic is a heterogeneous condition. The cause of colic is still obscure and controversial, and there is therefore a lack of an appropriate strategy for the management and treatment of this condition. This lack of a consensus on etiology of colic, despite decades of research, has resulted in a trial and error approach to treatment. In infants whose colic is due to lactose malabsorption, the application of lactase to feed or the consumption of reduced lactose/no added lactose formulas may lead to symptomatic improvement by reducing the enzyme activity needed to fully digest the lactose. Due to the increased risk of contamination when adding lactase to formula, reduced lactose/no added lactose formulas represent a legitimate first-line approach to the treatment of infantile colic.

Cow milk-based infant formulas contain either a reduced content of lactose and/or no added lactose in order to be easier to digest, reducing the amount of active lactase required for lactose digestion. These formulas are designed to be gentle on the infants developing GI system, taking into account that transient lactase deficiencies do occur throughout infancy.

References

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