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Prevention of type 2 diabetes mellitus in women with previous gestational diabetes mellitus

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Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, is characterized by underlying maternal defects in the β-cell response to insulin during pregnancy. Women with a previous history of GDM have a greater than 7-fold higher risk of developing postpartum diabetes compared with women without GDM. Various risk factors for postpartum diabetes have been identified, including maternal age, glucose levels in pregnancy, family history of diabetes, pre-pregnancy and postpartum body mass index, dietary patterns, physical activity, and breastfeeding. Genetic studies revealed that GDM shares common genetic variants with type 2 diabetes. A number of lifestyle interventional trials that aimed to ameliorate modifiable risk factors, including diet, exercise, and breastfeeding, succeeded in reducing the incidence of postpartum diabetes, weight retention, and other obesity-related morbidities. The present review summarizes the findings of previous studies on the incidence and risk factors of postpartum diabetes and discusses recent lifestyle interventional trials that attempted to prevent postpartum diabetes.

Keywords: Diabetes, gestational; Diabetes mellitus, type 2; Epidemiology; Risk factors; Clinical trial

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. In parallel to the current obesity epidemic, the prevalence of GDM has continuously increased globally [2]. In Korea, the prevalence of GDM has increased in past decades and reached 10.5% in 2011 [3]. Older maternal age and widespread screening for GDM have contributed to the increased prevalence of GDM in Korea [4].

GDM has its clinical implications for both perinatal and postpartum maternal outcomes [5]. Perinatal outcomes include preeclampsia, Cesarean section, macrosomia, neonatal hypoglycemia, and hyperbilirubinemia, of which the risk is increased in women with GDM. In addition, GDM has implications for postpartum metabolic conditions, as it is characterized by underlying defects in β-cell response due to increased insulin resistance during pregnancy. A prospective cohort study showed that women with previous GDM had a faster deterioration of β-cell secretory capacity and insulin

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sensitivity compared with their counterparts without GDM after delivery [6]. Therefore, women with a history of GDM are at elevated risk of postpartum diabetes and complications and may develop diabetes at an earlier age than women without GDM [7,8]. Metabolic impairments including dyslipidemia and vascular dysfunction are other possible complications in women with previous GDM [9,10]. This review will focus on the incidence of and risk factors for postpartum diabetes in women with a history of GDM and discuss recent interventional trials that aimed to improve postpartum metabolic phenotypes.

DIAGNOSIS OF GDM AND POSTPARTUM DIABETES

Gestational diabetes mellitus

The diagnostic criteria of GDM has its better clinical implication when it properly classify women at risk of poor pregnancy outcomes. The traditional 'two-step approach' (an 1-hour 50 g glucose challenge test for screening and a 3-hour 100 g oral glucose tolerance test [OGTT] for confirmation) has been widely used to evaluate maternal hyperglycemia at 24 to 28 weeks of pregnancy [1,11]. Two representative criteria are available as confirmatory tests. The National Diabetes Data Group (NDDG) recommends criteria based on the results of O'Sullivan and Mahan [12], which require two or more of the following: fasting plasma glucose ≥ 105 mg/dL, 1-hour levels ≥ 190 mg/dL, 2-hour levels ≥ 165 mg/dL, and 3-hour levels ≥ 145 mg/dL. Nearly 50% of the women who were diagnosed with GDM using these criteria developed postpartum glucose intolerance in follow-up studies [13]. Later, Carpenter and Coustan [11] suggested more inclusive criteria for the GDM confirmatory test; they suggested that two or more of the following be present for a diagnosis of GDM: fasting plasma glucose ≥ 95 mg/dL, 1-hour levels ≥ 180 mg/dL, 2-hour levels ≥ 155 mg/dL, and 3-hour levels ≥ 140 mg/dL. Using these criteria, an additional 50% of women tested were diagnosed with GDM compared with those diagnosed using the NDDG criteria [14,15]. These criteria were recommended by the Fifth International Workshop Conference on Gestational Diabetes Mellitus [16].

The 'one-step strategy' for GDM diagnosis was suggested by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) in 2010 [17]. Using this strategy, women meeting one or more of the following criteria after a 2-hour 75 g OGTT are diagnosed with GDM: fasting plasma glucose ≥ 92 mg/dL, 1-hour levels ≥ 180 mg/dL, and 2-hour levels ≥ 153 mg/dL. These cutoff values, derived from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, predict adverse pregnancy outcomes with an odds ratio of 1.75 [18]. Challenges associated with using the IADPSG criteria for GDM diagnosis include a high prevalence of GDM (17.8% of all pregnancies in the HAPO study) and poor reproducibility [19]. Currently, both the Korean Diabetes Association and the American Diabetes Association (ADA) recommend both the one- and two-step approaches for the diagnosis of GDM [20,21].

