

# Lactation Intensity and Postpartum Maternal Glucose Tolerance and Insulin Resistance in Women With Recent GDM

The SWIFT cohort

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**OBJECTIVE**—To examine the association between breastfeeding intensity in relation to maternal blood glucose and insulin and glucose intolerance based on the postpartum 2-h 75-g oral glucose tolerance test (OGTT) results at 6–9 weeks after a pregnancy with gestational diabetes mellitus (GDM).

**RESEARCH DESIGN AND METHODS**—We selected 522 participants enrolled into the Study of Women, Infant Feeding, and Type 2 Diabetes (SWIFT), a prospective observational cohort study of Kaiser Permanente Northern California members diagnosed with GDM using the 3-h 100-g OGTT by the Carpenter and Coustan criteria. Women were classified as normal, prediabetes, or diabetes according to American Diabetes Association criteria based on the postpartum 2-h 75-g OGTT results.

**RESULTS**—Compared with exclusive or mostly formula feeding (>17 oz formula per 24 h), exclusive breastfeeding and mostly breastfeeding ( $\leq 6$  oz formula per 24 h) groups, respectively, had lower adjusted mean (95% CI) group differences in fasting plasma glucose (mg/dL) of  $-4.3$  ( $-7.4$  to  $-1.3$ ) and  $-5.0$  ( $-8.5$  to  $-1.4$ ), in fasting insulin ( $\mu\text{U/mL}$ ) of  $-6.3$  ( $-10.1$  to  $-2.4$ ) and  $-7.5$  ( $-11.9$  to  $-3.0$ ), and in 2-h insulin of  $-21.4$  ( $-41.0$  to  $-1.7$ ) and  $-36.5$  ( $-59.3$  to  $-13.7$ ) (all  $P < 0.05$ ). Exclusive or mostly breastfeeding groups had lower prevalence of diabetes or prediabetes ( $P = 0.02$ ).

**CONCLUSIONS**—Higher intensity of lactation was associated with improved fasting glucose and lower insulin levels at 6–9 weeks' postpartum. Lactation may have favorable effects on glucose metabolism and insulin sensitivity that may reduce diabetes risk after GDM pregnancy.

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Lactogenesis has favorable effects on maternal cardiometabolic blood profiles, including a less atherogenic lipid profile (1) and lower blood glucose and insulin concentrations (2,3), as a result of the noninsulin-mediated cellular uptake of glucose for milk production. Some evidence suggests that lactation

may be associated with greater insulin sensitivity (2). Among 809 Latinas with recent gestational diabetes mellitus (GDM), the lactating group had lower mean fasting and 2-h postglucose and higher HDL cholesterol at 4–12 weeks' postpartum compared with the nonlactating group (4). A second study reports improved

pancreatic  $\beta$ -cell function among 14 lactating versus 12 nonlactating women with previous GDM assessed via the disposition index (insulin sensitivity multiplied by acute insulin response to glucose) (5).

Lactation intensity (e.g., degree of milk feed supplementation), to our knowledge, has never been examined in relation to maternal postpartum glucose tolerance, metabolic profile, or insulin resistance among women with a history of GDM. In addition, the few studies comparing metabolic parameters among lactating versus nonlactating postpartum women with recent GDM are limited to Latinas (4) or fewer than 30 non-Hispanic white women (5); there are currently no published data from racially/ethnically diverse cohorts. The objective of this analysis is to examine the association between intensity of breastfeeding and formula feeding in relation to blood glucose and insulin levels as well as glucose tolerance based on the postpartum 2-h 75-g oral glucose tolerance test (OGTT) among women with recent GDM who enrolled in the Study of Women, Infant Feeding, and Type 2 Diabetes (SWIFT), a Kaiser Permanente Northern California postpartum GDM cohort.

## RESEARCH DESIGN AND METHODS

### Study population

The analysis includes participants enrolled between September 2008 and March 2011 into SWIFT, an ongoing prospective observational cohort study of Kaiser Permanente Northern California members, who met American Diabetes Association criteria for the 3-h 100-g OGTT at 24–32 weeks' gestation for a diagnosis of GDM and delivered a singleton, live birth  $\geq 35$  weeks' gestation (6). Eligible participants had no known major medical conditions, provided information on duration and intensity of breastfeeding and formula feeding, and were free of diabetes at 6–9 weeks' postpartum (confirmed by the 2-h 75-g OGTT) for inclusion in the follow-up cohort screened

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annually for diabetes. This prospective study enrolled women into one of two infant feeding groups: exclusive or mostly breastfeeding (giving  $\leq 6$  oz formula per 24 h) and exclusive or mostly formula feeding (giving  $\geq 14$  oz formula per 24 h), based on the infant feeding practices assessed via telephone using the women's record of formula supplementation (amount and number of feedings per 24 h) from delivery through 4–6 weeks' postpartum. At the 6–9 week postpartum enrollment visit (baseline), research staff queried women about their frequency of breastfeeding and formula supplementation (including quantity per 24 h) during the previous 7 days. The analytic sample consists of 522 women—505 free of diabetes and 17 classified with diabetes at 6–9 weeks' postpartum based on the 2-h 75-g OGTT results.

