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The Role of Lactation in GDM Women

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Abstract

Lactating women exhibit more favorable blood glucose and insulin profiles, as well as increased insulin sensitivity than nonlactating women. Yet, much less is known about whether these favorable effects on metabolic risk factors persist long-term among women with gestational diabetes mellitus (GDM). The evidence that lactation reduces incident type 2 diabetes after GDM pregnancy is limited and inconsistent. Well-controlled, prospective studies that measure lactation intensity and duration, and comprehensively screen for postpartum glucose tolerance are needed to conclusively determine whether lactation can lead to reduced risk of type 2 diabetes after GDM pregnancy.

Keywords

lactation; diabetes; gestational diabetes; breastfeeding; pregnancy; postpartum

Introduction

Gestational diabetes mellitus (GDM), referred to as glucose intolerance with first-onset during pregnancy, occurs in ~7% of all US pregnancies, and affects over 200,000 women per year.¹ A history of GDM confers a 4- to 7-fold higher risk of diabetes, depending on whether hyperglycemia is present before conception.^{2,3} Almost 50% of women with a GDM pregnancy will be diagnosed with type 2 diabetes mellitus within 5 to 8 years after pregnancy.^{3–5} Major predictors of subsequent diabetes or metabolic syndrome after GDM delivery include pancreatic β -cell dysfunction, glucose intolerance, and obesity in the early postpartum period.^{4,6–11} Much less is known about postpartum behaviors that influence progression to type 2 diabetes after GDM pregnancy. The Diabetes Prevention Program randomized women with impaired glucose tolerance to lifestyle intervention and found a reduction in diabetes risk among those with a history of GDM, but could not discern the impact of lactation and postpartum behaviors because participants had delivered pregnancies more than a decade earlier.¹²

Lactation is characterized by increased glucose utilization and lipolysis through non-insulin-mediated processes for milk production by the mammary gland, as well as higher maternal basal metabolic rates and mobilization of fat stores.^{13–15} Lactating women manifest lower blood glucose and insulin concentrations and higher glucose production rates resulting from increased glycogenolysis (not gluconeogenesis or increased use of free fatty acids).¹⁶ Emerging evidence indicates that lactation may have enhanced pancreatic β -cell mass and function, as well as decrease insulin resistance.^{17,18} Although these beneficial effects of lactation on maternal metabolism are known, evidence is less available that these effects influence the progression to glucose intolerance and overt diabetes in mid to late life, particularly among women with previous GDM. The scientific evidence that lactation influences metabolism in women with GDM is critically reviewed herein, as well as evidence for persistent influences on diabetogenesis in women with a history of GDM, and the need for future research on lactation measures and the potential protective benefits for women's metabolic health.

Lactation and Maternal Metabolism in Postpartum Women With Recent GDM Pregnancy

Table 1 summarizes the cross-sectional analyses of postpartum lactation and glucose tolerance among women with a history of GDM. Postpartum women with a recent GDM pregnancy have more favorable metabolic profiles, including glucose tolerance and blood lipids, among those lactating compared with those nonlactating. McManus et al¹⁸ reported that 14 lactating compared with 12 nonlactating women with previous GDM had higher insulin sensitivity, glucose effectiveness, and first-phase insulin response to glucose (AIRg) assessed by Bergman's Minimal Model, although statistical significance was not reached. However, the same study reported higher disposition index (insulin sensitivity multiplied by AIRg) was 2.5 times higher (129.9 ± 26.0 vs. $53.4 \pm 18.0 \times 10^{-4}/\text{min}$; $P < 0.05$) for lactating versus nonlactating women matched for age, weight, postpartum weight loss, and exercise habits.¹⁸ These findings support the hypothesis that lactation by women with a recent GDM pregnancy improves insulin sensitivity and β -cell function, at least in the short term.

