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Amelioration of Insulin Resistance after Delivery Is Associated with Reduced Risk of Postpartum Diabetes in Women with Gestational Diabetes Mellitus

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Background: Identifying risk factors for postpartum type 2 diabetes in women with gestational diabetes mellitus (GDM) is crucial for effective interventions. We examined whether changes in insulin sensitivity after delivery affects the risk of type 2 diabetes in women with GDM.

Methods: This prospective cohort study included 347 women with GDM or gestational impaired glucose tolerance, who attended the follow-up visits at 2 months postpartum and annually thereafter. Changes in insulin sensitivity were calculated using the Matsuda index at GDM diagnosis and at 2 months postpartum (ΔMatsuda index). After excluding women with pregestational diabetes or those followed up only once, we analyzed the risk of postpartum type 2 diabetes based on the ΔMatsuda index tertiles.

Results: The incidence of type 2 diabetes at the two-month postpartum visit decreased with increasing ΔMatsuda index tertiles (16.4%, 9.5%, and 1.8%, P=0.001). During a 4.1-year follow-up, 26 out of 230 women who attended more than two follow-up visits (11.3%) developed type 2 diabetes. Compared to the lowest tertile, subjects in the highest ΔMatsuda index tertile showed a significantly reduced risk of type 2 diabetes (hazard ratio, 0.33; 95% confidence interval, 0.12 to 0.93; P=0.036) after adjusting for confounders.

Conclusion: Improvement in insulin sensitivity after delivery is associated with a reduced risk of postpartum type 2 diabetes in women with GDM. Postpartum changes in insulin sensitivity could be a useful prediction for future type 2 diabetes development in women with GDM.

Keywords: Diabetes, gestational; Diabetes mellitus, type 2; Insulin resistance; Insulin sensitivity

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a prevalent pregnancy complication, affecting approximately one in six live births with hyperglycemia in pregnancy [1,2]. Its global prevalence is rising due to increasing maternal age and the escalating obesity epidemic among women of reproductive age [3,4]. GDM not only increases the risk of perinatal complications like macrosomia and cesarean section [5], but also raises significant concerns, as women with a history of GDM have a much higher risk of developing type 2 diabetes, with a reported lifetime risk of up to 10 times greater [6-8]. Furthermore, the metabolic disruptions experienced by women with GDM elevate their risk of cardiovascular disease by nearly three times compared to women without GDM [9-11]. This underscores the importance of implementing GDM management strategies that prioritize early detection and prevention of the subsequent type 2 diabetes. Identifying the risk factors associated with the development of postpartum type 2 diabetes in women with a history of GDM is therefore crucial for developing effective interventions to prevent this condition.

Previous studies have identified various risk factors associated with postpartum type 2 diabetes. Some, like maternal age, pre-pregnancy body weight, ethnicity, and genetic factors, are non-modifiable [7,8,12], while others, like postpartum body weight, lactation, physical activity, and diet, can be adjusted. Notably, most modifiable factors influence maternal insulin sensitivity [13,14]. Women with reduced insulin sensitivity during pregnancy or those requiring insulin are at increased risk for postpartum diabetes [15]. This suggests that insulin resistance plays a key role in progression to postpartum diabetes, especially for women with GDM who harbor impaired pancreatic β-cell function.

People who develop type 2 diabetes likely exhibit varying degrees of baseline insulin resistance and β-cell function [16]. As an illustration, despite Asians generally having leaner bodies and higher insulin sensitivity compare to Western populations, the incidence of GDM in Asians is comparable to that in Western populations [5,17,18]. Furthermore, pregnancy induces significant shifts in insulin sensitivity due to hormonal changes [19]. This has led to the hypothesis that postpartum changes in insulin sensitivity, rather than pre-pregnancy levels, may play a more significant role in determining postpartum diabetes risk in women with GDM.

In this multicenter prospective cohort study, we investigated whether alterations in insulin sensitivity before and after delivery affect the risk of type 2 diabetes in Korean women with a history of GDM.

METHODS

Study design

This multicenter, prospective cohort study involved participants diagnosed with GDM or gestational impaired glucose intolerance (GIGT) at two tertiary hospitals in Korea (Ajou University Hospital and Cheil General Hospital) between August 1995 and May 1997. Follow-up visits occurred annually starting at 2 months postpartum.