### Data collection

Women provided written, informed consent prior to enrollment at the in-person examination at 6–9 weeks' postpartum to obtain blood specimens, questionnaire data, and anthropometric measurements. In preparation for the 2-h 75-g OGTT, women were advised to consume adequate carbohydrates for the 3 days before the test, fast for at least 10 h before the test, and express their breast milk a few days before the test so they would have breast milk to feed their infant during the OGTT. Women reported the frequency and duration of breastfeeding during the fasting period before the OGTT, and those who breastfed their infant during the 2-h OGTT also reported the duration and number of breastfeeding episodes during the OGTT to the research assistant.

Kaiser Permanente Northern California electronic databases were used to retrieve prenatal laboratory results for GDM diagnosis, date of delivery, and length of gestation. Measurements of weight and height were performed by trained research assistants using standardized methods and equipment. Interviewer and self-administered questionnaires collected information on sociodemographics, hours fasting before the OGTT, medical conditions, contraception, and lifestyle behaviors, including infant feeding methods. On the basis of infant feeding data collected from delivery to enrollment (6–9 weeks' postpartum), participants were classified into one of four infant feeding groups: 1) exclusive breastfeeding (no formula or other feeds); 2) mostly breastfeeding, defined as  $\leq 6$  oz of formula per 24 h; 3) mixed or inconsistent feeding of breast

milk and formula, defined as 7–17 oz per 24 h or change in feeding status to increase formula; and 4) exclusive or mostly formula feeding, defined as  $> 17$  oz formula per 24 h. These categories were based on the average quantity of infant formula fed per 24 h from birth to 6 weeks (feeding diary) and the average amount of formula fed within 1 week before enrollment. We defined an intake of  $\leq 6$  oz of formula per day as mostly breastfeeding and  $> 17$  oz of formula per day as mostly formula feeding. These criteria are based on an average formula intake of 24 oz per day among infants aged 6–9 weeks (e.g., 450 kcal per day) (7,8). More than 17 oz of formula per day is estimated to be at least 70% of the overall intake, and  $\leq 6$  oz of formula per day is estimated to be  $\leq 25\%$  of the overall intake on average as formula.

### Biochemical assays

Plasma glucose assays were performed enzymatically by the University of Washington Northwest Lipid Metabolism and Diabetes Research Laboratory (Seattle, WA) with the Hitachi 917 Autoanalyzer using the combined catalytic activities of hexokinase and glucose-6-phosphate-dehydrogenase. The assay of total immunoreactive insulin, or total insulin, is performed by a double-antibody radioimmunoassay developed in the Diabetes Endocrinology Research Center Immunoassay Core Laboratory (Seattle, WA). The assay is a 48-h polyethylene glycol-accelerated assay involving a primary antibody, guinea pig anti-human insulin, and a secondary antibody, goat anti-guinea pig immunoglobulin. The guinea pig anti-human insulin antibody is available in a very large quantity as produced from the laboratory, therefore ensuring consistency of the assay throughout the years. Assay precision is excellent, with a coefficient of variation of 4.5% for the high quality control and 6.9% for the low quality control.

### Glucose tolerance classification

Women were classified by glucose tolerance as follows: normal; glucose intolerant (prediabetes defined as impaired fasting glucose between 100 and 125 mg/dL and/or impaired glucose tolerance for 2-h 75-g postglucose between 140 and 199 mg/dL); or diabetes based on the American Diabetes Association diagnostic criteria for the 75-g OGTT (fasting  $\geq 126$  mg/dL and/or 2 h  $\geq 200$  mg/dL), which included a repeat test on a separate occasion for women with elevated values (9).

### Insulin sensitivity and resistance indices

We calculated indices of insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) and insulin sensitivity (insulin sensitivity index [ISI<sub>0,120</sub>]) using data obtained from 0 and 120 min during the OGTT at 6–9 weeks' postpartum (10,11): HOMA-IR =  $(G_0 \times I_0)/22.5$  and  $ISI_{0,120} = (m/MPG)/\log MSI$ , where  $G_0$  = fasting glucose,  $I_0$  = fasting insulin,  $G_{120}$  = glucose post 2-h OGTT,  $I_{120}$  = insulin post 2-h OGTT,

$$m = [75,000 \text{ mg} + (G_0 - I_{120}) \times 0.19 \times \text{body weight}] / 120 \text{ min}$$

$MPG = (G_0 + G_{120})/2$ , and  $MSI = (I_0 + I_{120})/2$ , where MPG is mean of fasting and 2-h glucose concentrations (mg/dL) and MSI is mean of fasting and 2-h insulin concentrations (mU/L).