Postpartum screening of glucose tolerance status

Women with a previous GDM diagnosis are encouraged to be screened for postpartum glucose intolerance. The ADA and the American College of Obstetricians and Gynecologists recommend that women with previous GDM undergo an OGTT at 6 to 12 weeks postpartum and to have lifelong evaluations for diabetes at least every 3 years [20,22]. Measurement of fasting plasma glucose is insufficient as a screening tool, as only 34% of women with diabetes or impaired glucose tolerance had impaired fasting glucose in a previous study [16]. Earlier studies [23,24] applied the following World Health Organization (WHO, year 1985) criteria [25] for the diagnosis of postpartum diabetes: fasting plasma glucose ≥ 140 mg/dL or 2-hour levels ≥ 200 mg/dL. In contrast, recent studies [26-28] have used the following diagnostic criteria from the ADA or WHO (year 1999) [20,29]: fasting plasma glucose ≥ 126 mg/dL or 2-hour levels ≥ 200 mg/dL. This resulted in diagnosing more individuals with postpartum diabetes compared with the previous WHO (year 1985) criteria [30]. Since 2010, the ADA has used a glycosylated hemoglobin (HbA1c) value ≥ 6.5% for the diagnosis of diabetes; although this is widely used in clinical practice, it has yet to be applied to postpartum diabetes studies. Recent epidemiologic studies have reported that the increase in the prevalence of GDM and/ or type 2 diabetes is associated with the obesity epidemic [2,31], but changes in diagnostic criteria should be kept in mind when interpreting prevalence data.

POSTPARTUM DIABETES IN WOMEN WITH PREVIOUS GDM

Incidence of postpartum diabetes

Previous epidemiologic studies on postpartum diabetes were conducted primarily in North America and Europe. Metzger et al. [32] recruited multi-ethnic women with GDM in Chicago and reported a 5-year cumulative incidence of postpartum diabetes of nearly 50%. The incidence of postpartum diabetes increased more rapidly in the first 2 years postpartum. Retnakaran et al. [33] performed a prospective cohort study in Canada with a cohort consisting primarily of Caucasian individuals; this study found that 32.8% of women with GDM had either impaired glucose tolerance or diabetes at 3 months postpartum. A retrospective cohort study from Sweden reported a diabetes incidence of 35% among women with previous GDM during a 15-year follow-up period [34]. A systematic review by Kim et al. [7] found that the prevalence of postpartum diabetes ranged from 2.6% to 70%, with rates differing according to study design, diagnostic methods, and ethnicity. Bellamy et al. [35] reviewed published cohort studies and demonstrated a 7.43-fold higher risk of postpartum diabetes in women with GDM compared with women who were normoglycemic during pregnancy.
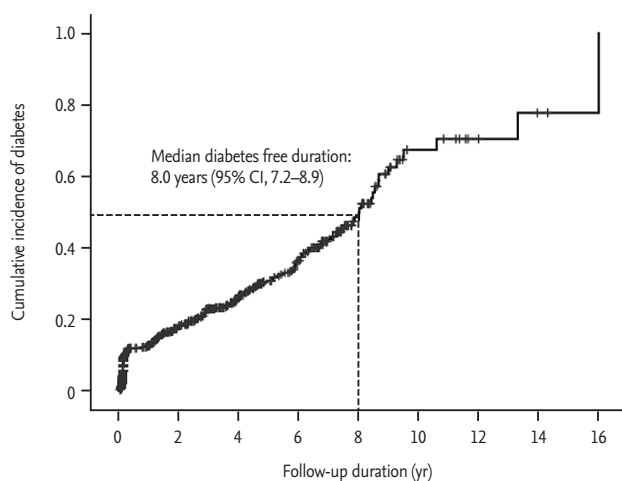
A prospective cohort study in Korea reported a cumulative incidence of postpartum diabetes of 23.8% for a median duration of 4 years, and it expected an incidence of 50.0% during an 8-year follow-up period among women with previous GDM (Fig. 1) [36]. Another prospective cohort study by Cho et al. [37] reported an incidence of 12.8% and 13.2% of postpartum diabetes and impaired glucose tolerance, respectively, during a 6-year follow-up period (mean, 2.1 ± 1.8 years). The risk of postpartum diabetes in Korean women with GDM was 3.5-fold greater than that in women without GDM [38]. The incidence of postpartum diabetes in Korean women with GDM seems to be similar to that found in other studies conducted abroad.

Factors affecting the incidence of postpartum diabetes

Ethnicity

East Asians have a relatively low body mass index (BMI), and the underlying pathophysiology of diabetes in this population is thought to differ from that in other ethnicities [39]. In previous studies, the development of diabetes in Korean individuals was attributed to a genetic predisposition to β-cell dysfunction and/or impaired β-cell compensation to insulin resistance [40,41].