Study participants

Screening for GDM began at 24 to 28 weeks of gestation with a 50-g oral glucose challenge. A 1-hour glucose value of 130 mg/dL or higher triggered a subsequent 3-hour, 100-g oral glucose tolerance test (OGTT) for confirmation. GDM diagnosis followed the Third International Workshop-Conference on Gestational Diabetes Mellitus recommendations, adopted during the study's enrollment phase [5]. Two or more of the following criteria defined GDM, while one criterion sufficed for GIGT: fasting plasma glucose ≥105 mg/dL or greater, 1-hour glucose ≥190 mg/dL, 2-hour glucose ≥165 mg/dL or greater, or 3-hour glucose ≥145 mg/dL.

A total of 475 women diagnosed with GDM or GIGT who attended at least one follow-up were enrolled (Supplemental Fig. S1). Women with pregestational diabetes (n=39), defined by glycated hemoglobin (HbA1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL, were excluded [20]. After excluding subjects with missing data (n=89), 347 women remained eligible for analysis. Their insulin sensitivity was assessed using a standard 75-g OGTT, and postpartum type 2 diabetes was diagnosed if applicable. All participants volunteered and provided informed consent. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1007-105-007) and was conducted according to the Declaration of Helsinki.

Postpartum follow-up examination

Obstetric history, including pre-pregnancy weight, weight at GDM or GIGT diagnosis, gestational weight gain, and pregnancy outcome, was extracted from medical records. At the initial postpartum visit, a standardized questionnaire collected information about the individual's past medical and reproductive history, as well as their family history of diabetes. Subsequent visits, starting at 2 months postpartum, included anthropometric

measures (body weight, height, blood pressure, and body composition), a standard 75-g OGTT, and fasting glucose and lipid profile measurements.

Following an overnight fast of at least 8 hours, subjects underwent a 75-g OGTT. Plasma glucose levels were measured enzymatically using an automated analyzer (YSI 2300-STAT, Yellow Springs Instrument Co., Yellow Springs, OH, USA) via the glucose oxidase method. Plasma insulin levels were determined by radioimmunoassay (Linco Research Inc., St. Charles, MO, USA). Total cholesterol, triglycerides, and high-density lipoprotein cholesterol were analyzed with an enzymatic assay using a Beckman analyzer from Beckman Instruments. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.

Definitions and glycemic assessment

Insulin sensitivity and β-cell function were derived from plasma glucose and insulin concentrations measured during annual postpartum 75-g OGTT. Insulin sensitivity was estimated using the Matsuda index [21]: 10,000/(fasting glucose×fasting insulin×mean glucose×mean insulin). The insulinogenic index [22] was calculated as follows to assess insulin secretion: [insulin (30 min)–insulin (0 min)]/[glucose (30 min)–glucose (0 min)]. The disposition index [23] was used to evaluate the combined effect of insulin secretion and sensitivity on glucose metabolism: Matsuda index×insulinogenic index. During pregnancy, insulin sensitivity and β-cell function were derived from the 100-g OGTT, and glucose and insulin concentrations at 60 minutes were used instead of 30 minutes for the insulinogenic index calculation. The homeostasis model assessment of β-cell function (HOMA-β) and insulin resistance (HOMA-IR) were further calculated from fasting plasma glucose and insulin levels [24].

Changes in insulin sensitivity including ΔMatsuda index, or β-cell function alterations were defined as the difference between the initial postpartum (2 months after delivery) value and the gestational value, determined using glucose and insulin values from two separate OGTTs. The diagnostic 100-g OGTT for GDM provided data from fasting, 1-, 2-, and 3-hour values of glucose and insulin, while the 75-g OGTT conducted at the initial postpartum visit yielded values from fasting, 30, 60, 90, and 120 minutes. The ΔMatsuda index served as the primary variable for subsequent analysis.

Statistical analysis

Subjects were divided into tertiles based on their ΔMatsuda index for analysis. Differences between the groups were assessed using independent *t*-tests or analysis of variance for continuous variables, and chi-squared tests or linear-by-linear association for categorical variables. A Cox proportional hazards model was used to investigate the association between the ΔMatsuda index and the risk of developing type 2 diabetes. Adjustments were made for factors known to influence postpartum type 2 diabetes, including fasting blood glucose, postpartum body mass index (BMI), breastfeeding, age at birth, familial history of diabetes, and parity. Additional analyses adjusted for covariates were found significant in the multivariate analysis.

Data are presented as the mean±standard deviation or median (interquartile ranges) for continuous variables, and number (%) for categorical variables. Statistical significance was defined as $P<0.05$. All analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Inc., Armonk, NY, USA).

