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REVIEW ARTICLE

Potential protective effect of lactation against incidence of type 2 diabetes mellitus in women with previous gestational diabetes mellitus: A systematic review and meta-analysis

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Summary

Lactation may protect women with previous gestational diabetes mellitus (GDM) from developing type 2 diabetes mellitus, but the results of existing studies are inconsistent, ranging from null to beneficial. We aimed to conduct a systematic review to gather available evidence. Databases MEDLINE, CINAHL, PubMed, and EMBASE were searched on December 15, 2015, without restriction of language or publication year. A manual search was also conducted. We included observational studies (cross-sectional, case-control, and cohort study) with information on lactation and type 2 diabetes mellitus incidence among women with previous GDM. We excluded case studies without control data. Data synthesis was conducted by random-effect meta-analysis. Fourteen reports of 9 studies were included. Overall risk of bias using RoBANS ranged from low to unclear. Longer lactation for more than 4 to 12 weeks postpartum had risk reduction of type 2 diabetes mellitus compared with shorter lactation (OR 0.77, 95% CI 0.01-55.86; OR 0.56, 95% CI 0.35-0.89; OR 0.22, 95% CI 0.13-0.36; type 2 diabetes mellitus evaluation time < 2 y, 2-5 y, and >5 y, respectively). Exclusive lactation for more than 6 to 9 weeks postpartum also had lower risk of type 2 diabetes mellitus compared with exclusive formula (OR 0.42, 95% CI 0.22-0.81). The findings support the evidence that longer and exclusive lactation may be beneficial for type 2 diabetes mellitus prevention in women with previous GDM. However, the evidence relies only on observational studies. Therefore, further studies are required to address the true causal effect.

KEYWORDS

gestational diabetes mellitus, lactation, meta-analysis, prevention, systematic review, type 2 diabetes mellitus

1 | INTRODUCTION

At present about 415 million adults suffer from diabetes, of which about 90% are type 2 diabetes mellitus.[1] Diabetes is associated with life-threatening morbidity, making the disease not only personal but also socioeconomic problem. In 2015, about 5 million people died because of diabetes.[1]

Gestational diabetes mellitus (GDM) is defined as "diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes."[2] The GDM occurs in nearly 14% of live births.[1] Although hyperglycemia usually normalizes immediately after delivery, the risk of lifetime type 2 diabetes mellitus in women who had GDM is more than 7-fold higher compared with in women with normoglycaemic pregnancies.[3] Furthermore,

up to 50% of women who had GDM developed type 2 diabetes mellitus within 5 years postpartum.[4] Therefore, women with GDM are recognized to be at high risk of developing diabetes at younger ages and are therefore the target of preventive measures.

Intensive lifestyle modification is effective in preventing or delaying type 2 diabetes mellitus in women with previous GDM.[5] However, postpartum women may face difficulties in adopting a healthy lifestyle mainly because of a lack of time.[6,7]

Meanwhile, lactation is increasingly being recognized for its potential benefits on maternal glycemic metabolism. Childbearing itself is suggested to put women at risk for type 2 diabetes mellitus when compared with nulliparous women,[8,9] and breastfeeding may "reset" the burden[10] and lower the risk of diabetes in dose-response manner.[11,12] Although etiological evidence is yet to be established, several hypotheses for this beneficial effect have been proposed such as extra energy expenditure for milk production,[13] visceral fat mobilization,[10] and pancreatic beta-cell rescue by prolactin[14] and/or oxytocin.[15]

It is of great interest whether women with previous GDM, the high risk population for type 2 diabetes mellitus, benefit as well from breastfeeding practice. To date, several observational studies investigating the association between lactation and type 2 diabetes mellitus incidence after GDM pregnancy have been conducted with mixed results. Although there are several reviews written on this topic,[16,17] none was conducted systematically. Only few GDM guidelines recommend breastfeeding for maternal health with minimal evidence.[18–20] To cover all the available evidence and to synthesize the data if available, we aimed to systematically review current findings on lactation for type 2 diabetes mellitus prevention in women with previous GDM.