Cross-sectional findings from a study of Latinas with history of GDM showed marked differences in glucose tolerance and lipid metabolism for lactating compared with nonlactating women.¹⁹ For example, lactating women had better glucose tolerance at 4 to 16 weeks postpartum; a lower total area under the glucose tolerance curve (17.0 ± 4.2 vs. 17.9 ± 5.0 g/min/dL), and lower fasting serum glucose (93 ± 13 vs. 98 ± 17 mg/dL) and 2-hour oral glucose tolerance test glucose levels (124 ± 41 vs. 134 ± 49 mg/dL) after controlling for body mass index (BMI), maternal age, and insulin use during pregnancy.¹⁹ In addition, lactating versus nonlactating women with recent GDM had a lower prevalence of type 2 diabetes mellitus; 4.2% versus 9.4%, respectively.¹⁹ A second study that examined 122 Latinas with normal fasting glucose and no insulin use during GDM pregnancy reported that lactation was less likely in those with diagnosis of diabetes within 6 months postpartum than women with normal glucose tolerance (42% vs. 71%; $P = 0.03$), respectively.²⁰ Other studies have reported that women with overt diabetes have reduced insulin requirements when lactating during the postpartum period.²³ In a study of women from the Atlantic Diabetes

and Pregnancy Study, women who were classified as lactating versus nonlactating at the time of the 2-hour oral glucose tolerance test had a 60% lower odds of persistent dysglycemia defined by the World Health Organization criteria for impaired glucose tolerance and diabetes adjusted for maternal BMI, age, treatment during pregnancy, and family history of diabetes.²¹ However, other lifestyle behaviors and lactation duration or intensity was not assessed in this study.

The Study of Women, Infant Feeding, and Type 2 Diabetes after GDM pregnancy (SWIFT), evaluated the relationship between lactation duration and intensity and postpartum glucose tolerance among women with a previous GDM pregnancy at the study baseline visit.²⁴ SWIFT reported that higher lactation intensity at 6 to 9 weeks postpartum was inversely associated with lower fasting plasma glucose and insulin concentrations in a graded monotonic manner.²² Specifically, compared with exclusive or mostly formula feeding (>17 oz formula per 24 h), exclusive breastfeeding and mostly breastfeeding (<6 oz formula per 24 h) groups, respectively, had lower adjusted mean (95% CI) fasting plasma glucose (mg/dL) of -4.3 (-7.4, -1.3) and -5.0 (-8.5, -1.4), fasting insulin (μ U/mL); -6.3 (-10.1, -2.4) and -7.5 (-11.9, -3.0), and 2-hour insulin; -21.4 (-41.0, -1.7) and -36.5 (-59.3, -13.7); all *P*-values <0.05. Higher lactation intensity was also linked to lower prevalence of prediabetes among obese women as well as nonobese women with exclusive or mostly breastfeeding groups had lower prevalence of diabetes or prediabetes (*P*=0.02).²²

The findings from cross-sectional analyses support the hypothesis that lactation has immediate favorable effects on glucose tolerance, but leaves open the possibility of reverse causation, with improved metabolic status determining lactation practices as some studies did not evaluate confounding by lifestyle behaviors, or control of metabolic status during pregnancy. Therefore, longitudinal studies with standardized screening methods for diabetes onset are required to determine whether lactation may have persistent protective effects on metabolism that lower risk of developing diabetes in women after GDM pregnancy. Studies that have investigated lactation duration or current lactation status during the postpartum period in relation to future development of type 2 diabetes after GDM pregnancy are described in Table 2.

LACTOGENESIS AND HISTORY OF GDM

GDM is a heterogeneous disorder that includes women with preexisting diabetes during pregnancy. Women with pregestational diabetes may experience delayed lactogenesis related to insulin resistance²⁹ and inadequate blood glucose control, although the mechanisms are known.³⁰ Delayed lactogenesis in women with a recent GDM pregnancy has been described in a few studies. One small clinical study of women with recent GDM reported no marked delays in lactogenesis based on similar concentration of lactose in the colostrum at 40 to 50 hours postpartum for GDM women compared with control women.²⁹ However, GDM women had more difficulty expressing colostrum from their breasts during the first 2 days of lactation.²⁹ One study reported a higher incidence of delayed OL among primiparas with previous GDM (*n*=27) as compared to women without GDM (*n*=397); 63% vs. 43%, *p*=0.04).³¹ Strong risk factors for delayed lactogenesis in the general prenatal population include primiparity, prematurity, and maternal obesity.^{32,33} Maternal obesity

may delay the onset of lactogenesis^{32,34} because of lower physiological levels of prolactin in response to suckling.³⁴

Delayed milk production is an important predictor of breastfeeding persistence, and has been associated with lower rates of breastfeeding and shorter duration among obese women.³² Furthermore, medical management of newborns of diabetic mothers that involves provision of supplemental milk feedings (ie, indicated by neonatal hypoglycemia) may also interfere with maternal milk production.