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Clinical characteristics and metabolic phenotypes of subjects

Our analysis included 347 women, with a median follow-up of 2.9 examinations (interquartile range, 1.0 to 4.0). A total of 60 out of 347 subjects (17.3%) developed type 2 diabetes. Compared to those who remained diabetes-free, women who developed type 2 diabetes were more likely to be obese before pregnancy and lactated less (Table 1).

Subjects who developed postpartum type 2 diabetes also displayed higher glucose levels during and after pregnancy, as determined by their OGTT results. They exhibited elevated fasting insulin levels and blunted glucose-stimulated insulin secretion, indicating insulin resistance and impaired β-cell function. Consequently, their postpartum Matsuda index, insulinogenic index, and disposition index were consistently lower.

Interestingly, subsequent analysis revealed that changes in β-cell function (Δinsulinogenic index and ΔHOMA-β) after delivery did not differ between women who did or did not develop type 2 diabetes. However, changes in insulin sensitivity (ΔMatsuda index and ΔHOMA-IR) did show a difference. This finding prompted us to investigate further whether changes in insulin sensitivity after delivery could predict the future development of type 2 diabetes.

Table 1. Clinical Characteristics and Metabolic Phenotypes according to Development of Postpartum Type 2 Diabetes

Characteristic	Did not develop T2DM (*n*=288)	Progression to T2DM (*n*=59)	*P* value
Age at delivery, yr	31.6±4.1	32.1±4.4	0.396
Body mass index, pregestational, kg/m^2	21.9±3.1	24.5±3.5	<0.001
BMI change, kg/m^2	–0.1±1.3	0.0±1.2	0.978
Parity, *n*	2.1±1.6	1.9±1.7	0.369
Exercise	99 (34.4)	25 (41.7)	0.283
Breastfeeding	102 (35.4)	9 (15.0)	0.002
100-g OGTT at mid-gestation			
Glucose (fasting), mg/dL	87.9±11.2	100.5±14.1	<0.001
Glucose (1-hour), mg/dL	185.9±28.4	203.7±36.6	<0.001
Glucose (2-hour), mg/dL	172.7±27.1	195.8±33.9	<0.001
Glucose (3-hour), mg/dL	145.6±25.8	165.3±31.8	<0.001
Insulin (fasting), μIU/mL	8.7±6.8	9.3±3.8	0.023
Insulin (1-hour), μIU/mL	65.2±49.0	45.9±37.8	0.004
Insulin (2-hour), μIU/mL	88.1±61.7	64.3±50.8	0.005
Insulin (3-hour), μIU/mL	75.7±52.2	60.9±38.6	0.033
75-g OGTT at initial postpartum visit (postpartum 2 months)			
Glucose (fasting), mg/dL	90.2±8.9	121.1±46.2	<0.001
Glucose (30-minute), mg/dL	154.9±25.7	200.4±57.9	<0.001
Glucose (60-minute), mg/dL	160.2±36.4	241.5±82.8	<0.001
Glucose (90-minute), mg/dL	138.4±33.3	231.7±78.2	<0.001
Glucose (120-minute), mg/dL	122.5±28.4	208.4±86.1	<0.001
Insulin (fasting), μIU/mL	10.2±5.3	12.0±6.2	0.026
Insulin (30-minute), μIU/mL	42.3±25.6	32.0±19.1	0.003
Insulin (60-minute), μIU/mL	52.0±34.5	42.1±24.9	0.035
Insulin (90-minute), μIU/mL	48.5±33.3	53.8±40.2	0.288
Insulin (120-minute), μIU/mL	43.4±31.3	53.3±46.5	0.042
Longitudinal changes in glycemic measures			
Matsuda index			
Antepartum	5.2±2.7	5.0±2.8	0.524
Postpartum	5.3±2.3	3.9±2.2	<0.001
P value[a]	0.717	0.010	
Mean difference	0.1±3.0	–1.0±3.3	0.011
HOMA-IR			
Antepartum	1.9±1.1	2.3±1.0	0.002
Postpartum	2.3±1.3	3.8±3.5	<0.001
P value[a]	<0.001	0.003	
Mean difference	0.4±1.4	1.4±3.5	<0.001
Insulinogenic index			
Antepartum	0.7±1.9	0.4±0.3	0.195
Postpartum	0.6±0.4	0.3±0.2	<0.001
P value[a]	0.201	0.028	
Mean difference	–0.1±1.8	–0.1±0.3	0.872

