Lactation Duration and Long-term Risk for Incident Type 2 Diabetes in Women With a History of Gestational Diabetes Mellitus

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OBJECTIVE

We examined the association of lactation duration with incident type 2 diabetes among women with a history of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS

We monitored 4,372 women with a history of GDM participating in the Nurses' Health Study II for incident type 2 diabetes over 25 years up to 2017. Lactation history was obtained through follow-up questionnaires to calculate lactation duration. Follow-up blood samples were collected from a subset of these women at median age of 58 years through the Diabetes & Women's Health Study.

RESULTS

We documented 873 incident cases of type 2 diabetes during 87,411 person-years of follow-up. Longer duration of lactation was associated with lower risk of type 2 diabetes for both total lactation (hazard ratio 1.05 [95% CI 0.83–1.34] for up to 6 months, 0.91 [0.72–1.16] for 6–12 months, 0.85 [0.67–1.06] for 12–24 months, and 0.73 [0.57–0.93] for >24 months, compared with 0 months; *P*-trend = 0.003) and exclusive breastfeeding (*P*-trend = 0.002) after adjustment for age, ethnicity, family history of diabetes, parity, age at first birth, smoking, diet quality, physical activity, and prepregnancy BMI. Longer duration of lactation was also associated with lower HbA_{1c}, fasting plasma insulin, and C-peptide concentrations among women without type 2 diabetes at follow-up (all adjusted *P*-trend ≤0.04).

CONCLUSIONS

Longer duration of lactation is associated with a lower risk of type 2 diabetes and a favorable glucose metabolic biomarker profile among women with a history of GDM. The underlying mechanisms and impact on diabetes complications, morbidity, and mortality remain to be determined.

As women undergo changes in metabolism to meet the demands of the growing fetus and to prepare for delivery and lactation (1), they often experience deterioration in insulin sensitivity during normal pregnancy (2). Although most women maintain glucose homeostasis by a compensatory increase in insulin secretion (1,3), this compensatory mechanism is insufficient in some women, resulting in gestational diabetes mellitus (GDM), which affects ~5–9% of pregnancies in the U.S. (4,5). Because women with a history of GDM are at higher risk for type 2 diabetes later in life (6,7), it is critical to identify modifiable determinants of type 2 diabetes risk prevention specific for these high-risk women.

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Breastfeeding has a potential role in women's cardiometabolic health (8,9), including type 2 diabetes prevention (10–12). In ongoing large-scale prospective cohorts of >150,000 parous women in the U.S. (13), longer duration of lactation was associated with lower risk for type 2 diabetes later in life. More recent investigations from other prospective studies in the U.S. and Europe demonstrated that the protective association was also evident among women with a history of GDM (14–16). In addition to women with a history of GDM being at a higher risk for type 2 diabetes progression later in life (6,7), women with diabetes during pregnancy experience breastfeeding challenges in early postpartum, including delayed onset of "milk coming in," also known as lactogenesis II (17). Therefore, targeting breastfeeding has a preventive potential, especially among these high-risk women with a history of GDM.

In addition to larger-scale prospective data, previous short-term investigations have reported the favorable recovery of insulin sensitivity among women who breastfeed in the early postpartum period (18,19). However, data are lacking on the association between lactation duration and biomarkers of glucose metabolism long-term after the index pregnancy. We therefore measured fasting plasma insulin and C-peptide concentrations among middle-aged women with a history of GDM. The objective of this study was to determine the associations of lifetime lactation duration with incident type 2 diabetes risk and biomarkers of glucose metabolism later in life among women with a history of GDM.