2 | METHODS

This systematic review was performed according to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines[21] and the Cochrane Handbook for Systematic Reviews for Intervention.[22] The protocol was registered in advance on PROSPERO (CRD42016032699) and is accessible at http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016032699.

2.1 | Eligibility criteria and study selection

A study was considered eligible if (1) the participants were women with previous GDM, (2) it assessed the lactation intensity and/or duration of any lactation, and (3) it included the incidence of postpartum type 2 diabetes mellitus in the outcome. Observational studies (cross-sectional, case-control, and cohort study) were included. Studies with unclear number/rate of type 2 diabetes mellitus onset were excluded (eg, "high" incidence of diabetes, incidence rate of "dysglyceamia").

After eliminating duplicate literatures in EndNote X7.1, 2 reviewers (K.T.N. and M.K.) independently selected potentially eligible reports with titles and abstracts. Full texts of reports that the 2 reviewers agreed on for inclusion were obtained for final selection and were reviewed separately. Any disagreement during the selection process was resolved through discussion with or consulting a third reviewer (E.O.).

2.2 | Search strategy

Literature search was conducted by an information specialist on December 15, 2015, using databases MEDLINE, CINAHL, PubMed, and EMBASE. The search keywords included terms for "lactation" and "GDM." The full search strategy for each database is provided in Table S1. No language or time restriction was applied. We also investigated the references lists of the retrieved papers for the search of additional relevant studies.

2.3 | Data extraction and data synthesis

Information collected was as follows:

1. Study design, study period, and country where the study was conducted
2. Population number and characteristics (ie, age at delivery, non-pregnant body mass index [BMI], race/ethnicity)
3. Exclusion criteria
4. Lactation measures (ie, intention, initiation, intensity, and duration)
5. Diagnostic methods of GDM and type 2 diabetes mellitus
6. Type 2 diabetes mellitus evaluation time-point, incidence rate, and hazard/risk ratio
7. Adjusted confounders for the analysis of breastfeeding and type 2 diabetes mellitus incidence
8. Conclusion on breastfeeding and type 2 diabetes mellitus incidence

One reviewer (K.T.N.) extracted data, and another reviewer (M.K.) checked for its integrity. We planned to contact authors or check original protocols for additional information if needed.

We conducted meta-analysis for studies with comparable results using Review Manager software version 5.3 (RevMan5.3). The number of women with GDM and type 2 diabetes mellitus incidence in relation to breastfeeding measures were obtained from the reports or estimated through calculation by RevMan5.3. We used ruler to estimate the number/percentage in reports providing only graph without exact number.[23] We combined odds ratio for dichotomous data using random-effect models. All data were presented with 95% confidence intervals. We regarded heterogeneity as substantial when the I-squared is greater than 60% and conducted subgroup analyses in such a case.

2.4 | Risk of bias assessment and quality of evidence evaluation

Two researchers (K.T.N. and M.K.) independently assessed the methodological quality of each selected study. Again, any disagreement was resolved through discussion or consulting a third reviewer (E.O.). We used the Risk of Bias Assessment Tool for Nonrandomized Studies

(RoBANS)[24] for making judgments. We evaluated the quality of evidence with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach using GRADEpro GDT.[25]

3 | RESULTS

3.1 | Study selection

A total of 1410 reports were identified through electronic search (Figure 1). Eight reports were added through hand search. Selection first with title and abstracts followed by full-text screening yielded 14 reports for this review. The lists of excluded reports with reason for exclusion are shown in Table S2.

3.2 | Characteristics of included studies

Fourteen reports included in this review were from 9 studies (4 reports for one study, and 2 reports each for 2 studies) involving more than 3600 women with GDM (Table 1).