(Continued to the next page)

Table 1. Continued

Characteristic	Did not develop T2DM (*n*=288)	Progression to T2DM (*n*=59)	*P* value
HOMA-β			
Antepartum	141.7±98.3	109.6±98.4	0.023
Postpartum	150.8±112.4	100.7±63.8	0.001
P value[a]	0.288	0.531	
Mean difference	9.1±145.4	–8.9±107.9	0.369
Disposition index			
Antepartum	2.6±3.3	1.6±1.1	0.023
Postpartum	2.7±2.3	1.0±1.0	<0.001
P value[a]	0.646	0.002	
Mean difference	0.1±3.9	–0.6±1.3	0.195

Values are expressed as mean±standard deviation or number (%). ΔMatsuda index was defined as the difference between the initial postpartum Matsuda index and the gestational Matsuda index. *P* values are for the *t* test or chi-square test to compare subjects with and without the occurrence of type 2 diabetes.
T2DM, type 2 diabetes; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.
[a]Paired *t* test from antepartum to postpartum values within each group.

Table 2. Incidence of Type 2 Diabetes at 2 Months Postpartum Visit by ΔMatsuda Index

Variable	ΔMatsuda index			Total (*n*=347)	*P* value
	Lowest tertile (*n*=116)	Middle tertile (*n*=116)	Highest tertile (*n*=115)		
Postpartum T2DM	19 (16.4)	11 (9.5)	2 (1.8)	32 (9.2)	0.001
Postpartum prediabetes and T2DM	67 (57.8)	52 (44.8)	32 (28.1)	151 (43.6)	<0.001

Values are expressed as number (%). ΔMatsuda index was defined as the difference between the initial postpartum Matsuda index and the gestational Matsuda index. Lowest tertiles ranged from –10.9 to –1.1, middle tertile from –1.0 to 1.0, highest tertile ranged from 1.0 to 8.5. *P* values are for the chi-square test to compare the occurrence of postpartum T2DM and combined with postpartum prediabetes across the tertiles.
T2DM, type 2 diabetes.

Postpartum changes in insulin sensitivity and development of type 2 diabetes

The subjects were categorized into tertiles based on their ΔMatsuda index. The numerical ranges for the lowest, middle, and highest tertiles of ΔMatsuda index were –10.9 to –1.1, –1.0 to 1.0, 1.0 to 8.5, respectively. Cross-sectional analysis showed a decreasing trend in type 2 diabetes at their 2-month postpartum visit as the tertile of ΔMatsuda index increased (Table 2). The incidence was 16.4%, 9.5%, and 1.8% in the lowest, middle, and highest tertiles, respectively (*P*=0.001), and the trend persisted for the combined incidence of postpartum prediabetes and type 2 diabetes, as detailed in Table 2.

Excluding women diagnosed with type 2 diabetes on their first postpartum visit and those who visited only once after childbirth, 230 subjects remained eligible for longitudinal analysis (Supplemental Fig. S1). At baseline, no significant differences were observed in age at delivery, pregestational BMI, postpartum BMI, or gestational weight gain between the ΔMatsuda index tertiles (Supplemental Table S1). Although HbA1c during pregnancy did not differ across tertiles, insulin levels were higher in the highest tertile. Blood pressure and lipid profiles were similar among the groups.

We further investigated the association between the ΔMatsuda index and the incidence of type 2 diabetes using a time-to-event analysis (Supplemental Table S2). During a median follow-up of 4.1 years (3.0 to 5.1) and 3.8 visits (2.0 to 5.0), 26 out of 230 women (11.3%) developed type 2 diabetes. The number of subjects who developed type 2 diabetes was 11 (14.5%), nine (11.7%), and six (7.8%) in the lowest, middle, and highest tertiles, respectively. Notably, the number of subjects who developed prediabetes or type 2 diabetes steadily decreased across the ΔMatsuda index tertiles, from 51.3% to 48.1% to 36.4%.

