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Environmental determinants of human milk composition in relation to health outcomes

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Abbreviations:

BC – body composition

BMI – body mass index

DDE – dichlorodiphenyldichloroethylene

DDT – dichlorodiphenyltrichloroethane

FAs – fatty acids

HGF – hepatocyte growth factor

HM – human milk

HMOs – human milk oligosaccharides

PCBs – polychlorinated biphenyls

PFAS – per- and polyfluoroalkyl substances

POPs – persistent organic pollutants

SCFAs – short chain fatty acids

sIgA – secretory immunoglobulin A

TGFβ – transforming growth factor beta

Abstract

Humans are exposed to environmental factors at every stage of life including infancy. The aim of this mini-review was to present a narrative of environmental factors influencing human milk composition. Current literature shows lactation is a dynamic process and is responsive to multiple environmental challenges including geographical location, lifestyle, persistent pollutants and maternal factors (ethnicity, diet, stress, allergy and adiposity), that may influence human milk composition in a synergistic manner and should be considered in order to improve infant and maternal outcomes on a populations scale. Further interventional studies on larger international cohorts are needed to elucidate these complex relationships.

Conclusion: Lactating women should aim for a healthy lifestyle and maintain a healthy body composition prior to and throughout the reproductive period, including during lactation.

Key Notes

- Human milk is a modifiable biological system that responds to environmental challenges.
- Multiple environmental factors, such as geographical location, lifestyle, persistent pollutants and maternal factors may modify human milk composition and potentially affect infant health and development.
- Maintaining a healthy adiposity, diet and lifestyle prior and during lactation may be beneficial for infant health, growth and developmental outcomes.

KEYWORDS

human milk composition, environmental factors and contaminants, maternal and infant body composition, breastfeeding and lactation, breastfed infant growth and development

1 INTRODUCTION

In this narrative mini-review, we focus on human milk (HM) composition in relation to effects of environmental factors. HM is a complex biological system which is influenced by maternal genetics, health, diet, adiposity and exposure to environmental stress.[1] Data from a variety of studies suggest that factors such as country of maternal origin and residence, diet, exercise, and exposure to smoke or a farming environment may influence HM composition. These factors are not affecting HM in isolation but have synergistic effects (Figure 1). The direct or indirect evidence of these exposures altering infant outcomes via the HM is more difficult to identify, as it is not always ethical to conduct a randomised control trial.

2 GEOGRAPHICAL FACTORS

Whilst it is known that genetic variations in some nutrient-specific genes are associated with altered HM composition (zinc, calcium, sodium, fatty acids (FA)),[2, 3] the data on genetic and ethnic differences in humans are still being accumulated; among them are interesting findings on the effects of geographical factors and lifestyle, which are often difficult to isolate from other environmental influences. Findings from samples collected from 11 populations worldwide (the large, geographically and socio-culturally diverse INSPIRE cohort) reflect on the biodiversity of HM, with concentrations of multiple milk components including multiple HM oligosaccharides (HMOs),[4] lactose and protein[5] and a number of immune compounds[6] being related to location and lifestyle. HMOs promote the growth of beneficial microbiota and protect the infant gut from pathogen proliferation and inflammation. Further, individual HMOs[7, 8] and immunomodulatory proteins[9] have been linked to infant body composition (BC) development, showing differential relationships with fat and lean body mass.

Another study established that concentrations of HM growth factors (hepatocyte growth factor (HGF) and transforming growth factor beta (TGFβ1,2,3) vary between three geographical locations (Italy, Russia, United Kingdom).[10] Interestingly, none of the maternal variables, such as demographics, mould and pet presence at home, maternal diet, smoking or allergy status explained the difference. The effect of these growth factors on infant health is not fully understood, with the majority of current studies showing no associations between TGFβ and infant allergic outcomes.[11]

Another multicentre study (China, Northern Europe, Spain) reported geographic origin as the most important factor (more important than mode of delivery) for the observed differences HM microbiota and lipid composition.[12] The associations between the HM lipid profile and microbiota suggest lipids are influencing the HM microbial profile and likely contributing to the development of the infant gut microbiota. An increased supply of HM long chain fatty acids (FAs) was associated with higher infant subcutaneous fat,[13] which is associated with protection against obesity late in life.[14] Additionally, another study has focused on short chain FAs (SCFAs; acetate, butyrate, and formate), the microbial metabolites in HM, and reported differences in levels in HM collected in an international cohort (Australia, Japan, Norway, South Africa, USA).[15] These findings are not attributed to ethnicity or location only and are potentially explained by lifestyle, diet and allergy status.

