Duration of Lactation and Maternal Adipokines at 3 Years Postpartum

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Duration of Lactation and Maternal Adipokines at 3 Years Postpartum

Alison M. Stuebe,1,2 Christos Mantzoros,3 Ken Kleinman,4 Matthew W. Gillman,4,5 Sheryl Rifas-Shiman,4 Erica P. Gunderson,6 and Janet Rich-Edwards7,8

OBJECTIVE—Lactation has been associated with reduced maternal risk of type 2 diabetes, the metabolic syndrome, and cardiovascular disease. We examined the relationship between breastfeeding duration and maternal adipokines at 3 years postpartum.

RESEARCH DESIGN AND METHODS—We used linear regression to relate the duration of lactation to maternal leptin, adiponectin, ghrelin, and peptide YY (PYY) at 3 years postpartum among 570 participants with 3-year postpartum blood samples (178 fasting), prospectively collected lactation history, and no intervening pregnancy in Project Viva, a cohort study of mothers and children.

RESULTS—A total of 88% of mothers had initiated breastfeeding, 20% had breastfed ≥12 months, and 42% had exclusively breastfed for ≥3 months. In multivariate analyses, we found that duration of total breastfeeding was directly related to PYY and ghrelin, and exclusive breastfeeding duration was directly related to ghrelin (predicted mean for never exclusively breastfeeding: 700.6 pg/mL vs. ≥6 months of exclusive breastfeeding: 1,008.1 pg/mL; P < 0.01) at 3 years postpartum, adjusting for pregravid BMI, gestational weight gain, family history of diabetes, parity, smoking status, and age. We found a nonlinear pattern of association between exclusive breastfeeding duration and adiponectin in multivariate-adjusted models.

CONCLUSIONS—In this prospective cohort study, we found a direct relationship between the duration of lactation and both ghrelin and PYY at 3 years postpartum. Diabetes 60:1277–1285, 2011

Type 2 diabetes causes substantial morbidity and mortality, affecting >9 million women in the U.S. Recent epidemiologic data (1–4) suggest that lactation may reduce a woman’s risk for this disease. Lactation also has been associated with more favorable lipid profiles after weaning (5), reduced metabolic syndrome risk (6,7), and lower rates of hypertension (3,8) and myocardial infarction (3,9).

These findings suggest that lactation may be a modifiable risk factor for metabolic disease in women. We have previously hypothesized that lactation mobilizes maternal adipose stores, resetting maternal metabolism after pregnancy (10). Adipose tissue produces cytokines called adipokines, and these endocrine markers are associated with subsequent metabolic disease risk. High leptin levels are associated with adverse metabolic profiles (11,12), although these associations are attenuated with adjustment for fat mass. High ghrelin (13–16) and adiponectin (17–20) levels are associated with reduced diabetes and metabolic disease risk. The protein peptide YY (PYY) also plays a key role in metabolism and appetite regulation, and low PYY levels are associated with obesity (21,22). No studies, to our knowledge, have measured the association between lactation and maternal levels of leptin, adiponectin, ghrelin, or PYY after weaning. We therefore examined the association between lactation duration and these markers at 3 years postpartum in Project Viva, a prospective cohort study of maternal and infant health. We hypothesized that longer durations of lactation would be associated with lower leptin and higher adiponectin, ghrelin, and PYY.

RESEARCH DESIGN AND METHODS

Women were recruited for Project Viva at their first prenatal visit at one of eight urban and suburban obstetrical offices of a multispecialty group practice in eastern Massachusetts. To be eligible for the study, potential participants were required to be fluent in English, <22 weeks’ gestation, and have a singleton pregnancy; 65% of eligible women were recruited. All participants provided written informed consent. The human studies committee of Harvard Pilgrim Health Care approved all procedures in accordance with ethical standards for human experimentation.

Of 2,128 participating women who gave birth, 1,579 were invited to a 3-year follow-up examination because they had completed dietary questionnaires during pregnancy; 761 of these women were eligible for the current analysis because they had not delivered another child since the birth of the index child 3 years previously, they did not have type 1 or type 2 diabetes, and they attended the 3-year visit. Of these women, 611 provided a blood sample. We excluded women missing breastfeeding duration (n = 30), gestational weight gain (n = 4), gestational diabetes (n = 4), or adipokine measurements (n = 3), leaving 570 women for analysis. Fasting blood samples were available for 175 of 570 women.