3.3 | Study design, country

Three studies were prospective cohort study,[26,30,31] 2 were retrospective cohort study,[23,38] and 4 were cross-sectional study.[32,34–36] There was no randomized control trial. Most studies were conducted in the United States, except for one in Germany[31] and one in South Korea.[34]

3.4 | Population

In each study 122 women[32] to 1035 women[26] with GDM were enrolled. Two studies did not provide the population number.[36,38]

The GDM diagnostic criteria were available in 8 studies. Two studies used the Carpenter-Coustan criteria,[26,34] 2 studies used the National Diabetes Data Group criteria,[23,35] 1 study used the recommendation of the Third International Workshop-Conference on GDM[32], 1 study used local criteria,[31] and 2 were based on self-report.[30,38]

The mean/median age at delivery, mostly in the early 1930s, was provided in 6 studies,[23,26,31,32,34,35] mostly in early 1930s. The mean nonpregnant BMI was available in 5 studies,[23,26,32,34,35] with all in overweight or obese range except in one study[34] conducted in South Korea (<25 kg/m^2). The race/ethnicity of the population was provided in 5 studies, 2 were multiracial,[26,30] and 3 consisted mainly of Hispanic populations.[23,32,35]

Exclusion of preexisting diabetes was clearly stated in 2 studies,[26,30] and presumably an additional 5 studies did do so because the diagnosis of GDM was based on glucose tolerance test and not on self-report.[23,31,32,34,35] Early postpartum DM was excluded in 2 studies.[23,26] Women with positive islet autoantibodies were excluded in 2 studies (one study with ICA-positive[32] and one study with GADA-positive[34]). One study conducted subgroup analysis with positive islet autoantibody versus negative islet autoantibody results,[31] and we used the data of the autoantibody-negative population only.

