

## Evolution of Diagnostic Criteria for Gestational Diabetes Mellitus and Risk Factors of Progression to Postpartum Type 2 Diabetes from Gestational Diabetes Mellitus

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### Abstract

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that is not type 1 or type 2 diabetes mellitus (T1DM or T2DM). There are many different GDM diagnostic criteria in clinical use. However, regardless of which diagnostic criteria are used, it has been shown that women with GDM are at increased risk for postpartum T2DM and that, among women with T2DM, as many as one third of women have experienced a pregnancy of GDM. Various risk factors for postpartum T2DM have been identified, including body weight/ body mass index of pre-pregnancy and postpartum, gestational age at diagnosis, ethnicity, and family history of diabetes, genetic risk factors and breastfeeding etc. This paper reviews diagnostic criteria for GDM established by different organizations and summarizes the findings of the incidence and risk factors of postpartum T2DM and the recent lifestyle interventional trials that aimed to prevent postpartum T2DM in women with a history of GDM

**Keywords:** Gestational diabetes mellitus (GDM), Diagnosis, Screening, Fasting plasma glucose, Type 2 diabetes, Risk factors

### 1. Introduction

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that is not type 1 or type 2 diabetes mellitus (T1DM or T2DM) (Agarwal, 2016). T1DM is caused by absolute insulin deficiency with positive autoimmune markers which destroy pancreatic  $\beta$ -cells, while T2DM is induced by insulin resistance or relative insulin deficiency. Clearly, GDM is distinct from both these types of diabetes (American Diabetes Association, 2016). GDM is also associated with many maternal (preeclampsia, increase in cesarean sections, birth injuries) and fetal problems (macrosomia, hypoglycemia, shoulder dystocia) (Hartling et al, 2012). GDM has long been recognized clinically. In 1916, a case of diabetes presented in pregnancy, resolved with delivery, and recurred in her later life (Joslin, 1916). No standardised criteria for GDM diagnosis were devised until 1964. In 1964, O'sullivan and Mahan (1964) carried out 3-h 100 g oral glucose tolerance tests (OGTT) on 752 patients at different stages of pregnancy. Women with 2 out of 4 values that were greater than 2 standard deviations (rounded to the nearest 5 mg/dL) above the mean glucose levels determined in this cohort were classified as having GDM. These criteria (with some modification) have continued in clinical use over the following several decades. Women with a previous history of GDM have a greater than 7-fold higher risk of developing T2DM compared with women without GDM (Moon et al, 2017). This review will focus on the evolution of diagnostic criteria for GDM and the risk factors for developing to T2DM and discuss the prevention trials that aimed to prevent woman with a history of GDM to develop to postpartum T2DM.

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## **2. Oral glucose tolerance test (OGTT) as the gold standard for GDM diagnosis and screening, its advantages and disadvantages**

All the expert panels agree that the OGTT is the “gold standard” for GDM diagnosis. The diagnosis of GDM is confirmed by the 75 g or 100 g OGTT. The screening of GDM generally involves a one-step or a two-step strategy though the ideal screening method for GDM is without consensus. The “one-step strategy” for GDM diagnosis was suggested by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) in 2010. In the “one-step strategy”, all patients undergo the diagnostic OGTT. In the “two-step strategy”, screening is done by: (1) the first step is assessing the clinical risk factors; the second step is that patients who have clinical risk factors undergo the diagnostic OGTT; or (2) the first step is venous plasma glucose is measured one hour after 50 g oral glucose (glucose challenge test, GCT) usually at 24-28 wk gestation; the second step is that patients who exceed a specific GCT screening threshold undergo the diagnostic OGTT.