When we compared women who provided fasting samples with those who provided nonfasting samples, we found no differences in adiponectin, leptin, breastfeeding duration, prepregnancy BMI, gestational weight gain, age, race, parity, gestational glucose tolerance, or family history of diabetes. We excluded from our analysis lactation analysis women missing data on the timing of introduction of formula or complementary foods (n = 130).

Assessment of lactation. At approximately 28 weeks’ gestation, study participants provided information on their intention to breastfeed. Shortly after delivery, participants again reported their intention and initiation of breastfeeding. At the 6-month follow-up visit, we asked women whether they were breastfeeding and whether they had introduced formula or solid foods. Women reported timing of weaning and introduction of supplemental foods in months, weeks, or days. We similarly assessed breastfeeding at 12 months postpartum.

From the 1Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill; the 2Department of Maternal and Child Health, University of North Carolina Gillings School of Global Public Health, Chapel Hill, North Carolina; the 3Department of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Boston, Massachusetts; the 4Obesity Prevention Program, Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, Massachusetts; the 5Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the 6Division of Research, Epidemiology and Prevention Section, Kaiser Permanente, Oakland, California; the 7Consortium for Women’s Health and Gender Biology, Brigham and Women’s Hospital, Boston, Massachusetts; and the 8Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.

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© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.
For our categorical analysis, we coded duration of lactation as 0, >0 to <3, \( \geq 3 \) to <6, \( \geq 6 \) to <12, and \( \geq 12 \) months. We defined exclusive lactation as time to first introduction of solid foods, formula, or juice. We coded duration of exclusive lactation in the categories of 0, >0 to <1, 1 to <3, 3 to <6, and \( \geq 6 \) months.

We used data on duration of breastfeeding, reasons for weaning or supplementing, and mothers’ planned duration reported at 28 weeks’ gestation to define “curtailed breastfeeding” as \( J \) weaning before 3 months among mothers who planned to breastfeed at 3 months or 2) introduction of formula before 3 months among mothers who planned to exclusively breastfeed at 3 months. We defined the curtailed breastfeeding group may have had physiologic lactation failures that did not affect women who was planned to wean before 3 months. At the 6-month interview, mothers who were not exclusively breastfeeding identified reasons for introducing formula from a structured list. We classified women as having problems with milk supply if they endorsed any of the following: “I wasn’t producing enough breast milk to satisfy my baby,” “I had difficulty or didn’t like pumping breast milk,” or “My baby was not gaining enough weight with breastfeeding.” We used categories of never breastfeeding, curtailed breastfeeding with low milk supply, curtailed breastfeeding without low milk supply, and successful breastfeeding to assess whether low milk production was associated with maternal adipokines at 3 years postpartum.

Assessment of adipokines at 3 years postpartum. Women returned with their children at 3 years postpartum for a physical examination that included anthropometric measurements and a blood sample. We tested all blood samples from their children at 3 years postpartum for a physical examination that included kine levels at 3 years postpartum.

to assess whether low milk production was associated with maternal adipo-
categories of never breastfeeding, curtailed breastfeeding with low milk supply, curtailed breastfeeding without low milk supply, and successful breastfeeding to de-
714.8 pg/mL for no lactation, \( P = 0.32 \). We found no association between duration category and adiponectin or PYY.