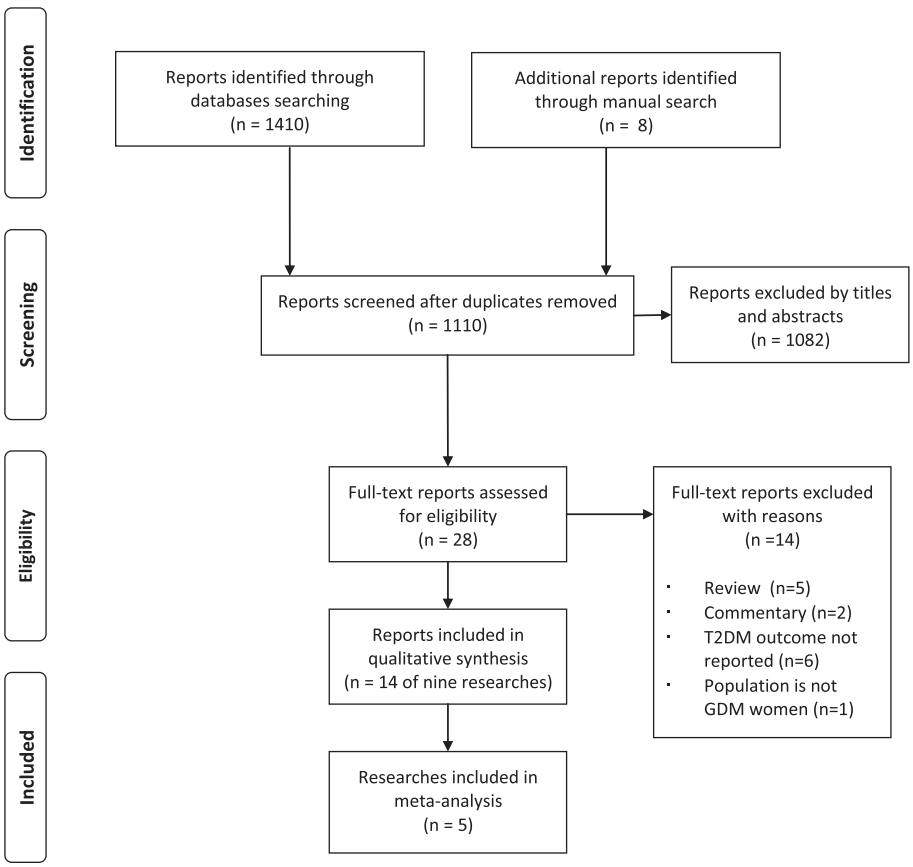

FIGURE 1 PRISMA flow diagram of search and selection

TABLE 1 Characteristics of included studies

First author, year, country, study name, reference	GDM definition	Study period	GDM (n)	Population characteristics (age at delivery, nonpregnant BMI, race/ethnicity)	Major exclusion criteria	Lactation measure[1]
Prospective cohort						
Gunderson, 2015, USA, SWIFT,[26–29]	Carpenter-Coustan criteria	2 y	1035	Mean age (y): 33.9 (DM group), 33.3 (No DM group). Mean pre-pregnancy BMI (kg/m^2): 33.4 (DM group), 29.0 (No DM group). Race/ethnicity: mixed.	Pre-existing DM, DM at 6-9 wk postpartum, mixed or inconsistent feeding within 4-6 wk postpartum.	- Intensity at 6-9 wk postpartum (exclusive lactation; mostly lactation; mostly formula and mixed or inconsistent lactation; exclusive formula)- Duration
Gunderson, 2014, USA, CARDIA[30]	Self-report	25 y	154	Age: NG. BMI: NG. Race/ethnicity: 50% white, 50% black.	Pre-existing DM at baseline and/or DM before the first post-baseline delivery.	Duration (lifetime)
Ziegler, 2012, Germany[31]	German Diabetes Association criteria	19 y	304	Median age (y): 31. BMI: NG. Race/ethnicity: presumably white	(Islet-autoantibody positive)	- Intensity (Full lactation with duration) - Duration
Cross-sectional						
Buchanan, 1998, USA[32,33]	Recommendation of the third international workshop-conference on GDM	NA	122	Mean age (y): 30.8 (NGT group), 32.3 (DM group). Mean pre-pregnancy BMI (kg/m^2): 30.4 (NGT group), 29.1 (DM group). Ethnicity: Latino.	ICA-positive, on insulin therapy during pregnancy, not all FBG <7.2 mmol/L since the diagnosis of GDM	Status at 6 mo postpartum
Kim, 2011, Korea[34]	Carpenter-Coustan criteria	NA	381	Mean age (y): 33.6 (NGT group), 34.9 (DM group). Mean pre-pregnancy BMI (kg/m^2): 22.5 (NGT group), 24.9 (DM group). Race/ethnicity: presumably Asian	GADA-positive.	Status at 6-12 wk postpartum
Kjos, 1993, USA[35]	NDDG criteria	NA	809	Mean age (y): 31.6 (Lactating group), 30.5 (Non-lactating group). Mean BMI (kg/m^2): 28.8 (Lactating group), 28.8 (Non-lactating group). Ethnicity: 95% Latino.		Status at 4-12 wk postpartum
Urs, 2015, USA, NHANES[36]	NG	NA	NG	Age, BMI, Race/ethnicity: NG.		Initiation
Retrospective cohort						
Kjos, 1998, USA[23,37]	NDDG criteria	7.5 y	809 (Non-hormonal only; 443)	Mean age (y): 31.3, mean postpartum BMI (kg/m^2): 29.6. Ethnicity: >97% Latino.	DM at 4-16 wk postpartum.	Status at 4-16 wk postpartum
Steube, 2005, USA, NHS II[38]	Self-report	14 y	NG	Age, BMI, Race/ethnicity: NG.		Duration (lifetime)

(*Continues*)

TABLE 1 (Continued)