However, the screening and diagnosis of GDM remains inconsistent due to different diagnostic criteria for GDM recommended by different organizations (Table 1). The major feature of these criteria was that they defined a cohort of women with a greatly increased future risk of developing to T2DM, demonstrating a lifetime risk of up to 60% (Noctor and Dunne, 2015). The National Diabetes Data Group (NDDG) criteria (Table 1) proposed in 1979 changed the O’Sullivan/Mahan criteria (O’Sullivan and Mahan, 1964) from whole blood to plasma values. The Carpenter-Coustan criteria (Carpenter and Coustan, 1982) also changed the O’Sullivan/Mahan criteria to plasma values, however in addition, took a change in enzymatic methods into account. Studies directly comparing the prevalence of GDM by either NDDG or Carpenter-Coustan criteria showed significant differences with an about 50% relative increase in GDM prevalence if the Carpenter-Coustan criteria were used (Cheng et al., 2009; Ferrara et al., 2002). In addition, the American Diabetes Association (ADA) also allowed for the use of a 75 g, 2-h OGTT to make a diagnosis of GDM, using the same one- and two-hour cut-offs as the three-hour 100 g OGTT. The World Health Organization (WHO) also recommended alternative criteria for the diagnosis of GDM beginning in 1980. In addition to these major criteria, multiple different diagnostic criteria are in use worldwide, some related to older criteria, some derived on the basis of local data. Therefore, the situation still exists where different centers in the same country or even the same region may employ different criteria for GDM diagnosis.

Although OGTT is regarded as the gold standard for GDM diagnosis, the OGTT has many disadvantages. OGTT is time consuming, expensive and demanding for both the patient and the laboratory; in addition, it is also quite unpleasant, not physiologic, uncorrected for body weight and its predictive value often alters with ethnicity due to varying prevalence of GDM (Hanna and Peters, 2002). The most serious defect being that it is not reproducible (Davidson, 2002).

## **3. Fasting plasma glucose (FPG) as a screening test for GDM, its advantages and disadvantages**

The screening and diagnostic criteria for GDM have evolved over time. FPG as a screening test for GDM has had a checkered history. Mortensen et al (1985) firstly used FPG (along with glycosuria) to screen pregnant women. When the expert committee of the ADA preferred using the FPG with lower thresholds rather than the OGTT for DM diagnosis in non-pregnant adults, the interest in studying FPG as a screening test for GDM increased. In 1999, the WHO approved this ADA approach and then FPG became even more accepted and popular (Atilano et al., 1999). Initially, the WHO recommended a fasting glucose threshold of 8 mmol/L (Table 1). These recommendations were revised again in 1985 (fasting glucose threshold lowered to 7.8 mmol/L, recommendation to treat impaired glucose tolerance added), 1999 (fasting glucose threshold reduced to 7.0 mmol/L), and 2013 (fasting glucose threshold reduced to 5.1 mmol/L) (Table 1). The European Association for the Study of Diabetes also proposed new GDM criteria in 1996 using a fasting value of 6.0 mmol/L and a two-hour post 75 g glucose load value of 9.0 mmol/L (Brown et al., 1996).

The advantages of FPG as a screening test for GDM are reproducible, reliable, cheap, and FPG does not induce vomiting as seen with the OGTT/GCT. FPG can be carried out in women unable to tolerate glucose drink and it takes less time than GCT. The FPG usage makes GDM screening and diagnosis patient friendly (Rey, 1999). However, the value of FPG for GDM screening remains uncertain and it also has some problems. In many poorer countries, multiple studies confirmed that women find it hard to come to a clinic fasting.

In some countries, fasting becomes hard due to cultural beliefs that pregnant women should not fast for a long time. The dropout rate is high when a pregnant woman is asked to come again for an OGTT after the clinic appointment. The FPG is inherently much lower in some Asian populations than Caucasians but the postprandial is very high (Wijeyaratne et al., 2006).

#### **4. GDM is the risk of postpartum T2DM**

It has been shown that women with GDM are at increased risk for future T2DM and that, among women with diabetes, as many as one third of women have experienced a pregnancy of GDM (Cheung and Helmink, 2006; Agarwal, 2016).

Bellamy et al. (2009) found that women with GDM had an increased risk of developing T2DM compared with women without GDM (relative risk 7.43, 95% CI 4.79–11.51) via a comprehensive systematic review and meta-analysis. A study recruited multi-ethnic women with GDM in Chicago showed a 5-year cumulative incidence of postpartum T2DM of nearly 50% (Metzger et al., 1993). The incidence of postpartum T2DM increased more rapidly in the first 2 years postpartum. Retnakaran et al. (2008) conducted a prospective cohort study in Canada with a cohort consisting primarily of Caucasian individuals; this study demonstrated that 32.8% of women with GDM had either impaired glucose tolerance or T2DM at 3 months postpartum. A retrospective cohort study from Sweden proved a T2DM incidence of 35% among women with previous GDM during a 15-year follow-up period (Linne et al., 2002). Kim et al. (2002) reported that the prevalence of postpartum T2DM ranged from 2.6% to 70%, with rates differing according to study design, diagnostic methods, and ethnicity. A systematic review by Bellamy et al. (2009) summarized published cohort studies and proved a 7.43-fold higher risk of postpartum T2DM in women with GDM compared with women without GDM during pregnancy.

