Metabolic Syndrome

Chapter 6

The Negative Lifestyles in the 21st Century that Modifies Breast Milk and Contributes to the Rising Infant Obesity Pandemic

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Abstract

The lifestyle in the 21st century has risen the prevalence of infant obesity in worldwide, representing a public health challenge. Also, non-communicable diseases (NCDs) in youths associated with metabolic syndrome (MetS) has increased in the last few years. The prevention of MetS starts with the treatment of maternal risk factors beginning in the period before conception until weaning. On this way, breast milk represents a unique metabolic entity that exerts direct effects on the infant's health. Additionally, proper balance of maternal substances transferred to the offspring by milk has a strong impact in the prevention for developing future chronic diseases during adulthood, however, breast milk could also have a negative impact in the offspring metabolic programming. Persistent Organic Pollutants (POPs), a group of worldwide distributed chemicals derived from the growing industrial activities of the 21 century with negative metabolic outcomes for life can also reach the fetus via trans placental route and the newborn thought breast milk. In addition, unhealthy metabolic maternal state caused by unbalanced maternal diet and unhealthy lifestyle habits also could affect the milk composition.

1. Introduction

Worldwide in 2016, 39 % of adults aged 18 years and older were overweight, and 13% were obese [1]. According to the Global Burden Study, 5.02 million people died in 2019 because of high BMI (Body Mass Index) [2]. These trends were first detected in developed countries, but recent studies show a similar tendency in developing countries. Results from the Global Nutrition Report 2020 [3] have reported that obesity affects more women than men (obese women (393.5 million, 15.1%); men (284.1 million, 11.1%). Additionally, the recent Lancet series estimates that 20% of women will be obese by 2025, a problem of significant concern as obese women in reproductive age represents a major public health problem worldwide. Obesity during pregnancy not only affects the woman's health by increasing her risk of gestational diabetes, type 2 diabetes and cardiovascular diseases, but also puts the offspring at risk for developing childhood obesity with later health consequences. This means that obesity during maternal stage can become an intergenerational problem [4]. Worldwide, the number of infants and young children (0-5 years) with overweight or obesity increased from 32 million in 1990 to 41 million in 2016. If current trends continue, the number of overweight infants and young children will increase to 70 million by 2025 [4]. Moreover, obese children are more likely to carry this extra weight into adulthood, negatively affecting their overall health and well-being [5]. Furthermore, once established, obesity is extremely difficult to reverse [6]. In this context, it is essential to highlight infant obesity as this problem increases the susceptibility to metabolic syndrome (MetS), however, most of the attention about which factors lead to obesity, now considered an pandemic, is a shift in the diet since the 1980s with introducing processed food with a high caloric load. On this regard, scientific literature shows that the beginning of this problem lies in the pre and postnatal period, where the practice of breastfeeding plays a critical role [7]. Scientific evidence revealed that exclusive breastfeeding for at least the first 6 months of life significantly decreases the odds of overweight and obesity [8]. Unfortunately, according to the World Health Organization (WHO), nearly 2 out of 3 infants are not exclusively breastfed for the recommended 6 months; 3 in 5 babies are not breastfeed in the first hour of life [9] and only 45% of young children continue to be breastfed during their first 2 years of life [10]. Parallel to this scenario, there is an increase in the use and commercialization of milk artificial formulas. In Mexico, the situation is critical as the official national survey of health, ENSANUT (Encuesta Nacional de Salad y Nutrition), exclusive breastfeeding rates are alarmingly low, with just 28 % in 2018 [11] and a prevalence of overweight and obesity affecting over 75% of adults and 35.6% of the child population. Interestingly, according to the Organization for Economic Cooperation and Development (OECD), Mexico is the 6th most obese country in the world [12]. 21st century lifestyles involving intrinsic and extrinsic environmental conditions to which the lactating woman is exposed such as Persistent Organic Pollutants (POPs), unhealthy metabolic maternal state caused by unbalanced maternal diet and unhealthy lifestyle habits could affect the milk

composition with deleterious effects for the offspring. Therefore, in this chapter, we highlight: 1) the importance of breastfeeding and its relationship with childhood obesity that leads to non-communicable diseases (NCDs) associated with metabolic syndrome (MetS); 2) Modern day lifestyles to which vulnerable groups such as breastfeeding women are exposed and 3) How this is affecting the perfect composition of breast milk. Scientific literature was collected from articles published in scientific journals indexed in PubMed, Science Direct, NCBI, and official websites.

