The Milk of Paradise?: New Research on Maternal Obesity, Breast Milk Quality, and Infant Metabolic Health

Ellen W. Demerath, PhD
Associate Professor,
Division of Epidemiology and Community Health
School of Public Health
University of Minnesota
Minneapolis, MN

Patricia L. Fontaine, MD, MS
Senior Clinical Investigator,
Health Partners Institute for Education and Research
Minneapolis, MN

David A. Fields, PhD
Associate Professor,
Endocrinology Section
Department of Pediatrics
University of Oklahoma College of Medicine
Oklahoma City, OK
The public health goal of universal breast-feeding

- Breast-milk is currently recommended as the sole source of nutrition for infants through age 6 months because of well-documented benefits for:
  
  - **Mothers** *(post-partum weight loss, longer birth spacing, lower cost)*
  
  - **Infants** *(passive immunity yields lower rate of infectious disease, higher performance on tests of cognitive development; emotional and psychological benefits of the bonding experience; ‘optimal nutrition’ with composition varying to suit maturity)*

The public health goal of universal breast-feeding

- Breastfeeding is also associated with lower obesity risk in children in numerous studies.
- A systematic review found a 4% reduction in risk of overweight or obesity per month of breastfeeding (Harder et al., 2005).
- Possible mechanisms: lower kcal and protein in milk than formula, poorer appetite regulation in the formula fed infant.

- However, there are important race/ethnic, socioeconomic, and obesity-related disparities in breast feeding that must be considered…
Disparities in breastfeeding in the US

- **Race/ethnicity**
  - Initiation is highest in Hispanic women (79%) 
  - Initiation is lowest in Black non-Hispanic women (62.4%)

- **Education**
  - Initiation is lower in women with ≤ high school education (64%), as compared to women with > high school education (79%)

Maternal obesity is now a common condition in the US

- The percentage of US mothers with pre-pregnancy BMI in the overweight or obese range has increased from 29.7% in 1983 to 53.7% in 2011; ~25% of US deliveries are to obese women.

- In contrast to men, obesity in women increases as education decreases:
  - College graduates = 23.4%
  - HS graduates = 39.8%
  - Less than HS = 42.1%

- These SES relationships with obesity are already evident in early childhood:
  - 8.4% of all 2-5 year old children in the US are obese
  - 14.4% of 2-5 children living in poverty are obese

Maternal obesity is associated with 2-3 fold increase in child obesity risk…..Why?

- Correlated obesogenic environments (e.g., pollutant exposure; similar dietary intake)
- Shared genetic risk transmitted from mother (and father) to child
- Epigenetic variation altered by in utero environment and across generations
- Parenting behavior and styles affecting infant and child feeding patterns and behavior
- Different patterns of breast-feeding and breast milk composition in obese mothers
Rapid decline in exclusive breast-feeding in overweight women in the Twin Cities region

- $HR_{adj}$ Exclusive Breast-feeding Cessation (Overweight/Obese vs Normal weight):
  - 1.42 (1.02-2.00)

From Hauff and Demerath, 2012 *Am J Hum Biol,*
Maternal obesity, breastfeeding, and breast milk

- Obese women are just as likely to intend to breastfeed as normal weight women (Hauff and Demerath, AJHB 24:339-49, 2012; Hauff et al., AJCN 99(3):524-34, 2014).

- However, obese women are 1.38-3.09 times less likely to initiate breastfeeding, and breastfeed for ~4 weeks less than normal weight women (Amir and Donath, BMC Pregnancy and Childbirth, 7:9, 2007).

- Why?
  - **Physiology:** delayed lactogenesis II, lower prolactin response
  - **Behavior:** difficulty in latching on; positioning, poorer body image
  - **Social factors:** public breastfeeding as “indecent”, sexualized
  - **Health beliefs:** Low SES mothers perceive formula as safe, reliable, and nutritious, while poor diet and illness can make breast milk “dangerous” for the infant (Nommsen-Rivers et al., Breastfeeding Medicine 5(1):25-33, 2010)
Maternal obesity, breast feeding, and breast milk

- Once maternal obesity (and SES) are accounted for, the relationship of breast-feeding to child obesity risk is greatly diminished. What does this mean? Is breast feeding not important for infant metabolic health?

- No: Milk varies greatly between women, depending on maternal diet, day-to-day, and within feeds, and much of this variation is currently poorly understood.