Table 1: Baseline characteristics of study population by total duration of lactation. Data from 570 participants in Project Viva who presented for follow-up at 3 years postpartum without an intervening birth

<table>
<thead>
<tr>
<th>Months of lactation</th>
<th>None</th>
<th>0 to &lt;3</th>
<th>3 to &lt;6</th>
<th>6 to &lt;12</th>
<th>( \geq 12 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 70 ) Mean (SD) Mean (SD) Mean (SD) Mean (SD) Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td>26.8 (6.0)</td>
<td>26.9 (7.3)</td>
<td>24.9 (5.0)</td>
<td>24.8 (5.2)</td>
<td>23.7 (3.8)</td>
</tr>
<tr>
<td>Gestational weight gain (kg)</td>
<td>15.1 (6.7)</td>
<td>14.6 (6.2)</td>
<td>15.7 (5.5)</td>
<td>14.5 (5.2)</td>
<td>14.9 (5.0)</td>
</tr>
<tr>
<td>Postpartum weight retention at 3 years (kg)</td>
<td>3.7 (7.5)</td>
<td>1.8 (10.0)</td>
<td>2.9 (5.7)</td>
<td>2.4 (5.6)</td>
<td>1.8 (5.7)</td>
</tr>
<tr>
<td>Age at 3 year visit</td>
<td>36.0 (4.8)</td>
<td>36.8 (6.0)</td>
<td>37.2 (5.3)</td>
<td>38.2 (4.6)</td>
<td>38.8 (5.0)</td>
</tr>
</tbody>
</table>

Race | 0.10
---|---
Asian | 0 (0) | 5 (5) | 7 (6) | 5 (4) | 5 (3) |
Black | 12 (17) | 16 (17) | 21 (18) | 13 (9) | 19 (13) |
Hispanic | 2 (3) | 9 (10) | 11 (9) | 8 (6) | 7 (5) |
Other | 3 (4) | 4 (4) | 8 (7) | 3 (2) | 6 (4) |
White | 53 (76) | 58 (63) | 70 (60) | 112 (79) | 113 (75) |

Parity | 0.006
---|---
1 | 12 (17) | 39 (42) | 37 (32) | 33 (23) | 41 (27) |
2 | 36 (51) | 40 (44) | 57 (49) | 73 (52) | 64 (43) |
\( \geq 3 \) | 22 (31) | 13 (14) | 23 (20) | 35 (25) | 45 (30) |

Gestational glucose tolerance | 0.74
---|---
Gestational diabetes | 3 (4) | 6 (7) | 4 (3) | 4 (3) | 5 (3) |
Impaired glucose tolerance | 3 (4) | 2 (2) | 8 (7) | 5 (4) | 6 (4) |
Transient hyperglycemia | 5 (7) | 12 (13) | 13 (11) | 14 (10) | 11 (7) |
Normal | 59 (84) | 72 (78) | 92 (79) | 118 (84) | 128 (85) |

Parental history of diabetes | 0.85
---|---
Yes | 11 (16) | 17 (19) | 19 (16) | 20 (14) | 20 (13) |
No | 59 (84) | 75 (82) | 98 (84) | 121 (86) | 130 (87) |

Hormonal contraception† | 0.04
---|---
Yes | 4 (10) | 16 (28) | 7 (10) | 17 (21) | 16 (15) |
No | 37 (90) | 42 (72) | 64 (90) | 65 (79) | 92 (85) |

Current smoker | \(<0.001\)
---|---
Yes | 8 (11) | 13 (14) | 7 (6) | 7 (5) | 3 (2) |
No | 50 (71) | 73 (79) | 104 (89) | 129 (91) | 139 (93) |
Missing | 12 (17) | 6 (7) | 6 (5) | 5 (4) | 8 (5) |

Plan to exclusively breastfeed at 3 months ‡ | \(<0.001\)
---|---
Yes | 1 (1) | 12 (13) | 26 (22) | 74 (52) | 100 (67) |
No | 69 (99) | 80 (87) | 91 (78) | 67 (48) | 50 (33) |

Fasting sample | 0.34
---|---
Yes | 16 (23) | 30 (33) | 40 (34) | 38 (27) | 51 (34) |
No | 54 (77) | 62 (67) | 77 (66) | 103 (73) | 99 (66) |

*ANOVA \( P \) value for continuous variables, \( \chi^2 \) \( P \) value for categorical variables. †Using hormonal contraception at 2–3 years postpartum, as reported at the 6-year follow-up visit. Missing for 210 participants. ‡At the 28-week interview, each participant reported how she intended to breastfeed her infant at 3 months postpartum.