2. Early Origins of Health and Disease

To date, literature has increasingly focused on adult comorbidities and the obesity pandemic while overlooking the factors in early life that lead to such comorbidities. Intrauterine life and postnatal periods are of high plasticity and susceptibility to metabolic disorders. Current evidence suggests that changes in the environment during these critical periods, in particular metabolic and nutritional status, result in predictive health effects of the fetus or infant [6]. As a result, the physiological function of the body is permanently altered, which can lead to energy balance dysfunction and long-term diseases such as obesity, diabetes, and cardiovascular disorders in adulthood [7]. In this context, it is important to recognize that maternal obesity can cause complications in the mother and fetus during and after postnatal life. During pregnancy, obese women face an increased risk of complications such as gestational diabetes, preeclampsia and other metabolic alterations that can lead the infant to an obesity profile for later life, including intergenerational effects. During postnatal life, one of the most important factors that may be affected by maternal obesity is the breast milk composition as well as breastfeeding establishment, which is a critical factor for the mother-infant pair health [13].

3. Maternal Nutrition and its Impact on Breastfeeding

It is now well recognized that nutritional practices and the maternal metabolic status during pregnancy and postnatal life can have far-reaching and long-lasting consequences for a child's its subsequent generations [14]. In this context, in the course of maternal obesity exposure to the fetus or postnatal infant, the programming of a childhood obesity profile could be direct, such as through epigenetic modifications in utero, Trans placental transfer of inflammatory factors, or through breast milk during lactation [15]. Breastfeeding not only provides the macronutrients necessary for the healthy growth and development of the infant, but is also a direct route by which other bioactive molecules including maternal immune cells, hormones, metabolites and microbes have a strong influence on child development. This could mean resilience or establishment of obesity [15]. Scientific evidence has shown that the components of breast milk (vs. formula), and the length of breastfeeding can reduce the incidence of infant obesity [8]. However, it has been recently suggested that maternal

metabolic status and diet can alter breast milk composition, resulting in a high risk of obesity, diabetes, and cardiovascular diseases in the infant with possible intergenerational effects [15].

Several factors affect breast milk composition, including the stage of lactation, circadian rhythms, preterm delivery, mother's age, number of parity, mother's diet and environmental factors. On this regard, there is emerging evidence about effects on the breast milk composition caused by maternal physiological conditions and environmental adverse factors [16-21]. In particular, metabolic effects of obese women can change negatively the composition of human milk, however to date, it is still not completely understood how this occurs. Consequently, there is still a lack of knowledge regarding the possible adverse effects of the changes in milk composition in terms of the development and health of the infant and its long-term effect.

Studies on the impact of the maternal diet on breast milk compounds are scarce, but evidence shows that maternal nutritional habits can modify the breast milk composition. For example, Rydlewski et al [22] revealed that maternal diet modifies the lipid profile of human milk. In the study, colostrum and transitional milk was analyzed for its fatty acid composition and triacylglycerol's lipid profile including eicosapentaenoic and docosahexaenoic acids, finding that milk from obese women had alterations in the long-chain polyunsaturated fatty acids (LC-PUFAs). Hu et al. [16] using a dietary pattern classification in 122 Chinese lactating women, found higher fat and lower protein concentrations in colostrum in the maternal groups with high proportions of animal foods as well as with the plant based foods group, however, only carbohydrates were affected in mature milk of the high in animal food group. In animal models, Pomar et al. [19], analyzed the changes in milk triacylglycerol's (TG) in relation to both maternal diet and maternal obesity. The results demonstrated that the intake of an obesogenic diet during lactation can alter TG profile in milk, and the maternal fat reserves may affect TG milk composition only at initial stages of lactation. Tan et al. [20] examined the association between maternal dietary intake and breast milk mineral concentrations in 20 Malaysian Malay postpartum mothers, reporting an inadequate maternal intake of several micro minerals (Cu, Mn, I) as well as a decrease in essential mineral concentrations (K, Fe, Zn and Cu) in breast milk, by contrast, Na concentration exceeded the recommendation by 1.5-2.5 times.

On the other hand, a key compound in the composition of breast milk is protein content; mature breast milk has a serum: casein ratio of 60:40, by contrast, cow's milk has a serum casein ratio of 20:80. On this respect, it is known that infant formulas that replace breast milk are made based on the main components of cow's milk and it has been shown that there are substantial differences in the composition and concentration of total protein between cow's milk and human milk, which puts at high risk the infant health [23]. Lactoferrin is the main whey protein in all mammalian milk, and it is found in high amounts in human breast milk compared to cow's milk. Among all of the bioactive substances found in human milk, lactoferrin is well

known for its anti-infective actions, moreover, this protein positively impacts infant gut health and gut immune development [24].

Liu et al. [25] in a cohort study with 206 breastfeeding women found a positive correlation with lactoferrin concentrations in mature human milk with protein, cholesterol and vitamin and eggs intake. The protein components of breast milk have been exhaustively studied to improve the nutritional composition of infant formulas, however, breast milk is a personalized and dynamic food that changes according to the needs of each infant, a process currently unreachable to milk formulas industry despite the biotechnological advances.

