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Lactation intensity and duration to postpartum diabetes and prediabetes in women with gestational diabetes

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Abstract

Objective: To investigate the association of lactation intensity and duration with postpartum diabetes and prediabetes risks among Chinese women with a history of GDM.

Methods: We included 1260 women with a history of GDM who participated in the whole population's GDM universal screening survey by using World Health Organization's criteria. Lactation intensity and lactation duration were collected by a standardized questionnaire. Postpartum diabetes and prediabetes were confirmed by an oral glucose tolerance test.

Results: During a mean postpartum period of 3.65 years, we identified 114 cases of diabetes and 417 cases of prediabetes. The multivariable-adjusted hazard ratios based on different lactation intensity (exclusive formula, mixed feeding, exclusive lactation) were 1.00, 0.68, 0.45 for diabetes ($P_{\text{trend}} = 0.008$), and 1.00, 0.74, and 0.61 for prediabetes ($P_{\text{trend}} = 0.006$), respectively. The multivariable-adjusted hazard ratios associated with different lactation duration (none, 0–6 months, 6–12 months, 12–18 months, 18 months) were 1.00, 0.66, 0.42, 0.66, and 0.25 for diabetes ($P_{\text{trend}} = 0.013$), and 1.00, 0.82, 0.62, 0.67, and 0.63 for prediabetes ($P_{\text{trend}} = 0.021$),

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Author Contributions:

Y.S., and G.H. designed the study, acquired data, performed statistical analyses, and drafted the manuscript. J.L., W.L., S.Z., H.L., P.S., P.W., L.W., H.T. and J.T. designed the study and critically revised the manuscript for important intellectual content. C.Z., X.Y., Z.Y. and L.H. critically revised the manuscript for important intellectual content. G.H. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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respectively. A restricted cubic spline curve showed a graded inverse association of lactation duration with the risks of diabetes and prediabetes ($P_{\text{trend}} < 0.001$).

Conclusions: Higher lactation intensity and longer lactation duration were significantly associated with lower risks of postpartum diabetes and prediabetes among Chinese women with a history of GDM.

Keywords

gestational diabetes; lactation; diabetes; prediabetes

Introduction

Women with gestational diabetes (GDM) are well known to suffer great risks of type 2 diabetes and prediabetes in their postpartum life ¹. Diabetes is recognized as a major risk factor of cardiovascular diseases, while in recent years, prediabetes is also found to be associated with an increased risk of composite cardiovascular diseases and all-cause mortality ². Recently, lactation has been considered as potential benefit for maternal postpartum weight retention and glycemic metabolism ^{3,4}. Several studies have found a graded association between lactation duration and the risk of diabetes ^{5–11}. However, self-reported diagnoses of diabetes were used in some of these studies rather than the lab measurement to define the major outcome ^{5,9}. Moreover, few studies have assessed the association of lactation intensity and duration with postpartum diabetes risk among women with GDM, and their results remain inconsistent due to the relatively small sample sizes of women with GDM, few cases of type 2 diabetes ^{10,11}, and short follow-up time ^{7,11}. Evidence of the contribution of lactation to the progression of diabetes and prediabetes in Asian women with GDM is limited. The aim of this study was to investigate the contribution of lactation intensity and duration to the postpartum diabetes and prediabetes among Chinese women with prior GDM in the Tianjin GDM observational study.

Subjects and Methods

Tianjin GDM screening project

Tianjin is the fourth largest city in China with only 30 minutes away from the Capital Beijing by train. There are six central districts in Tianjin with about 4.3 million residents. Since 1999, the Tianjin Women's and Children's Health Center launched a universal screening of GDM using WHO's criteria in all six central districts ¹². The screening rate was reported to be >91% between 1999 and 2008 ¹². We used a 1-hour glucose screening test with 50g glucose load at 26–30 gestational weeks. If the 1-hour glucose level was over 7.8 mmol/L, another 2-h oral glucose tolerance test (OGTT) with 75g glucose load would be performed at the Tianjin Women's and Children's Health Center. GDM diagnosis was made as per WHO criteria: a 75-g glucose 2-h OGTT result confirming either diabetes (fasting glucose ≥ 7 mmol/l or 2-hour glucose ≥ 11.1 mmol/l) or impaired glucose tolerance (IGT) (2-hour glucose ≥ 7.8 and < 11.1 mmol/l) ¹³.