Interestingly, two studies compared populations from higher and lower altitude regions of Tibet, reporting that living at higher altitude had no effect on HM macronutrient content,[16] but was related to higher HM adiponectin and lower leptin concentrations, however this could be in part explained by the higher body mass index (BMI) of mothers from lower altitude,[17] or lower circulating leptin as an adaption to colder climate in mothers from higher altitudes.[18]

3 ENVIRONMENTAL CONTAMINANTS

Unsurprisingly, synthetic, non-endogenous chemicals present in our environment are of interest in HM research, and it is important to understand if they affect milk composition and therefore the newborn infant. Many environmental and dietary contaminants have the potential to leach into soil, water sources and air, and include mercury, lead, and pesticides and other persistent organic pollutants (POPs).[19] After entering the bloodstream by inhalation, ingestion or direct skin contact, POPs in particular are transported around the body via transport proteins and lipoproteins, and accumulate in adipose tissue, including breast tissue. The transfer of POPs into HM likely occurs through diffusion through the intracellular spaces while tight junctions remain open, and then through the lactocyte after tight junctions close (following secretory activation) however the mechanisms in humans are not yet described. Accordingly, many POPs and their breakdown products have been identified in HM and increase in infant circulation with increasing breastfeeding duration.[20]

Numerous polychlorinated biphenyls (PCBs) have been measured in HM (range: ~1–400 ng/g of lipid). The highest HM PCB concentrations are typically measured in populations residing in industrial areas, or in those with high dietary fish consumption.[20] Similarly, HM dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) are found in the highest concentrations in rural communities, where pesticide use is prevalent (52–17170 ng/g of lipid). Most recently, historic per- and polyfluoroalkyl substances (PFAS) have been measured in HM and show a clear decrease since 1995, e.g. perfluorooctanesulfonic acid has halved from approximately 6 to 3 pg/mL across Europe, Asia, and North America. However, new PFAS species are increasing in concentration in HM.[21]

Exposure to POPs has been linked to reproductive, developmental, endocrine, and many other adverse health effects and infants are at highest risk during rapid growth and development in early life. Although there are few HM POPs intake studies, the concentrations and infant intake appears to be below acceptable daily intakes, decreasing throughout lactation, but now decreasing across many populations.[22, 23] In a Western Australian study DDE intake has been shown to be much lower than the tolerable level, and no relationships were seen between DDE intake and infant growth.[22] Studies agree that the benefits of breastfeeding outweigh any possible environmental contaminant risks; however, populations exposed to high levels of discontinued and emerging POPs and other xenobiotics should be considered in future research.[19]

4 MATERNAL ADIPOSITY

Maternal adiposity has been associated with concentrations of several HM components, including hormones, proteins, carbohydrates, and fat. Multiple studies report inconclusive relationships of HM insulin with maternal adiposity, negative associations with ghrelin, no associations with adiponectin, and positive associations with leptin,[24-26] and glucocorticoids, cortisol and cortisone.[27]

Maternal adiposity is generally associated with higher HM fat content,[28] which is the most variable component, although the directions of associations vary for individual FAs.[3] HM protein and lactose concentrations are unlikely to differ in relation to maternal adiposity as indicated by the quantitative analysis,[28] however, the qualitative synthesis points to a possible positive association between maternal adiposity and HM proteins. This is supported by positive relationships between maternal adiposity and both total,[29] and whey protein concentrations,[30] however, immunomodulatory proteins lactoferrin, lysozyme and sIgA are not related to maternal BC.[9]

Overall, multiple studies report the associations between maternal adiposity and HM composition, however, the data are limited and conflicting due to heterogeneity in study design, sample collection, and time postpartum.[25] Therefore, careful interpretation of results is needed since the mechanisms by which maternal adiposity may influence HM composition, and potentially the infant, are still unclear.[25]

