Review

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Review

Recognizing and Mitigating Long-Term Cardiometabolic Risks Following Gestational Diabetes

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Abstract

Gestational diabetes (GDM) is associated with long term risk of diabetes and cardiovascular disease. Offspring of mothers with GDM also have elevated cardiometabolic risk in their lifetime. This article reviews risk factors that may predict progression to Type 2 or Type 1 diabetes after history of GDM, recurrence risk of GDM in a future pregnancy and discusses what evidence is available for risk mitigation in reducing long term adverse health outcomes in both mothers with GDM and their children.

Keywords: gestational diabetes; progression to diabetes; cardiometabolic risk; risk factors; risk mitigation

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1. Introduction:

Gestational diabetes (GDM) is known to be associated with increased long-term risk of both Type 2 diabetes (T2DM) [1] and Type 1 diabetes (T1D) [2]. The metabolic derangements in GDM have been shown to affect long term health outcomes in the offspring resulting in increased lifetime risk of diabetes [3] and cardiovascular disease [4] in the offspring.

Early recognition of risk factors that may be associated with progression to Type 2 or Type 1 diabetes after GDM may help in facilitating timely interventions to prevent future diabetes. In addition, appropriate glycemic management during pregnancy affected by GDM and in early childhood may further help mitigate the long term cardiometabolic risks. This article aims to review current evidence regarding risk factors that suggest increased propensity for long term dysglycemia, and cardiovascular morbidity in patients and their offspring, discuss prevention strategies for development of recurrent GDM, progression from GDM to diabetes and risk reduction in offspring.

2. Risk Factors for Development of Type 2 Diabetes After GDM:

As compared with women without a history of GDM, women with a history of GDM have a nearly 10-fold increased risk for the development of T2DM [5]. While the incidence appears to be higher in the first 5-10 years postpartum, the cumulative incidence was found to be up to 70% in studies with follow-up as long as 28 years [6]. Factors associated with greater risk are listed in in Table 1 and include elevated BMI, family history of DM, and nonwhite race/ethnicity among others. In a study with 5.5 years of postpartum follow up after GDM pregnancy, risk factors for abnormal glucose tolerance postpartum included polycystic ovarian syndrome and fasting glucose ≥5.4 mmol/L (97 mg/dl) and 2-h glucose ≥9.3 mmol/L (168 mg/dl) on the screening oral glucose tolerance test taken during pregnancy [7]. Postpartum weight gain, independent of BMI before and during pregnancy, is also associated with diabetes risk. Women with obesity at baseline who gained ≥5 kg after having GDM had a 43-times higher risk of developing T2DM compared with women with normal weight at baseline and who gained <5 kg after having GDM [8]. Interestingly, factors which were NOT associated with the development of T2DM were parity, birth weight, macrosomia, and gestational weight gain. Repeated episodes of GDM increase the risk of developing T2DM postpartum as noted in an observational cohort study of multiparous women with where incidence of diabetes diagnosis at 6 months postpartum was 4 times higher in those with recurrent GDM compared to those with first episode of GDM [9].

Exciting research in the field of metabolomics is ongoing that can help develop predictive models to identify which patients with GDM will ultimately develop T2DM. Such models could help guide further inquiries into what interventions might be the most useful to prevent the development of T2DM. In an effort to characterize metabolic changes associated with gestational diabetes, one study found postpartum elevations in branched-chain amino acids (leucine, isoleucine, and valine) in patients with gestational diabetes during pregnancy compared to normoglycemic pregnancies [10]. Another study looking at serum medium chain acylcarnitines [(M)-acylCs], among women with GDM and in early stages of T2DM onset found that that an elevation in circulating M-acylCs is associated with GDM and early stages of T2D onset and that this elevation directly impairs β-cell function [11]. Furthermore, 3 specific lipids have been found to be positively associated with development of T2DM in women who have had GDM. These include cholesteryl ester 20:4, alkenylphosphatidylethanolamine PE (P-36:2), and phosphatidylserine PS 38:4 [12]. Yet another promising potential predictor of the development of T2DM after GDM involves a preliminary genetic study which found the TCF7L2 rs7903146 and FTO rs8050136 polymorphisms predict diabetes after GDM [13].

The population of patients with a history of GDM who eventually develop diabetes is heterogeneous. For instance, Khan et al. identified 3 different clusters of patients at 6-9 weeks postpartum in a nondiabetic state after GDM, who ultimately developed diabetes over a 12-year period [14]. One cluster had beta cell dysfunction, another had insulin-resistance, and a third had mixed features. Understanding the different populations may help to characterize the risk for development of T2DM but also to personalize successful intervention measures.

