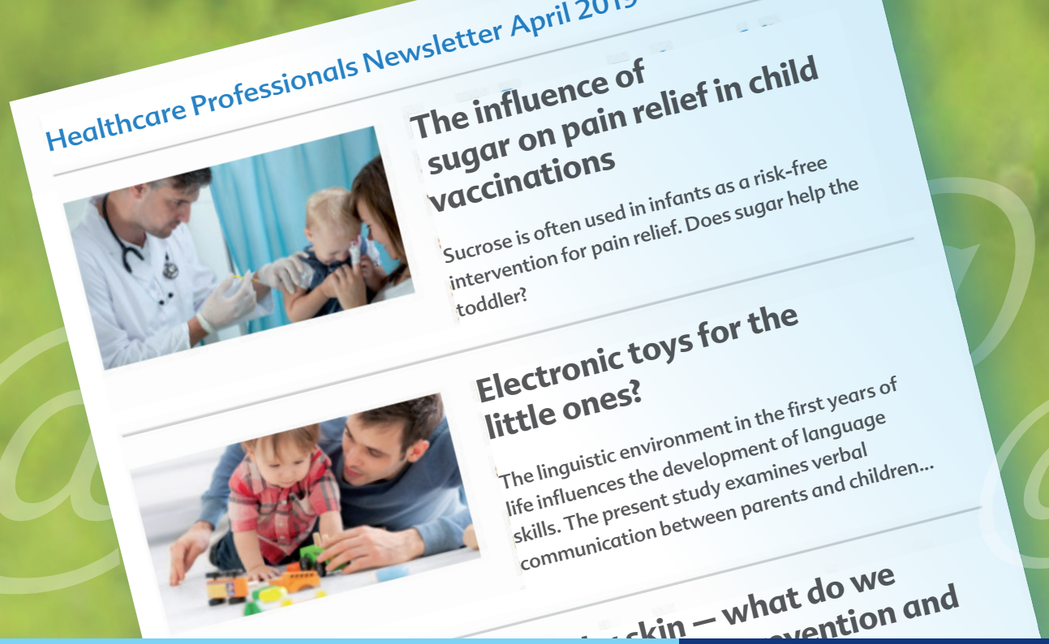

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It's All About the Mother: Maternal Factors Influencing Human Milk Composition

Friday, 07 June 2019
07:15 to 08:15 am
SEC Glasgow
Lomond Hall

Chair:
Catherine Stanton
University College Cork
Ireland

Michelle McGuire
University of Idaho, USA

Milk Microbiome: Origin and Impact of Maternal Diet?

Human milk provides sole-source nutrition for exclusively breastfed infants. In addition to the traditional nutrients, milk contains myriad biologically active substances such as hormones, immune factors and cells, nucleic acids, and enzymes. Although long believed sterile, milk is also a rich source of microbes. Substantial research is needed to understand the importance of these microbes to maternal and infant health, but experts postulate that they may be involved in maintaining breast health and colonizing the infant's gastrointestinal (GI) and respiratory tracts with specific taxa that confer early-life and life-long health and wellbeing[6], including optimization of the immune system[4, 8, 9].

The origin of the microbial communities in milk is still controversial but thought to be multifactorial including via transport from the mother's GI tract (enteromammary pathway), retrograde inoculation from the infant's mouth during suckling, and the breast skin. Indeed, elegant studies with women suffering from mastitis have shown that maternal consumption of probiotics can result in the appearance of the same bacterial species in the milk produced by these women[1,3], supporting an enteromammary pathway. In a recent report from the CHILD study which included 393 mother-infant dyads, Azad and colleagues provided convincing evidence that whether a mother exclusively feeds her infant at the breast or uses a pump to express her milk is related to variation in the microbiome of her milk: women who pumped produced milk with a lower prevalence of a Bifidobacterium spp. than what is found in milk produced by women who exclusively fed at the breast. The researchers posit that their data provide additional evidence for the retrograde inoculation hypothesis. Biagi (2018) also found that the milk microbiome changes as women transition from exclusively pumping to feeding their infants at the breast. In addition, we and others have found strong correlations among variations in milk, infant oral, and maternal fecal microbiomes[10, 13], suggesting that these microbial communities are linked and likely interacting with each other. Importantly, even women who have never breastfed have a rich microbial community in their mammary glands[11], illustrating that these microbes are reaching the breast via routes not related to suckling. Carefully conducted, controlled intervention studies are needed to unequivocally determine whether the milk microbiome can be predictably altered via oral and/or topical provision of live bacteria (probiotics) to breastfeeding mothers and/or their infants.