### Statistical methods

Differences in participant characteristics by infant feeding groups were assessed using  $\chi^2$  statistics for categorical variables (race, education, BMI, and breastfeeding during OGTT or fasting period) and by comparison of means for continuous variables (blood glucose, insulin, HOMA-IR, and ISI<sub>0,120</sub>) using *F* statistics from ANOVA. All *P* values presented are for two-sided tests; statistical significance was defined as  $P < 0.05$ .

Unadjusted and multivariable adjusted means (95% CI) and adjusted mean group differences in measures of glucose tolerance among the four infant feeding groups were estimated from linear regression models (ANOVA, *F* statistics) adjusted for covariates. Statistically significant *P* values and CIs were corrected for multiple comparisons of infant feeding groups using the Dunnett procedure in SAS for Windows 9.1.3 (SAS Institute Inc., Cary, NC). Covariates evaluated as potential confounders based on a priori hypotheses included race/ethnicity, maternal BMI, education, parity, and age. We also examined time fasting and breastfeeding during the fasting period as potential confounders based on 10% change in model coefficients for infant feeding groups.

**RESULTS**—Participants' age ranged from 21 to 45 years with a mean (SD) age of 33.2 (5.0) years, and overall race/ethnicity of the cohort was 73% minority (36% Asian, 8% black, and 29% Hispanic). Among the analytic sample of 522 women (Table 1), 211 reported exclusively breastfeeding, 99 reported mostly breastfeeding

Table 1—Participant characteristics according to intensity of the infant feeding methods†

Characteristic	Exclusive BF (n = 211)	Mostly BF (n = 99)	Mixed or inconsistent (n = 77)	Exclusive or mostly FF (n = 135)	P value
Race/Ethnicity, n (%)					
Non-Hispanic white	75 (35.5)	21 (21.2)	17 (22.1)	30 (22.2)	0.002
Non-Hispanic black	12 (5.7)	2 (2.0)	9 (11.6)	18 (13.3)	
Hispanic	51 (24.2)	35 (35.3)	22 (28.6)	43 (31.8)	
Asian/Other	73 (34.6)	41 (41.4)	29 (37.7)	44 (32.6)	
Parity, n (%)					
1	80 (38.0)	37 (37.4)	32 (41.6)	51 (37.8)	0.95
2	72 (34.1)	33 (33.3)	27 (35.1)	42 (31.1)	
3 or more	59 (27.9)	29 (29.3)	18 (23.3)	42 (31.1)	
Education, n (%)					
High school or less	35 (16.6)	22 (22.2)	22 (28.6)	49 (36.2)	0.44
Some college	63 (29.9)	30 (30.3)	23 (29.9)	46 (34.1)	
College ≥4 years	113 (53.5)	47 (47.5)	32 (41.5)	40 (29.7)	
Contraception method, n (%)					
Norplant or Depo-Provera	4 (1.9)	4 (4.0)	5 (6.5)	4 (3.0)	0.34
Intrauterine device	14 (6.6)	9 (9.0)	5 (6.5)	17 (12.6)	
Oral contraceptive	26 (12.3)	17 (17.1)	11 (14.3)	19 (14.1)	
Barrier methods or none	167 (79.2)	69 (69.9)	56 (72.7)	95 (70.3)	
BF during fasting period, n (%)	205 (97.2)	96 (96.0)	59 (76.6)	29 (21.5)	<0.001
BF during OGTT, n (%)	68 (32.2)	9 (9.0)	9 (11.7)	2 (1.5)	<0.001
Age					
Years, mean (SD)	33.7 (4.9)	32.7 (5.0)	32.7 (5.1)	33.2 (5.0)	0.28
Range	23–44	21–45	22–44	20–44	
Prenatal 3-h 100-g OGTT glucose (mg/dL), mean (SD)					
Fasting	91.3 (13.4)	91.9 (11.8)	93.3 (11.3)	93.2 (12.6)	0.48
1 h	202.8 (24.6)	197.2 (22.0)	203.6 (23.7)	200.0 (26.1)	0.20
2 h	180.4 (27.3)	175.8 (27.6)	176.8 (33.2)	178.9 (30.1)	0.57
3 h	122.8 (34.2)	125.1 (31.9)	130.3 (32.4)	128.6 (34.9)	0.26
6–9 weeks' postpartum, mean (SD)					
BMI (kg/m <sup>2</sup> )	29.4 (5.7)	30.5 (6.6)	30.4 (6.7)	32.7 (7.8)	<0.001
Postpartum (weeks)	6.8 (3.8)	7.1 (1.0)	7.2 (1.0)	7.3 (1.2)	0.25
Amount of formula fed (oz per 24 h)	0.0 (0.0)	3.1 (1.9)	14.4 (7.2)	29.1 (8.1)	<0.001
Time, mean (SD)					
Fasting before OGTT (h)	11.8 (1.4)	11.7 (1.4)	11.9 (1.5)	12.2 (2.2)	0.10
BF during fasting period (min)	60.5 (35.5)	57.4 (47.0)	41.9 (42.8)	8.8 (23.4)	<0.001
BF during OGTT (min)††	15.3 (8.8)	18.0 (9.3)	18.0 (8.1)	13.5 (9.2)	0.68

BF, breastfeeding; FF, formula feeding. †Range for amount of formula fed (oz per 24 h): Exclusive BF = 0; mostly BF = 0.03–6; mixed = 7–17; exclusive or mostly FF >17–60. ††Time (min) is for the sample of women who breastfed their child during the OGTT.