RESEARCH DESIGN AND METHODS

Study Population

The Nurses' Health Study (NHS) II is an on-going prospective cohort of 116,671 female registered nurses from the U.S. aged 25–42 years in 1989. Participants were monitored biennially using validated questionnaires on medical history and lifestyle. NHS II participants were eligible for inclusion in the current study if they reported a history of GDM in 1991 or incident GDM through the biennial questionnaires up to 2001 or through a 2009 pregnancy questionnaire, which inquired about physician diagnoses of GDM. In a review of medical records among 120 women, 94% were confirmed to have a "definite or probable" diagnosis of GDM (20). In a random sample of parous women (n = 100), a high level of GDM surveillance was documented in this cohort, with 83% reporting they underwent a glucose challenge test during pregnancy and 100% reporting frequent prenatal urine screening. Participants were excluded if they reported cancer, cardiovascular disease, or multiple-birth pregnancy before the GDM pregnancy or were missing important data such as lactation information and BMI at age 18 years. We therefore included 4,372 women with a history of GDM. Between 2012 and 2014, the NHS II participants who reported a history of GDM were invited to participate in the Diabetes & Women's Health (DWH) Study. Details of the DWH study protocol have been published previously (21). Fasting blood samples were collected from 934 women (21), and the baseline characteristics of those who provided blood samples were similar to the entire study population of women with a history of GDM. The current biomarker analysis included DWH study participants in NHS II who were free from type 2 diabetes, defined as hemoglobin A_{1c} (HbA_{1c}) <6.5% (48 mmol/mol) at the follow-up blood collection and who had data on duration of lactation and samples assayed for fasting insulin and C-peptide (n = 543). The Brigham and Women's Hospital Institutional Review Board and the Harvard T.H. Chan School of Public Health Human Subjects Committee Review Board approved the study protocol.

Exposure Assessments

Lactation history was obtained from three NHS II follow-up questionnaires. In 1993, participants were asked "how many months in total (all births combined) did you breastfeed?" with the following response options: did not breastfeed, <1, 1–3, 4–6, 7–11, 12–17, 18–23, 23–35, 36–47, ≥48 months, cannot remember. Similar questionnaires were sent in 1997 and 2003 to update and overwrite lactation information with the latest response. Lifetime duration of lactation was calculated from the sum of the number of months after each birth that the participant reported any breastfeeding. Duration of exclusive breastfeeding was similarly calculated using the reported timing of introduction of formula or solids after each birth.

Information on other potential risk factors, including medical, demographic, and reproductive histories, lifestyle practices, and body weight, were collected through NHS II biennial questionnaires. The validity of these assessments has been documented previously (22). Parity was defined as the number of pregnancies lasting >6 months and updated through follow-up questionnaires. Age at first birth was collected through the NHS II biennial questionnaire in 2007. To reflect the earliest available lifestyle information during reproductive years, lifestyle data collected in 1991 were used. Dietary intake was assessed using a validated semiquantitative food frequency questionnaire in 1991 (23,24). Diet quality was assessed using the Alternate Healthy Eating Index 2010 score, which was developed to determine scores for foods and nutrients most consistently associated with lower chronic disease risk (25). Physical activity was ascertained in 1991, and MET-hours per week was derived (26). As a surrogate prepregnancy BMI measure, BMI at age 18 years was calculated as self-reported weight (kg) at age 18 years divided by the square of height (m^2). The previous validation study showed self-reported weights were highly correlated with measured weights (r = 0.97) (27).

Type 2 Diabetes Ascertainment

The baseline questionnaire and all biennial follow-up questionnaires asked participants about the incidence of physician-diagnosed diabetes. Participants who reported such a diagnosis received a supplementary questionnaire asking about symptoms, diagnostic tests, and treatment to confirm the diagnosis. The validity of the supplementary questionnaire for type 2 diabetes has been documented previously (28,29), in which self-reported diagnosis of diabetes was confirmed by medical records reviewed by an endocrinologist blinded to the supplementary questionnaire information for 61 of 62 (98%) participants randomly selected in the NHS.

The diagnosis was confirmed if at least one of the following was reported according to the National Diabetes Data Group criteria (30): *1*) at least one symptom (excessive thirst, polyuria, weight loss, or hunger) plus fasting glucose ≥7.8 mmol/L or random glucose ≥11.1 mmol/L; *2*) in the absence of symptoms, at least two elevated glucose concentrations on different occasions (fasting glucose >7.8 mmol/L, random glucose ≥11.1 mmol/L,

and/or 2-h postload ≥11.1 mmol/L at an oral glucose tolerance test); or *3*) treatment with insulin or oral hypoglycemic medication. For the cases identified after 1998, the revised American Diabetes Association criteria were applied using the fasting glucose cutoff of 7.0 mmol/L (31).