First author, year, study name, reference	T2DM definition	T2DM evaluation time	T2DM incidence among GDM women	Adjusted co-variables for the analysis of lactation and T2DM incidence	Conclusion
Prospective cohort					
Gunderson, 2015, SWIFT,[26–29]	ADA criteria	OGTT at 1 and 2 y postpartum	113 of 959 (11.8%) developed T2DM. Overall incidence rate was 5.64 cases per 1000 person-mo (95% CI; 4.60-6.68).	Age; race/ethnicity; education; pre-pregnancy BMI; GDM treatment; sum of prenatal 3-h, 100-g OGTT Z score; gestational age at GDM diagnosis; subsequent birth during follow-up; total PA, GI, animal fat intake; weight change from delivery to 1 y; LGA vs not LGA, newborn's hospital stay >3 d, NICU admission	The lactation intensity and duration of breastfeeding inversely associated with T2DM incidence in a graded manner (all $P < .05$).
Gunderson, 2014, CARDIA,[30]	NG	Questionnaire at 7, 10, 15, 20, and/or 25 y after enrollment	46 of 154 (29.9%) developed T2DM. Overall incidence rate was 17.9 per 1000 person-years.	Pre-pregnancy BMI; age; parity; family history; race; education.	Shorter lactation (0-1 mo vs >9 mo) was associated with higher incidence of T2DM (Adjusted RH 3.0, 95% CI; 2.1-13.3).
Ziegler, 2012,[31]	ADA criteria	OGTT at 2 and 9 mo; 2, 5, 8, 11, 15, and 19 y postpartum	147 of 304 (48.4%) developed T2DM. The 15-year cumulative risk was 63.6% (95% CI 55.8-71.4).	Age at delivery; insulin treatment during pregnancy; BMI at early pregnancy; smoking during pregnancy; parity status; recruitment year	Longer lactation (>3 mo vs no or <3 mo) was associated with 30% risk reduction in 15-y DM incidence ($P = .0002$). Full lactation duration was inversely associated with DM incidence ($P = .001$).
Cross-sectional					
Buchanan, 1998,[32,33]	NG	OGTT within 6 mo postpartum	12 of 122 (9.8%) developed T2DM.	Not adjusted	Lactation rate 42% in DM, 49% in IGT and 71% in NGT group ($P = .03$)
Kim, 2011,[34]	ADA criteria	OGTT at 6 to 12 wk postpartum	30 of 573 (5.2%) developed T2DM.	Not adjusted	Lactation status did not affect postpartum glycemic status.
Kjos, 1993,[35]	NDDG criteria	OGTT at 4 to 12 wk postpartum	55 of 809 women (6.8%) developed T2DM	Not adjusted	T2DM incidence rate was 4.2% in lactating group and 9.4% in non-lactating group ($P = .01$).
Urs, 2015, NHANES,[36]	NG	NA	NG	Age; BMI; race/ethnicity; income; education; age at DM; number of live births	Adjusted OR for incident DM after GDM (vs no GDM) was 0.6 lower in women who breastfed compared to women who did not breastfeed.
Retrospective cohort					
Kjos, 1998,[23,37]	NDDG criteria	OGTT within 7.5 y	Average annual incidence rate was 8.7% (non-hormonal group).	insulin treatment during index pregnancy; glucose AUC at initial postpartum OGTT; weight change from initial postpartum weight; completion of additional pregnancy; and prior use of OC	No significant difference in T2DM risk between women who were breastfeeding vs who were not breastfeeding.
Steube, 2005, NHS II,[38]	Self-report	Questionnaire up to 12 y	Incidence rate: 624 cases per 100 000 person-years	parity, BMI at age 18 years, current BMI, dietary score quintile, PA, family history of DM, smoking status, birth weight of mother, and multivitamin use.	Lifetime lactation duration did not affect diabetes risk.

[1]Duration, evaluation of any lactation period; Initiation, evaluation of lactation experience; Intensity, evaluation of lactation or formula feeding exclusiveness; Status, evaluation of the lactation practice at the point of survey.

Abbreviations: ADA, American Diabetes Association; GI, glycemic index; IGT, impaired glucose tolerance; LGA, large for gestational age; NICU, neonatal intensive care unit; OC, oral contraceptive; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test; OR, odds ratio; PA, physical activity; RH, relative hazards; T2DM, type 2 diabetes mellitus.