We found a nonlinear association between adiponectin and duration of total breastfeeding in a multivariate-adjusted three-knot quadratic spline model (Fig. 1D) (likelihood ratio test, \( P = 0.04 \)). To determine whether breastfeeding intensity was associated with maternal metabolic markers at 3 years postpartum, we compared adipokine levels among women with different exclusive breastfeeding durations. In unadjusted models, we found higher adiponectin and lower ghrelin levels among women who had never exclusively breastfed (Table 3). When we adjusted for prepregnancy BMI and other risk factors, we found that differences in ghrelin levels were somewhat attenuated, but the association of exclusive breastfeeding with leptin was strengthened (leptin: multivariate adjusted mean predicted value for \( \geq 6 \) months of breastfeeding, \( P = 0.03 \)).
### Table 2

Adipokines at 3 years postpartum, by breastfeeding duration category: predicted values* from linear regression models

<table>
<thead>
<tr>
<th>Months of lactation</th>
<th>None</th>
<th>&gt;0 to &lt;3</th>
<th>3 to &lt;6</th>
<th>6 to &lt;12</th>
<th>≥12</th>
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<tr>
<td>n</td>
<td>503</td>
<td>503</td>
<td>503</td>
<td>503</td>
<td>503</td>
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<tr>
<td><strong>Leptin (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>69</td>
<td>116</td>
<td>138</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>Multivariable</td>
<td>69</td>
<td>116</td>
<td>138</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td><strong>Adiponectin (µg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>7.0</td>
<td>9.2</td>
<td>11.5</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Multivariable</td>
<td>7.0</td>
<td>9.2</td>
<td>11.5</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td><strong>Ghrelin (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>566</td>
<td>20.1</td>
<td>20.9</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td>Multivariable</td>
<td>566</td>
<td>20.1</td>
<td>20.9</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td><strong>PYY (pg/mL)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>177</td>
<td>53.4</td>
<td>56.1</td>
<td>56.1</td>
<td></td>
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<tr>
<td>Multivariable</td>
<td>177</td>
<td>53.4</td>
<td>56.1</td>
<td>56.1</td>
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</tbody>
</table>

Data from 570 participants in Project Viva who presented for follow-up at 3 years postpartum without an intervening birth. *For the multivariate adjusted model, data presented are mean predicted values for a participant with a prepregnancy BMI of 25.1 kg/m², the mean for the study population, modeled using a three-knot quadratic spline model for BMI. The participants were a white woman aged 35–40 years, has two children, has no parental history of diabetes, had normal glucose tolerance, is a non-smoker, and gained 15 kg during the index pregnancy. †Partial F test P values for differences among categories. ‡Results presented for PYY are geometric means. Because this outcome was not normally distributed, it was modeled on the log scale. Predicted values are exponentiated for presentation to improve interpretability.

**Discussion**

Consistent with our hypothesis, we found that long duration of both total and exclusive breastfeeding was associated with higher maternal adipokine and pancreatic PYY levels in unadjusted models (Fig. 2A). In our multivariate-adjusted models, we found the lowest leptin levels among women with a history of curtailed breastfeeding and supply problems (713.4 pg/mL), those who never breastfed (721.8 pg/mL), and curtailed breastfeeding without supply problems (774.0 pg/mL), those who were highest among women who breastfed successfully (824.4 pg/mL), followed by those who breastfed successfully but had supply problems (789.1 pg/mL), and those who did not breastfeed (872.3 pg/mL). We did not find any pattern of association between maternal adipokine and pancreatic PYY levels and breastfeeding duration.

To test our hypothesis that failed lactation would be associated with higher leptin and lower ghrelin, we adjusted for a variable for infants who were never breastfed, a variable for those who breastfed successfully without supply problems (224.4 pg/mL), followed by those who breastfed successfully, and those who did not breastfeed (224.4 pg/mL). We did not find any pattern of association between maternal adipokine and pancreatic PYY levels and breastfeeding duration.