Biochemical Analysis

Blood sample collection was described in detail previously (21). Briefly, a phlebotomy kit and instructions for fasting blood collection were sent to participants in 2012–2014. Samples were returned via overnight shipping to a central laboratory where blood was processed according to standardized procedures and stored at −80°C. HbA_{1c} was measured using a nonporous ion exchange high-performance liquid chromatograph assay (Tosoh Automated Analyzer HLC-723G8; Tosoh Bioscience, Inc., San Francisco, CA) (interassay coefficient of variation [CV] <1.2%). C-peptide concentrations were measured using C-peptide micro-ELISA (Quansys Biosciences, Logan, UT) (interassay CV 10.0% at 3.6 ng/mL and 7.3% at 1.9 ng/mL). Insulin concentrations were measured using the cobas 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN) (interassay CV 3.1% at 121.2 pmol/L and 3.1% at 377.9 pmol/L).

Statistical Analysis

Distributions of continuous variables were assessed for normality, and natural log transformations of skewed biomarkers were used in subsequent analyses. Descriptive statistics for continuous variables are summarized as mean ± SD, and categorical variables are summarized using proportions according to lactation duration categories.

Participants contributed to person-time from the date of the GDM diagnosis to the date of the type 2 diabetes diagnosis, death, or the end of follow-up, whichever came first. We used multivariable time-dependent Cox proportional hazards models to estimate hazard ratio (HR) and 95% CI, and the time scale for the left-truncated survival model was age (months). Model 1 was age adjusted. Model 2 was additionally adjusted for ethnicity (white/nonwhite), family history of diabetes (yes/no), parity, and age at first birth (<25, 25–29, 30–34, ≥35 years). Model 3 was additionally adjusted for ever smoking assessed in 1991 (yes/no), diet quality assessed in 1991 (tertiles), physical activity in 1991 (tertiles), and prepregnancy BMI (≤23, >23–25, >25–27, >27–30, >30 kg/m^2). For age at first birth (1% missing), missing indicators were generated to treat missing as a separate category. Tests for trend were conducted by assigning a median value to each category and modeling this value as a continuous variable. General linear models were used to assess associations of lactation duration with glucose metabolic biomarkers among women free of type 2 diabetes at the follow-up blood draw, defined as HbA_{1c} <6.5% (48 mmol/mol). Potential interactions were tested by adding an interaction term of lactation duration (continuous) with age (continuous), parity (continuous), primipara (yes/no), prepregnancy BMI (continuous), and age at index GDM diagnosis (continuous) with adjustment for covariates included in model 2.

For all statistical analyses, two-sided $P < 0.05$ was considered to be statistically significant. All data analyses were performed using SAS 9.4 software for UNIX (SAS Institute, Cary, NC).

RESULTS

We documented 873 incident cases of type 2 diabetes among 4,372 women with a history of GDM during 87,411 person-years of follow-up. Women were a median age 31.8 (95% CI 25.2–40.2) years at the index GDM diagnosis and 49.8 (39.2–61.5) years at the type 2 diabetes diagnosis. The age-standardized characteristics of study participants are presented according to lifetime duration of lactation in Table 1.

Lactation Duration and Type 2 Diabetes

HRs for developing type 2 diabetes are presented in Table 2 with models adjusting for other risk factors. A longer lifetime duration of lactation was associated with lower risk for type 2 diabetes (Table 2). When lactation was treated as a continuous variable per year increase, the association remained (HR 0.89 [95% CI 0.83–0.96]) with the model 3 adjustment. When model 3 was additionally adjusted for marital status (yes/no), the significant association remained (HR 1.05 [95% CI 0.82–1.34] for up to 6 months, 0.91 [0.71–1.15] for 6–12 months, 0.84 [0.67–1.06] for 12–24 months, and 0.73 [0.57–0.93] for >24 months compared with 0 months; P for trend = 0.004). There was no statistically significant effect modification in the association between lactation duration and type 2 diabetes by age, parity, primipara, prepregnancy BMI, or age at the index GDM diagnosis.