(1) GDM: Hedderson et al. [42] compared ethnic differences in the prevalence of GDM based on BMI. Asian women had a higher prevalence of GDM compared with Caucasian women in the same BMI categories. This finding suggests that Asian women may have impaired β-cell compensation compared with women of other ethnicities with a similar extent of insulin resistance (or obesity). This suggest that the BMI goals for Asian women during pregnancy should be lower than those of Caucasian women. For instance, among Asian women at 17 weeks of gestation, BMIs less than 19 kg/m² (compared with those 19.0 to 21.9 kg/m²) exerted protective effects on the development of GDM, whereas Caucasian women with BMIs less than 19 kg/m² did not show protective effects.

(2) Postpartum diabetes: Kousta et al. [43] recruited 368 women of European, Asian, and African ethnicities with previous GDM and demonstrated increased prevalences of impaired glucose tolerance (44% vs. 28%) and metabolic syndrome (49% vs. 28%) among Asian women compared with European women at 20 months postpartum. Ignell et al. [44] compared postpartum glucose homeo-

Figure 1. Cumulative incidence of type 2 diabetes after gestational diabetes mellitus pregnancy. CI, confidence interval. Adapted from Kwak et al. [36], with permission from Endocrine Society.

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stasis between Asians and Europeans. Women of Asian ethnicity had a 5-fold higher risk of developing diabetes 1 to 2 years postpartum and showed a 22% decrease in their β-cell compensation measured using the disposition index. Further multi-ethnic studies are warranted to investigate the hypothesized increased susceptibility of postpartum diabetes among Asian populations.

Duration after delivery

It is known that the incidence of postpartum diabetes varies widely according to the duration of follow-up [7,35], but changes in incidence over time have not been well studied. In a systematic review, Kim et al. [7] argued that the incidence of postpartum diabetes increased steeply within the first 5 years postpartum and reached a plateau after 10 years. However, this should be carefully interpreted, as individual studies did not distinguish the incidence of early postpartum diabetes (≤ 8 weeks after delivery) from that of late conversion to diabetes but only determined the average incidence after several years of follow-up in each study. Studies from Korea reported that the incidence of early postpartum diabetes (6 to 8 weeks) was higher than 10% [36,45]. This incidence rate (incidence per unit time) during the early postpartum period was much higher than the rate of ~50% of postpartum diabetes in following 5 to 10 years [7]. Early converters to diabetes had greater impairment in their β-cell function during pregnancy than did late converters [36]. Studies with a longitudinal follow-up > 15 years showed that the incidence rates of postpartum diabetes remained relatively stable 10 to 20 years after the period of early conversion to diabetes [26,34,46]. The incidence of diabetes over time seems to increase with aging, which is another major risk factor for diabetes. Overall, the incidence of postpartum diabetes is higher during the early postpartum period and remains stable thereafter.

Other factors

Study designs and methods may affect the reported incidence of postpartum diabetes. For instance, the incidence of GDM and postpartum diabetes can vary when different diagnostic criteria are applied. Exclusion of pre-gestational diabetes is not always successful because the majority of studies recruit subjects upon pregnancy. The postpartum follow-up loss of women with GDM

has been a barrier in many studies and also exists in clinical practice. Only ~25% of women with previous GDM underwent glucose screening at 6 to 12 weeks of postpartum [47]. The main factors that contributed to loss of postpartum follow-up included time pressure, emotional stress in adjusting to a baby, and fear of being diagnosed with diabetes [48,49]. Women with autoantibodies, including the glutamic acid decarboxylase antibody, are expected to increase the risk of developing postpartum diabetes [50,51].

RISK FACTORS FOR POSTPARUM DIABETES

Genetic risk factors

Gestational diabetes mellitus

Many genetic variants that were previously reported to be associated with type 2 diabetes have been shown to be associated with GDM. Cho et al. [52] found that 18 single-nucleotide polymorphisms associated with type 2 diabetes, including *CDKAL1*, *CDKN2A/2B*, *HHEX*, *IGF2BP2*, *SLC30A8*, and *TCF7L2*, were associated with GDM in Korean women. Associations of *MTNR1B* [53] and *KCNQ1* [54] with GDM were also identified in Korean studies. Meta-analyses investigating the association between common type 2 diabetes genetic variants and GDM discovered up to nine genetic variants at or near *TCF7L2*, *GCK*, *KCNJ11*, *KCNQ1*, *CDKAL1*, *IGF2BP2*, *MTNR1B*, and *IRS1* [55,56]. The genetic variants found in these meta-analyses were commonly associated with GDM in both East Asians and Caucasians, but the allele frequencies of each variant differed among study populations [55].