A relevant factor for pediatric nutrition research is to evaluate the effect of dairy products consumption by breastfeeding women as nature designed cow's milk to be ingested by calf's and not by other mammals. Despite its relevance, the scientific literature in this area is also scarce. Cutignano et al. [26], in a preliminary multi analytical study, assessed short term effects of maternal dietary bovine milk on the fatty acid composition of breast milk, finding that a single administration of bovine milk might induce slight fluctuations of long-chain fatty acids in the breast milk. Other studies have demonstrated that maternal genetic defects, adiponectin, as well as inappropriate maternal dietary, can affect the breast milk composition triggering systemic inflammation and metabolic disorders in offspring [21].

4. Our Lifestyle is Affecting our Lifespan

Human activities have always a goal in mind, and due to the natural tendency of change, our activities are also constantly changing. Modern days bring greater problems if compared to a more simplistic human lifestyle, therefore, bigger problems may require bigger solutions. Industrialization of basically everything is a human activity that has been growing at surprisingly high rates in almost every country, and many of its achievements have a significant and direct impact on our lifestyle. Chemically speaking, every industry has an urge to use better and cheaper compounds to allow them more production and growth, but everything has a price. Environmental pollution is a nowadays subject that although overlooked for several years, is regaining the attention it deserves. Persistent Organic Pollutants or simply "POPs" are a group of compounds with long half-lives due to specific industrial purposes which mainly possess lipophilic nature that causes them to bio accumulate, mainly in adipose tissue. Pollutant discharges due to the increasing industrial and agricultural activities can also contaminate water bodies and affect negatively human and animal life [27], and due to their high persistency, they are worldwide distributed as there is evidence of POPs presence in rural areas far from industrial pollution sources [28]. Clean water can also get contaminated through chemical leaching from plastic containers. Examples of these compounds are polychlorinated biphenyls (PCBs), dioxins, organochlorine pesticides and Hex chlorobenzene (HCB). They can enter the biological chain during consumption of contaminated water or fatty foods although they can

also be inhaled or absorbed through the skin. Mechanism of action is not completely understood but some POPs are classified as endocrine-disrupting chemicals (EDCs) which are defined by the Endocrine Society as "An exogenous (non-natural) chemical, or a mixture of chemicals, that interferes with any aspect of hormone action" [27]. The normal biological function of hormones includes growth, development and reproductive health [29]. To date, a wide number of compounds are classified as EDCs and they can be grouped as industrial chemicals such as dioxins, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs) and pesticides like dichlorodiphenyltrichloroethane (DDT), chlorpyrifos and methoxychlor. Plastics such as bisphenol A (BPA) and plasticizers such as phthalates are not as persistent as other pollutants but due to their widespread use, they are also found in the environment. EDCs act via several receptors through a different mechanism that includes epigenetic modifications or disturbance of hormonal balance having, as a result, a wide array of health disorders that can affect life in different stages. Abnormalities EDCs produce can be at a developmental, neurologic, immunologic or reproductive level and can also affect growth patterns or increase the presence of hormone-sensitive cancers. They can also be transferred to children through human breast milk or to the fetus via the trans placental route, situations of significant concern as these early stages of life are highly susceptible [28]. Complications derived from this early contact could not be immediately observed but recent evidence shows there might be a link between EDCs exposure with an increase in susceptibility to non-communicable diseases in adult life [27].

5. It's not all about Food: Pollutants as non-communicable Disease Enhancers

Obesity and overweight are growing problems that although initially affected high-income countries only, are now also present in middle and low-income countries. Both children and adults are at risk of becoming over weighted or obese, and globally, numbers are increasing [30], thus, it is of no surprise that this problem is also referred to as "obesity pandemic" [27]. Genetics, high energy intake, low physical activity, sleep deprivation and sedentarism are classic factors that are known to contribute to the conversion of a healthy individual into an overweight/obese phenotype [27], however, changes in our chemical environment appear to be a negatively-modifying factor in the obesity pandemic [27]. This includes pollutants such as POPs and EDCs that end up in the environment due to the industrialization of human activities and its increase is also linked to higher recurrence of obesity, cancer, pulmonary complication, cardiovascular diseases and metabolic diseases such as type 2 diabetes and metabolic syndrome (MetS) [27,28,31]. These health problems are part of the named "non-communicable diseases" which are chronic illnesses that can be largely prevented by adopting healthy lifestyle habits [30] but that ironically, solely in 2019, represented 7 of the 10 leading causes of death worldwide [32]. Of these, metabolic syndrome is a complex disorder composed of dyslipidemia (elevated triglycerides and Apo lipoprotein B; low HDL cholesterol), high arterial blood pressure, dysregulated glucose homeostasis, abdominal obesity and insulin