Study samples

Totally 76,325 women were screened from 2005 to 2009, and 4644 women were diagnosed as GDM (Figure 1) ¹⁴. We invited these 4644 women with GDM and finally 1263 of them finished the study survey including a questionnaire and an OGTT after August 2009. There were no differences in age, 2 h glucose, fasting glucose, the prevalence of IGT and diabetes at 26–30 gestational weeks, and OGTT tests between those returned and those not returned. Among the 1263 women, 83 were newly diagnosed diabetes using an OGTT and 1180 GDM women received randomization into the intervention group (n=586) and the “usual care” control group (n=594) for another clinical trial. This study was approved by the Human Subjects Committee of the Tianjin Women’s and Children’s Health Center. All the participants provided written informed consent. In the current analysis, 1260 women with GDM were included after excluding 3 GDM women with missing information for lactation duration.

Measurements

All study participants filled in a questionnaire about their socio-demographics (age, marital status, education, income, and occupation), history of GDM (fasting and 2-h glucose in the OGTT were measured/available from the central lab in the Tianjin Women’s and Children’s Health Center and treatment of GDM during the pregnancy), family history of diabetes, medical history (hypertension, diabetes, and hypercholesterolemia), pregnancy outcomes (pre-pregnancy weight, weight gain in pregnancy, and number of children), lactation (exclusive formula, mixed or exclusive breast) and lactation duration, dietary habits (a self-administered food frequency questionnaire (FFQ) to measure the frequency and quantity of intake of 33 major food groups and beverages during the past year) ¹⁵, alcohol intake, smoking habits, passive smoking, and physical activity (the frequency and duration of leisure time and sedentary activities) at the postpartum baseline survey. They also completed the 3-day 24-hour food records using methods for dietary record collections taught by a dietician. The performance of 3-day 24-hour food records ¹⁵, the FFQ ¹⁵, and the above questionnaire on assessing physical activity ^{16,17} have been validated in the China National Nutrition and Health Survey in 2002.

Body weight and height were measured using the standardized protocol by specially trained research doctors. BMI was calculated as the body weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the horizontal level between the inferior costal margin and the iliac crest on the mid-axillary line with women in their standing position. Blood samples were collected in all participants after an overnight fast of at least 12 hours. Participants without a self-reported history of diabetes were given a standard 75-g glucose OGTT test. Plasma glucose was measured on an automatic analyzer (Toshiba TBA-120FR, Japan).

Diagnosis of postpartum diabetes and prediabetes

We used the American Diabetes Association (ADA)’s criteria ¹⁸ for the diagnosis of diabetes and prediabetes. Diabetes was defined as fasting glucose ≥ 7.0 mmol/L, and/or 2-h glucose ≥ 11.1 mmol/L. Prediabetes was defined as either impaired fasting glucose (fasting glucose ≥ 5.6 mmol/L and < 7.0 mmol/L) or IGT (2-h glucose ≥ 7.8 mmol/L and < 11.1 mmol/L).

Those using antidiabetic drugs in the examination were also included into the type 2 diabetes cases.

Statistical analysis

One-way ANOVA and chi-square test were used to compare the mean levels of continuous variables and the prevalence of categorical variables among women with different glycemic status. Cox proportional hazard regression analysis was used to assess risks of postpartum diabetes and prediabetes in women with different lactation intensity and duration. We used the restricted cubic spline nested in time-dependent Cox models to test whether there was a dose-response or nonlinear association of lactation duration as a continuous variable with the risks of diabetes and prediabetes. All analyses were adjusted for pregnant age (Model 1), and then for education, family income, family history of diabetes, treatment of GDM, smoking, passive smoking, alcohol drinking, leisure-time physical activity, sleeping time, dietary fiber, sweetened beverage drinking, energy intakes of fat, protein, and carbohydrate, and pre-pregnancy BMI (Model 2), and further for 2-hour glucose during pregnancy (Model 3). $P < 0.05$ was considered statistically significant. All statistical analyses were performed by IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA), and SAS for Windows, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