Table 1. Risk for Development of Type 2DM after GDM.

Risk Factor	Risk
Elevated BMI	2 fold greater risk#
Family history of DM	70% greater risk*
Nonwhite race/ethnicity	50% greater risk*
Postpartum weight gain [15]	43 times greater risk¥,∆
Higher fasting glucose	>3 fold greater risk*
Insulin requirement	3.7 fold greater risk*
Elevated A1c	2.6 fold greater risk*
Advanced maternal age	20% greater risk*

Rayanagoudar et al. Diabetologica. 2016;59(7):1403-11. * Ingram et al.Aust N Z J Obstet Gynaecol. 2017 Jun;57(3):272-279. ¥ Bernstein J et al. Prev Med 2018 August;113:1-6. ∆ Chorell E et al. Metabolism Clinical and Experimental 72(2017) 27-36.

3. Risk Factors for Development of Type 1 Diabetes After GDM:

Multiple studies have shown an increase in diagnosis of Type 1 diabetes in adulthood, after GDM pregnancy. In a Finnish cohort study [16] of 391 GDM patients and age-and parity- matched controls who were followed for 23 years, Type 1 diabetes developed in 5.7% during the first 7 years after GDM pregnancy. In this cohort, risk factors for future development of type 1 diabetes were identified as needed for insulin treatment in pregnancy and 2-hour value in OGTT of >11.9mmol/dl (214 mg/dl).

This same group subsequently published data regarding predictive value of autoantibodies for type 1 (T1DM) after gestational diabetes (GDM) in their 23-year follow-up study [17]. Four

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autoantibodies were analyzed in first-trimester blood samples: islet cell autoantibodies (ICAs), glutamic acid decarboxylase autoantibodies (GADAs), insulin autoantibodies (IAAs) and insulinoma-associated antigen-2 autoantibodies (IA-2As). Detection of ICA, GADA and/or IA-2A autoantibodies decreased T1DM-free survival time and time to diagnosis. All subjects with three positive autoantibodies developed T1DM within seven years from the GDM pregnancy. Development of T2DM after GDM occurred independent of autoantibody positivity.

An earlier study investigating the predictive value of autoantibody markers in gestational diabetes pregnancy with 7-year follow up, found the risk of type 1 diabetes was 3% by 9 months and 7% within 2 years after a GDM pregnancy, in their cohort of 437 patients. By 2 years postpartum, 29% of patients positive for at least one antibody developed type 1 diabetes, compared with 2% of antibody-negative patients ($P < 0.0001$). The risk for type 1 diabetes increased with the number of positive antibodies: from 17% for one antibody, to 61% for two antibodies, and to 84% for 3 antibodies. Risk of progression to type 1 diabetes postpartum was also associated with the status of parity. Women with one or more pregnancies before the index pregnancy had a higher risk for type 1 diabetes 2 years after delivery than women having their first (i.e., index) pregnancy (14.7% vs 5%, $P < 0.006$)[18].

Despite this association, most major US guidelines, including those from the American Diabetes Association and American College of Obstetrics and Gynecology, do not recommend universal screening for diabetes related autoantibodies in patients with GDM. However, selective screening can be considered in patients who have a cluster of high-risk clinical features: young age, normal to low pre-pregnancy BMI, requiring insulin therapy early in pregnancy or have a family history of autoimmune disorders [19].

4. Cardiovascular and Other Morbidity After GDM:

In addition to the increased risk for the development of diabetes, people with a history of gestational diabetes have an increased risk for development of other diseases associated with cardiovascular disease and obesity such as hypertension, dyslipidemia, ischemic heart disease [20], vascular dysfunction, chronic inflammation [21], metabolic associated fatty liver disease [22], and chronic kidney disease [23]. A study of 67,356 of women with GDM and 1.003.311 without GDM followed for up to 25.5 year after delivery found GDM was associated with a higher risk of ischemic heart disease (HR 1.23, 95% CI 1.12-1.36), myocardial infarction (HR 2.14, 95% CI 1.15-2.47), coronary angioplasty (HR 2.23, 95% CI 1.87-2.65), and coronary artery bypass graft (HR 3.16, 95% 2.24-4.47). The increased risk of cardiovascular disease is not necessarily dependent on the development of Type 2 DM [24] In a pooled analysis of 9 studies of 5,390,591 women, women with GDM had a 2-fold higher risk of cardiovascular event (RR 1.98 (95% confidence interval 1.57-2.50). Among the women with GDM who did not develop type 2 diabetes there was a 56% increased risk of future cardiovascular events (RR 1.56, 95% CI 1.04-2.32). The authors concluded that even without progressing to type 2DM, women with GDM are at increased risk for cardiovascular disease.