Lactation and Changes in Metabolic Risk Factors Postweaning

Direct biochemical evidence that lactation influences cardiometabolic risk factors is available from a longitudinal study of women without a history of GDM. Gunderson and colleagues examined changes in metabolic parameters from before pregnancy to an average of 13 months postweaning (range, 2 to 24 mo). This study reported that lactation duration for 3 months or longer was associated with 6 mg/dL higher plasma high density lipoprotein-cholesterol, but no difference in BMI, adjusted for lifestyle behaviors and sociodemographic attributes.³⁵ Given the strong inverse association between plasma HCL-C and incidence of type 2 diabetes in women,³⁶ these findings provide direct biochemical evidence that lactation may have lasting favorable effects on metabolic risk factors postweaning, and supports the hypothesis that lactation may have lasting beneficial effects on glucose tolerance in women.

Lactation and Incidence of Type 2 Diabetes Among Women With a History of GDM

Less evidence is available to determine whether lactation has lasting effects on glucose metabolism to prevent development of type 2 diabetes in women with a history of GDM. The studies reporting findings related to lactation measures and subsequent diabetes among women with a history of GDM are shown in Tables 1 and 2. The study limitations include the retrospective designs, lack of detailed lactation measures, variable testing for diabetes after pregnancy, self-report of subsequent type 2 diabetes mellitus, and lack of control for major confounders, including lifestyle behaviors. For example, several studies focused on lactation status (any vs. none) at the time of the postpartum glucose tolerance test (ie, 1 to 4 mo postpartum) and did not assess lactation duration. Kjos et al⁷ reported that lactation at 4 to 16 weeks postpartum was not associated with development of type 2 diabetes within 7.5 years after delivery in Latinas with variable follow-up screening. Another study of 91 Latinas in whom lactation status (yes/no) was assessed at the time of the glucose tolerance testing, lactation was not associated with type 2 diabetes diagnosis at 11 to 26 months after GDM pregnancy.²⁵

Only 2 studies report findings regarding lactation duration and subsequent incidence of type 2 diabetes among women with a history of GDM, and provide inconclusive evidence. A retrospective analysis of women with a history of GDM from the Nurses' Health Study cohort found no association between lifetime lactation or other lifestyle behaviors (ie, diet, exercise habits) and incidence of type 2 diabetes several years after delivery.²⁶ In the

Nurses' Health Study cohort, diabetes status was ascertained only by self-report, and confirmed by review of clinical records, and women retrospectively reported GDM status. A second study by Ziegler et al²⁸ among 264 women with recent GDM reported that the lowest risk of diabetes occurred in women who had lactated for longer than 3 months after controlling for GDM treatment and maternal BMI. However, this study did not control for any lifestyle behaviors or other confounders that may determine both lactation duration and diabetes risk. Thus, reverse causation in which greater insulin resistance may lead to delayed lactogenesis and shorter lactation duration cannot be ruled out. Prospective studies are needed that engage in standardized screening methods for diabetes at regular intervals, assess both lactation duration and exclusivity, and control for potential confounders including gestational glucose tolerance, maternal lifestyle behaviors, and sociodemographics. Studies within racially and ethnically diverse cohorts of women with GDM are needed to determine whether lactation measures influence future diabetes onset.

Lactation Duration and Incidence of the Metabolic Syndrome After GDM Pregnancy

The Coronary Artery Risk Development in Young Adults Study assessed lifestyle behaviors and biochemical measures during a 20-year period to investigate whether lactation influences future disease risk in women with a history of GDM. Gunderson and colleagues (Table 2) assessed lactation and the incidence of metabolic disease among women with a history of GDM in a carefully controlled longitudinal cohort study that overcomes the study design weaknesses outlined above. The CARDIA Study²⁷ prospectively measured cardiometabolic risk factors, both before and after pregnancies as well as lactation duration for each pregnancy. The incidence of the metabolic syndrome was ascertained every 5 years among women with previous GDM as well as those without GDM. The study found that increasing lactation duration (1 mo and up to >9 mo vs. 0 to <1 mo) was strongly associated with lower relative hazards of incident metabolic syndrome in black and white women; lower by 39% to 50% among non-GDM and by 49% to 86% among GDM groups adjusted for all metabolic syndrome components measured before pregnancy, obesity, lifestyle behaviors, and weight gain during the 20-year follow-up. These findings suggest that the long-term effects of lactation on women's cardiometabolic health are beneficial and that they are not mediated by weight changes. The study provides the first direct biochemical evidence that link lactation duration to long-term favorable effects on women's cardiometabolic health, and these protective effects were also reported among women with a history of GDM.²⁷