Kwak et al. (2013a) performed a prospective cohort study in Korea; the study found a cumulative incidence of postpartum T2DM 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. Another prospective cohort study showed an incidence of 12.8% of postpartum T2DM during a 6-year follow-up period (Cho et al., 2006). The risk of postpartum T2DM in Korean women with GDM was 3.5-fold greater than that in women who were normoglycemic during pregnancy (Lee et al., 2008). A prospective cohort study showed that women with previous GDM had a faster deterioration of  $\beta$ -cell secretory capacity and insulin sensitivity compared with their counterparts without GDM after delivery. Therefore, women with a history of GDM are at elevated risk of postpartum T2DM and complications and may develop T2DM at an earlier age than women without GDM (Kim et al., 2002; Jang, 2011).

#### **5. The risk factors of developing to postpartum T2DM from GDM**

Despite the heterogeneity of the cohorts, many studies have identified similar risk factors predicting progression to postpartum T2DM. In this paper, we review the most commonly associated factors. Table 2 summarizes the representative studies for risk factors of developing to postpartum T2DM from GDM.

##### **5.1 Body weight / body mass index (BMI) of pre-pregnancy**

The information on pre-pregnancy factors is limited since most studies retrospectively assess pre-pregnancy risk factors (Noctor and Dunne, 2015). An exception to retrospective recall of pre-pregnancy factors is the large long-term longitudinal cohort study of 4554 women from the Nurses' Health Study II, which have detailed information preceding the index pregnancy (Bao et al., 2014). Of pre-pregnancy variables assessed, body weight or body mass index (BMI) is the most common measure, and is commonly associated with increased risk of progression to T2DM (Cao et al., 2008; Russell et al., 2008; Jang, 2011). Specifically, pre-pregnancy BMI was associated with significantly increased risk of future T2DM after a GDM delivery; for every 1 kg increase in pre-pregnancy weight, there was a 40% increase in odds of developing T2DM (odds ratio 1.40, 95% CI 1.20–1.60) (Kim, 2014). Capula et al. (2014) reported that the strongest predictors of T2DM were FPG  $\geq 100$  mg/dl (5.6 mmol/l) at GDM diagnosis and pre-pregnancy BMI  $\geq 25$ .

##### **5.2 Body weight/BMI post-pregnancy**

A number of studies have reported that body weight (or associated measures) after pregnancy are related with progression to T2DM (Bao et al., 2015; Ziegler et al., 2012; Steinhart et al., 1997; Wang et al., 2014; Persson et al., 1991). This correlation appears stronger than that seen with pregnancy weight/BMI, which often loses significance in multivariable models.

An examination of weight change post-partum reported by Peters et al. (1996) showed that there was a twofold increase in the risk of T2DM for every 4.5-kg increase in weight even after adjustment for other factors including post-partum BMI, oral glucose tolerance test results and breastfeeding. In a Korean cohort, Cho et al. (2006) compared the strength of association between post-partum BMI, weight, skin thickness, waist-hip ratio and waist circumference and risk of T2DM.

All of the body mass measures were related with T2DM risk, but waist circumference was one of the key risk factors for the onset of T2DM in Korean women with previous GDM. The study from 1,695 women with GDM as a part of the Nurses' Health Study demonstrated that the incidence of T2DM increased by 27% for each 5 kg of weight gain (baseline BMI not given) (Bao et al., 2015). Interestingly, Wang et al (2014) reported that both waist circumference and body fat performed better than BMI in predicting T2DM in a Chinese population, while Jang (2011) proved that waist circumference showed a stronger association than BMI in a Korean cohort. This may help to explain why some Asian cohorts have not proved an association between BMI and future T2DM despite longer-term follow-up (Cho et al., 2005; Lee et al., 2011).