(≤6 oz formula per 24 h), 77 reported mixed breast milk and formula (7–17 oz per 24 h) or inconsistent feeding, and 135 reported exclusive or mostly formula feeding (>17 oz per 24 h). Women who exclusively or mostly breastfed their infants had higher education attainment and were more likely to breastfeed during the OGTT, have lower BMI at 6–9 weeks' postpartum, and be of non-Hispanic white race. The amount of formula provided to the infant within a 24-h period was higher among formula feeding than breastfeeding groups as expected ( $P < 0.001$ ). The time interval spent breastfeeding during the fasting period and during

the OGTT was higher among exclusively and mostly breastfeeding groups than other groups.

Plasma glucose and insulin and insulin resistance or sensitivity indices (HOMA-IR and ISI<sub>0,120</sub>) from unadjusted and adjusted multivariable linear regression models followed a dose-response pattern with increasing means directly associated with higher quantities of formula feeding (Table 2). Unadjusted and fully adjusted means (95% CI) for fasting plasma glucose, fasting plasma insulin, 2-h insulin concentrations, and HOMA-IR levels were significantly lower among exclusive breastfeeding and mostly breastfeeding groups

compared with the exclusive or mostly formula feeding group ( $P$  ranges from <0.05 to <0.001). Higher intensity of lactation (exclusive and mostly breastfeeding groups vs. exclusively or mostly formula feeding) was associated with lower adjusted mean group differences (95% CI) in fasting plasma glucose (mg/dL) by  $-4.3$  ( $-7.4$  to  $-1.3$ ) and  $-5.0$  ( $-8.5$  to  $-1.4$ ), respectively ( $P < 0.01$ ), and fasting insulin ( $\mu\text{U/mL}$ ) by  $-6.3$  ( $-10.1$  to  $-2.4$ ) and  $-7.5$  ( $-11.9$  to  $-3.0$ ), respectively ( $P < 0.001$ ) (Table 2). Similar associations were found with lower 2-h insulin values of  $-21.4$  ( $-41.0$  to  $-1.7$ ) for exclusive breastfeeding ( $P < 0.05$ ) and  $-36.5$

Table 2—Plasma glucose and insulin levels and insulin resistance/sensitivity indices by infant feeding groups for the 2-h 75-g OGTT at 6–9 weeks' postpartum