resistance [33] represents the largest burden of non-communicable diseases worldwide [34]. MetS directly increase the risk of preventable and often fatal diseases such as coronary heart disease, cardiovascular atherosclerosis and diabetes mellitus type 2 [33] which are illness also related to pollutants such as POPs and EDCs [27,31]. Mechanism of actions that turns these chemicals into biological threats is not fully understood as controlled scenarios in research laboratories are far from recreating the natural situation where organisms tend to be exposed chronically to a wide mixture of pollutants at frequently unknown concentrations [28,35], however, several mechanisms have been proposed. EDCs can disturb hormonal balance through several pathways such as hormone-mimicking, disruption of hormone synthesis, alteration of the development of hormone receptors, modification of natural hormone binding process and hormonal antagonism [27]. EDCs are also thought to cause dysbiosis of gut microbiota, where such compounds could also be metabolized by these microbes giving as a result byproducts that can be taken up by the host and affect its glucose homeostasis [31]. Recently, gut dysbiosis has also been associated with MetS [34] therefore this could be part of the missing links between such pollutants and metabolic traits.

6. Pollutant Leaching from Mother to Son

POPs are a nowadays problem as they are distributed all around the globe, no mattering the industrial activity situation of the areas as the presence of these pollutants has been described in the population of rural areas with no industrial activity [36] or remote areas such as in the Inuit population in the Artic [37]. The presence of these compounds can have negative effects on human life, and prenatal contact can affect both the mother and the newborn [28]. Maternal transfer of pollutants related to metabolic aberrations begins early in life as these chemicals can reach the fetus through the trans placental route, or to the newborn via breast milk, acting in both scenarios at the hormonal level [27]. Such events can happen as these compounds have high lipophilicity, therefore, they can easily travel coupled to the lipid fractions that come from mother to child. In fetal life, effects can be seen at embryonic development and sex differentiation; later in life, puberty and reproductive systems can be affected. Non-communicable diseases can also be programmed for coming years as these early stages represent a highly plastic window that allows positive or negative health programming [27]. Different organochlorine pesticides, especially p,p'-DDE, a DDT metabolite considered as a risk factor for overweight [38] has been identified in cord blood samples with a positive correlation between birth weight and the pollutant's presence. In this sense, higher levels mean higher birth weight and this tendency seems to be sex-related as girls show a stronger correlation when the DDT metabolite is present [28,35]. The prenatal presence of p,p'-DDT is also positively correlated with bodyweight outcome in girls [35] and similar effects have also been described with birth weight and cord blood levels of HCB [28]. The presence in cord blood of the bromodiphenyl ether (BDE) BDE-47 is also associated with increased birth

weight in a possible sex-dependent as this effect is seen only in girls [28]. In contrast, the cord blood presence of PCB congeners PCB-52 and specially PCB-28 have shown an inverse sex-specific influence in fetus development as there is an inverse association with birth weight in boys and PCB-52 has a similar effect in girls [28].

Thyroid hormones have important roles in human health as they influence metabolism and development, and during fetal life, it influences brain development [36], unfortunately, the presence of pollutants in mothers such as BDE congeners (BDE-153) and polychlorinated dibenzo-p-dioxins and furans (PCDD/F) can negatively affect these hormones during early pregnancy, a period when this hormone has an impact in fetal development [36]. The latter is to be considered as birth weight is a strong indicator of fetal growth and development. Factors such as genetics, placental circulation and proper maternal nutrition naturally impact the newborn's weight [39], unfortunately, the analyzed evidence shows that pollutants can affect negatively the birthweight and this outcome can be difficult to study as some pollutants show more effects on one sex than another one, and mixtures of pollutants can interfere with the effects. In addition, birthweight is also related to the development of chronic diseases in later life. Small birth size has been linked with cardiovascular diseases whereas large birth size might predict obesity or cancer [40] are examples of these outcomes, therefore, pollutants in the early stages of life should not be overlooked.

7. Conclusions

Breast milk has a wide array of biologic effects as it can regulate infant postnatal growth and development with positive outcomes in the off springs health, however, alterations in its composition can influence the susceptibility to develop chronic diseases in adulthood. This doesn’t mean that breastfeeding should be omitted as the benefits highly overcome the risks. In this sense, our objective as a responsible society is to protect breastfeeding practice and increase its prevalence, since breast milk is an irreplaceable food for the infant, not only for its contribution in achieving optimal growth and development, but also for its metabolic, psychological, economic and environmental benefits for the mother-child pair. Therefore, is urgent to increase the understanding of the impact of environmental factors on breast milk quality and their critical role in the programming of metabolic diseases including their negative effects in the offspring. This could represent an initial step towards preventing and reducing the growing metabolic syndrome pandemic, with an aim in early stages of life. Consequently, rigorous clinical trials are required to further elucidate the effect exerted by metabolic maternal state, dietary and environmental factors to which the mother is exposed that could in turn, modify the breast milk composition and affect the infant's health in future life stages.

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