To assess whether the ΔMatsuda index was an independent predictor of incident type 2 diabetes, we adjusted for multiple

Table 3. Hazard Ratio of Postpartum Type 2 Diabetes by ΔMatsuda Index Tertile and Associated Variables by Cox Analysis

Variable	Univariate[a]		Multivariate[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
ΔMatsuda index tertile				
Lowest tertile	1 (reference)		1 (reference)	
Middle tertile	0.72 (0.29–1.79)	0.484	0.52 (0.21–1.33)	0.175
Highest tertile	0.59 (0.22–1.59)	0.293	0.33 (0.12–0.93)	0.036
Fasting plasma glucose	1.05 (1.03–1.08)	<0.001	1.06 (1.03–1.09)	<0.001
Postpartum body mass index	1.18 (1.06–1.32)	<0.001	1.16 (1.03–1.30)	0.015
Age at birth	0.99 (0.90–1.09)	0.869	0.93 (0.84–1.04)	0.203
Family history of diabetes	1.00 (0.47–2.17)	0.992	0.98 (0.43–2.19)	0.950
Parity	0.90 (0.69–1.16)	0.414	0.87 (0.67–1.13)	0.305

HR of postpartum type 2 diabetes are calculated using Cox proportional model including ΔMatsuda index and variables associated with postpartum type 2 diabetes. ΔMatsuda index was defined as the difference between the initial postpartum Matsuda index and the gestational Matsuda index. Lowest tertiles ranged from –10.9 to –0.9, middle tertile from –0.8 to 1.2, highest tertile ranged from 1.2 to 8.8.
HR, hazard ratio; CI, confidence interval.
[a]ΔMatsuda index and factors associated with postpartum type 2 diabetes (gestational fasting blood glucose, postpartum body mass index, age at birth, familial history of diabetes, parity) were included in the multivariate Cox model; [b]ΔMatsuda index tertile was included as a covariate in addition to factors associated with postpartum type 2 diabetes in the multivariate Cox model.

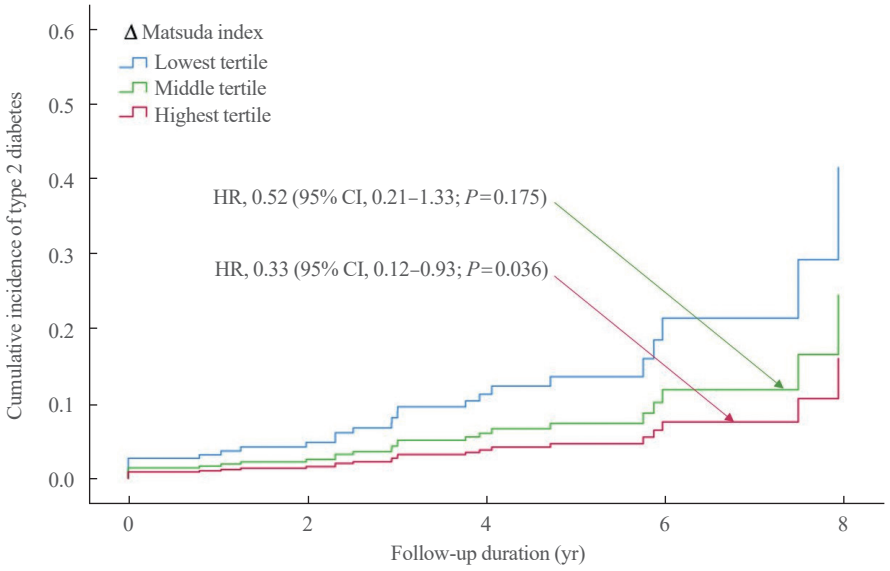

Fig. 1. Cumulative incidence of type 2 diabetes according to ΔMatsuda index. ΔMatsuda index was defined as the difference between the initial postpartum Matsuda index and the gestational Matsuda index. Lowest tertiles ranged from –10.9 to –0.9, middle tertile from –0.8 to 1.2, highest tertile ranged from 1.2 to 8.8. Hazard ratio (HR) of postpartum type 2 diabetes are calculated using Cox proportional model including ΔMatsuda index and variables associated with postpartum type 2 diabetes (gestational fasting blood glucose, postpartum BMI, age at birth, familial history of diabetes, parity). CI, confidence interval.

clinical risk factors within a Cox proportional hazards model (Table 3). Higher gestational fasting plasma glucose and postpartum BMI were independently associated with increased risk of type 2 diabetes (univariate model). After adjusting for known risk factors, participants in the highest tertile, demonstrating the greatest improvement in insulin sensitivity after delivery, had a significantly lower risk of developing type 2 diabetes compared to the lowest tertile (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.12 to 0.93; $P=0.036$) (multivariate model in Table 3, Fig. 1).

The observed trend held true when the ΔMatsuda index was treated as a continuous variable (HR, 0.76; 95% CI, 0.46 to 1.25; P=0.281), but statistical significance was not attained, possibly due to insufficient statistical power. We also investigated the association of gestational or postpartum Matsuda index alone with type 2 diabetes risk, but neither showed statistical significance.