	Mean (95% CI)				Trend P value	Mean group difference (95% CI)		
	Exclusive BF (n = 211)	Mostly BF (n = 99)	Mixed or inconsistent (n = 77)	Exclusive or mostly FF (n = 135)		Exclusive BF vs. exclusive or mostly FF	Mostly BF vs. exclusive or mostly FF	Mixed vs. exclusive or mostly FF
Glucose (mg/dL)								
Fasting								
Unadjusted	93.2 (92.4–93.9)	93.1 (92.0–94.2)	97.4 (96.2–98.7)	99.3 (98.3–100.2)	<0.001	–6.1*** (–9.0 to –3.1)	–6.2*** (–9.7 to –2.6)	–1.9 (–5.7 to 2.0)
Adjusted†	93.8 (93.0–94.6)	93.2 (92.1–94.3)	97.5 (96.2–98.7)	98.1 (97.1–99.1)	<0.001	–4.3** (–7.3 to –1.2)	–4.9** (–8.4 to –1.4)	–0.6 (–4.4 to 3.2)
Fully adjusted‡	93.8 (93.0–94.6)	93.2 (92.1–94.3)	97.5 (96.2–98.8)	98.2 (97.2–99.1)	<0.001	–4.3** (–7.4 to –1.3)	–5.0** (–8.5 to –1.4)	–0.7 (–4.4 to 3.1)
2 h								
Unadjusted	115.4 (113.1–117.7)	116.4 (113.0–119.7)	122.7 (118.9–126.5)	116.5 (113.6–119.3)	0.51	–1.1 (–10.1 to 7.9)	–0.1 (–11.0 to 10.7)	6.2 (–5.5 to 17.9)
Adjusted†	115.3 (112.9–117.7)	114.4 (111.0–117.8)	120.4 (116.7–124.2)	112.1 (109.2–115.1)	0.93	3.2 (–5.9 to 12.3)	2.3 (–8.3 to 12.9)	8.3 (–3.0 to 19.7)
Fully adjusted‡	115.4 (113.0–117.8)	114.5 (111.2–117.9)	120.3 (116.5–124.0)	111.3 (108.4–114.3)	0.88	4.1 (–5.0 to 13.2)	3.2 (–7.4 to 13.8)	8.9 (–2.4 to 20.2)
Insulin (μU/mL)								
Fasting								
Unadjusted	20.1 (19.0–21.2)	21.4 (19.9–23.0)	25.4 (23.7–27.2)	31.2 (29.9–32.5)	<0.001	–11.1*** (–15.3 to –6.9)	–9.8*** (–14.8 to –4.8)	–5.8* (–11.2 to –0.3)
Adjusted†	21.5 (20.5–22.5)	20.4 (19.0–21.8)	24.5 (22.9–26.1)	27.8 (26.6–29.1)	<0.001	–6.4*** (–10.2 to –2.5)	–7.4*** (–11.9 to –3.0)	–3.3 (–8.1 to 1.4)
Fully adjusted‡	21.5 (20.5–22.5)	20.4 (18.9–21.8)	24.5 (22.9–26.0)	27.8 (26.6–29.1)	<0.001	–6.3*** (–10.1 to –2.4)	–7.5*** (–11.9 to –3.0)	–3.4 (–8.1 to 1.4)
2 h								
Unadjusted	92.0 (87.0–97.0)	88.0 (80.7–95.3)	116.0 (107.7–124.3)	126.7 (120.5–133.0)	<0.001	–34.7*** (–54.4 to –15.0)	–38.7*** (–62.4 to –15.0)	–10.7 (–36.3 to 14.8)
Adjusted†	88.9 (83.8–94.0)	74.3 (66.9–81.6)	102.8 (94.7–111.0)	109.6 (103.3–116.0)	<0.001	–20.7* (–40.3 to –1.2)	–35.4*** (–58.2 to –12.6)	–6.8 (–31.2 to 17.6)
Fully adjusted‡	89.1 (84.0–94.2)	73.9 (66.6–81.2)	103.0 (94.8–111.1)	110.4 (104.1–116.8)	<0.001	–21.4* (–41.0 to –1.7)	–36.5*** (–59.3 to –13.7)	–7.5 (–31.9 to 16.9)
HOMA-1R								
Unadjusted	4.74 (4.45–5.03)	5.01 (4.59–5.44)	6.35 (5.87–6.83)	7.89 (7.52–8.25)	<0.001	–3.15*** (–4.30 to –2.00)	–2.88*** (–4.25 to –1.50)	–1.54* (–3.02 to –0.05)
Adjusted†	5.14 (4.86–5.41)	4.78 (4.38–5.18)	6.12 (5.68–6.56)	6.96 (6.62–7.30)	<0.001	–1.82*** (–2.88 to –0.77)	–2.18*** (–3.41 to –0.95)	–0.84 (–2.16 to 0.48)
Fully adjusted‡	5.16 (4.88–5.43)	4.77 (4.37–5.16)	6.11 (5.67–6.55)	6.95 (6.61–7.30)	<0.001	–1.79*** (–2.86 to –0.73)	–2.18*** (–3.42 to –0.95)	–0.84 (–2.16 to 0.48)
ISI <sub>0-120</sub>								
Unadjusted	1.66 (1.62–1.69)	1.61 (1.57–1.65)	1.45 (1.40–1.50)	1.44 (1.40–1.47)	<0.001	0.22*** (0.10–0.34)	0.17** (0.03–0.31)	0.01 (–0.14 to 0.16)
Adjusted†	1.67 (1.64–1.71)	1.68 (1.63–1.72)	1.52 (1.47–1.57)	1.55 (1.51–1.58)	<0.001	0.13* (0.01–0.24)	0.13 (0.00–0.26)	–0.03 (–0.17 to 0.11)
Fully adjusted‡	1.67 (1.64–1.71)	1.68 (1.63–1.72)	1.52 (1.47–1.57)	1.55 (1.51–1.59)	<0.001	0.12* (0.002–0.24)	0.13 (–0.01 to 0.26)	–0.03 (–0.17 to 0.11)

BF, breastfeeding; FF, formula feeding. P values adjusted for multiple comparisons using the Dunnett test. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001. †Adjusted for race, baseline parity, age, BMI, and education. ‡Fully adjusted for race, baseline parity, age, BMI, education, weeks' postpartum, and hours of fasting before the test.

(−59.3 to −13.7) for mostly breastfeeding ( $P < 0.001$ ) versus exclusive or mostly formula feeding. HOMA-IR was significantly lower and  $ISI_{0, 120}$  was significantly higher with greater intensity of lactation compared with exclusive or mostly formula feeding women ( $P < 0.001$ ). No differences in metabolic parameters were found for mixed or inconsistent feeders (similar amounts of breast milk and formula) compared with the formula feeding group. Breastfeeding during the OGTT had no significant impact on the metabolic parameters (data not shown).