- If variation in the exact formulation and dosage of a putative drug treatment would weaken an RCT, so too we should be looking at milk as medicine and not simply comparing the effect of “any milk to formula”, but also examining specific nutritive and non-nutritive components of milk as they relate to infant outcomes.
Animal models provide strong support for the role of “lactational programming” by maternal obesity

- 10-fold greater **leptin** concentration in obese than lean rat dams (Oben et al., *J. Hepatol.*, 2010)
- 128% greater milk **insulin** and 50% lower **PUFA** concentration in milk of obese vs. lean dams (Gorski et al, *Am., J. Physiol.*, 2006)
- At maturity, offspring of lean dams nursed by an obese female had higher:
  - Caloric intake
  - Body fat
  - Plasma insulin and leptin
  - Blood pressure and hepatic steatosis
- …and conversely, nursing by lean dams **normalized** the body composition and metabolic health of offspring of obese dams (Gorski et al., 2006)
However, extrapolating results from rodents to humans requires caution, due to the large, qualitative species differences in milk composition, growth trajectories and developmental maturity at birth.
As in non-human species, human milk contains numerous non-nutritive factors, including appetite, growth, and obesity-related hormones and inflammatory factors:
- Leptin, IGF-1, glucose, insulin, ghrelin, IL-6, C-reactive protein, and TNF-α

Early work suggested elevated risk of obesity and glucose intolerance in breastfed offspring of diabetic mothers (e.g., Rodecamp et al., *Diabetes Care*, 2005)

Growing evidence that obesity-related hormones and adipokines in human milk may be altered by maternal nutritional status, and influence infant body composition
Milk is synthesized by mammary epithelial cells by transforming substrates derived from the blood and interstitial fluid, as well as from the surrounding stroma including adipocytes.

It is reasonable, therefore, that circulating factors in the blood that are increased in obesity (inflammatory factors, hormones) may also be increased in milk.

Figure from: Milk Secretion, an Overview  
http://mammary.nih.gov/reviews/lactation/Neville001/
Increasing evidence for association of maternal adiposity and milk composition in humans

- 26 studies included in this 2014 systematic review
- 11/15: positive association of maternal BMI and milk leptin
- 2/9: positive association of maternal BMI and milk adiponectin
- Associations with insulin, ghrelin, resistin, obestatin, Peptide YY and Glucagon-Like Peptide 1 were inconclusive
- High degree of variability across studies in collection, preparation and analysis of breast milk samples
Leptin strongly positively associated with maternal BMI
Produced in mammary epithelial cells and in milk (20-fold lower concentration than serum)
Conflicting evidence from a number of studies on association with infant weight or adiposity

# Appetite and Satiety-Related Hormones and Adipokines in Breast milk at 1 month, N=35

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (N=17)</th>
<th>Overweight/Obese (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>25 ± 9</td>
<td>25 ± 9</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>7.5 ± 10</td>
<td>6.1 ± 8</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>6.2 ± 6</td>
<td>5.2 ± 5</td>
</tr>
<tr>
<td>Insulin (pg/mL)</td>
<td>664 ± 632</td>
<td>963 ± 745*</td>
</tr>
<tr>
<td>Leptin (pg/mL)</td>
<td>580 ± 456</td>
<td>1,222 ± 900*</td>
</tr>
<tr>
<td>NPY (ng/ml)</td>
<td>2.4 ± 1.5</td>
<td>2.0 ± 0.9</td>
</tr>
</tbody>
</table>

* = p<0.05

Fields and Demerath, under review
Gestational Weight Gain May Also Play a Role

- N=35 exclusively breast feeding women seen at 1 and 6 months; N obs =59
- Linear mixed effect model
- Excess gestational weight gain was associated with higher milk leptin, independent of pre-pregnancy BMI

<table>
<thead>
<tr>
<th>Effect on [LnLeptin]</th>
<th>Estimate</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Pregnancy BMI (kg/m²)</td>
<td>0.07</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Excess GWG (yes)</td>
<td>0.52</td>
<td>0.23</td>
<td>0.03</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>-0.04</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>Timepoint (1, 6 months)</td>
<td>0.01</td>
<td>0.03</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Demerath and Fields, under review
Evidence for possible lactational programming: Relationship of milk hormones and cytokines on infant body composition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glucose</th>
<th>Ln Insulin</th>
<th>Leptin</th>
<th>Ln TNF-α</th>
<th>Ln IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.39**</td>
<td>-0.32*</td>
<td>-0.20</td>
<td>-0.36**</td>
<td>-0.43***</td>
</tr>
<tr>
<td>Weight Δ 0-1 m</td>
<td>0.23</td>
<td>-0.29*</td>
<td>-0.32*</td>
<td>-0.18</td>
<td>-0.35**</td>
</tr>
<tr>
<td>%fat</td>
<td>0.14</td>
<td>0.20</td>
<td>0.20</td>
<td>-0.14</td>
<td>-0.36**</td>
</tr>
<tr>
<td>Total Fat Mass</td>
<td>0.31*</td>
<td>-0.08</td>
<td>-0.02</td>
<td>-0.31*</td>
<td>-0.43***</td>
</tr>
<tr>
<td>Trunk Fat Mass</td>
<td>0.31*</td>
<td>-0.05</td>
<td>-0.05</td>
<td>-0.32*</td>
<td>-0.44***</td>
</tr>
<tr>
<td>Total Lean Mass</td>
<td>0.39**</td>
<td>-0.32*</td>
<td>-0.23</td>
<td>-0.37**</td>
<td>-0.34**</td>
</tr>
</tbody>
</table>
Corroborates finding in mice: Lager et al., 2011, Perinatal lack of maternal IL-6 promotes increased adiposity during adulthood in mice. *Endocrinology* 152:1336-46.
Evidence supporting potential bioactivity of breast-milk peptides

