HMOs and the infant microbiota

An error meant that an early, incomplete draft of this article was printed in a previous issue of* British Journal of Midwifery. *The final version has therefore been published here

Breast milk will always be the ideal food for all babies: the benefits that it offers in encouraging health, growth and development cannot be replicated. But for mothers who are unable to feed their infants the natural product, formula milk is the only suitable alternative. A growing understanding of the composition and function of breast milk is helping to produce infant formula milks that are closer in composition to breast milk, with the aim of improving outcomes for infants who are formula-fed.

It has been known since the 19th century that there is a direct relationship between early diet and health. Breastfed infants had been shown to have lower incidence of infectious diseases and a higher survival rate than those fed formula. Researchers then realised that this could be linked to the effects of diet on the bacterial population, which differed markedly in the bowels of breast- and bottle-fed infants.

Researchers also realised that the benefits of human milk on the immune system could be linked to the differences in the gut bacterial population (microbiota), which differed markedly between breast- and bottle-fed infants. This led to the study of the effects of prebiotics (non-digestible fibres that stimulate the growth of beneficial gut bacteria) and probiotics (solutions of live bacteria or yeasts with similar effects).

Glenn Gibson, professor of microbiology at the University of Reading, explained that the human gut microbiota contains more than 1000 bacterial species and that pre- and probiotics have a vital role in establishing and maintaining a balanced gut microbiota. This influences other body systems, and there is growing evidence of the importance of the microbiota in a wide range of conditions such as atopic disease, obesity and various cancers.

In the guts of healthy breastfed babies, the microbiota is dominated by Bifidobacteria (beneficial bacteria). Professor Sharon Donovan, Professor of Nutrition at the University of Illinois, presented the evidence for the unique relationship that has evolved between these bacteria and the human species.

Bifidobacteria use human milk oligosaccharides (HMOs) as their preferred source of food to grow. HMOs are a diverse group of complex carbohydrates that have a prebiotic effect. HMOs cannot be broken down by human digestive enzymes and instead pass into the colon. While these HMOs can be metabolised by other components of the microbiota, bifidobacteria are more efficient at absorbing and processing these compounds and will often out-compete other bacteria, including potentially harmful strains.

HMOs are much more abundant and structurally complex than oligosaccharides present in the milk of other mammals. To date, more than 150 different HMOs have been identified, present at levels of between 5–15g/litre of HMO compared to <0.05g/litre in bovine milk.

The pattern of HMO production varies between women, but most will produce around eight compounds. This variation is largely genetic. HMO levels in the milk of individual women will also vary both seasonally and according to the stage of lactation, but factors such as maternal diet and the sex of the infant have not been shown to have any effect.

Fermentation of these HMOs by bifidobacteria produces short chain fatty acids and lowers the pH of the colon, which has protective effects in inhibiting the growth of potentially pathogenic bacteria. But HMOs also have direct effects on the intestinal epithelium, preventing disease by blocking the ability of pathogenic organisms to attach themselves to the cells of the gut wall and colonise its surface (Bode et al, 2012). Each HMO acts as a receptor analogue, binding to the cell surface proteins of a particular microorganism, such as *Escherichia coli*, *Campylobacter* or *Calicivirus,* that causes neonatal diarrhoea. An observational study of breast-fed infants demonstrated in infants fed milk with different HMO concentrations, which showed that moderate-to-severe diarrhoea was significantly less common in infants receiving higher levels of these compounds (Morrow et al, 2004).

A small proportion of the HMOs present in the gut will be absorbed and can be detected in the blood and urine. There is some evidence to suggest that this contributes to the lower frequencies of respiratory and urinary tract infections that have been recorded in breastfed infants compared with those receiving formula. It has also been suggested that if milk rejected by the breastfeeding infant runs into the ears, this may be responsible for the lower incidence of otitis media infections in this group (Bode, 2012).