Classification as having diabetes ( $n = 17$ ), prediabetes ( $n = 171$ ), or normal ( $n = 334$ ) glucose tolerance based on the 2-h 75-g OGTT was inversely associated with lactation intensity ( $P = 0.02$ ), with higher prevalence of glucose intolerance as the

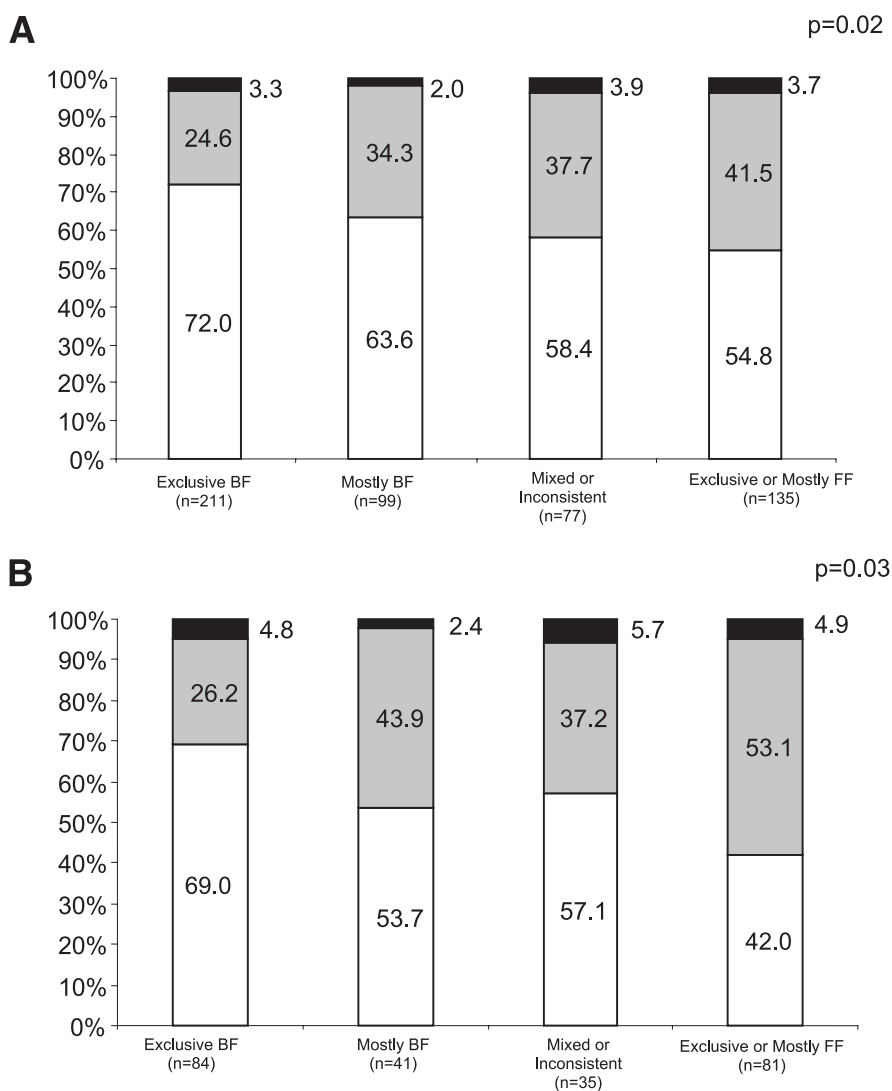
amount for formula fed increased across the infant feeding groups (Fig. 1A). When stratified by maternal obesity (Fig. 1B), the association between glucose tolerance categories and infant feeding groups remained among the 241 obese women ( $P = 0.03$ ).

**CONCLUSIONS**—Our large epidemiologic study in a racially and ethnically diverse cohort found a dose-response relationship between increasing intensity of lactation (ranging from exclusive breastfeeding to exclusive or mostly formula feeding) and decreasing fasting plasma glucose and both fasting and 2-h insulin, as well as improved insulin sensitivity at 6–9 weeks' postpartum. Intensively lactating women displayed 4–5 mg/dL lower mean fasting plasma glucose

compared with women who intensively formula fed, but no differences in 2-h glucose. These findings are consistent with the only prior study to examine lactation and metabolic profiles among women with recent GDM. Kjos et al. (4) reported 5 mg/dL lower fasting blood glucose for any intensity of lactation versus no lactation groups in a retrospective cohort of Latinas. However, 2-h glucose levels were 10 mg/dL lower between lactating versus nonlactating groups in this study, but this difference was not observed in our study. Differences in study design, particularly our comparison of intensively lactating women, standardized prenatal screening criteria, and our diverse racial and ethnic groups with lower risk of diabetes, may explain the discrepant findings. The study of Latinas included a longer time period for OGTT screening (up to 12 weeks) and a higher prevalence of postpartum diabetes (6.7 vs. 3% in our study), which may have enhanced differences in the 2-h OGTT results among the two infant feeding groups (lactating vs. nonlactating) reported by Kjos et al. (4).