Following the era of the candidate gene approach, the first genome-wide association study evaluating the risk of GDM was conducted in Korea by Kwak et al. [57]. A two-stage analysis, which included a total of 1,399 women with GDM and 2,025 nondiabetic control subjects, was performed. Two loci (rs7754840 in *CDKAL1* and rs10830962 near *MTNR1B*) were found to be associated with GDM. In that study, eight of 34 type 2 diabetes-associated loci were also shown to be associated with GDM (*IGF2BP2*, *CDKAL1*, *CDKN2A/2B*, *IDE/HHEX*, *KCNQ1*, *CENTD2*, and *MTNR1B*). As the number of subjects was not sufficient to fully power a genome-wide association

study, genetic variants specifically associated with GDM but not with type 2 diabetes may be identified in future studies.

The majority of genetic alterations associated with GDM, except *IRS1*, are functionally associated with β-cell insulin secretion but not insulin resistance. *PPARG*, which is associated with insulin resistance, was not associated with GDM [55,56]. Inherited genetic alterations affecting pancreatic β-cell function seem to play an important role in the development of GDM.

Postpartum diabetes

In contrast to genetic studies on GDM, not many studies have evaluated the genetic risk factors for postpartum diabetes. A total of 21 genetic variants associated with type 2 diabetes were genotyped among 634 Korean women with previous GDM, and genetic variants near *CDKN2A/2B* and *HHEX* were associated with early conversion (≤ 8 weeks postpartum) to postpartum diabetes, and those near *CDKAL1* were associated with late conversion (> 1 year postpartum) (Fig. 2) [36]. Kwak et al. [58] generated a genetic risk score (GRS) that consists of 48 genetic variants associated with type 2 diabetes and validated that adding GRS to clinical models significantly increased the predictability of postpartum diabetes among 395 Korean women with previous GDM (net reclassification index 0.430, $p = 7.0 \times 10^{-5}$). To our knowledge, no genome-wide association study has been conducted to discover specific genetic variants related to postpartum diabetes in women with previous GDM.

GDM and postpartum diabetes are not separate diseases but rather exist on a continuum among women predisposed to insufficient β-cell capacity. Women with genetic variants for GDM and/or type 2 diabetes are expected to have a higher risk of postpartum diabetes, but further studies are needed to discover the specific genetic variants associated with postpartum diabetes.

Environmental risk factors

Various risk factors for postpartum diabetes in women with GDM have been identified, including maternal age [59], family history of diabetes [60], extent of hyperglycemia during pregnancy [61], insulin treatment in pregnancy [50], and pre-pregnancy and postpartum BMI [30,62]. Among these, fasting plasma glucose level in pregnancy was consistently associated with postpartum diabetes in various major studies [24,61,63-65]. Other glycemic indices, including 1-hour [66] and 2-hour plasma glucose on OGTT [30,32], the area under the curve on OGTT [64], basal and stimulated insulin [32,36,67], and β-cell compensation in response to insulin resistance [59,66], were associated with the development of postpartum diabetes. A number of studies conducted in Korea identified risk factors consistent with previous findings. Kwak et al. [36] demonstrated that pre-pregnancy BMI, a higher area under the curve on OGTT, low fasting insulin, and decreased β-cell secretion were independent risk factors for early conversion to postpartum diabetes. Jang et al. [30] found that pre-pregnancy weight, age, 2-hour
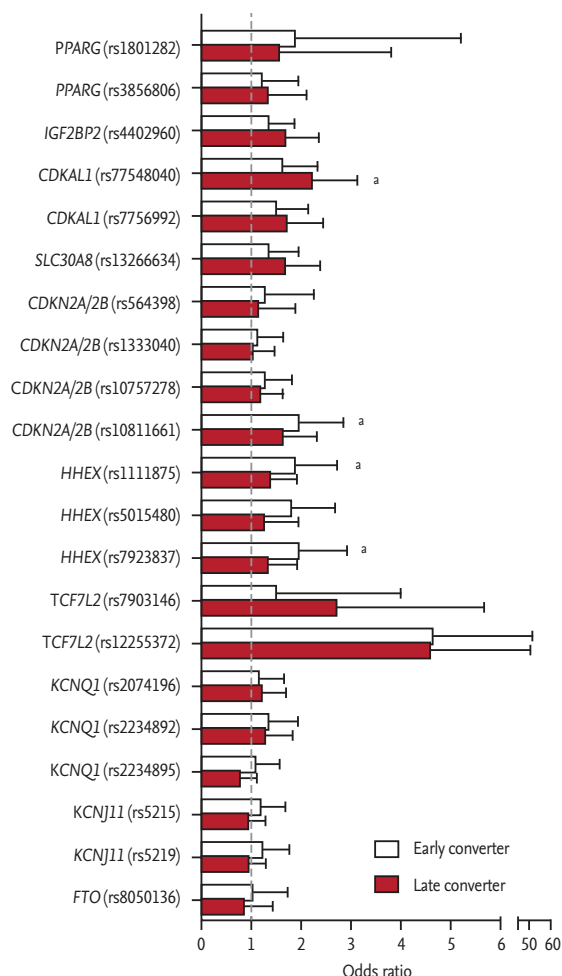

Figure 2. Genetic risk factors for early (≤ 8 weeks) and late (> 1 year) conversion to postpartum diabetes. [a]*p* value < with the significance after Bonferroni correction (0.05/10/2 = 0.0025).