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1. **Diabetes, Vol. 60, April 2011**
2. diabetes.diabetesjournals.org
3. LACTATION AND ADIPOKINES AFTER WEANING
4. TABLE 2
5. Adipokines at 3 years postpartum, by breastfeeding duration category: predicted values* from linear regression models
6. | Months of lactation | None | >0 to <3 | 3 to <6 | 6 to <12 | ≥12 |
7. |---------------------|------|--------|--------|---------|-----|
8. | n                   | 503  | 503    | 503    | 503     | 503 |
9. | **Leptin (ng/mL)**  |      |        |        |         |     |
10. | Unadjusted          | 69   | 116    | 138    | 149     |     |
11. | Multivariable       | 69   | 116    | 138    | 149     |     |
12. | **Adiponectin (µg/mL)** |      |        |        |         |     |
13. | Unadjusted          | 7.0  | 9.2    | 11.5   | 11.5    |     |
14. | Multivariable       | 7.0  | 9.2    | 11.5   | 11.5    |     |
15. | **Ghrelin (pg/mL)** |      |        |        |         |     |
16. | Unadjusted          | 566  | 20.1   | 20.9   | 20.9    |     |
17. | Multivariable       | 566  | 20.1   | 20.9   | 20.9    |     |
18. | **PYY (pg/mL)**     |      |        |        |         |     |
19. | Unadjusted          | 177  | 53.4   | 56.1   | 56.1    |     |
20. | Multivariable       | 177  | 53.4   | 56.1   | 56.1    |     |
21. Data from 570 participants in Project Viva who presented for follow-up at 3 years postpartum without an intervening birth. *For the multivariate adjusted model, data presented are mean predicted values for a participant with a prepregnancy BMI of 25.1 kg/m², the mean for the study population, modeled using a three-knot quadratic spline model for BMI. The participants were a white woman aged 35–40 years, has two children, has no parental history of diabetes, had normal glucose tolerance, is a non-smoker, and gained 15 kg during the index pregnancy. †Partial F test P values for differences among categories. ‡Results presented for PYY are geometric means. Because this outcome was not normally distributed, it was modeled on the log scale. Predicted values are exponentiated for presentation to improve interpretability.
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Our results confirm and extend earlier work relating breastfeeding to differences in maternal metabolic outcomes after weaning. In large epidemiologic studies, we and others have reported associations between longer duration of lactation and reduced risk of diabetes (1–3), hypertension (8), higher HDL cholesterol levels post-weaning adjusted for preconception levels (5), metabolic syndrome (6,7), and cardiovascular disease (3,9,27). The mechanism underlying this association is unknown. Lactation appears to mobilize adipose tissue accrued during pregnancy, and we have previously hypothesized that breastfeeding "resets" maternal metabolism after pregnancy, reducing disease risk (10).

In this study, we did not find any association between lactation duration and maternal leptin levels, once we adjusted for pregravid BMI. It is likely that unadjusted
LACTATION AND ADIPOKINES AFTER WEANING

We found a modest direct association between breastfeeding duration and levels of ghrelin and PYY, two gut-secreted peptide hormones that regulate appetite through reciprocal effects on hypothalamic orexigenic and anorexigenic pathways (28). In the fasting state, low PYY levels and high ghrelin levels stimulate hunger, whereas after feeding, PYY levels rise and ghrelin levels fall. Paradoxically, low ghrelin levels are associated with obesity, insulin resistance, hypertension, and type 2 diabetes in cross-sectional studies (13,14,16). In a small study (n = 18) of women at 4–5 weeks postpartum, Larson-Meyer et al. (29) found slightly higher fasting levels of ghrelin in lactating versus nonlactating mothers (971.8 [208.9] vs. 798.8 [271.8] pg/mL), but this difference was not statistically significant. PYY did not differ between lactating and nonlactating women. Among five women in that study who exclusively breastfed, ghrelin levels did not change from baseline to 24 weeks postpartum, despite reductions in total body fat and BMI (29). Ilcol et al. (30) measured ghrelin concentrations during lactation in 16 women and found increases in total ghrelin from 0–3 to 4–14 days postpartum, followed by slightly lower but stable levels from 15 to 30 days postpartum. The same authors measured total ghrelin in a cross-section sample of 150 women and found stable levels from 15 to 180 days postpartum.