5 MATERNAL DIET

Maternal diet is another factor that has been found to relate to HM composition. Many observational studies have linked specific dietary factors with HM macro- and micronutrients. These studies have focused mainly on FAs and demonstrate a positive association between maternal intake of FAs and their concentrations in HM.[3, 31] FAs provide energy to the infant and support neurological development. HM micronutrients, including vitamins (A, E, C, B1, B12), calcium and copper have been shown to associate positively with maternal dietary intake levels.[31] To date, only two interventional studies have assessed the effect of maternal diet on HM macronutrient composition.[26, 32] An 8-day high-fat diet intervention resulted in increased HM total lipid concentrations. The same women then followed a low-fat diet for the same period, with no change in HM lipid content. Both dietary interventions did not alter HM protein and lactose concentrations.[32] In the second study, a 14-day low-fat and low-sugar dietary intervention did not result in any changes in HM macronutrient concentrations (protein, lactose, and total lipid) despite a reduction in maternal adiposity, however the concentrations of HM hormones insulin, leptin, and adiponectin significantly decreased.[26]

Among other components of HM, HMOs support infant health by promoting the development of the gut microbiome and immune system. Findings of previous observational studies on maternal diet and HMO composition are conflicting.[33] A randomised cross-over study showed that concentration of total sialylated HMO decreased in the milk of mothers who had a high-fat diet compared to a highcarbohydrate diet, while the concentration of total fucosylated HMO was decreased in the milk of mothers who underwent the glucose diet intervention relative to the galactose diet.[34] Further, the HM microbiome also contributes to the infant oral and gut microbiome which are associated with the programming of lifelong health. Five observational studies have demonstrated associations between maternal diet and HM bacterial composition.[35] Collectively, these studies highlight the influence of maternal diet on HM composition; however, interventional studies on larger cohorts are needed to elucidate these relationships.

6 ALLERGY

Early allergen exposure is important for inducing regulatory immune responses and tolerance[36]. For breastfed infants, the first exposure to dietary allergens and their corresponding antigens is via HM. This exposure is important for developing oral tolerance to common allergens and may have a protective effect against allergy; thus, several research groups are working on establishing the optimal time and dose for the allergen introduction. After consumption of allergenic foods, such as eggs, bovine milk, or peanuts, the related allergen is shed into the mother's milk, however, allergens appear to be cleared rapidly from HM, and are not detected after consumption in all women.[37] Egg and peanut allergens in HM have been associated with protection from food allergy in offspring, however the opposite effect has been reported for house dust mite derived (airborne) allergens.[37, 38] Apart from the dust mites, there are no data on airborne allergens from sources such as pollen, mould or animal dander.[37]

Due to accumulating evidence suggesting that milk allergens may promote early immune tolerance, recent guidelines do not recommend mothers to eliminate dietary allergens while breastfeeding.[39] However, in the case of cow's milk protein allergy, a restricted maternal diet has been suggested.[40, 41] This is highly controversial, with more recent analyses suggesting that infant cow's milk allergies are often over-diagnosed and that concentrations of cow's milk allergens in HM are not sufficient to trigger allergy.[42, 43] While breastfeeding and avoiding allergens, such as cow's milk protein, may not lead to reduced risk of developing allergy, short-term supplementation with formula may actually increase that risk.[44] The mechanisms by which allergens and antigens are transported to milk and how they affect infants are not fully elucidated, and the potential impact of HM allergens on infant immune development should not be overlooked.

In addition to dietary and environmental allergens, HM may also play a role in programming early-life immune tolerance by exposing the infant to maternal microbial metabolites. Although the presence and function of HM microbial metabolites remains understudied, there is evidence that immune-modulating metabolites, such as HM SCFAs, may play a role in early immune tolerance. SCFAs are produced by gut bacteria upon their fermentation of dietary fibre (including HMOs) and are distributed systemically. They elicit a broad range of host responses including promotion of regulatory T-cells and gut barrier integrity and inhibition of inflammation. [45, 46] Early-life exposure to SCFAs has been shown to protect against atopy in mice and is speculated to protect against obesity, although human studies are sparse.[46] Furthermore, high maternal serum acetate levels during pregnancy are associated with a reduced risk of infant wheeze over the first year of life.[45] Interestingly, allergic mothers have lower levels of SCFAs in their milk compared to healthy mothers,[15] potentially suggesting a role for these metabolites in the intergenerational transmission of allergic disease. HM SCFAs and other immune-modulating metabolites produced by the maternal gut microbiota warrant further investigation for their potential role in early-life immune programming.