DISCUSSION

Women with a history of GDM have a significantly higher risk of developing type 2 diabetes postpartum, with up to a 10-fold increase compared to those without GDM [6]. While the American College of Obstetrics and Gynecology and the American Diabetes Association recommend postpartum glucose testing at 4 to 12 weeks postpartum, and subsequently every 1 to 3 years thereafter [25,26], less than half of women return for follow-up visits [27]. This highlights the importance of early identification of high-risk women, ensuring they receive accurate risk information, and establish a comprehensive follow-up plan. Our prospective cohort study demonstrates that postpartum changes in insulin sensitivity, measured by the ΔMatsuda index, are significantly associated with the risk of developing type 2 diabetes after pregnancy in women with a history of GDM. Therefore, this study provides evidence that monitoring insulin sensitivity changes from pregnancy to the early postpartum period can serve as an additional predictor of future type 2 diabetes risk in this specific population.

The risk of type 2 diabetes after GDM hinges on various factors, including non-modifiable ones like maternal age and genetic predisposition, potentially modifiable ones influenced by lifestyle modification [7,8,12,28]. Among modifiable factors, lactation and weight change are well-established contributors to improved insulin sensitivity after delivery.

Studies consistently show that longer lactation duration is associated with improved fasting glucose levels, lower insulin levels, and a sustained beneficial effect on glucose metabolism and insulin sensitivity over time [14,29,30]. Postpartum weight change also impacts glucose metabolism and type 2 diabetes risk. A study by Peters et al. [25] found a two-fold increase in type 2 diabetes risk with a 4.5 kg postpartum weight gain. Similarly, our findings revealed that women who gained weight after postpartum had a roughly two-fold higher risk compared to those who lost weight [26]. Furthermore, *post hoc* analysis of the Diabetes Prevention Program [27] showed a 16% reduction in diabetes risk for every kilogram of weight loss.

Collectively, existing research supports promoting breastfeeding [29-31] and weight loss [25-27] among women with GDM as effective strategies for reducing their type 2 diabetes risk. This study's Cox model identified postpartum BMI as a significant factor associated with postpartum diabetes, aligning with prior findings. This reinforces the importance of encouraging lifestyle modifications in women with GDM to mitigate their diabetes risk.

Regarding the link between postpartum weight change and insulin sensitivity, our previous work revealed a noteworthy finding: individuals with a greater postpartum BMI change experienced significant deterioration in insulin sensitivity [26]. Kew et al. [32] also reported that sustained weight loss at 3 and 12 months postpartum was associated with improved insulin sensitivity, as well as improved lipid profiles and higher adiponectin levels. Building on this research, our study provides clinical implications for lifestyle modifications, like weight loss, while also shedding light on predictive factors for postpartum type 2 diabetes risk.

Insulin resistance, alongside β-cell dysfunction, is recognized as key pathophysiological factors for type 2 diabetes [33-35]. In individuals who develop diabetes, the frequent co-occurrence of these factors has made it challenging and controversial to unravel their individual contributions to the disease's development. Interestingly, our study showed no difference in β-cell function changes after delivery between those who progressed to type 2 diabetes and those who did not, while differences in insulin sensitivity changes were observed. However, when examining postpartum β-cell function in individuals who later developed diabetes, it was significantly lower compared to those who did not. This observation suggests a potential interplay, where weight gain and insulin resistance ultimately impact β-cells by increasing their secretory demands. While our findings offer a glimpse into this relationship, further studies are warranted to elucidate the relative contributions of insulin resistance and secretary insufficiency to type 2 diabetes risk in women with a history of GDM.

To our knowledge, this is the first prospective study to investigate postpartum changes in insulin sensitivity as a predictor of type 2 diabetes after GDM. In this study, the Matsuda index was employed as a measure of insulin sensitivity, validated in pregnancy and demonstrating stronger correlations with the euglycemic hyperinsulinemic clamp measures compared to other insulin sensitivity models such as HOMA-IR [36]. However, this study has some limitations. Firstly, widespread access to fasting and postprandial insulin assays in primary care settings remains

limited. Secondly, follow-up duration and intervals varied among participants. However, it is important to note that the mean follow-up duration within each ΔMatsuda index tertile was comparable, and we employed a Cox proportional hazards model to address this potential limitation. Additionally, Matsuda index calculation from the 100-g OGTT during mid-gestation utilized fasting, 1-, 2-, and 3-hour values of glucose and insulin, while the Matsuda index calculation from the initial postpartum 75-g OGTT utilized fasting, 30-, 60-, 90-, and 120-minute values of glucose and insulin. This difference in time points poses a challenge and may affect how we interpret insulin sensitivity and β-cell function throughout pregnancy and postpartum. Lastly, while the multivariate model showed a significant association, the univariate analysis did not reach statistical significance. This limitation highlights the necessity for larger sample sizes to validate the findings observed in this study.