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Table 1. Summary of representative studies for modifiable risk factors of postpartum diabetes

	Study	Ethnicity	Study subjects	Mean age (baseline), yr	Independent variable	Follow-up duration	Major findings
Obesity	Peters et al. [70]	Hispanic	666 Women with previous GDM	30	Postpartum weight change	Mean 22 mon	Postpartum weight gain (10 lb) increased risk of postpartum diabetes by 1.95-fold
	Bao et al. [46]	Mostly Caucasians	1,695 Women with a history of GDM from Nurses' Health Study II	~40	Baseline BMI, most recent BMI, postpartum weight gain	1991 to 2009 (median 14.0 yr)	Each 1 kg/m² (~2.6 kg) increase in baseline BMI and most recent BMI increased postpartum diabetes by 16% and 16%. Each 5 kg increment of postpartum weight gain increased postpartum diabetes by 27%.
	Moon et al. [45]	Korean	418 Women with previous GDM or gestational impaired glucose tolerance	32	Postpartum BMI change	Median 4.0 yr	Each 1 kg/m² (~2.6 kg) increase in postpartum BMI change increases postpartum diabetes by 27%. Subjects in highest tertile (1.8 kg/m²) had 2 times higher risk of postpartum diabetes and worsened blood pressure and lipid profile compared to subjects in lowest tertile (~1.6 kg/m²)
Diet	Tobias et al. [76]	Mostly Caucasians	4,413 Women with a history of GDM from Nurses' Health Study II	38	aMED, DASH, aHEI	1991 to 2005	Adherence to healthy diet (highest quartile of aMED, DASH, aHEI) had 40%, 46%, and 57% decreased risk of postpartum diabetes
Physical activity	Bao et al. [79]	Mostly Caucasians	4,554 Women with a history of GDM from Nurses' Health Study II	38	Physical activity (MET-hour/week)	1991 to 2007	Higher physical activity (5 MET-hour/week or 100 minutes/week of moderate-intensity physical activity) decreased postpartum diabetes by 9%. Increase in physical activity during follow-up (7.5 MET-hour/week or 150 minutes/week of moderate-intensity physical activity) decreased postpartum diabetes by 47%.
Breastfeeding	Ziegler et al. [82]	German	304 Women with previous GDM	31	Breastfeeding (and duration)	Up to 19 yr	Median time to postpartum diabetes was 12.3 years for women who breastfed vs. 2.3 years for women who did not breastfeed. Women who breastfed for > 3 months had lower risk of diabetes than women who breastfed for ≤ 3 months ($p = 0.029$)

GDM, gestational diabetes mellitus; BMI, body mass index; aMED, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; aHEI, alternate Healthy Eating Index; MET, metabolic equivalent of task.

glucose, and 3-hour insulin levels were independently associated with postpartum diabetes. In a recent Korean study, women with postpartum diabetes were found to have higher HbA1c and all (1-, 2-, and 3-hour) glucose levels on 100-g OGTTs [68].

The risk factors mentioned above, including age, family history of diabetes, and glycemic indices during pregnancy, are factors that are not modifiable after delivery. In contrast, postpartum weight reduction, healthy diet, exercise, and breastfeeding are factors that can be ameliorated using lifestyle interventions for women with previous GDM (Table 1). Therefore, clinicians should focus on improving these modifiable risk factors to aid in the prevention of postpartum diabetes.

Obesity

Weight gain is a well-known risk factor for type 2 diabetes in the general population [69]. There are several studies from North America that reported the association between weight gain and increased risk of postpartum diabetes in women with previous GDM. Peters et al. [70] followed 666 Hispanic women with GDM and demonstrated that a 4.5 kg (10 lb) weight gain increased the risk of developing diabetes by 1.54-fold during a 2.2-year follow-up period (baseline BMI, 29.4 kg/m²). Bao et al. [46] analyzed 1,695 women with GDM as a part of the Nurses' Health Study, and the incidence of diabetes increased by 27% for each 5 kg of weight gain (baseline BMI not given). Xiang et al. [71] demonstrated that weight gain was strongly associated with declining β-cell secretory capacity measured using the disposition index.