Since the 1990s, formula milk manufacturers have tried to reproduce the health benefits of breast milk by including two prebiotic components, galactooligosaccharide (GOS) and fructooligosaccharide (FOS) in their products. However, GOS/FOS are compounds that have a much simpler structure than HMOs. The latter will often contain two more saccharides, either fucose or sialic acid and tend to be more biologically active. But with advances

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in technology, it has been possible to produce two structurally identical HMOs, 2'-fucosyllactose (2'-FL) and lacto-N-neotetraose (LNnT), in sufficient quantities to be included in commercial products. This has also allowed the first randomised controlled trials on the effects of supplementation in the infant (all previous research on the effects of HMOs has been *in vitro* or has used animal models).

Professor Donovan described the results of the first two of these studies. One from Columbus, Ohio (Marriage et al, 2015) confirmed the safety of 2'FL supplemented infant formula, showing that factors such as growth rates and stool consistency in babies given experimental formula containing 0.2 or 1g/litre were equivalent to those receiving the standard product. In the second phase of that study (Goehring et al, 2016), the 2'-FL milk was shown to have similar positive effects on the immune system, in terms of reduced levels of proinflammatory cytokines and increased circulating T-cell populations, as breast milk.

Meanwhile, a study by Puccio et al (2017) tested infant formula containing both 2'-FL and LNnT. The results showed that growth and digestive tolerance were similar in infants receiving the new formula and in those given traditional bovine milk-based formula.

However, the parents of infants given the new formula reported a lower incidence of respiratory tract infections and bronchitis, and reduced need for antibiotics and antipyretics compared with those given standard formula. Although the feeding trial lasted only 6 months, there were detectable differences between the two groups for a further 6 months.

Further articles based on this study are expected in the coming months, but Professor Donovan did reveal that analysis of the gut microbiota in these babies had shown that those infants receiving the HMOs developed a gut flora that was much closer to that of breastfed babies.

The availability of a greater range of HMOs over the next few years will mean that intervention studies in human infants will become an increasingly active area of paediatric research, Professor Donovan noted. One obvious target will be an examination of new strategies for preventing necrotising enterocolitis in pre-term infants. It has already been shown that the administration of a different HMO, disialyllacto-N-tetraose (DSLNT) may prevent the equivalent condition occurring in a rodent disease model (Jantscher-Krenn et al, 2012). It has also been noted that mothers of babies that developed the condition produced lower levels of the DSLNT in their milk. This would not be an easy compound to produce synthetically, but it is likely that significant efforts will be going into producing DSLNT in laboratories around the world, she said.

There is therefore growing evidence that HMOs are multifunctional carbohydrates that confer multiple benefits. Their recent introduction into commercial formula products has helped to narrow the gap between formula and breastfed infants in terms of microbiota, immune function and possibly in cognition. Although Professor Donovan admitted that only two of the approximately 150 compounds are available, it is likely that others will be produced in quantities that allow further investigations in future. These must first be tested for their bioactivity, which will stimulate the search for other components in human breast milk that may act synergistically with HMOs, she said. **BJM**

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***Important notice**: The World Health Organization (WHO) has recommended that pregnant women and new mothers be informed on the benefits and superiority of breastfeeding—in particular the fact that it provides the best nutrition and protection from illness for babies. Mothers should be given guidance on the preparation for, and maintenance of, lactation, with special emphasis on the importance of a well-balanced diet both during pregnancy and after delivery. Unnecessary introduction of partial bottle-feeding or other foods and drinks should be discouraged since it will have a negative effect on breastfeeding. Similarly, mothers should be warned of the difficulty of reversing a decision not to breastfeed. Before advising a mother to use an infant formula, she should be advised of the social and financial implications of her decision: for example, if a baby is exclusively bottle-fed, more than one can (400g) per week will be needed, so the family circumstances and costs should be kept in mind. Mothers should be reminded that breast milk is not only the best, but also the most economical food for babies. If a decision to use an infant formula is taken, it is important to give instructions on correct preparation methods, emphasising that unboiled water, unsterilised bottles or incorrect dilution can all lead to illness.*

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