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Review

Exploring the contribution of maternal antibiotics and breastfeeding to development of the infant microbiome and pediatric obesity

Dominick J. Lemas [a, *], Shanique Yee [a], Nicole Cacho [b], Darci Miller [a], Michelle Cardel [a], Matthew Gurka [a], David Janicke [c], Elizabeth Shenkman [a]

[a] University of Florida, Department of Health Outcomes and Policy, Gainesville, FL, USA
[b] University of Florida, Department of Pediatrics, Division of Neonatology, Gainesville, FL, USA
[c] University of Florida, Department of Clinical and Health Psychology, Gainesville, FL, USA

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SUMMARY

Pediatric obesity, a significant public health concern, has been associated with adult premature mortality and the development of type 2 diabetes and cardiovascular disease. Evidence has suggested that the gut microbiota is associated with pediatric obesity. Establishment of the infant gut microbiome is dependent on a dynamic maternal–infant microbiota exchange during early life. The objective of this review is to describe maternal factors such as feeding practices and antibiotic use that may influence the infant gut microbiome and risk for obesity. The complex components in human milk have many nutritional benefits to the infant; however, the microbiome in human milk may be an important factor to help regulate the infant's weight. We discuss maternal antibiotics and the effects on breast milk as critical exposures that alter the infant's gut microbiome and influence the risk of pediatric obesity.

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1. Introduction

Pediatric obesity has significant public health importance due to increasing risk of adult premature mortality, type 2 diabetes, and cardiovascular disease [1,2]. Currently there is no universally accepted definition of obesity in children aged <2 years [3]; however, growth curves and estimates of adiposity have been associated with infant adiposity [4], rapid weight gain [5], and subsequent pediatric obesity [6]. In the USA between 2011 and 2012, 23% of children were overweight or obese entering kindergarten [7] and 8% of infants are greater than the 95th percentile of sex-specific weight for recumbent length [7]. Moreover, longitudinal data demonstrate that children obese at age 5 years are four times as likely to remain obese at age 14 years, with nearly one in three of these children delivered with a birth weight ≥4000 g [8]. Emerging evidence suggests that an altered intestinal microbiota during early life, potentially resulting from mode of delivery, maternal diet, antibiotic use, hormones, and/or breastfeeding may seed an "obesogenic" microbiome that contributes to the development of obesity in early life [9]. Exclusive breastfeeding has been associated with protection against pediatric obesity [10]; however, these observations do not appear to be universal across all populations [11]. The objective of this review is to examine the development of the infant gut microbiome concerning breastfeeding and antibiotic exposure that may influence and/or obscure the relationship between breastfeeding and protection from obesity.

2. Infant gut microbiome

The human gut microbiome is described as a community of micro-organisms that live in and on the human body [12]. In the last decade, the gut microbiota has been associated with body weight, energy homeostasis and inflammation [13]. Bacterial colonization patterns have also been associated with obesity [14]. The infant gut microbiome is influenced by several factors including genetics, gestational age, mode of delivery, feeding practices (breastfeeding vs formula feeding) [15], and exposure to antibiotics [16]. The initial development of the infant gut microbiome is dependent on prenatal and postnatal maternal–offspring interactions [17]. Prenatal inoculation of the infant microbiome includes transmission of bacteria and bacterial-derived metabolites via umbilical cord blood, amniotic fluid, and the infant's first

* Corresponding author. Address: University of Florida, Department of Health Outcomes and Policy, College of Medicine, 1329 SW 16th St, Gainesville, FL 32608, USA. Tel.: +1 (352) 294 5971.
E-mail address: djlemas@ufl.edu (D.J. Lemas).

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postpartum bowel movement called meconium [17]. Postnatal transmission of the infant microbiome includes exposure to maternal vaginal flora during birth; breastfeeding; and skin-to-skin contact [18]. Importantly, delivery by cesarean section is associated with aberrant infant gut colonization and increased risk of pediatric obesity [19]. Although the founding individual microbiota composition in newborns largely reflects the maternal transfer during birth, accumulating data demonstrates that the postnatal assembly of the human microbiota through breastfeeding plays an important role in resistance to pathogen invasion, immune stimulation, and other important developmental cues early in life [20].

3. Human milk composition

The macronutrient composition of human milk (HM) is dependent upon a variety of factors including maternal environment, time of delivery, stage of lactation, maternal diet, nursing frequency, and maternal body mass index (BMI) [21]. Structure of the macronutrients in HM provides support for infant development of protective microbiota. Specifically, glycosylated proteins passed to the infant through HM act as defense mechanisms against potential pathogens within the infant gut. Whereas many of the proteins in HM are associated with positive health outcomes, formula contains additional protein and different types of protein than HM. During lactogenesis, nutrients in the HM are derived from amalgamation in the lactocyte using dietary stores in the maternal microbiome [21]. Throughout lactation, content and quality of macronutrients and appetite-regulating hormones in HM may affect infant biology and feeding behaviors [22]. Macronutrient concentration is highly variable, especially in the first month of infant life, with fat content being the most variable macronutrient in milk [23]. Fat content increases as the breast is emptied, and is considerably higher during afternoon and evening feedings relative to feedings in the morning and at night [23]. This excess intake of fat and protein in early childhood is linked to increased levels of adiposity [10]. The macronutrient content of HM has been associated with the maternal gut microbiome [24] and differs between normal weight and obese women [25]; however, there is currently limited information that describes how the micronutrient composition of HM influences the infant gut microbiome and pediatric obesity.