Although the effect of weight gain on postpartum diabetes is assumed to be similar, the baseline maternal BMI of Asians is usually lower than that of Caucasians. For this reason, a prospective cohort study was conducted in Korea by Moon et al. [45] which included 418 Korean women with GDM (baseline BMI 23.3 kg/m2). This study demonstrated that subjects in the highest tertile of postpartum BMI change had ~2-fold higher risk of developing diabetes compared with women in the lowest tertile (mean BMI change in each tertile, 1.6 and –1.8 kg/m², respectively) [45]. In this study, postpartum weight gain did not merely affect development of diabetes but was also associated with other metabolic phenotypes, including lipid profile, blood pressure, and dynamic glycemic parameters (e.g., Matsuda and insulinogenic
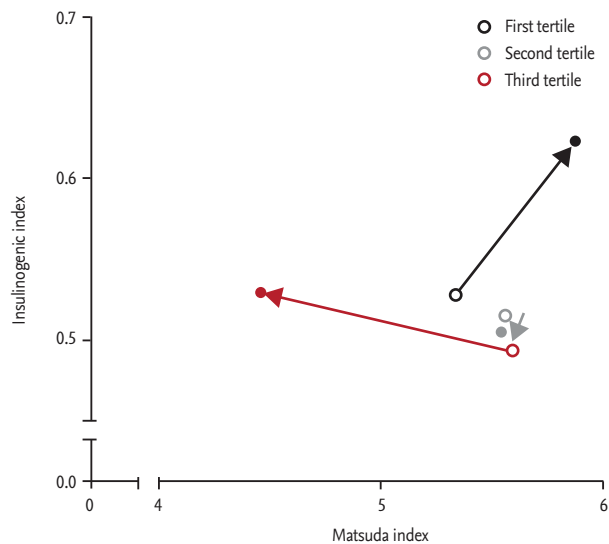

Figure 3. Changes in insulin sensitivity (Matsuda index) and insulin secretory function (insulinogenic index) according to postpartum body mass index (BMI) change during 4 years of follow-up. Changes in insulin sensitivity and secretory function by tertiles of postpartum BMI change were depicted (open circle, initial postpartum visit; closed circle, last follow-up). Subjects in the first tertile (who lost weight during follow-up) showed improvements in both insulin sensitivity and insulin secretion, whereas subjects in the third tertile (who gained weight during follow-up) had significant deterioration in insulin sensitivity but were not able to compensate by increasing their insulin secretion during follow-up. Adapted from Moon et al. [45], with permission from Endocrine Society.

indices) (Fig. 3).

Obesity parameters other than BMI or weight were also found to be associated with postpartum diabetes. Cho et al. [37] demonstrated that a series of obesity parameters, including waist circumference, skinfold thickness, and body fat weight were associated with postpartum diabetes, with waist circumference being the strongest predictor. Lim et al. [72] performed frequently sampled intravenous glucose tolerance tests in women with previous GDM with impaired glucose tolerance and demonstrated that high visceral fat content contributed to the development of impaired postpartum glucose tolerance. High homocysteine [73], high RBP-4 [74], and low adiponectin [74] were also associated with the severity of postpartum glucose intolerance. These findings highlight that increased adiposity or insulin resistance may accelerate the progression to postpartum

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diabetes when β-cells fail to compensate.

Diet

Dietary patterns are closely associated with the development of diabetes [75]. Women with GDM in the Nurses' Health Study who showed greater adherence to healthier diets as evidenced by a score in the highest quartile for the alternate Mediterranean diet, Dietary Approaches to Stop Hypertension diet, and alternate Healthy Eating Index diet had a 40% to 57% lower risk of developing postpartum diabetes compared with women in the lowest quartile [76]. In Korea, carbohydrates represent more than 70% of total energy intake [77]. It is not known whether the Korean diet has deleterious effects on glucose metabolism, but women with previous GDM should be careful not to consume too many calories and/or carbohydrates.

Physical activity

Physical activity is known to reduce the incidence of type 2 diabetes [78]. Women with GDM who had physical activity levels higher than a 7.5 metabolic equivalent of task-hours/week had a 47% lower risk of postpartum diabetes [79]. Several lifestyle interventional trials involving dietary changes and exercise encouragement among women with previous GDM were conducted to decrease the incidence of postpartum diabetes. These trials are further discussed in detail below.

Breastfeeding

Breastfeeding provides benefits to both the mother and her offspring. In a previous study, neonates who were breastfed were less likely to become overweight [80] and to develop type 2 diabetes in adulthood [81]. Ziegler et al. [82] followed German women with GDM for up to 19 years and found that breastfeeding > 3 months reduced postpartum diabetes by 46%. Amelioration of lipid profiles [83] and reduced postpartum weight retention [84] were also observed in studies involving women with GDM. In the Nurses' Health Study, each additional year of breastfeeding reduced the risk of diabetes by 15% even in mothers without GDM [85]. Breastfeeding was also associated with increased weight loss and decreased skinfold thickness [86]. These benefits are partly mediated by decreased circulating estrogen levels during lactation [87,88]. Breastfeeding should be strongly encouraged in women with a previous GDM diagnosis to promote both maternal and offspring health.