Similarly, a longer lifetime duration of exclusive lactation was associated with a lower risk for type 2 diabetes (Table 3).

Table 1—Characteristics of NHS II participants according to lifetime duration of lactation (N = 4,372)

	0 months (n = 766)	>0 to 6 months (n = 770)	>6 to 12 months (n = 871)	>12 to 24 months (n = 1,082)	>24 months (n = 883)
Age at index GDM, years†	32.1 ± 4.8	32.5 ± 4.8	32.3 ± 4.7	32.2 ± 4.7	33.2 ± 4.8
White	89	88	90	92	94
Family history of diabetes	30	28	25	24	24
Age at first birth, years†	27.3 ± 5.1	28.6 ± 5.4	28.4 ± 5.2	27.5 ± 4.8	26.1 ± 4.1
Prepregnancy BMI, kg/m^2	22.3 ± 4.4	21.7 ± 3.7	21.2 ± 3.1	21.0 ± 3.2	21.0 ± 2.7
Parity in 1991	1.9 ± 0.9	1.8 ± 0.8	1.9 ± 0.8	2.3 ± 0.9	3.0 ± 1.1
Ever smoking in 1991	38	37	34	31	29
AHEI in 1991	40.7 ± 10.6	42.5 ± 10.5	43.7 ± 10.1	43.7 ± 10.7	43.1 ± 10.5
Total activity in 1991, MET-h/week	17.0 ± 23.5	16.4 ± 19.7	15.9 ± 18.2	18.3 ± 22.1	17.3 ± 21.7

Values are means ± SD or percentages and are standardized to the age distribution of the study population. AHEI, Alternate Healthy Eating Index.
†Value is not age adjusted.

Table 2—HR (95% CI) for type 2 diabetes among women with a history of GDM, according to lifetime duration of total lactation in NHS II (N = 4,372)

	0 months	>0 to 6 months	>6 to 12 months	>12 to 24 months	>24 months	*P* for trend
Cases/person-years	178/14,553	155/12,769	151/16,007	205/22,253	184/21,828	
Model 1	1	1.01 (0.80–1.28)	0.82 (0.64–1.03)	0.78 (0.62–0.97)	0.67 (0.54–0.84)	<0.0001
Model 2	1	1.04 (0.82–1.32)	0.85 (0.67–1.08)	0.78 (0.62–0.98)	0.64 (0.51–0.82)	<0.0001
Model 3	1	1.05 (0.83–1.34)	0.91 (0.72–1.16)	0.85 (0.67–1.06)	0.73 (0.57–0.93)	0.003

Model 1 adjusted for age. Model 2 additionally adjusted for ethnicity (white/nonwhite), family history of diabetes (yes/no), updated parity, and age at first birth (<25, 25–29, 30–34, ≥35 years). Model 3 additionally adjusted for baseline ever smoking (yes/no), baseline diet quality (tertiles), baseline physical activity (tertiles), and prepregnancy BMI (≤23, >23–25, >25–27, >27–30, >30 kg/m^2).

Lactation Duration and Biomarkers of Glucose Metabolism Among Women Free of Type 2 Diabetes

Multiple regression models were constructed to assess whether duration of lactation was associated with glucose metabolic biomarkers among women who provided blood samples in 2012–2014 (Table 4). At the follow-up blood collection, women were a median age of 58.2 (95% CI 51–65) years and 26.3 (95% CI 15.7–34.1) years since the GDM index pregnancy. Among women free of type 2 diabetes at the blood collection, a longer lactation duration was significantly associated with HbA_{1c}, fasting insulin, and C-peptides (Table 4).

CONCLUSIONS

Among 4,372 women with a history of GDM during 87,411 person-years of follow-up, longer lifetime lactation duration was associated with a lower risk of type 2 diabetes after adjustment for age at first birth, ethnicity, family history of diabetes, parity, smoking, diet quality, physical activity, and prepregnancy BMI. Further, longer lifetime duration of lactation was associated with lower concentrations of HbA_{1c}, fasting insulin, and C-peptide among middle-aged women without type 2 diabetes.