5. Intergenerational Effect of GDM

Hyperglycemia during pregnancy is associated with multiple short- and long-term outcomes in the offspring. In the short term, GDM is associated with increased risk of stillbirth, macrosomia, and shoulder dystocia due to the large size of fetus, and neonatal hyperbilirubinemia. Several metabolic alterations have been proposed to lead to these complications. Maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia that then stimulates fetal metabolism, resulting in increased oxygen consumption. In addition, increased glycosylation of hemoglobin in maternal circulation from elevated glucose levels can alter the structure and function of hemoglobin, leading to an increase in oxygen affinity and decreased oxygen delivery to fetus. These alterations result in a metabolically induced oxygen deficit in the fetus of varying degrees and duration, that may result in the risk of

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birth asphyxia and stillbirth [25]. Fetal hypoxia is also thought to induce increased erythropoietin production, leading to polycythemia in the fetus and eventual hyperbilirubinemia in the neonate [26].

Large size at birth is a consequence of fetal hyperinsulinemia and subsequent increased fetal production of insulin-like growth factor-1 [27]. Adiponectin may also play a direct role in fetal macrosomia in GDM. Adiponectin impairs the transport of amino acids across the placenta, limiting fetal growth and reducing the risk of fetal macrosomia. An inverse correlation between adiponectin levels and infant birth size has been demonstrated in several studies [28–31]. The production of this adipokine is reduced in mothers with gestational diabetes [32].

Infants born large for gestational age (LGA) after exposure to GDM in utero, are at an increased risk of having excess fat mass, increased body fat, and less fat-free mass (muscle, bone, etc.) at birth, compared with LGA infants not exposed to GDM [33]. The increase in body fat mass has been noted even in appropriate for gestational age (AGA) infants born to GDM mothers [34]. These differences in adiposity are known to persist into childhood as overweight and obesity [35,36]. The link between childhood obesity and long-term health outcomes including early onset of diabetes [37] and cardiovascular disease [38], is well established. In addition, there is mounting evidence for an increase in diabetes and cardiovascular risk in offspring of GDM mothers irrespective of BMI. The Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS), which included over 4000 children aged 10-14 whose mothers had a 75-g oral glucose tolerance test (OGTT) at ~28 weeks of gestation, showed that offspring of mothers with GDM had higher prevalence of impaired glucose tolerance and reduced insulin sensitivity compared with children of mothers without GDM [39]. Notably, adjustments for maternal BMI, child BMI, and family history of diabetes did not alter the association. Similarly, Maternal GDM has been shown to be associated with higher blood pressure [40] and abnormal lipid profile [41] in the offspring. In a meta-analysis of 5 studies exploring the link between gestational diabetes and subsequent development of cardiovascular disease in the offspring, a positive correlation was noted between GDM and early onset of cardiovascular disease including stroke, ischemic heart disease, and heart failure [42].

6. Risk Mitigation After GDM

6.1. Reducing Future Risk of Type 2 Diabetes:

Both lifestyle and pharmacologic interventions have been investigated and showed benefit in reducing future risk of Type 2 diabetes. In a systematic review of RCTs of postpartum lifestyle interventions to prevent type 2 diabetes in women with prior GDM, a significant decrease in insulin resistance-related measures and weight-related measures was noted in the intervention group compared with the comparison group [43].

Breastfeeding has been shown to decrease the risk for development of T2DM after GDM. A prospective cohort study of 1010 ethnically diverse women with history of GDM were followed for 2 years after pregnancy with lactation measures for the development of diabetes. Higher lactation intensity and duration of lactation were independently associated with lower incidences of DM after GDM [44]. Breastfeeding also reduced future cardiometabolic risk in patients with prior GDM [45]. Stuebe found that a lifetime breastfeeding duration of over 23 months was associated with a 0.77 (95% confidence interval 0.62-0.94) multi-variate adjusted hazard ratio of incident myocardial infarction as compared with never having breastfed [46].

Counseling and assisting people who have had GDM on weight management is important for health improvement. In the Diabetes and Women's Health Study, women with obesity at baseline who gain over 5 kg after GDM had a 43 times higher risk of developing T2DM as compared with normal weight women who gained less than 5kg [47].