### 5.3 Gestational age at diagnosis

Another commonly reported association with T2DM is gestational age at diagnosis (Jang, 2011; Dalfrà et al., 2001; Albareda et al., 2003). However, many of the studies also specify a screening protocol that involves screening higher-risk women in early pregnancy, causing a significant bias. Women diagnosed with GDM in early pregnancy before insulin resistance begins to rise (Stanley et al., 1998; Mills et al., 1998) are likely to have a greater degree of hyperglycaemia, and therefore an increased likelihood of progression to T2DM. In a word, many studies demonstrated that gestational age at diagnosis remains a risk factor (Albareda et al., 2003; Catalano et al., 1991; Kjos et al., 1995).

### 5.4 Ethnicity

There are few studies specifically examining the effects of ethnicity, although these studies have found an increased prevalence among those women of ethnicity other than white European origin (Ali and Alexis, 1990; Dornhorst et al., 1992; Sinha et al., 2003). Other studies have found no association (Dacus et al., 1994; Catalano et al., 1991), though the reasons for this are unclear. The prevalence of GDM is higher among ethnic groups who are not of white European origin, while the prevalence of GDM increases at a lower BMI in the Asian populations studied (Hedderston et al., 2012). Kousta et al. (2006) 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. It has been shown that women of Asian ethnicity had a 5-fold higher risk of developing T2DM 1 to 2 years postpartum and showed a 22% decrease in their  $\beta$ -cell compensation measured using the disposition index (Ignell et al., 2013). In addition, adoption of the IADPSG criteria may induce a disproportionate rise in GDM prevalence among Asian populations, which will be of relevance when determining the future risk of T2DM in these populations (Jenum et al., 2012). In addition to the studies outlined above examining this question, comparison between studies does suggest a higher proportion of women of non-white European ethnicity progress to abnormal glucose tolerance (Girgis et al., 2012).

### 5.5 Family history of diabetes

Although some studies proved family history has an independent effect (Capula et al., 2014; O'Reilly et al., 2011; Kim et al., 2011; Kwak et al., 2013b), several studies examining family history have found no effect (Lam et al., 1991; Damm et al., 1992), it appears to be small, and the association is often not seen when analysed as part of a multivariate model (Coustan et al., 1993; Vambergue et al., 2008). Therefore, family history does not appear to play a major independent role in predicting future risk of diabetes or abnormal glucose tolerance.

### 5.6 Genetic risk factors

Not many studies have evaluated the genetic risk factors for postpartum T2DM. A total of 21 genetic variants associated with T2DM were genotyped among 634 Korean women with a history of GDM, and genetic variants near *CDKN2A/2B* and *HHEX* were associated with early conversion ( $\leq 8$  weeks postpartum) to postpartum T2DM, and

those near *CDKAL1* were associated with late conversion (> 1 year postpartum) (Kwak et al., 2013a). It has been shown that a genetic risk score (GRS) consisting of 48 genetic variants was associated with T2DM. Adding GRS to clinical models significantly increased the predictability of postpartum T2DM among 395 Korean women with a history of GDM (net reclassification index 0.430,  $p = 7.0 \times 10^{-5}$ ) (Kwak et al., 2013b). To our knowledge, no genome-wide association study has been conducted to discover specific genetic variants related to postpartum T2DM in women with a history of GDM.

Women with genetic variants for T2DM are expected to have a higher risk of postpartum T2DM, however further studies are needed to discover the specific genetic variants associated with postpartum T2DM.

### 5.7 Breastfeeding

It has been shown that breastfeeding among women with GDM is related with improved glycaemic indices in the early postpartum period (O'Reilly et al., 2011; Gunderson et al., 2012). Breastfeeding provides benefits to both the mother and her offspring. It has been shown that neonates who were breastfed were less likely to become overweight (Grummer-Strawn and Mei, 2004) and to develop T2DM in adulthood (Pettitt et al., 1997). Women with GDM ( $n = 304$ ) participating in the prospective German GDM study were followed from delivery for up to 19 years postpartum for T2DM development.

The results found that breastfeeding >3 months reduced postpartum T2DM by 46 % (Ziegler et al., 2012). The Nurses' Health Study reported that each additional year of breastfeeding reduced the risk of T2DM by 15% even in mothers without GDM (Stuebe et al., 2005). It also has been shown that breastfeeding was related with increased weight loss and decreased skinfold thickness (Dewey et al., 1993). Thus, breastfeeding should be strongly encouraged in women with a previous GDM diagnosis to promote both maternal and offspring health.