Issues and Gaps

Evidence is insufficient that lactation has lasting effects that prevent diabetes among women with previous GDM. We know very little about the metabolic effects of lactation intensity and duration in women with GDM, or whether delayed lactogenesis is a significant problem during the early postpartum period for women with GDM. The heterogeneity in GDM according to the severity of the gestational glucose intolerance may also be of major importance in determining the long-term impact of lactation on women's metabolic health and disease risk, as greater insulin resistance may result in delayed lactogenesis.³³

Conclusions

Relatively few studies have examined lactation and postpartum glucose intolerance or dysglycemia, and subsequent development of incident type 2 diabetes after GDM pregnancy. Of 36 studies that screened for postpartum glucose tolerance in women with previous GDM,^{4,10,11,21,22,26,28,37,38} only 9 of 36 study samples assessed lactation measures,^{7,18–22,25,26,28} and of these, only 3 controlled for lifestyle behaviors and/or sociodemographics.^{18,22,26} Six studies defined lactation as “any” versus “none,”^{7,18–21,25} 1 study assessed lactation intensity²² and 2 studies assessed lactation duration up to one or more years postpartum.^{26,28} A retrospective analysis among nurses reporting a history of GDM showed a null association with incident type 2 diabetes by self-report.²⁶ Another study in German women prospectively assessed diabetes onset after pregnancy among 264 women with previous GDM, and reported that lactation for >3 months was associated with lower incidence of type 2 diabetes, but lifestyle behaviors were not controlled in this study.²⁸ Limitations of the studies include primarily qualitative measures of lactation (current, ever vs. never), 25% to 45% lost-to-follow-up rates, select populations (white only, nurses or Latinas attending family planning clinics), nonuniform GDM diagnostic criteria, and nonstandardized ascertainment of diabetes outcomes (ie, variable postpartum diabetes screening, self-reported diabetes), and lack of data on prenatal glycemia or postpartum lifestyle behaviors as potential confounders.

The SWIFT study was designed to prospectively assess lactation intensity and duration in relation to the 2-year incidence of type 2 diabetes mellitus in women with recent GDM.²⁴ Follow-up of the SWIFT cohort is currently underway to assess glucose tolerance among a large, racially and ethnically diverse (75% minority; Asian, Hispanic, and Black) cohort of 1,035 women diagnosed with GDM via Carpenter and Coustan criteria.²⁴ SWIFT prospectively measured lactation, as well as lifestyle behaviors and other major confounders, and is the largest cohort of women with GDM in whom standardized postpartum screening for glucose tolerance is being carried out at regular intervals.

Lactation has favorable effects on maternal glucose tolerance during the postpartum period after GDM pregnancy, but evidence is insufficient to conclude that these effects endure postweaning, or lactation influences development of type 2 diabetes in women years later. However, among women with GDM, evidence for lasting effects of lactation on long-term risk of type 2 diabetes and the metabolic syndrome is much less available. Well-controlled, prospective studies with more precise and complete measures of lactation, (ie, intensity) and control for lifestyle behaviors, are needed to conclusively determine whether lactation lowers the risk of type 2 diabetes among women with a history of GDM. Longitudinal assessment of glucose intolerance, including prediabetes and diabetes, at defined intervals is necessary to determine whether favorable effects of lactation persist years after delivery. Specifically, biochemical measurements are needed to substantiate the epidemiologic evidence that lactation influences diabetogenesis beyond the childbearing years. Lactation is a modifiable health behavior that may play an important role in future disease risk not only for women with a history of GDM, but for their offspring as well.

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TABLE 1

Cross-sectional Analyses of Glucose Tolerance and Metabolism From 1 to 6 Months Postpartum Among Women With Previous GDM by Lactation Status (Any vs. None) or Lactation Intensity