The flow diagram of the study was presented in Figure 1. General characteristics of the study participants were presented in Table 1. GDM women who were diagnosed prediabetes and diabetes during postpartum period had significantly higher pre-pregnancy BMI, fasting and 2-hour glucose during pregnancy, postpartum fasting glucose, postpartum 2-hour glucose, postpartum HbA1c, lower education and family income, and were more often with a family history of diabetes compared with GDM women with a normal glucose.

During a mean 3.65 ± 2.17 years postpartum, we confirmed 114 cases of diabetes and 417 cases of prediabetes by OGTT. There were inverse associations of lactation intensity and duration with the risks of postpartum diabetes and prediabetes (Table 2). The multivariable-adjusted (age, education, family income, family history of diabetes, treatment of GDM, smoking, passive smoking, alcohol drinking, leisure-time physical activity, sleeping time, dietary fiber, sweetened beverage drinking, energy intakes of fat, protein, and carbohydrate, pre-pregnancy BMI, and 2-hour glucose during pregnancy) hazard ratios based on different lactation intensity (exclusive formula, mixed feeding, exclusive lactation) were 1.00, 0.68 (95% confidence interval [CI] 0.41–1.15), 0.45 (95% CI 0.27–0.75) for diabetes (P for trend = 0.008), and 1.00, 0.74 (95% CI 0.55–1.00), and 0.61 (95% CI 0.46–0.84) for prediabetes (P for trend = 0.006), respectively.

The multivariable-adjusted hazard ratios associated with different lactation duration (none, 0–6 months, 6–12 months, 12–18 months, 18 months) were 1.00, 0.66, 0.42, 0.66, and 0.25 for diabetes (P for trend = 0.013), and 1.00, 0.82, 0.62, 0.67, and 0.63 for prediabetes (P for trend = 0.021), respectively. When lactation duration was considered as a continuous variable, multivariable-adjusted hazard ratios for each 1-month increase in lactation duration

were 0.95 (95% CI 0.92–0.98) for postpartum diabetes, and 0.98 (95% CI 0.96–0.99) for postpartum prediabetes.

When lactation duration was considered as a continuous variable by using restricted cubic splines, a graded inverse association of lactation duration with the risks of diabetes and prediabetes was observed (P for trend <0.001) (Figure 2). The relatively lower risk of diabetes occurred when lactation duration was found around 6 months, then the risk slightly increased and finally became much lower when lactation duration was over 18 months. This curve trend was consistent with the findings in Table 2 when lactation duration was considered as a categorical variable. Similar results could also be found in the analysis regarding the risk of prediabetes.

Discussion

Our study found that exclusive breast feeding was related to 55% and 39% lower risks of postpartum diabetes and prediabetes respectively when compared with exclusive formula feeding in Chinese women with prior GDM. This study indicated an inverse and graded association of lactation duration with the risks of diabetes and prediabetes among women with prior GDM. Our findings were strengthened and more plausible due to the accurate diagnosis of postpartum diabetes and prediabetes by performing an OGTT and the multivariable adjustments for pre-pregnancy BMI, treatment of GDM, 2-hour glucose during pregnancy, lifestyle and sociodemographic factors.