- Gastrointestinal epithelial cell receptors for milk hormones suggest they may enter the infant circulation

- Human milk contains antiproteases that retard proteolysis

- Normal developmental delay in production of gastric acid and digestive enzymes for 4-6 months may favor survival of cytokines and adipokines in the young infant

- Proof of principle: oral leptin supplementation in suckling rats results in increased serum leptin concentrations acutely; there is transport of large peptides from the gut to the circulation
State of the Human Lactational Programming Literature in 2015

- Studies predominantly small (N<100), cross-sectional, wide inclusion criteria, lack of control for infant age and breast feeding exclusivity
- Recruited after initiation of breast-feeding; open to confounding by prenatal conditions (e.g., maternal circulating hormones, physical activity and diet)
- Narrow range of milk factors measured; effects could be due to uncontrolled correlation with true causal factors
- Macronutrient and caloric content of the milk generally not adjusted for in analysis
- Wide range of milk expression and collection methods
- Infant outcomes generally limited to weight and length
Our research seeks to understand how health inequalities can “get into the milk” of breast feeding women, specifically in regard to the role of:

- Excess adiposity before pregnancy
- Excess weight gain during pregnancy
- Post-pregnancy weight loss and retention during lactation

in altering milk composition in ways that matter for infant obesity risk
- Prospective observational cohort of N=360 non-diabetic mothers who plan to exclusively breast-feed their infants, recruited in the second trimester of pregnancy
- Equal numbers of normal weight, overweight, and obese women

### Table 1. Data Collection Flow

| Aim 1 and 2 (N=360)                      | Pregnancy | Delivery/Discharge | 1-month | 2-months | 3-months | 6-months | 12-months |
|-----------------------------------------|-----------|--------------------|---------|----------|----------|----------|----------|----------|
|                                          | Consent   | Delivery records   | Questionnaires | Milk output | Milk sample | Infant ADP | Maternal anthropometry | Questionnaires | Milk output | Milk sample | Infant ADP | Maternal anthropometry |
|                                          | Questionnaires |                | Questionnaires | Milk output | Milk sample | Infant ADP | Maternal anthropometry | Questionnaires | Milk output | Milk sample | Infant ADP | Maternal anthropometry |
|                                          | Ob/gyn records |              | Questionnaires | Milk output | Milk sample | Infant ADP | Maternal anthropometry | Questionnaires | Milk output | Milk sample | Infant ADP | Maternal anthropometry |

**Additional data for Aim 3 (N=60)**
- Maternal serum
- Cord Blood
- Infant ADP
- Maternal DXA

**Surveillance sub-study:** dyads breast-fed < 1 mo.
(Questionnaires at 1, 3, and 6 months; infant pediatric records for weight and length)
Conclusion

- The ultimate goal of our research is to support women and their infants during a crucial phase for development of life-long health risks.
- Exclusive breastfeeding to 6-months is recommended for all infants but very little is yet known about how the evolutionarily novel condition of pervasive maternal obesity influences milk composition and thereby alters the trajectory of growth and health for the next generation.
- In addition to identifying potentially novel intervention targets to prevent child obesity, the study will be a valuable biospecimen resource for additional exploratory analyses.
- With the help of an advisory board of lactation consultants and pediatricians, results will be disseminated to augment lactation education for breastfeeding women.
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    - Katy Smith, MS (Coordinator)
  - **University of Minnesota**
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    - Heather Gray, MPH (Data Management, Analyst)
    - Neely Miller, MS (Lab Manager)
    - Tonya Schoenfuss, PhD (Dairy Sciences)
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    - David Jacobs, PhD (Biostatistician)
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