Rodent studies (31,32) provide conflicting evidence regarding ghrelin’s role in energy balance during lactation; however, cows bred for milk production have higher plasma ghrelin levels and greater energy intake during lactation (33). It is possible that long-term lactation and the associated negative energy balance induce changes in fasting ghrelin levels that persist after weaning, reducing the risk for metabolic disease. Alternatively, women with higher baseline ghrelin levels may produce more milk, allowing them to continue breastfeeding longer. In this case, long breastfeeding durations would be a marker for reduced maternal metabolic risk.

Pancreatic PYY is an appetite-inhibiting peptide hormone secreted by the intestine in response to a meal (22). Obese individuals secrete less PYY than normal-weight individuals, suggesting an impaired response to satiety cues. Unlike the leptin resistance that can develop with obesity, overweight individuals retain a normal appetite response to infused PYY. We found a direct association between the duration of lactation and fasting PYY levels. This difference could improve energy balance, leading to more weight loss or less weight gain among women with longer durations of lactation. In support of this speculation, we previously found that women in our cohort with >6 months of exclusive breastfeeding had a lower BMI and reduced pregnancy-associated weight retention at 3 years, compared with women who had never breastfed exclusively (34).

When we measured the association between adipokine levels and curtailed breastfeeding, we found lower leptin and higher ghrelin levels among women who reported problems with milk supply, compared with women with curtailed breastfeeding who did not report supply

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**Table 3: Adipokines at 3 years postpartum, by exclusive breastfeeding duration: predicted values from linear regression models**

<table>
<thead>
<tr>
<th>Months of exclusive lactation</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0 to &lt;1</td>
<td>n</td>
<td>Mean (95% CI)</td>
<td>Unadjusted</td>
<td>Multivariable-adjusted</td>
<td>n</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>488</td>
<td>12.3 (10.2–14.5)</td>
<td>10.2 (8.9–11.6)</td>
<td>9.0 (7.7–10.6)</td>
<td>8.8 (7.3–10.1)</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>56</td>
<td>19.8 (16.2–23.4)</td>
<td>21.4 (19.1–23.5)</td>
<td>21.9 (19.1–23.5)</td>
<td>22.9 (20.6–25.9)</td>
</tr>
<tr>
<td>Ghrelin (pg/mL)</td>
<td>136</td>
<td>665.1 (422.9–907.4)</td>
<td>721.5 (602.2–890.9)</td>
<td>772.8 (639.1–912.6)</td>
<td>805.0 (679.4–942.6)</td>
</tr>
<tr>
<td>PYY (pg/mL)</td>
<td>136</td>
<td>57.0 (42.6–76.2)</td>
<td>56.7 (47.4–75.9)</td>
<td>56.4 (46.5–74.8)</td>
<td>62.0 (52.9–72.6)</td>
</tr>
</tbody>
</table>

*P* values from linear regression models for association between breastfeeding duration and adipokines. Predicted values are exponentiated for presentation to improve interpretability.
problems. We acknowledge that we had only limited ability to capture biologic versus cultural or social reasons for weaning; however, our results do not support the hypothesis that difficulty with milk production is a marker for an adverse adipokine profile.

No other studies to our knowledge have measured associations between the duration of breastfeeding and ghrelin or PYY levels after weaning; however, there is tentative evidence that lactation is associated with long-term changes in other hypothalamic neuroendocrine pathways. During lactation, breastfeeding women have reduced autonomic and adrenal responses to stressors, compared with nonlactating postpartum control subjects (35-39). Differences in hypothalamic-pituitary-adrenal activity may...
Breastfeeding,
no problems
with milk supply*
Curtailed
breastfeeding,
problems with milk supply*
Successful
breastfeeding*
\(P\)