In conclusion, our findings suggest that improvements in insulin sensitivity after delivery are associated with a reduced risk of postpartum type 2 diabetes in Korean women with GDM. While the assessment of insulin sensitivity lacks a standardized approach, the ΔMatsuda index can be a valuable tool for clinicians to predict postpartum type 2 diabetes risk in this population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: H.S., J.H.M., S.H.K., H.C.J. Acquisition, analysis, or interpretation of data: H.S., J.H.M., S.H.K., H.C.J. Drafting the work or revising: H.S., J.H.M., S.H.C., N.H.C., S.H.K., H.C.J. Final approval of the manuscript: H.S., J.H.M., S.H.C., N.H.C., S.H.K., H.C.J.

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Supplemental Table S1. Clinical Characteristics and Metabolic Phenotypes according to ΔMatsuda Index Tertiles

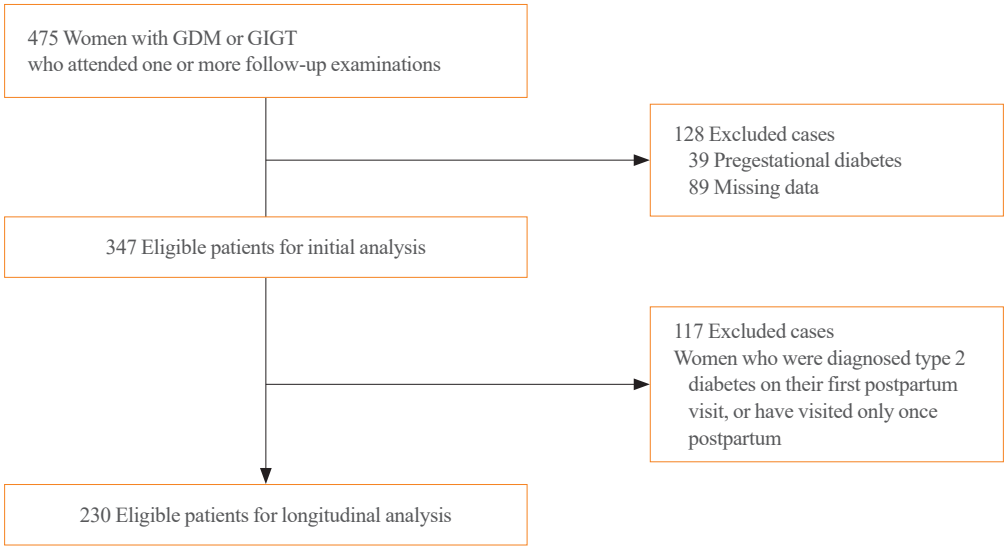
Characteristic	ΔMatsuda index			*P* value
	Lowest tertile (*n*=116)	Middle tertile (*n*=116)	Highest tertile (*n*=115)	
Gestational Matsuda index	7.6±2.8	4.2±1.9	3.7±1.6	<0.001[a,b]
Postpartum Matsuda index	4.2±1.8	4.2±1.8	6.6±2.2	<0.001[b]
ΔMatsuda index	–3.4±2.0	0.0±0.6	2.9±1.7	<0.001[a,b]
Age at delivery, yr	32.0±4.2	31.2±4.3	31.7±3.9	0.311
Body mass index, pregestational, kg/m^2	22.4±3.6	22.3±3.08	22.3±3.3	0.936
Body mass index, postpartum, kg/m^2	23.6±3.8	23.4±3.2	23.4±3.4	0.865
Gestational weight gain, kg	10.6±4.0	11.7±4.5	11.4±4.5	0.078
SBP, postpartum, mm Hg	110.0±11.1	110.8±11.7	107.8±12.0	0.131
DBP, postpartum, mm Hg	68.4±8.4	68.0±8.4	66.5±8.8	0.207
Parity, *n*	2.2±1.7	2.1±1.8	1.9±1.4	0.243
Breastfeeding	36 (31.0)	38 (32.8)	36 (31.3)	0.092
Duration of follow-up, yr	3.3±2.0	3.4±2.4	3.4±2.0	0.889
Gestational glycemic measurements phenotypes				
Glucose (fasting), mg/dL	87.1±12.9	92.0±12.7	91.2±11.9	0.007[a,b]
Glucose (1-hour), mg/dL	179.7±34.2	193.4±29.1	194.4±25.8	<0.001[a,b]
Glucose (2-hour), mg/dL	173.4±32.6	180.7±30.2	176.0±25.4	0.166
Glucose (3-hour), mg/dL	154.3±25.7	147.8±30.9	144.9±26.1	0.029[b]
AUC (glucose)	473.8±65.2	494.0±61.6	488.4±48.0	0.027[a]
Insulin (fasting), μIU/mL	5.9±2.5	9.7±4.3	18.1±77.7	0.110
Insulin (1-hour), μIU/mL	34.8±18.1	67.8±44.5	83.6±57.7	<0.001[a,b]
Insulin (2-hour), μIU/mL	48.2±27.0	93.9±60.0	110.3±68.4	<0.001[a,b]
Insulin (3-hour), μIU/mL	52.8±26.7	76.7±51.1	90.4±60.1	<0.001[a,b]
HbA1c	5.1±0.8	5.1±1.1	5.3±0.9	0.354
Postpartum glycemic and lipid phenotypes				
Glucose (fasting), mg/dL	100.4±31.8	96.8±22.9	89.7±10.2	0.002[b]
Glucose (30-minute), mg/dL	173.2±42.2	167.2±39.7	148.0±23.5	<0.001[b]
Glucose (60-minute), mg/dL	193.5±70.2	177.6±51.1	151.8±35.1	<0.001[b]
Glucose (90-minute), mg/dL	173.5±71.6	155.0±50.7	135.1±35.1	<0.001[a,b]
Glucose (120-minute), mg/dL	155.9±69.7	134.5±49.2	121.6±33.3	<0.001[a,b]
Insulin (fasting), μIU/mL	12.3±7.3	11.4±4.3	8.0±2.8	<0.001[b]
Insulin (30-minute), μIU/mL	42.1±23.2	47.3±31.2	32.3±15.6	<0.001[b]
Insulin (60-minute), μIU/mL	53.6±30.3	61.3±42.0	36.1±17.5	<0.001[b]
Insulin (90-minute), μIU/mL	55.2±33.5	59.8±43.1	33.6±15.2	<0.001[b]
Insulin (120-minute), μIU/mL	54.6±43.9	51.0±33.5	29.9±13.2	<0.001[b]
Total cholesterol, mg/dL	189.7±34.8	192.2±34.7	193.6±44.8	0.740
Triglycerides, mg/dL	118.5±67.1	133.0±96.2	109.9±81.1	0.099
HDL cholesterol, mg/dL	47.9±11.1	47.7±10.7	50.1±12.8	0.227
LDL cholesterol, mg/dL	118.0±31.1	117.9±32.4	121.5±41.4	0.671