Our study also enhances our knowledge about the effect of lactation on insulin sensitivity and resistance in women with recent GDM. Our findings support the hypothesis that lactation spares insulin response required for similar or even improved levels of glucose control. Glucose (~50 g/day) is diverted for lactogenesis (the process of milk synthesis and secretion) via noninsulin-mediated pathways of uptake by the mammary gland (12) and, thus, lower levels of insulin with increasing intensity of lactation is expected. Thus, lactating women exhibit lower blood glucose and insulin concentrations along with higher rates of glucose production and lipolysis compared with nonlactating women (2). In our study, both exclusively and mostly lactating women experienced similar lowering of glucose and insulin levels relative to formula feeding women. The diversion of glucose and lipids into milk production may unload the pancreatic  $\beta$ -cells and preserve long-term insulin production in women. The impact of maternal metabolic profiles on breast milk composition has not been assessed in women with a history of GDM.

Also, we found that indices of insulin sensitivity were associated with higher lactation intensity. The indices were most favorable for exclusive or mostly breastfeeding compared with formula feeding but mixed feeders did not differ from formula feeders. A few small studies (sample size



**Figure 1**—Glucose tolerance categories (2-h 75-g OGTT) among infant feeding groups at 6–9 weeks' postpartum. A: Entire cohort ( $n = 522$ ). B: Obese women only ( $n = 241$ ). Normal (white bar), prediabetes (gray bar), diabetes (black bar). BF, breastfeeding; FF, formula feeding.

<30) measured insulin and glucose as well as insulin response to any lactation, and results are consistent with our findings. McManus et al. (5) reported improved insulin response and glucose tolerance among lactating women with recent GDM at 3 months' postpartum. A total of 14 lactating compared with 12 nonlactating women had higher insulin sensitivity, glucose effectiveness, and first-phase insulin response to glucose assessed by Bergman minimal model, but statistical significance was not reached, possibly as a result of the small sample size (5). However, the disposition index (insulin sensitivity multiplied by first-phase insulin response to glucose) was 2.5 times higher ( $129.9 \pm 26.0$  vs.  $53.4 \pm 18.0 \times 10^{(-4)} \text{ min}^{(-1)}$ ;  $P < 0.05$ ) in lactating compared with nonlactating women matched for age, weight, postpartum weight loss, and exercise habits (5). Other small cross-sectional studies report that lactating women with recent GDM had lower insulin levels (3) and insulin-glucose ratios (12) than nonlactating women. In sum, these data suggest improved insulin sensitivity and  $\beta$ -cell function in postpartum women with a history of GDM who breastfeed, but previous studies did not examine intensity of breastfeeding.

Our study strengths include the racially and ethnically diverse sample of women who were diagnosed with GDM via standardized criteria and the detailed and systematic prospective assessment of lactation intensity and duration. There were also some limitations, including the lack of direct measures of insulin sensitivity in women during or after pregnancy and no direct measures of overall or regional adiposity in the cohort based on magnetic resonance imaging or dual X-ray absorptiometry methodologies. BMI is a crude measure of overall adiposity, and we controlled for this potential confounder in the multivariable models as a surrogate marker for healthy lifestyle behaviors that may be associated with infant feeding practices. Because it is unethical to randomize women to breastfeeding or formula feeding, residual confounding may play a role in the improved metabolic control observed with greater lactation intensity. Poorer metabolic status, obesity, or other physiologic traits could influence a woman's ability to successfully establish lactation (e.g., delayed lactogenesis) and, potentially, the findings may be due to reverse causation. This possibility is minimized because the SWIFT infant feeding groups were comparable in severity of GDM based on the 3-h 100-g OGTT blood

glucose results obtained at similar gestational age and the fact that over 50% of obese women in our sample lactated successfully (exclusive or mostly breastfeeding). Our findings are robust given the large sample size of women diagnosed with GDM via standardized methodologies and the more favorable metabolic profiles for lactating women even after adjustment for potential confounders such as prepregnancy BMI, education, race/ethnicity, parity, age, and fasting time period.

Previous evidence consistently shows that women with a history of GDM who lactate manifest improved metabolic profiles as well as enhanced pancreatic  $\beta$ -cell compensation (5) and exhibit a lower prevalence of type 2 diabetes in the early postpartum period (4). Yet direct evidence that links these acute metabolic effects to persistent metabolic changes postweaning or assesses whether they confer protection against future disease onset has been unavailable. Our findings may have important implications for determination of glucose tolerance based on results from the postpartum OGTTs, including the diagnosis of diabetes as well as glucose intolerance (prediabetes). Because intensive lactation results in lower fasting and 2-h glucose levels from the OGTT, it may be advisable to repeat the OGTT postweaning, particularly for women whose glucose values are within 10% below cutoffs for diagnosis of diabetes.