Our incident type 2 diabetes results are in general similar to recent reports from prospective studies in the U.S. and Europe (14–16). In 155 women with a history of GDM participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study (14), lactation duration had a graded inverse association with diabetes incidence. Although longer duration of lactation was associated with lower risk for type 2 diabetes in the NHS and NHS II (13), the association was not statistically significant in a sensitivity analysis among women with a history of GDM in the previous analysis of NHS II using up to 2001 follow-up. Having follow-up data up to 2017 enabled us to perform updated analyses among women with a history of GDM in NHS II. In these updated analyses monitoring women up to ages in their early-60s, as opposed to the earlier report of monitoring up to their mid-40s, we observed a significant association of longer lifetime duration of lactation with lower risk for type 2 diabetes among women with a history of GDM. Since U.S. women between ages mid-40s and early-60s experience a sharp increase in the incidence of type 2 diabetes (32), this increased power is likely to have contributed to the detection of a significant association of longer lifetime duration of lactation with lower risk for type 2 diabetes among women with a history of GDM.

Previously, the favorable recovery of postpartum glucose homeostasis has been documented among women who adopt breastfeeding behavior in the early postpartum period (18,19,33). In a clinical study among 26 women with recent GDM (14 breastfeeding and 12 nonbreastfeeding) at 3 months postpartum, the disposition index, which is the product of insulin sensitivity times the amount of insulin secreted in response to blood glucose concentrations, was higher in the breastfeeding group (19). However, whether this early favorable recovery might have a sustained long-term impact on glucose homeostasis was unclear. In a study with 3-year postpartum follow-up, women who breastfed for longer tended to have lower fasting insulin concentrations, although the association did not reach statistical significance after multiple adjustment (34); however, these women in their 30s might recover their glucose homeostasis to some extent by 3 years postpartum. We have performed biochemical analysis of fasting insulin and C-peptide concentrations in women at a median age of 58 years to assess the association between earlier lactation behavior and glucose metabolic biomarkers later in life. We report the associations of longer lactation duration with lower fasting insulin and C-peptide concentrations as indicators

Table 3—HR (95% CI) for type 2 diabetes among women with a history of GDM, according to lifetime duration of exclusive lactation in NHS II (N = 4,006)

	0 months	>0 to 6 months	>6 to 12 months	>12 months	*P* for trend
Cases/person-years	363/30,531	200/19,235	155/18,318	109/14,013	
Model 1	1	0.89 (0.74–1.08)	0.73 (0.59–0.89)	0.66 (0.53–0.83)	<0.0001
Model 2	1	0.92 (0.76–1.11)	0.73 (0.60–0.90)	0.64 (0.50–0.82)	<0.0001
Model 3	1	0.96 (0.79–1.16)	0.79 (0.64–0.98)	0.70 (0.54–0.90)	0.002

Model 1 adjusted for age. Model 2 additionally adjusted for ethnicity (white/nonwhite), family history of diabetes (yes/no), updated parity, and age at first birth (<25, 25–29, 30–34, ≥35 years). Model 3 additionally adjusted for ever smoking (yes/no), diet quality (tertiles), physical activity (tertiles), and prepregnancy BMI (≤23, >23–25, >25–27, >27–30, >30 kg/m^2).

Table 4—Least-squares mean (95% CI) biomarker concentrations of glucose metabolic biomarkers according to lifetime duration of lactation among women free of diabetes (HbA_{1c} <6.5% [48 mmol/mol]) with a history of GDM (n = 543)