Findings from the present study on the inverse association are in general consistent with those from previous studies. For instance, in the SWIFT (Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy SWIFT) study including 959 women with GDM found an inverse association of lactation intensity (exclusive formula, mixed formula, and exclusive lactation) and lactation duration with the risk of postpartum 2-year diabetes⁷. One recent meta-analysis⁴ including the SWIFT⁷, another prospective cohort¹⁰, 2 cross-sectional studies^{19,20} and 1 retrospective cohort study²¹ has indicated that longer lactation for more than 4 to 12 weeks postpartum compared with shorter lactation among women with GDM showed a reduced risk of type 2 diabetes at postpartum 2 years (odds ratio 0.56, 95% CI 0.35–0.89), and more than 5 years (odds ratio 0.22, 95% CI 0.13–0.36), but not within 12 weeks postpartum (odds ratio 0.77, 95% CI 0.01–55.9). However, these previous studies are largely limited by small sample sizes of women with GDM (except SWIFT study) and few cases of type 2 diabetes ($n=12-113$) with limited power, by the cross-sectional design^{19,20}, short follow-up time (2 studies within 12 weeks postpartum^{19,20}, and 1 study at 2 years postpartum⁷), insufficient multivariable adjustment for major diabetes risk factors^{10,19-21}, and incomplete ascertainment of diabetes by self-reported records⁵.

The association of lactation intensity and duration with type 2 diabetes risk has been assessed in the western population. Due to one-child policy from 1979 to 2015 in China^{22,23}, no parity bias is caused and considered in the present analysis. The present study with large sample sizes of women with GDM, long follow-up, and enough cases of postpartum diabetes and prediabetes identified by an OGTT during follow-up demonstrated that exclusive breast feeding compared with exclusive formula feeding reduced 61% risk of

postpartum diabetes after adjusting major diabetes risk factors. In addition, we found an inverse and graded association of lactation duration with the risk of postpartum diabetes among women with prior GDM.

The present study was the first to assess the association of lactation intensity and lactation duration with the long-term risk of postpartum prediabetes identified by an OGTT among Chinese women with prior GDM. Although most women with GDM return to a normal glucose status after delivery, about 30% women with GDM develop prediabetes during early postpartum¹⁴. Prediabetes has been reported associated with an increased risk of cardiovascular and renal diseases^{2,24}. We have indicated a 39% reduction of prediabetes risk among women with exclusive lactation versus exclusive formula. We also found an inverse and graded association of lactation duration with the risk of postpartum prediabetes among women with prior GDM. It is noteworthy that lactation of over six months should be the first priority of childbearing in women with prior GDM, which will be beneficial for both their children and themselves.

Our findings manifested the WHO recommendation that infants should be exclusively lactated in the first six months²⁵. However, in a national survey of breastfeeding rate in China, the crude breastfeeding rate of infants under 6 months was reported to be only 20.7%²⁶. Policies and national supports regarding the extension of the lactation duration among parous women especially those with prior GDM are needed to relieve the increasing healthcare burden of diabetes and its complications in China.

Several mechanisms are plausible to explain the lower risks of diabetes and prediabetes associated with lactation. Lactation was reported to reduce the postpartum weight retention in several studies^{27,28}, and weight retention was considered to be one of the risk factors of postpartum diabetes²⁹. Meanwhile, prolactin may also play an important role in reducing the risks of diabetes and prediabetes postpartum. Moderately increasing level of prolactin during pregnancy and later lactation has been proven to be beneficial to β cell function and hepatic insulin resistance³⁰. Another cross-sectional study also found that increasing prolactin level was associated with reduced risks for both diabetes and prediabetes³¹. Further prospective studies are warranted to see whether there is a causal relationship between prolactin and diabetes and prediabetes.

Strengths of this study include the relatively large sample size of women with prior GDM. In addition, diagnoses of GDM and postpartum diabetes and prediabetes were based on an OGTT. However, we did not use HbA1c as one of the diagnostic criteria of diabetes or prediabetes postpartum mainly because several studies showed that using HbA1c in isolation to predict glucose tolerance in women with a history of GDM was limited due to its poor sensitivity, which may cause missing diagnosis of incident diabetes or prediabetes^{32,33}. One limitation of this study is the return rate of the initial invitation with only 27% of all GDM women, which may cause the selection bias. Second, we have no data on 1 h glucose and 3 h glucose during pregnancy since we used the WHO's diagnostic criteria for GDM. Third, lactation intensity and duration were based on self-reported data which might be influenced by multiple factors, such as pre-pregnancy obesity, and treatment during pregnancy. However, we have controlled all these factors and other major confounding factors in the

multivariable-adjusted analyses. Finally, due to the retrospective design of this study, the causal relationship between lactation and hyperglycemia could not be well clarified. Further prospective studies were necessary.