Factors influencing variation in the human milk microbiome are likely extensive and may include maternal health, nutritional status and dietary patterns, antibiotic use, time postpartum, genetics, and cultural practices. However, substantial inconsistencies exist in the literature regarding these relationships, and this may be due to a plethora of mediating factors. For instance, data from the INSPIRE study which involved 412 relatively healthy mothers and infants living in 8 countries provide rigorous evidence that the milk microbiome varies around the world[5]. We have also shown previously that an infant's social environment (e.g., number of caregivers) is associated with the microbial diversity of his/her mother's milk[7]. As such, studies relating maternal and environmental factors to the milk microbiome should take into consideration culture, geography, and behaviors. The potential impact of maternal diet is one such factor. Although very little is known about whether a mother's acute and chronic dietary patterns influence the microbial community structure of her milk, evidence from our research group and several others suggests that this is a distinct possibility. For instance, in a study of 21 healthy women living in the Pacific northwest region of the US, we found that women who consumed more energy and higher amounts of protein, saturated fat, monounsaturated fat, carbohydrates, and fiber produced milk with relatively higher amounts of Firmicutes [12]. We also found striking patterns relating essential and nonessential amino acid intakes with variation in the milk microbiome. Specifically, women consuming more amino acids produced milk with higher levels of Proteobacteria. There were also relationships between micronutrient intakes and the milk microbiome. For instance, vitamin D intake was negatively correlated with relative abundance of Firmicutes, and iodine intake positively correlated with Fusobacteria. We hypothesize that maternal diet might influence milk microbiome via at least 3 routes: [1]alteration of the mother's GI microbiome and subsequently the bacteria trafficked to the mammary gland via the enteromammary pathway, [2]alteration of the mammary nutrient milieu, thus influencing the microbial communities that thrive in that environment, and [3]in the case of dietary probiotics, directly seeding the mother's GI tract with live bacteria. Again, carefully conducted, controlled intervention studies are needed to investigate and understand better these possibilities.

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Current Insights into Maternal Genetic Contributions to Human Milk Composition

The complex composition of human milk is influenced by a variety of factors including stage of lactation, diet, environmental factors, and maternal genetics. Although widely studied in the animal agriculture field, the influence of genetic polymorphisms on milk composition has only been studied for a few components in human milk. This talk will briefly discuss a few examples of this.

Fatty acids

In 2008, Innis and coworkers (2008) first reported that single nucleotide polymorphisms (SNPs) in the fatty acid desaturase (FADS) 1 and FADS2 genes were associated with concentrations of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in human milk. Since that time, others[(e.g., 9,10, 3,16)] have provided supporting evidence that not only genetic variation in FADS genes but also polymorphisms in fatty acid elongase genes (e.g., ELOVL2 and ELOVL5) are associated with varying levels of long-chain polyunsaturated fatty acids (LC-PUFAs) such as EPA, AA, and DHA in colostrum and mature milk. Most recently, Wu and coworkers (2019) reported associations between polymorphisms in both ELOVL2 and ELOVL5 genes, which encode elongation enzymes that are vital in the synthesis of LC-PUFA from linoleic (LA) and α-linolenic acid (ALA), and PUFA concentrations in milk of healthy lactating Chinese Han women. In addition to investigating SNPs in individual genes of interest, associations between polymorphisms across the genome and milk composition can also be investigated through genome-wide association studies (GWAS). Once again, although GWAS have been extensively used in bovine milk research, only one GWAS on human milk composition has been published. This GWAS examined associations between genome-wide SNPs and concentrations of fatty acids in milk from Bangladeshi mothers. In this study, Mychaleckyj and coworkers (2018) identified several SNPs in the FADS1/2/3 region of chromosome 11 associated with AA concentration.

Immune factors

Even fewer studies have determined the extent to which maternal genetic variation is associated with the concentrations of immune factors in human milk. Guerra and coworkers (2004) identified associations between 2 SNPs in the CD14 gene and concentrations of soluble CD14 in milk of Hispanic and non-Hispanic Caucasian mothers. This result, however, is in contrast to that of Snijders and coworkers (2010) who did not find associations between SNPs in CD14 and concentrations of soluble CD14 in milk from mothers in the Netherlands. More work is needed to disentangle these seemingly conflicting results. Baumgartel and coworkers (2016) recently investigated associations between concentrations of cytokines interleukin-4 (IL-4), IL-6, and IL-10 in milk and SNPs found in the promoter regions of their respective genes. Although their sample size was small, they did detect associations between the SNPs investigated and IL-6 and IL-10 concentrations in milk; no associations were detected between SNPs and IL-4 concentration.

HMO

Perhaps the most widely known components in human milk influenced by maternal genotype are the human milk oligosaccharides (HMO). Since the late 1960s, a correlation between the occurrence of 2'fucosyllactose and blood group secretor and Lewis secretor status has been documented[(5)]. Since then, several studies have reported differing profiles of HMO in relation to secretor activity regulated by fucosyltransferase enzymes [(7,2,15)]. For example, women who synthesize various HMO such as 2'-fucosyllactose (2'FL), difucosyllactose (DFLac), and lacto-N-fucopentaose I (LNFP I) in their mammary glands are referred to as "secretors" and are believed to have an active α-1,2-fucosyltransferase enzyme encoded by the FUT2 gene. Recently, we conducted a multi-site cross-sectional study in 8 countries with 11 cohorts[(8)] and subsequently investigated the contribution of maternal genetic variation to the differences observed in milk composition by utilizing a genome-wide association analysis. We genotyped women using the Illumina Multi-Ethnic Global array which contains over 1.7 million SNPs and investigated potential associations between SNPs and HMO concentrations. Several significant associations were detected between SNPs in key genes such as FUT2 and FUT3 and concentrations of 2'FL, DFLac, and LNFP I (Williams unpublished).

Conclusion and Future directions

These studies suggest that genetic variation among women does influence the complex composition of human milk. However, there are still a plethora of components in human milk that have yet to be studied along with the genes that regulate their synthesis and/or secretion into milk. Since human milk composition has been linked to not only short-term health [(11;13)], but also potentially long-term health of the infant [(4)], it is crucial to continue to study and better understand genetic factors that regulate or alter milk composition. We are primed to do so now with new methodologies that allow us to examine not only how polymorphisms in genes and/or DNA are associated with milk composition, but also how epigenetic DNA methylation, histone modification, and RNA splicing might influence expression of genes involved in lactation and thus, ultimately, human milk composition.

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