### 5.8 Other factors

Although some studies have shown that there is no association between age at diagnosis of GDM and future T2DM (Löbner et al., 2006; Kaufmann et al., 1995), another studies did show the association (Dalfrà et al., 2001; Malinowska-Polubiec et al., 2012; Chodick et al., 2010; Vambergue et al., 2008). The association is rarely significant when other variables are taken into account (Chodick et al., 2010). Parity, most commonly classified as a binary variable (multiparous or nulliparous) has been identified as potentially associated with higher risk of progression later (Ekelund et al., 2010; Kerimoğlu et al., 2010; Corrado et al., 2007), however this finding is inconsistent (Kaufmann et al., 1995).

Kjos et al. (1998) reported that patients using progestin-only oral contraceptive developed T2DM more rapidly during the first 2 years of use. Although the increasing prevalence of T2DM with advancing age in the general population, this is not a universal finding (Cypryk et al., 1994; Cho et al., 2005) especially in multivariate analysis (Göbl et al., 2013). This may be due to the relatively small difference in ages within the population of women involved in these studies, compared to the cohorts as a whole.

## 6. Prevention of postpartum T2DM

Interventional trials that aimed to prevent postpartum T2DM in women with a history of GDM were conducted among Hispanic, Chinese, et al populations (Buchanan et al., 2002; Shek et al., 2014). The Troglitazone in Prevention of Diabetes (TRIPOD) study recruited young Hispanic women (mean age, 34 years) who were diagnosed with GDM within 4 years postpartum. Patients who were given troglitazone had a 55% reduction in the risk of T2DM progression (12.1% per year for placebo, and 5.4% per year for troglitazone) (Buchanan et al., 2002). In the Pioglitazone in Prevention of Diabetes (PIPOD) study, the patients were given pioglitazone; the incidence rate of T2DM was 4.6% per year, which was considerably lower than the T2DM rate for the placebo group in the TRIPOD study (Xiang et al., 2006).

The Diabetes Prevention Program Outcomes Study (DPPOS) proved that intensive lifestyle modifications and metformin reduced the cumulative incidence of T2DM in women with a history of GDM diagnosis by 35% and 40%, respectively, compared with the placebo group (Aroda et al., 2015). Women (mean age, 43) had their last delivery a mean of 12 years before enrollment, as this trial did not primarily aim women with prior GDM. The results of this study showed that interventions, such as lifestyle modifications and/ or metformin treatment, were effective for preventing the progression to T2DM, even years after delivery.

A study on interventional trial in Chinese women with previous GDM who had impaired glucose tolerance on postpartum OGTT offered suggests on diet and exercise (Shek Et al., 2014). Fewer women who were provided the lifestyle intervention developed postpartum T2DM during a 3-year follow-up period compared with the control group; however this was without statistical significance. 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 T2DM and dyslipidemia.

Lifestyle interventions have shown better or equivalent effects on reducing postpartum T2DM when compared with antidiabetic medications (Knowler et al., 2002; Ratner et al., 2008). 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.

## 7. Conclusions

Distinct heterogeneity across studies of women with a history of GDM with regard to the diagnostic criteria used limits the ability to compare findings across studies. However, regardless of which criteria are used, women with previous GDM have more than a 7-fold higher risk of developing postpartum T2DM compared with women without GDM. The risk factors predicting progression remain similar across cohorts. These risk factors, including gestational age at diagnosis, ethnicity, family history of diabetes, genetic factors, are factors that are not modifiable after delivery. In contrast, postpartum body weight reduction and breastfeeding etc are factors that can be ameliorated using lifestyle interventions for women with a history of GDM. Asians have a different genetic predisposition to T2DM 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 T2DM and the metabolic benefits of lifestyle modifications are deemed to be similar, further studies investigating the prevention of postpartum T2DM in Asian populations are suggested.