In conclusion, among parous women with prior GDM, exclusive lactation was associated with significantly reduced risks of postpartum diabetes and prediabetes. Findings from Chinese women along with those in other population supported the potential of lactation in lowering risks of type 2 diabetes. Lactation of over 6 months may be a practical, low-cost intervention during an early postpartum period to prevent diabetes and prediabetes among women with prior GDM.

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Figure 1.
Flow chart of the study.

Figure 2.

Hazard ratios of diabetes and prediabetes by lactation duration among women with GDM. Adjustments were made for age, pre-pregnancy body mass index, education, family income, family history of diabetes, treatment of GDM, current smoking, passive smoking, current alcohol drinking, leisure time physical activity, sleeping time, dietary fiber, sweetened beverage drinking, energy intakes of fat, protein, and carbohydrate, and 2-hour glucose during pregnancy.

Table 1. Characteristics of women with gestational diabetes by different glycemic status confirmed by postpartum oral glucose tolerance test

	Normal glucose	Pre-diabetes	Diabetes	P value [†]
No. of participants	729	417	114	
Age at delivery, years	30.0±3.31	30.4±3.81	29.7±3.55	0.637
Age at baseline, years	33.5±3.93	34.5±4.50	32.8±3.63	0.410
Pre-pregnancy body mass index, kg/m ²	22.4±2.98	23.7±3.37	25.6±3.64	<0.001
Duration after delivery, years	3.50±2.10	4.08±2.37	3.04±1.53	0.411
Weight gain during pregnancy, kg	17.2±5.85	16.5±6.07	15.3±6.28	0.001
Fasting glucose during pregnancy, mmol/l	5.17±0.69	5.44±0.81	5.93±0.81	<0.001
2-hour glucose during pregnancy, mmol/l	8.99±1.14	9.12±1.18	10.3±1.75	<0.001
Treatment of gestational diabetes				
Daily self-monitoring of blood glucose, %	14.0	14.9	23.7	0.020
Diet control or physical activity only, %	40.6	36.0	30.7	0.449
Diet control + physical activity, %	45.4	48.2	53.5	0.030
Insulin, %	2.61	3.12	21.1	<0.001
Lactation intensity				0.007
Exclusive formula, %	11.9	15.1	22.8	
Mixed feeding, %	43.6	42.7	41.2	
Exclusive lactation, %	44.4	42.2	36.0	
Lactation duration, months	9.05±6.16	8.43±6.12	7.60±6.45	0.010
Body mass index, kg/m ²	23.1±3.35	25.4±4.01	27.7±4.27	<0.001
Waist circumference, cm	77.9±8.15	82.9±9.65	89.1±9.44	<0.001
Fasting glucose postpartum, mmol/l	5.00±0.37	5.67±0.54	7.35±1.94	<0.001
2-hour glucose postpartum, mmol/l	5.89±0.98	7.87±1.63	13.5±3.01	<0.001
HbA1c postpartum, mmol/mol	36±6	38±6	50±12	<0.001
HbA1c postpartum, %	5.5±0.6	5.7±0.5	6.8±1.1	<0.001
Education, %				
<13 years	19.9	25.2	29.8	0.001

	Normal glucose	Pre-diabetes	Diabetes	χ^2 P value
13–16 years	71.3	68.6	66.7	
16 years	8.8	6.2	3.5	
Family income, %				0.003
<5000 yuan per month	24.7	29.0	40.4	
5000–8000 yuan per month	38.7	34.1	35.1	
8000 yuan per month	36.6	36.9	24.6	
Family history of diabetes, %	31.6	37.4	56.1	<0.001
Current smoking, %	2.6	2.2	2.6	0.810
Passive smoking, %	42.8	42.0	36.0	0.248
Current alcohol drinkers, %	26.2	28.1	25.4	0.809
Leisure time physical activity, %				0.116
0 min per day	70.6	72.2	78.9	
1–29 min per day	26.3	24.7	19.3	
30 min per day	3	3.1	1.8	
Sleeping time, hours/day	7.71±1.00	7.64±1.02	7.79±1.09	0.859
Energy consumption, kcal/day *	1673±416	1754±455	1714±427	0.020
Fiber, g/day	12.1±4.39	12.7±4.95	12.4±4.74	0.091
Fat, % energy	33.0±5.99	33.2±6.28	33.3±6.32	0.567
Carbohydrate, % energy	50.3±6.98	50.1±7.12	50.3±7.12	0.715
Protein, % energy	16.7±2.71	16.7±2.70	16.4±2.42	0.671
Sweetened beverage drink, %	77.2	80.6	74.6	0.813