4. Human milk hormones

Appetite-regulating hormones including adiponectin, leptin, insulin, ghrelin, and resistin are present in HM and have been associated with the development of pediatric obesity; however, their contribution to the infant gut microbiome is not well established [22]. Milk adiponectin is present at higher concentrations relative to other milk adipokines (i.e., leptin, ghrelin) and has been related both positively and negatively with obesity risk and adiposity in later life [26–28]. Further, milk adiponectin concentrations have also been associated with adiposity and weight gain in infants who are breastfed [26,29,30]. Milk resistin is correlated with anthropometric indices and gestational age [31] whereas milk ghrelin is a hunger-stimulating hormone [27,31]. HM insulin and leptin concentrations at the age of one month were associated with lower infant body weight and adiposity in a cohort of exclusively breastfed infants [32]. Importantly, dietary insulin affects the neonate at the mucosal level via insulin receptors localized along the intestinal tract, and systemically via direct absorption through loose tight-junctions into the bloodstream [33–35]. Moreover, HM leptin is an important factor regulating infant body weight control [36] and gastric leptin has been linked to the gut microbiota [37]. In adult mice, gastric leptin and the gut leptin receptor were shown to regulate the gut microbiota by increasing mRNA expression of gut antimicrobial peptides, independent of food intake [38]. Recent data from a cohort of exclusively breastfed infants suggest that maternal obesity may adversely impact the early infant intestinal microbiome at age 2 weeks; however, HM insulin and leptin were independently associated with beneficial microbial metabolic pathways predicted to increase intestinal barrier function and reduce intestinal inflammation [39]. Given the role of appetite-regulating hormones present in HM that contribute to neonatal gut barrier function and development of the intestinal mucosa [40–42], additional investigations should consider the role of HM hormones in the development of the infant gut microbiome as potential mechanisms to attenuate the risk of pediatric obesity.

5. Human milk microbiome

Breastfeeding, as the initial food source for the infant, introduces new microbial communities that stimulate growth and development of the infant gut microbiome [43]. Investigations have examined the infant gut microbiome in breast- and formula-fed infants [15]; however, surprisingly little is known about HM composition and its impact on the development of the early infant gastrointestinal tract [19]. Bifidobacteria are Gram-positive bacteria that are dominant in the microbiota of breastfed infants; the colonization of the infant gut by Bifidobacteria occurs due to the ability to utilize HM oligosaccharides [44]. *Bifidobacterium* species within the milk microbiome have been shown to have positive effects on infant health, including the prevention of infection by pathogenic bacteria and anticarcinogenic capabilities [45]. Moreover, *Bifidobacterium* species in HM were observed to be higher in mothers who delivered at term as compared to preterm delivery [19]. Additionally, HM from mothers who delivered by cesarean section had a lower count of *Bifidobacterium* [19] that may be related to perinatal antibiotic exposure [46]. Collectively, these data suggest that cesarean sections in combination with maternal antibiotics have independent and synergistic effects on the development of the infant gut microbiome that reduce bifidobacteria [14] and may play an important part in the postnatal development of the immune system [47] and obesity [48].

6. Maternal antibiotic exposure

Antibiotics utilization in the USA has increased over the past decade due to changes in lifestyle and health care systems [49]. In recent years, our ubiquitous use of antibiotics in obstetrics means that many infants are exposed to antibiotics prenatally, perinatally, and postnatally. Prenatally, maternal antibiotics are often prescribed due to urinary tract infection, sinus infection, ear infection or any other common infections. During peripartum, use of antibiotics is most likely given due to prolonged rupture of membranes, Group B streptococcus (GBS) colonization, cesarean section or chorioamnionitis. According to the Centers for Disease Control and Prevention (CDC), ~25% of women are colonized with GBS. The current recommendation from CDC and American Congress of Obstetricians and Gynecologists (ACOG) for prevention of early onset GBS disease includes providing antibiotics during labor, referred to as intrapartum antimicrobial prophylaxis (IAP) [50,51]. Additional data from the CDC (2013) show that there are about four million births per year in the USA, translating to ~1 million pregnant mothers qualifying for IAP [52]. The maternal IAP decreases neonatal colonization after birth and this decreases invasive early onset neonatal GBS infections.

The use of antibiotics is even higher in cases of preterm deliveries [53]. A meta-analysis on use of antibiotics in the setting of preterm labor versus preterm premature rupture of membranes (PPROM) suggests a possible reduction in neonatal infection with

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