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**Table 1.** Comparison of diagnostic criteria for GDM

Criteria	Year	Glucose load (g)	Fasting glucose mmol/L	1-h glucose mmol/L	2-h glucose mmol/L	3-h glucose mmol/L	Values for diagnosis
NDDG	1979	100	5.8	10.6	9.2	8.1	$\geq 2$
O'Sullivan <i>et al</i>	1964	100	5	9.2	8.1	6.9	$\geq 2$
Carpenter and Coustan	1982	100	5.3	10	8.6	7.8	$\geq 2$
ADA (C and C)	2003 (1982)	100	5.3	10.0	8.6	7.8	$\geq 2$
ADA	2011	75	5.1	10.0	8.5	--	$\geq 1$
CDA	2013	75	5.3	10.6	9.0	--	$\geq 1$
EASD	1996	75	6.0	--	9.0	--	$\geq 1$
NICE	2015	75	5.6	--	7.8	--	$\geq 1$
ADIPS	2014	75	5.1	10.0	8.5	--	$\geq 1$
NZSSD	1998	75	5.5	--	9.0	--	$\geq 1$
JDS	2013	75	5.1	10.0	8.5	--	$\geq 1$
IADPSG	2010	75	5.1	10.0	8.5	--	$\geq 1$
WHO 1980	1980	75	8	--	8	--	$\geq 1$
WHO 1985	1985	75	7.8	--	7.8	--	$\geq 1$
WHO 1999	1999	75	7	--	7.8	--	$\geq 1$
WHO 2013	2013	75	5.1	10.0	8.5	--	$\geq 1$

NDDG: National Diabetes Data Group; ADA: American Diabetes Association; C and C: Carpenter-Coustan; CDA: Canadian Diabetes Association; EASD: European Association for the Study of Diabetes; NICE: National Institute for Health and Care Excellence; ADIPS: Australasian Diabetes in Pregnancy Society; NZSSD: New Zealand Society for the study of diabetes; JDS: Japan Diabetes Society; IADPSG: International Association of Diabetes and Pregnancy Study Groups; WHO: World Health Organization.

**Table 2.** Summary of representative studies for risk factors of postpartum T2DM

Risk factors	Representative studies	Major findings
Body weight/BMI of pre-pregnancy	Cao et al., 2008; Russell et al., 2008; Capula et al., 2014	Of pre-pregnancy variables assessed, body weight or BMI is the most common measure, and is commonly associated with increased risk of progression to T2DM. Specifically, pre-pregnancy BMI was associated with significantly increased risk of future T2DM after a GDM delivery.
Body weight/BMI post-pregnancy	Bao et al., 2015; Wang et al., 2014; Persson et al., 1991 Peters et al., 1996 Cho et al., 2006 Bao et al., 2015	A number of studies have reported that body weight (or associated measures) after pregnancy are related with progression to T2DM. There was an increase in the risk of T2DM with the body weight increasing after pregnancy.
Gestational age at diagnosis	Dalfrà et al., 2001; Albareda et al., 2003 Catalano et al., 1991; Kjos et al., 1995	Women diagnosed with GDM in early pregnancy before insulin resistance begins to rise are likely to have a greater degree of hyperglycaemia, and therefore an increased likelihood of progression to T2DM.
Ethnicity	Dornhorst et al., 1992; Sinha et al., 2003 Kousta et al., 2006 Ignell et al., 2013	There is an increased prevalence of postpartum T2DM among those women of ethnicity other than white European origin.
Family history of diabetes	Capula et al., 2014; Kim et al., 2011; Kwak et al., 2013b Lam et al., 1991; Damm et al., 1992 Coustan et al., 1993; Vambergue et al., 2008	Some studies proved family history had an independent effect on devolving T2DM, but several studies examining family history have found no effect. Therefore, family history does not appear to play a major independent role in predicting future risk of diabetes.
Genetic risk factors	Kwak et al., 2013a Kwak et al., 2013b	A total of 21 genetic variants associated with T2DM were genotyped among 634 Korean women with a history of GDM, and genetic variants near CDKN2A/2B and HHEX were associated with early conversion ( $\leq 8$ weeks postpartum) to postpartum T2DM, and those near CDKAL1 were associated with late conversion ( $> 1$ year postpartum). A genetic risk score (GRS) consisting of 48 genetic variants was associated with T2DM. Adding GRS to clinical models significantly increased the predictability of postpartum T2DM among 395 Korean women with a history of GDM (net reclassification index 0.430, $p = 7.0 \times 10^{-5}$ ).
Breastfeeding	Ziegler et al., 2012 Stuebe et al., 2005	The results found that breastfeeding $>3$ months reduced postpartum T2DM by 46 %. The Nurses' Health Study reported that each additional year of breastfeeding reduced the risk of T2DM by 15% even in mothers without GDM. Thus, breastfeeding should be strongly encouraged in women with a previous GDM diagnosis to promote both maternal and offspring health.