7 STRESS

Maternal psychological stress (acute and chronic) that accompanies birth and childcare, has multiple origins and may impact HM composition, milk production and potentially infant outcomes, however the effects of stress on lactation are poorly understood and only few studies have investigated effect on HM composition with mixed results.[47] The measures of maternal stress are usually maternal questionnaires for long-term stress, and glucocorticoids (cortisol, measured in plasma or saliva) for both long- and short-term stress. A short period of anxiety (acute stress), such as during infant hospitalisation, does not seem to affect HM macronutrient content,[48] whereas long-term (chronic) stress results in the cumulative glucocorticoid burden and is associated with maternal diet and BC changes, thus may lead to HM composition changes. In a recent study perinatal psychosocial stress (the intensity and number of maternal stressor) was negatively associated with FAs concentration and energy density of HM, whilst stress reactivity (cortisol measured in saliva taken during the cold pressor test) associated positively with fat and FAs and negatively with lactose.[47] The HM immune factors though were not affected by natural variations in maternal distress (questionnaires for stress, anxiety and depressive symptoms).[49]

The level of cortisol in the amniotic fluid has been shown to be inversely correlated with infant cognitive development.[50] The glucocorticoids, cortisol and cortisone, are transferred to HM from maternal circulation and, unlike in plasma, cortisone concentrations in HM is higher than that of cortisol, and higher than in maternal plasma.[27] Cortisol in HM has been shown to associate positively with maternal psychosocial distress at 3 months postpartum.[49] Whilst their biological functions in infants are still being investigated, a recent longitudinal study showed positive relationships between HM cortisol and cortisone and maternal BC, as well as with infant growth, with higher levels associating with infant adiposity and head size, indicating their potential role in shaping infant BC and cognitive development.[27] Monitoring and improving maternal psychological status during lactation will promote breastfeeding and healthy infant nutrition.

8 CONCLUSION

In summary, multiple environmental factors influence HM composition and should be considered in order to improve infant and maternal outcomes. HM is a highly adaptable biological system that will potentially respond to interventions designed for improvement. Mothers should aim for a healthy diet and maintain a healthy body composition before and throughout the reproductive period, including during lactation.

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FIGURES

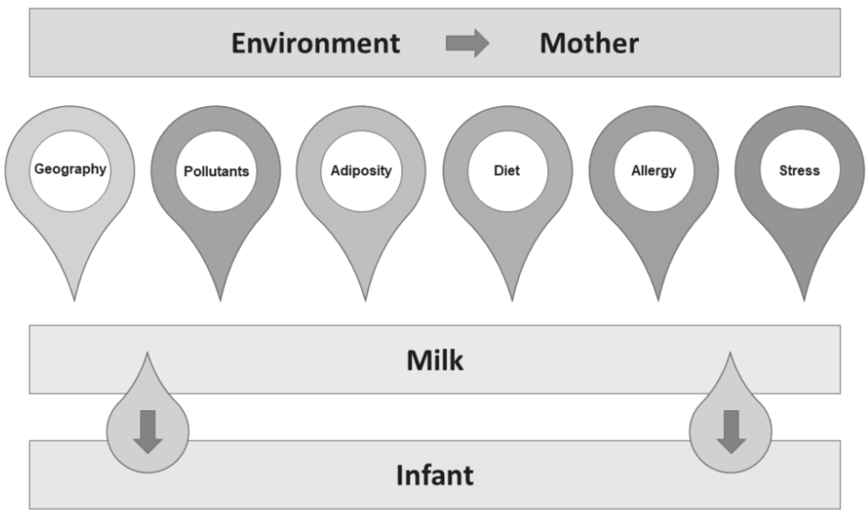

FIGURE 1. The reported synergistic effects of environmental factors on human milk composition.