INTERVENTIONAL MODALITIES IN WOMEN WITH GDM

Benefits of lifestyle interventions

A number of studies have demonstrated that lifestyle interventions can prevent or delay the onset of diabetes in high-risk populations. The Diabetes Prevention Program (DPP) is a representative multicenter randomized interventional trial that aimed to demonstrate that either intensive lifestyle modifications or metformin could prevent the development of diabetes in high-risk men and women with impaired glucose tolerance [89]. The lifestyle intervention reduced the incidence of diabetes by 58% during a 2.8-year follow-up period. This benefit was maintained during 10 years of follow-up, resulting in a 34% reduction in the incidence of diabetes in the lifestyle intervention group [90]. Systolic and diastolic blood pressure and triglyceride levels were also lower in subjects who underwent lifestyle modifications. Likewise, lifestyle interventional trials have been attempted among pregnant women.

Prevention of GDM

It is important to prevent high-risk pregnant women from developing GDM. Several lifestyle interventional trials have been conducted among obese pregnant women, but the effects of lifestyle modifications on gestational weight gain and GDM were inconsistent. Some trials succeeded in decreasing gestational weight gain [91-94], but others failed to decrease weight gain during pregnancy [95,96]. In a study from Denmark, although reduction in gestational weight gain was achieved, a significant number of women still exceeded the Institute of Medicine recommendations for gestational weight gain [94]. The Finnish Gestational Diabetes Prevention Study (RADIEL) is a representative study that succeeded in decreasing the incidence of GDM using a lifestyle intervention, which recruited 293 high-risk women with previous GDM or a pre-pregnancy BMI ≥ 30 kg/m² [97]. Individualized lifestyle interventions reduced GDM by 39% (13.9% for the intervention group and 21.6% for controls) and resulted in an additional weight loss of

Table 2. Summary of interventional trials for prevention of postpartum diabetes

Study	Study design	Study subjects	Mean age (baseline)	Intervention	Follow-up duration	Major findings
TRIPOD [98]	Intervention	High risk Hispanic women with previous GDM in the previous 4 years (266 women were randomized 1:1 to either troglitazone or placebo)	34 yr	Troglitazone 400 mg/day	Median 30 mon	Annual diabetes incidence rate during postpartum was 12.1 and 5.4%/year in women assigned to placebo and troglitazone, respectively. Troglitazone group showed reduction in endogenous insulin secretion (measured by IVGTT at 3 month).
PIPOD [99]	Intervention	95 women who were not diabetic at the end of TRIPOD study	39 yr	Pioglitazone 30 mg/day, then increased to 45 mg/day	Median 35.9 mon	Annual diabetes incidence rate during postpartum was 4.6%/year, which was much lower than 12.1%/year in placebo group in TRIPOD study. Pioglitazone stopped the decline in β-cell function that occurred during placebo treatment in the TRIPOD study.
DPPOS [100]	*Post hoc* analysis of DPP	350 women with previous GDM and 1416 women with previous live births (DPP initially enrolled high risk subjects with impaired glucose tolerance)	43 and 51 yr for women with and without previous history of GDM, respectively	ILS vs. metformin (850 mg twice a day) vs. placebo	10 yr	ILS reduced incidence of diabetes compared with placebo by 40% (11.4 and 7.6/100 person-years in placebo and ILS, respectively).
DEBI [101]	Intervention	197 women with GDM (enrolled during pregnancy)	Not available	Diet, exercise and breastfeeding Intervention	1 yr	Higher proportion of women reached postpartum weight goal who underwent intervention (37.5 vs. 21.4%, *p* = 0.07). The intervention decreased dietary fat intake and increased breastfeeding.
Chinese study [103]	Intervention	450 Chinese women with either impaired glucose tolerance or diabetes by 75 g OGTT during pregnancy	39 yr	Dietary advice and exercise	3 yr	Fewer women developed diabetes who underwent lifestyle intervention (15% vs. 19%, *p* value not given). BMI, systolic and diastolic blood pressure, and triglyceride concentration were lower with intervention.

TRIPOD, The Troglitazone in Prevention of Diabetes; GDM, gestational diabetes mellitus; IVGTT, intravenous glucose tolerance test; PIPOD, The Pioglitazone in Prevention of Diabetes; DPPOS, Diabetes Prevention Program Outcomes Study; DPP, Diabetes Prevention Program; ILS, intensive lifestyle intervention; DEBI, Diet, Exercise, and Breastfeeding Intervention; OGTT, oral glucose tolerance test; BMI, body mass index.

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0.58 kg. Thus, lifestyle interventions seem beneficial for preventing GDM and reducing gestational weight gain; however, further studies are required to confirm the soundness of this association.