* Dietary intakes are assessed by 3-day 24-h food records

χ^2 P for trend across different glycemic status.

Table 2.

Hazard ratios of diabetes and pre-diabetes by lactation intensity and duration

	No. of patients	No. of cases	Person-years	Hazard ratios (95% confidence intervals)		
				Model 1	Model 2	Model 3
Diabetes						
Lactation intensity	1260	114	4595			
Exclusive formula	176	26	600	1.00	1.00	1.00
Mixed feeding	543	47	1956	0.60 (0.37–0.97)	0.58 (0.35–0.96)	0.68 (0.41–1.15)
Exclusive lactation	541	41	2039	0.43 (0.26–0.71)	0.39 (0.23–0.64)	0.45 (0.27–0.75)
P for trend				0.004	0.001	0.008
Lactation duration (months)						
None	176	26	600	1.00	1.00	1.00
0–6	249	24	833	0.70 (0.40–1.22)	0.64 (0.36–1.14)	0.66 (0.37–1.19)
6–12	342	20	1350	0.34 (0.19–0.60)	0.39 (0.21–0.71)	0.42 (0.22–0.78)
12–18	377	39	1404	0.64 (0.39–1.05)	0.53 (0.32–0.89)	0.66 (0.39–1.12)
>18	116	5	408	0.28 (0.11–0.72)	0.19 (0.07–0.52)	0.25 (0.09–0.65)
P for trend				0.002	0.002	0.013
Lactation duration as a continuous variable (1 month increase)				0.96 (0.93–0.99)	0.95 (0.92–0.98)	0.96 (0.93–0.98)
Pre-diabetes	1146	417	4248			
Lactation intensity						
Exclusive formula	150	63	510	1.00	1.00	1.00
Mixed	496	178	1829	0.67 (0.50–0.90)	0.73 (0.55–0.98)	0.74 (0.55–1.00)
Exclusive lactation	500	176	1909	0.57 (0.43–0.76)	0.62 (0.46–0.83)	0.61 (0.46–0.84)
P for trend				0.001	0.006	0.006
Lactation duration (months)						
None	150	63	510	1.00	1.00	1.00
1–6	225	83	766	0.77 (0.55–1.07)	0.83 (0.59–1.16)	0.82 (0.59–1.15)
6–12	322	114	1296	0.55 (0.40–0.75)	0.61 (0.45–0.84)	0.62 (0.45–0.85)
12–18	338	122	1283	0.60 (0.44–0.82)	0.65 (0.48–0.89)	0.67 (0.49–0.91)
>18	111	35	393	0.63 (0.42–0.96)	0.62 (0.41–0.95)	0.63 (0.41–0.96)

	No. of patients	No. of cases	Person-years	Hazard ratios (95% confidence intervals)		
				Model 1	Model 2	Model 3
P for trend				0.001	0.014	0.021
Lactation duration as a continuous variable (1 month increase)				0.98 (0.96–0.99)	0.98 (0.96–0.99)	0.97 (0.96–0.99)

Model 1 adjusted for age; Model 2 adjusted for age, pre-pregnancy body mass index, education, family income, family history of diabetes, treatment of gestational diabetes, current smoking, passive smoking, current alcohol drinking, leisure time physical activity, sleeping time, sweetened beverage drinking, energy intakes, fiber, fat, protein and carbohydrate intakes; Model 3 adjusted for variables in Model 2 and also 2-hour glucose during pregnancy.