3.5 | Lactation measures

Four studies measured lactation by the duration of breastfeeding period,[26,30,31,38] 2 of 4 measured the sum of lifetime lactation[30,38] and 2 studies measured index pregnancy.[26,31]

Four studies assessed lactation status within the following: 6 months by Buchanan et al,[32] 6 to 12 weeks by Kim et al,[34] 4 to 12 weeks by Kjos et al,[35] and 4 to 16 weeks by Kjos et al[23] after delivery.

Lactation intensity was assessed in 2 studies with different methodology. One study evaluated the intensity at 6 to 9 weeks postpartum by measuring the amount of added formula milk to test the dose-response effect for type 2 diabetes mellitus prevention and divided the participants into 4 groups: exclusive lactation, mostly lactation, mostly formula and mixed or inconsistent lactation, and exclusive formula.[26] Another study assessed the full lactation period.[31]

3.6 | T2DM evaluation, incidence

The diagnostic criteria for the evaluation of type 2 diabetes mellitus incidence were described in 6 studies; 3 studies applied the American Diabetes Association criteria,[26,31,34] 2 studies used the National Diabetes Data Group criteria,[23,35] and one was based on self-report.[38]

Type 2 diabetes mellitus evaluation time ranged from 4 to 12 weeks to up to 19 years postpartum, and type 2 diabetes mellitus incidence rate increases in accordance with the evaluation time.

Covariables used to adjust for analyzing lactation measure and type 2 diabetes mellitus incidence varied by each study. The most frequently adjusted index was BMI, which was used in 5 studies.[26,30,31,36,38] Age at delivery and parity status were used in 4 studies.[26,30,31,36] Race/ethnicity,[26,30,36] education,[26,30,36] weight/BMI change,[23,26,38] and GDM treatment during pregnancy were used in 3 studies.[23,26,31] Family history of DM,[30,38] smoking,[31,38] physical activity,[26,38] diet,[26,38] OGTT results,[23,26] and subsequent birth were adjusted in 2 studies.[23,26] Oral contraceptive use,[23] multivitamin use,[38] gestational age at diagnosis of GDM,[26] income,[36] birth weight of mother,[38] enrollment year,[31] and age at DM[36] were used in one study.

As for the conclusions on type 2 diabetes mellitus incidence, 6 studies[26,30–32,35,36] reported results in favor of lactation, and 3 studies[23,34,38] reported null results.

3.7 | Risk of bias

The results of risk of bias assessment using RoBANS are summarized in Figure S1 and Table S3.

Selection biases that are caused by selection of participants were judged to be "low" for 7 studies[23,26,30–32,34,35] and "unclear" for 2 studies[36,38] because the baseline diabetes statuses were not given. Selection biases that are caused by confounding variables were judged to be "high" in most studies,[23,30–32,34–36] except 2 studies judged to be "low" because of adequate adjustment for covariables.[26,38] Performance biases indicating measurement of lactation were judged to be "low" for only one study[26] in which trained interviewers measured lactation, "high" for 3 studies[30,31,38] with self-report, and "unclear" for 5 studies.[23,32,34–36] All the studies were judged to be "low" for detection biases because type 2 diabetes mellitus incidence could not be influenced by the blinding methods for its assessment. Attrition biases were judged to be "unclear" in most studies except one[31] that stated there was no difference in lactation rate regarding dropout status. Reporting biases were judged to be "unclear" in most studies except one study with the experimental protocol available.[26]

3.8 | Synthesis of results

3.8.1 | Lactation duration (longer lactation vs shorter lactation)