<table>
<thead>
<tr>
<th></th>
<th>Never breastfed</th>
<th>Curtailed breastfeeding, problems with milk supply*</th>
<th>Curtailed breastfeeding, no problems with milk supply*</th>
<th>Successful breastfeeding*</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (ng/mL) ((n))</td>
<td>69</td>
<td>11.2 (9.7–12.6)§</td>
<td>7.9 (6.4–9.3)</td>
<td>9.0 (7.2–10.8)</td>
<td>8.7 (8.1–9.3)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>564</td>
<td>8.9 (7.6–10.1)§</td>
<td>6.8 (5.6–8.1)</td>
<td>7.5 (6.0–9.0)</td>
<td>8.0 (7.1–8.8)§</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>564</td>
<td>19.0 (17.0–21.0)</td>
<td>21.3 (19.2–23.3)</td>
<td>19.9 (17.4–22.4)</td>
<td>20.2 (19.4–21.1)</td>
</tr>
<tr>
<td>Adiponectin ((ug/mL)) ((n))</td>
<td>70</td>
<td>20.9 (18.6–23.3)</td>
<td>22.7 (20.3–25.1)</td>
<td>21.3 (18.5–24.1)</td>
<td>21.2 (19.7–22.8)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>566</td>
<td>574.7 (427.9–721.5)</td>
<td>78.9 (392.7–845.1)</td>
<td>682.2 (546.8–817.5)</td>
<td>775.7 (719.8–831.6)</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>177</td>
<td>721.8 (566.6–877.1)</td>
<td>774.0 (645.4–902.5)</td>
<td>713.4 (588.5–883.8)</td>
<td>824.4 (736.3–912.4)</td>
</tr>
<tr>
<td>Ghrelin (pg/mL) ((n))</td>
<td>17</td>
<td>53.4 (45.7–62.4)</td>
<td>57.5 (50.4–65.7)</td>
<td>56.5 (49.2–65.0)</td>
<td>60.2 (56.7–63.9)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>177</td>
<td>52.3 (43.0–63.5)</td>
<td>57.0 (48.5–67.0)</td>
<td>58.8 (49.1–70.3)</td>
<td>60.9 (54.5–68.0)</td>
</tr>
<tr>
<td>PYY (pg/mL) ((n))</td>
<td>17</td>
<td>53.4 (45.7–62.4)</td>
<td>57.5 (50.4–65.7)</td>
<td>56.5 (49.2–65.0)</td>
<td>60.2 (56.7–63.9)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>177</td>
<td>52.3 (43.0–63.5)</td>
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<td>60.9 (54.5–68.0)</td>
</tr>
</tbody>
</table>

Data from 570 participants in Project Viva who presented for follow-up at 3 years postpartum without an intervening birth. *We used data on mothers’ intended duration of breastfeeding, as reported at 28 weeks of pregnancy to define curtailed breastfeeding as either 1) weaning prior to 3 months among women who planned to breastfeed for more than 3 months or 2) introduction of formula prior to 3 months among women who planned to breastfeed exclusively for at least 3 months. At the 6-month interview, mothers who had weaned or were supplementing were considered to have curtailed breastfeeding. **For the multivariate-adjusted model, data presented are mean predicted values for a participant with a prepregnancy BMI of 25.1 kg/m², the mean for the study population, modeled using a three-knot quadratic spline for presentation to improve interpretability. \(\alpha\)Results presented for PYY are geometric means. Because this outcome was not normally distributed, it was modeled on the log scale. Predicted values are exponentiated for presentation to improve interpretability.

In conclusion, in a prospective study of maternal and infant health, we found that longer duration of breastfeeding was associated with higher maternal levels of ghrelin and PYY at 3 years postpartum. These two gut peptides regulate appetite and are associated with reduced risk of metabolic disease. Our findings provide tentative evidence that changes in hypothalamic appetite regulation may mediate associations between longer lactation and reduced risk of maternal metabolic disease. Additional studies will be needed to confirm these findings in other populations and to determine whether these associations are causal.

**ACKNOWLEDGMENTS**

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A.M.S. analyzed the data and wrote the manuscript. C.M. completed the laboratory assays, contributed to the
discussion, and reviewed and edited the manuscript. K.K. provided advice on statistical methods and reviewed and edited the manuscript. S.R.-S. analyzed the data and reviewed and edited the manuscript. E.P.G. contributed to the discussion and reviewed and edited the manuscript. M.W.G. and J.R.-E. researched the data, contributed to the discussion, and reviewed and edited the manuscript.

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