



Messaging and methodological considerations when researching breastfeeding and obesity

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To the Editor:

Identifying modifiable components of human milk that influence infant growth and adiposity is a clinically important objective with potential implications for public health. We commend Enstad and colleagues [1] for their efforts to identify associations between maternal body mass index (BMI) and human milk composition, and downstream associations with infant anthropometrics. This research adds new information to an understudied subject that we have also investigated [2, 3]. However, we are concerned that in several places, the authors' language implies that milk from mothers with an elevated BMI may predispose their infants to obesity. This is a potentially harmful message that is

unsupported by their data due to several methodological limitations. Additionally, this implication is made without acknowledging the extensive evidence that breastfeeding is associated with healthy growth patterns and lower odds of childhood obesity [4], even among children of mothers with obesity [5].

Methodological considerations

We appreciate the authors' attempt to address whether the association between maternal BMI and infant growth is attributed, in part, to human milk composition. However, answering this question using observational data requires a mediation analysis, which the authors acknowledge they were underpowered to perform because of the small study population ($n = 40$). Given this limitation, the implication of mediation in their conclusions is not supported.

The results presented do provide evidence for separate associations between maternal BMI and milk composition, and between milk composition and infant anthropometrics. However, only 1 of 6 milk components investigated (the n6:n3 polyunsaturated fatty acid [PUFA] ratio) was associated with both maternal BMI and infant growth trajectory, and without mediation analysis, it is not possible to confirm or quantify the mediating role of this milk component. Moreover, dozens of comparisons between multiple milk components and infant anthropometric measurements were tested without correction for multiple comparisons, which increases the likelihood of false positive results. Even if milk composition is a mediator to some (likely small) degree, other known but unmeasured mediators (e.g. epigenetic effects in utero resulting from pre-pregnancy BMI and associated conditions such as gestational diabetes; other infant feeding practices) [4, 6] are likely more impactful and therefore more important to target for intervention.

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We are also concerned that complementary feeding was not accounted for in this study, but may be an important confounder and/or mediator in the pathways under investigation. Mothers with obesity are more likely to introduce complementary foods early (before 4 months), which is associated with more rapid weight gain in their children [5, 7]. In addition, introduction to complementary foods corresponds with gradual weaning, which influences milk composition [8]. The omission of complementary feeding data is an important limitation since infants in this study were followed for 7 months.

Finally, details are lacking regarding milk collection procedures and the n-6:n-3 PUFA ratio. While we appreciate that the authors acknowledged the limitations of their milk collection protocol, appropriate milk collection and storage strategies are critically important for many human milk analytes, especially fat, which varies within a feed, diurnally, with maternal diet, and over the course of lactation [9]. Furthermore, results could be biased if collection methods differed between women with and without obesity, which is conceivable since feeding patterns and practices have been shown to differ between these groups [5, 10]. In addition, the authors do not identify the individual fatty acids included in the n-6:n-3 PUFA ratio calculation, nor report the actual values observed (e.g. mean, median, range), making comparison with existing literature difficult.

Messaging and context

As human milk scientists, population health researchers, lactation professionals, and maternity care providers, we are concerned with the messaging of the article. Importantly, the title is misleading in that it suggests causal links (“impact”) between maternal obesity, breast milk composition, and infant growth. This causal language is too strong for an observational study that does not use causal modeling. In addition, the authors use the unconventional term “breast milk inflammation,” which carries a negative connotation and is not defined anywhere in the article. This phrase alongside “developmental programming of infant growth” leads the reader to believe that proinflammatory constituents in milk have long-term negative effects on infant growth patterns - yet only a few select inflammatory biomarkers were assessed, and the duration of follow up was just 7 months.

Lastly, the findings are discussed without considering the broader context and complex reality of factors that influence infant feeding practices, nor the potential harm of discouraging women with obesity from breastfeeding. These issues are particularly concerning because women with obesity already struggle disproportionately with breastfeeding compared to their peers without obesity [11]. The connotation that milk from women with obesity might be

subpar or even hazardous for their infants may further add to their breastfeeding struggles and is unsupported given the data presented. Moreover, breastfeeding is generally associated with *reduced* risk of infant/child obesity compared to other infant feeding options [4], even among women with obesity [5], alongside many other benefits for maternal and child health [4]. It is important to situate the results of this research within this context.

In conclusion, we agree with Enstad et al. that identifying modifiable components of human milk that influence infant growth and adiposity is a clinically important objective. However, it must be pursued with rigor and caution - ideally using a transdisciplinary approach that includes experimental model systems where causal mechanisms can be tested. Most importantly, this research must be undertaken using a knowledge translation approach that accounts for the multifactorial causes and consequences of breastfeeding difficulties, human milk composition, and maternal and childhood obesity.

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Author contributions SMR, KM, DC, and MBA planned and wrote the initial draft correspondence. All authors provided feedback and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest. They report the following: MBA serves in a volunteer capacity as Secretary to the International Society for Research on Human Milk and Lactation (ISRHML) and as a member of the National Academy of

Sciences, Engineering and Medicine Committee on Scanning New Evidence on the Nutrient Content of Human Milk. She regularly speaks at conferences and workshops on infant nutrition, some sponsored by Medela, the Institute for the Advancement of Breastfeeding & Lactation Education, and Prolacta Biosciences. MBA, SMR, and MB have contributed to online courses on breast milk and the infant microbiome produced by Microbiome Courses. SMR serves as the scientific advisor for SimpliFed, created and operates Milk and Microbes, and is currently pursuing the development and patenting of a human milk pasteurizer. She also leads a systematic review for the International Milk Consortium (IMiC) on the associations between human milk analytes and infant/child growth in the first 2 years. ST serves in a volunteer capacity as Trainee Mentorship Series Coordinator to the Trainee Interest Group of ISRHML. KK and CR are co-founders of the Winnipeg Breastfeeding Center. They regularly give presentations to clinical professionals and trainees and about lactation support, without remuneration. NCN served in a volunteer capacity as the Scientific Chair for Breastfeeding at the American Public Health Association and served on the Executive Council for the International Society for Research in Human Milk and Lactation until April 2020. None of these entities had any involvement in the development or publication of this correspondence.

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