Five studies[23,26,31,34,35] enrolling 3408 women were included in the meta-analysis for longer (>4 to 12 wk postpartum) versus shorter (<4 to 12 wk postpartum) lactation of any intensity for preventing type 2 diabetes mellitus after GDM pregnancy (Figure 2). The remaining studies were not included because of different study design[30,38] and/or inadequate data.[30,32,36] Publication bias was not assessed as the number of included studies was fewer than 10. The heterogeneity yielded was substantial (I^2 = 85%) that we conducted subgroup analysis. In a

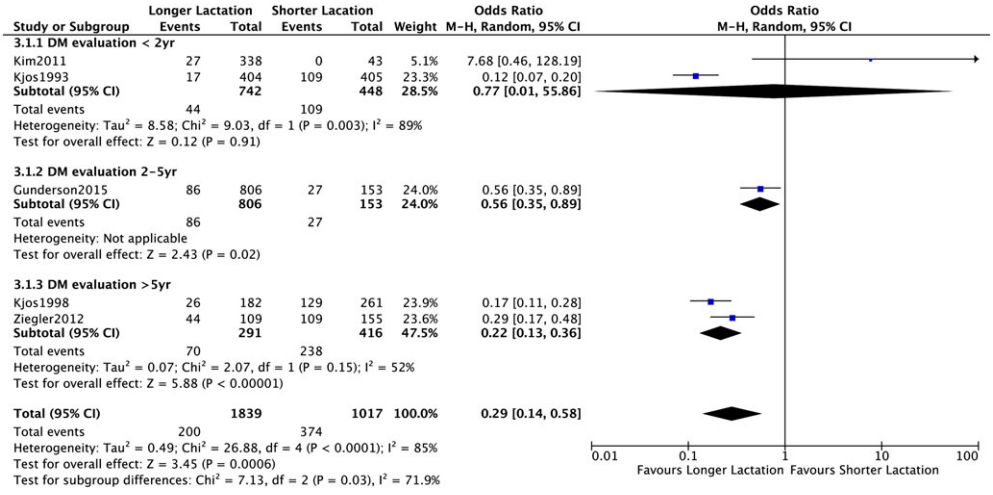

FIGURE 2 Forrest plot comparing "longer lactation" (>4-12 wk) with "shorter lactation" (<4-12 wk) with analysis of 3 subgroups on the basis of diabetes evaluation time; <2 y, 2-5 y, and >5 y

subgroup analysis comparing by T2DM evaluation time, <2 years versus 2 to 5 years versus >5 years, we found significant subgroup differences (P = .03). Meta-analysis (random-effect model) revealed significant risk reduction of T2DM incidence with longer lactation in subgroups with DM evaluation time longer than 2 years (OR 0.56, 95% CI 0.35-0.89 for 2 to 5 y; OR 0.22, 95% CI 0.13-0.36 for >5 y). The qualities of the evidence were judged to be "very low" with DM evaluation <2 years group and "low" with 2 to 5 years and >5 years group (Table S4).

3.8.2 | Lactation intensity (exclusive lactation vs exclusive formula)

Two studies have assessed lactation intensity[26,31]; however, only one of them compared the effect of exclusive lactation with exclusive formula for type 2 diabetes mellitus incidence.[26] The risk of bias of this study was low (Table S3). The quality of the evidence was judged to be "moderate" graded up by its large (OR 0.42, 95% CI 0.22-0.81) and dose-response effect even with observational study design with small sample size (Table S5).

4 | DISCUSSION

In this systematic review, we have shown that lactation of any intensity for more than 4 weeks to more than 12 weeks postpartum has statistically significant association with lower risk of type 2 diabetes mellitus in the long term (ie, >2 y). The effect of longer lactation was not obvious when diabetes was evaluated in early postpartum, but became more prominent with longer follow-up (OR 0.77 95% CI 0.01-55.86; OR 0.56 95% CI 0.35-0.89; OR 0.22 95% CI 0.13-0.36; <2 y, 2-5 y, and >5 y, respectively). One likely explanation is that type 2 diabetes mellitus incidence after GDM pregnancy increases with time,[4] and at least several years of follow-up are required to judge the effect of exposure. Also, women developing type 2 diabetes mellitus in early postpartum (ie, 4-12 wk postpartum) are definitely of the highest risk. The underlying etiology may be different from those who develop type 2 diabetes mellitus later. In fact, Ziegler et al reported that women with islet autoantibody developed diabetes much faster (median diabetes-free duration, 4.5 mo) compared with women negative for the autoantibody, and no protective effect of lactation was observed in those women.[31] All 3 studies in the subgroup evaluating type 2 diabetes mellitus at >3 years excluded early onset DM[23,26] or islet autoantibody-positive population,[31] suggesting a difference in population compared with the subgroup evaluating DM at <2 years (4-12 wk and 6-12 wk postpartum each).