	0 months	1–12 months	12–24 months	>24 months	*P* for trend
HbA_{1c}, %; mmol/mol					
Model 1	5.68 (5.59–5.77); 39 (38–40)	5.64 (5.59–5.70); 38 (38–39)	5.66 (5.61–5.72); 38 (38–39)	5.58 (5.53–5.63); 37 (37–38)	0.03
Model 2	5.69 (5.59–5.78); 39 (38–40)	5.65 (5.59–5.70); 38 (38–39)	5.66 (5.61–5.72); 38 (38–39)	5.57 (5.52–5.63); 37 (37–38)	0.02
Model 3	5.66 (5.56–5.75); 38 (37–39)	5.65 (5.60–5.71); 38 (38–39)	5.66 (5.61–5.72); 38 (38–39)	5.58 (5.53–5.63); 37 (37–38)	0.04
Insulin, pmol/L					
Model 1	71.6 (60.5–84.7)	61.3 (55.6–67.6)	54.7 (49.5–60.5)	51.3 (46.8–56.2)	0.0004
Model 2	69.7 (58.8–82.7)	60.6 (54.8–67.0)	54.7 (49.5–60.5)	52.2 (47.3–57.5)	0.005
Model 3	64.7 (54.6–76.8)	61.0 (55.2–67.3)	54.7 (49.5–60.4)	53.1 (48.2–58.5)	0.02
C-peptide, ng/mL					
Model 1	4.07 (3.67–4.52)	3.74 (3.52–3.97)	3.48 (3.27–3.70)	3.35 (3.17–3.55)	0.0006
Model 2	4.01 (3.61–4.46)	3.71 (3.49–3.95)	3.48 (3.27–3.70)	3.39 (3.19–3.60)	0.007
Model 3	3.88 (3.49–4.32)	3.73 (3.50–3.96)	3.47 (3.26–3.69)	3.42 (3.22–3.63)	0.02

Model 1 adjusted for age at follow-up blood draw. Model 2 additionally adjusted for ethnicity (white/nonwhite), family history of diabetes (yes/no), lifetime parity, and age at first birth (<25, 25–29, 30–34, ≥35 years). Model 3 additionally adjusted for ever smoking (yes/no), diet quality (high/low), baseline physical activity (high/low), and prepregnancy BMI (≤23, >23–25, >25–27, >27–30, >30 kg/m^2).

of insulin action in middle-aged women with a history of GDM and free of type 2 diabetes at follow-up. Although fasting plasma insulin and C-peptide concentrations to some minor extent are influenced by pancreatic insulin secretion capacity, there is consensus that fasting plasma insulin and C-peptide predominantly are a measure of insulin resistance in individuals without severe diabetes and β-cell defects.

This study has several notable strengths. It is the largest long-term prospective investigation of lactation, biomarkers of glucose metabolism, and type 2 diabetes prevention among women with a history of GDM to date, allowing assessment of long-term diabetes risk and glucose metabolic biomarkers specific to these high-risk women.

However, the study has several limitations. First, our study participants were nurses of primarily European ancestry; therefore, further investigations targeting specific populations of more diverse socioeconomic status are warranted to develop optimal prevention routes.

Second, our blood samples were shipped overnight after collection, then processed, and stored for 1–3 years at −80°C before biochemical analyses were performed. The process might have introduced molecular degradation, although stability of these biomarkers after delay in processing and long-term storage has been documented previously (35).

Third, we were not able to obtain valid measure of fasting plasma concentrations of glucose in these samples because of overnight shipping collection methods used; therefore, we were unable to assess HOMA estimates. However, fasting insulin was used as a surrogate marker for insulin resistance because insulin resistance and hyperinsulinemia rarely exist in isolation in a diabetes-free population (36). Further, the consistent association between lactation duration and C-peptide confirms that its association is unlikely influenced by exogenous insulin.

Fourth, the observed benefits of lactation may have been confounded by other healthful behaviors, although we attempted to account for these confounders through statistical adjustment of regression models.

Fifth, we did not have precise measurements of pregnancy and early postpartum clinical parameters, including weight gain and energy expenditure. Since gestational and postpartum weight gain (37), energy expenditure during lactation (38), and other pregnancy and postpartum clinical parameters including biochemical measurements and detailed fetus information may be involved in the mechanism behind the observed associations, we recommend carefully designed and controlled future studies to determine the causality and mechanisms and to examine life stage–specific questions.

In summary, longer lifetime duration of lactation is associated with incident type 2 diabetes and a favorable glucose metabolic biomarker profile among middle-aged women with a history of GDM. Prolonged breastfeeding should be encouraged during pregnancy, especially among women with GDM who are at increased risk for experiencing breastfeeding challenges in early postpartum (17) in addition to being at higher risk for type 2 diabetes progression later in life (6,7). It is furthermore important to understand the underlying mechanisms and additional potential benefits on diabetes complications, comorbidity, and mortality.

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