Our findings also support previous evidence that lactation may be beneficial to women's future health, including protection against development of metabolic diseases in midlife. The Coronary Artery Risk Development in Young Adults (CARDIA) study reports that longer duration of lactation (>1–5 months, >5–9 months, and >9 months vs. 0–1 month) was associated with lower incidence of metabolic syndrome in midlife (lower by 39–50% for non-GDM and by 49–86% among GDM groups independent of preconception metabolic profiles, weight gain, sociodemographics, and lifestyle behaviors) among black women, and white women followed prospectively (13). Other studies report that lactation had weak to modest effects in reducing metabolic diseases or cardiovascular risk factors (14–18). Only one study examined lactation duration and incident diabetes among women with a history of GDM, but it reports a null association based on the retrospective design (18). Thus, benefits of lactation for prevention of diabetes

are likely, but direct evidence is much less available in women with previous GDM. Moreover, none of the previous studies ever examined lactation intensity. The findings from the CARDIA study by Gunderson et al. (13) are unique because of the repeated measures longitudinal design that involved prospective data collection every 2–5 years (i.e., lactation duration, changes in lifestyle behaviors, body weight, and biochemical measures during the reproductive years), as well as control for prepregnancy metabolic syndrome components. Lactation duration beyond 6 months may be a proxy for higher intensity. Our study findings support the hypothesis that exclusive lactation for shorter time periods may confer additional long-term health benefits for women, particularly women with GDM who are up to seven times more likely to develop diabetes in midlife (19,20).

Postpartum screening for diabetes after GDM pregnancy is completed by only ~50% of women with GDM in various clinical settings (21), even though both the American Diabetes Association and the American College of Obstetrics and Gynecology recommend screening for early diagnosis and treatment of diabetes after pregnancy (22,23). Future studies are needed to better understand the mechanisms through which lactation may contribute to lasting improvements in metabolic profiles and the potential degree of benefit to long-term health according to various levels of intensity and duration of lactation.

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#### References

- Knopp RH, Walden CE, Wahl PW, et al. Effect of postpartum lactation on lipoprotein lipids and apoproteins. *J Clin Endocrinol Metab* 1985;60:542–547
- Tigas S, Sunehag A, Haymond MW. Metabolic adaptation to feeding and fasting during lactation in humans. *J Clin Endocrinol Metab* 2002;87:302–307
- Lenz S, Kühl C, Hornnes PJ, Hagen C. Influence of lactation on oral glucose tolerance in the puerperium. *Acta Endocrinol (Copenh)* 1981;98:428–431
- Kjos SL, Henry O, Lee RM, Buchanan TA, Mishell DR Jr. The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. *Obstet Gynecol* 1993;82:451–455
- McManus RM, Cunningham I, Watson A, Harker L, Finegood DT. Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. *Metabolism* 2001;50:715–719
- American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 2000;23 (Suppl. 1):S77–S79
- Lucas A, Ewing G, Roberts SB, Coward WA. How much energy does the breast fed infant consume and expend? *Br Med J (Clin Res Ed)* 1987;295:75–77
- Stunkard AJ, Berkowitz RI, Stallings VA, Schoeller DA. Energy intake, not energy output, is a determinant of body size in infants. *Am J Clin Nutr* 1999;69:524–530
- Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–1197
- Hanson RL, Pratley RE, Bogardus C, et al. Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *Am J Epidemiol* 2000;151:190–198
- Hanley AJ, Williams K, Gonzalez C, et al.; San Antonio Heart Study; Mexico City Diabetes Study; Insulin Resistance Atherosclerosis Study. Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. *Diabetes* 2003;52:463–469
- Butte NF, Hopkinson JM, Mehta N, Moon JK, Smith EO. Adjustments in energy expenditure and substrate utilization during late pregnancy and lactation. *Am J Clin Nutr* 1999;69:299–307
- Gunderson EP, Jacobs DR Jr, Chiang V, et al. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). *Diabetes* 2010;59:495–504
- Cohen A, Pieper CF, Brown AJ, Bastian LA. Number of children and risk of metabolic syndrome in women. *J Womens Health (Larchmt)* 2006;15:763–773
- Ram KT, Bobby P, Hailpern SM, et al. Duration of lactation is associated with lower prevalence of the metabolic syndrome in midlife—SWAN, the study of women's health across the nation. *Am J Obstet Gynecol* 2008;198:268, e1–e6
- Schwarz EB, Ray RM, Stuebe AM, et al. Duration of lactation and risk factors for maternal cardiovascular disease. *Obstet Gynecol* 2009;113:974–982
- Villegas R, Gao YT, Yang G, et al. Duration of breast-feeding and the incidence of type 2 diabetes mellitus in the Shanghai Women's Health Study. *Diabetologia* 2008; 51:258–266
- Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. *JAMA* 2005;294:2601–2610
- Gunderson EP, Lewis CE, Tsai AL, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetes* 2007;56:2990–2996
- Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009;373:1773–1779
- Ferrara A, Peng T, Kim C. Trends in postpartum diabetes screening and subsequent diabetes and impaired fasting glucose among women with histories of gestational diabetes mellitus: A report from the Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care* 2009;32:269–274
- American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 2004;27 (Suppl. 1):S88–S90
- Committee on Obstetric Practice. ACOG Committee Opinion No. 435: postpartum screening for abnormal glucose tolerance in women who had gestational diabetes mellitus. *Obstet Gynecol* 2009;113:1419–1421