Prolactin is one of the key factors for biochemical hypotheses of long-term effect.[39] Prolactin starts to elevate during pregnancy, peaks in term and stays above nonpregnant level with pulsatile secretion until weaning.[40] Research on prolactin receptor knockout mice has clarified that prolactin plays a physiological role in pancreatic islet formation and function.[41] Moderately elevated serum prolactin, which is the model for physiological elevation during pregnancy and postpartum, has also been shown to improve insulin secretion and insulin resistance in diabetic rats.[42] However, full biological etiologies to explain the beneficial effect lasting long after weaning are lacking. Therefore, further studies on this topic are needed.

We have also found from a study with moderate evidence quality that exclusive lactation at 6 to 9 weeks postpartum was associated with lower risk of long-term type 2 diabetes mellitus compared with exclusive formula (OR 0.42 95% CI 0.22-0.81).[26] The World Health Organization has recommended all mothers to exclusively breastfeed for the first 6 months followed by partial breastfeeding.[43] However, only 37% of women were exclusively breastfeeding under 6 months in upper-middle income countries.[44] In addition, women with previous GDM are known for even lower breastfeeding rate compared with women with nondiabetic pregnancies.[45–47] This may be due to increased risk of complications in both the mother and infant during the perinatal period,[48] delayed lactogenesis,[49] or the poor sucking pattern of infants.[50] Therefore, exclusive breastfeeding for at least 6 to 9 weeks postpartum may be more achievable for women with GDM.

There are several limitations in this study. First, the evidence of this review relies only on observational studies in which we cannot confirm the causal relationship between lactation and type 2 diabetes mellitus. The effect of unknown confoundings or reverse causation cannot be ruled out even in well-designed and adequately analyzed studies. This is because randomization of breastfeeding is infeasible both ethically and technically, although 2 randomized trials were conducted in the past when the benefits of breast milk were not proven.[51,52] Second, all the data used for the meta-analysis were crude data without adjustment. Only few of the included studies adequately adjusted for covariables. Breastfeeding practices were reported to be influenced by multiple factors such as obesity,[53] depression,[54] insulin treatment during pregnancy,[49] and how health conscious a mother is.[55] These factors are likely to influence diabetes incidence, and they should be adjusted for. Third, analyses with stratification by the participants' characteristics such as ethnicity or BMI were not possible because of inadequate information. This limitation may deter us from drawing tailored conclusion for each woman in real practice. However, subgroup analysis showed fairly heterogeneous results for long-term type 2 diabetes mellitus even in populations with diverse background, suggesting that the association remains.

5 | CONCLUSION

In conclusion, the women with previous GDM lactating for more than 4 to 12 weeks postpartum have lower risk (moderate quality of evidence) of type 2 diabetes mellitus compared with women with shorter lactation period. Also, women with GDM exclusively lactating for more than 6 to 9 weeks postpartum have lower risk of type 2 diabetes mellitus compared with women with formula feeding. The etiology behind this potential long-term beneficial effect of lactation remains poorly understood. The optimal support for women with GDM to breastfeed is not well studied. To investigate these unresolved issues between lactation and the prevention of type 2 diabetes mellitus, further studies are warranted in the future.

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CONFLICTS OF INTEREST

None of the authors has conflict of interest related to this review.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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