Prevention of postpartum diabetes

Interventional trials that aimed to prevent postpartum diabetes in women with previous GDM were conducted among non-Korean populations (Table 2). The Troglitazone in Prevention of Diabetes (TRIPOD) study recruited only young Hispanic women who were diagnosed with GDM within 4 years postpartum (mean age, 34 years) [98]. Subjects who were given troglitazone had a 55% reduction in the risk of diabetes progression (12.1% per year for placebo, and 5.4% per year for troglitazone). The authors hypothesized that reducing insulin resistance using thiazolidinedione preserved β-cell function by reducing insulin secretory demands. The Pioglitazone in Prevention of Diabetes (PIPOD) study was a subsequent study that included diabetes-free subjects who completed the TRIPOD study and were given pioglitazone; the incidence rate of diabetes was 4.6% per year, which was considerably lower than the diabetes rate for the placebo group in the TRIPOD study [99].

The 10-year observational cohort that followed the DPP study, the Diabetes Prevention Program Outcomes Study (DPPOS), demonstrated that intensive lifestyle modifications and metformin reduced the cumulative incidence of diabetes in women with a previous GDM diagnosis by 35% and 40%, respectively, compared with the placebo group [100]. Participants (mean age, 43) had their last delivery a mean of 12 years before enrollment, as this trial did not primarily target women with previous GDM. Nevertheless, the results of this study suggest that interventions, such as lifestyle modifications and/or metformin treatment, are effective for preventing the progression to diabetes, even years after delivery.

Ferrara et al. [101] performed a randomized controlled feasibility trial, the Diet, Exercise, and Breastfeeding Intervention (DEBI), among women with previous GDM. The intervention decreased dietary fat intake and increased breastfeeding with borderline significance, but physical activity levels did not differ. This resulted in a higher proportion of women reaching their postpartum weight goal (pre-pregnancy weight for women with pregravid BMI < 25 kg/m² and an additional 5% loss from pre-pregnancy weight for women with pregravid BMI ≥ 25 kg/m²), although this was statistically insignificant. In this trial, women who lost more than 2 kg exhibited reduced fasting and 2-hour glucose levels and increased 2-hour insulin levels at 12 months postpartum [102].

One interventional trial in Asia, which involved Chinese women with previous GDM who had impaired glucose tolerance on postpartum OGTT, offered advice on diet and exercise [103]. Fewer women who were provided the lifestyle intervention developed postpartum diabetes during a 3-year follow-up period compared with the control group, but this was without statistical significance (15% vs. 19%, *p* value not given). A subgroup analysis showed that women aged > 40 years had a significantly lower incidence of postpartum diabetes (9.3% vs. 22.5%, *p* = 0.018). BMI, systolic and diastolic blood pressure, and triglyceride concentrations were lower in the intervention group, but the significance of these results was inconsistent over time.

Several issues raised by the previous trials should be considered. First, weight reduction by lifestyle modification was modest in women with previous GDM compared with in non-GDM women. In the DPP study, the 3-year weight change in women with previous GDM was –1.6 kg, whereas it was –4.0 kg in women without GDM [104]. The reasons underlying this difference are unknown but may be due to predisposition or poor compliance with lifestyle interventions among women with GDM. A more active and comprehensive strategy should be sought to achieve distinct metabolic benefits among those with GDM. Next, although the weight-loss effect of these interventions was inconsistent when considering study design, lifestyle modifications should still be encouraged to prevent various obesity-related morbidities, including postpartum diabetes and dyslipidemia. Lifestyle interventions have shown better or equivalent effects on reducing postpartum diabetes when compared with antidiabetic medications [89,104]. Lastly, as Asian women have relatively lower BMIs than non-Asians, the effects of interventions may differ across populations. Indeed, further studies are warranted to clarify the metabolic benefits of lifestyle interventions in Asian populations.

CONCLUSIONS

Women with previous GDM have more than a 7-fold higher risk of developing postpartum diabetes compared with women without GDM. Various risk factors for postpartum diabetes, including age, glucose level in pregnancy, family history of diabetes, obesity, physical activity, and breastfeeding, were identified in previous studies. Recent interventional trials have shown that lifestyle modifications and/or antidiabetic medications have metabolic benefits, such as reducing postpartum diabetes, but these interventions were not as effective as they were in the non-gravid population. Nonetheless, lifestyle modifications are strongly recommended for women with previous GDM [105,106].

In clinical practice, the loss of women with GDM to follow-up evaluations after delivery is problematic. The majority of women with GDM understand the association between GDM and postpartum diabetes but do not perceive themselves at increased risk of developing diabetes [107]. Postpartum diabetes screening rates range from 19% to 73%, which are generally poor compared with expectations [48]. Automated reminders or notifications sent to women diagnosed with GDM would help to detect postpartum diabetes and guide women regarding subsequent follow-up [108,109].

Asians have a different genetic predisposition to diabetes and have relatively low BMIs compared with other ethnicities. However, many previous studies covered in this review were conducted in Western countries. Although the risk factors for postpartum diabetes and the metabolic benefits of lifestyle modifications are assumed to be similar, further studies investigating the prevention of postpartum diabetes in Asian populations are warranted.

Conflict of interest

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

Acknowledgments

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