References	Analysis, Years	GDM Pregnancy (n)	Study Population	Lactation Measure	Testing Method	Time After Delivery	Outcomes	Conclusions
Kjos et al ¹⁹	Cross-sectional, 1990–1991	809	Latinas attending family planning clinic	“Any” Yes/no	2-h 75 g OGTT	4–16 wk	Diabetes prevalence: 9.4% nonlactating 4.2% lactating	Lower prevalence of diabetes in lactating, $P = 0.01$
Buchanan et al ²⁰	Cross-sectional, 1993–1995	122 normal fasting glucose, diet-control	Latinas in central Los Angeles	“Any” Yes/no	2-h 75 g OGTT and FSIGTs	1–6 mo	Overall DM prevalence 10%	Diabetes less likely to be lactating than non-DM (42% vs. 71%) $P = 0.03$
McManus et al ¹⁸	Cross-sectional	26 women: 14 lactating 12 nonlactating		“Any” Yes/no	FSIGT Disposition index assessed by Bergman’s Minimal Model	3 mo	Disposition index	Higher disposition index (129.9 $\pm$ 26.0 vs. 53.4 $\pm$ 18.0 $\times 10^{-4}$ /min; $P < 0.05$) for lactating vs. nonlactating matched for age, weight, weight loss, exercise
O’Reilly et al ²¹	Cross-sectional 2006–2007	300	Ireland	“Any” Yes/no	2-h 75 g OGTT	12 wk	Persistent dysglycemia World Health Organization criteria	Breastfeeding; OR (95% CI) = 0.418 (0.199–0.888), $P = 0.022$
Gunderson et al ²²	Cross-sectional 2008–2011	522	Diverse: 26% white 32% Hispanic 28% Asian 9% black	Cumulative lactation intensity from birth to 6–9 wk	2-h 75 g OGTT	6–9 wk	Prevalence of prediabetes, diabetes, and fasting glucose, insulin, 2-h glucose, insulin	Lower fasting glucose and insulin ($P < 0.01$); lower prevalence of prediabetes with higher intensity of lactation in obese and nonobese

References	Analysis, Years	GDM Pregnancy (n)	Study Population	Lactation Measure	Testing Method	Time After Delivery	Outcomes	Conclusions
								women (n=100)

CI indicates confidence interval; FSGT, frequently sampled intravenous glucose tolerance test; GDM, gestational diabetes mellitus; OR, odds ratio.

TABLE 2

Incidence of Diabetes Mellitus or the Metabolic Syndrome by Lactation Status (Any vs. None) or Lactation Duration Among Women With Previous GDM

References	Study Design, Years	GDM Pregnancy (n)	Study Population	Lactation Measure	Type 2 DM Definition	Time Postpartum	Type 2 DM* Outcome	Conclusions
Kjos et al ⁷	Retrospective analysis 1987–1994	671	Latinas clinic attendees in central Los Angeles	Any vs. none at 4–16 wk postpartum	2-h 75 g OGTT	Variable time within 7.5 y	Incidence rate 1.1 cases/1000 person-years 95% CI, 0.9–1.9	Null association of lactation with DM in bivariate analyses
Buchanan et al ²⁵	Longitudinal 1993–1997	91	Latinas central Los Angeles	Any vs. none at 11–26 mo postpartum	75 g OGTT and FSGITs once	15-mo interval, 11–26 mo	Overall cumulative incidence 15%	Null between lactation and DM vs. normal OGTT (25% vs. 15.4%), $P = 0.41$
Stuebe et al ²⁶	Retrospective cohort 1989–2003	Not reported (n)	The Nurses' Health Study cohort; aged 24–43 y in 1989	Duration: months of lactation for pregnancies	Self-report of diabetes chart confirmation	Variable up to 14 y	Incidence rate: 6.24 cases per 1000 person-years	Null, nonsignificant association; adjusted for lifestyle behaviors
Gunderson et al ²⁷	Prospective cohort 1985–2006	702 non-GDM 84 GDM	CARDIA, multicenter 50% white 50% black; aged 18–30 in 1985–1986	Duration: total months of lactation, for all pregnancies	Fasting glucose, 2-h 75 g OGTT; and metabolic components* (examinations up to 6 times)	Average of 8 y postpartum 72% retention at 20 y	Metabolic syndrome incidence rate: 22.1 cases per 1000 person-years	44%–86% lower risk; >1–>9 mo vs. 0–1 mo adjusted for parity, race, smoking, prepregnancy biomarkers, and lifestyle behavior
Ziegler et al ²⁸	Prospective cohort 1989–1999	264 GDM	Germany, white	Duration 3 vs. >3 mo	Fasting glucose, 2-h 75 g OGTT (up to 8 times)	Up to 19 y postpartum	Incidence of diabetes; average 12 y to diabetes for lactating groups	Hazard ratio: 0.55, (95% CI, 0.35–0.85) adjusted for BMI, age, smoking, family history

* The metabolic syndrome.