Values are expressed as mean±standard deviation or number (%). ΔMatsuda index was defined as the difference between the initial postpartum Matsuda index and the gestational Matsuda index. *P* values are for analysis of variance (continuous) or linear-by-linear association (dichotomous).
SBP, systolic blood pressure; DBP, diastolic blood pressure; AUC, area under curve; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]*P*<0.05 for first vs. second tertile; [b]*P*<0.05 for first vs. third tertile.

Supplemental Table S2. Cumulative Incidence of Type 2 Diabetes by ΔMatsuda Index

Variable	ΔMatsuda index			Total (n=230)	P value
	Lowest tertile (n=76)	Middle tertile (n=77)	Highest tertile (n=77)		
Postpartum T2DM	11 (14.5)	9 (11.7)	6 (7.8)	26 (11.3)	0.423
Postpartum prediabetes and T2DM	39 (51.3)	37 (48.1)	28 (36.4)	104 (45.2)	0.148

Values are expressed as number (%). ΔMatsuda index was defined as the difference between the initial postpartum Matsuda index and the gestational Matsuda index. P values are for the chi-square test to compare the occurrence of postpartum type 2 diabetes and combined with postpartum prediabetes across the tertiles.
T2DM, type 2 diabetes.



Supplemental Fig. S1. Flowchart for study participants. GDM, gestational diabetes mellitus; GIGT, gestational impaired glucose intolerance.