Several pharmacologic interventions have been investigated in the prevention of progression to diabetes after GDM, with most robust data available for metformin. Intensive lifestyle modification and metformin reduced the progression to T2DM in women with a history of GDM by 35% and 40% respectively in The Diabetes Prevention Program Outcomes Study (DPPOS) as compared with

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placebo [48]. A 2024 meta-analysis of 26 studies consisting of a total of 8624 participants evaluating pharmacologic and lifestyle interventions found pharmacologic interventions to be associated with reduced risk of T2DM at 0.80 (95% confidence interval 0.64-1.0) [49]. The medications studied included metformin alone or in combination with sitagliptin, liraglutide or dapagliflozin. In the the PIPOD [50] (Pioglitazone In Prevention of Diabetes) and TRIPOD [51] (Troglitazone In Prevention Of Diabetes) studies, a significant reduction in risk of progression to diabetes, with enhanced insulin sensitivity and preserved pancreatic beta-cell function, was noted in Hispanic women with prior gestational diabetes. Troglitazone was withdrawn from clinical use in 2000 due to concern for hepatotoxicity.

Further study is needed to determine optimal interventions to prevent the development of Type 2DM in women with a history of GDM. One review of interventions for the prevention of diabetes in women after GDM, found that women reported a lack of postpartum care and demonstrated low knowledge of risk factors for developing Type 2 DM [52], highlighting the importance of education and follow up in this population. It is important to note that ALL patients with a history of GDM need monitoring for the development of future DM though it may be tempting to focus on only those with the most severe GDM. Bernstein, et al. found that despite an increase relative risk for the development of T2DM in higher-severity GDM group, the actual number of cases who developed T2DM from the lower-severity group was higher than that from the higher-severity group, such that a focus only on the higher-severity group would miss the majority of cases with early onset T2DM [53].

6.2. Reducing Future Risk Type 1 Diabetes:

An exhaustive review of the various interventions and trials for primary, secondary, and tertiary prevention of Type1Diabetes is beyond the scope of this article. No trials are studying interventions specifically for prevention of Type 1 diabetes after GDM pregnancy. Universal screening with diabetes antibodies is not recommended in the GDM population. However, if an individual has been identified as having diabetes related autoantibodies, a consensus guidance [54] recommends periodic medical monitoring, including regular assessments of glucose levels, regular education about symptoms of diabetes and DKA, psychosocial support and offering opportunities for participation in trials for prevention of overt Type 1 diabetes.

6.3. Reducing Risk of Recurrent GDM in a Future Pregnancy

GDM has a high likelihood of recurrence in a subsequent pregnancy. Preconception counseling is fundamental to optimizing pregnancy in general but essential in women with a history of GDM in a previous pregnancy. It is critical to ensure patients have not developed overt diabetes in the interim from previous pregnancy since controlling A1c at the time of conception prevents congenital anomalies, and patients should be aware of the need for intensive glucose monitoring and treatment required throughout pregnancy. Guidelines recommend monitoring A1c at least every 3 years after a pregnancy with GDM but it is reasonable to check yearly in women with multiple risk factors. Preconception counseling is also a time to discuss the importance of lifestyle modification both before and during pregnancy.

A systematic review and meta-analysis of 31 studies identified risk factors for GDM recurrences as follows: maternal age (especially over 40 years), ethnicity, parity, family history of diabetes, history of macrosomia, insulin treatment during index pregnancy, overweight or obesity before the index pregnancy, more abnormal oral glucose tolerance test values at the index pregnancy, weight gain between pregnancies, overweight or obesity prior to the subsequent pregnancy, weight gain before the oral glucose tolerance test in subsequent pregnancy, and fasting blood glucose levels in the early stages of the subsequent pregnancy [55]. Regardless of pre-pregnancy BMI, weight changes in-between pregnancies can affect GDM recurrence risk. A population-based cohort study of 2763 women in the Swedish and Norwegian Medical Birth Registries from 1992-2014 found that compared with women with stable weight between pregnancies, women with weight loss >2 BMI units had a

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20% lower risk of GDM recurrence [56]. Women who gained >4 BMI units had a 42% increased risk of GDM recurrence.

Wang, et al. did a systematic review and meta-analysis [57] of 30,871 pregnant women in randomized control trials of various diets including the Mediterranean Diet and Dietary Approaches to Stop Hypertension (DASH). They found a 15-38% reduced relative risk of GDM. The same study showed that compared to no physical activity at all, any pre-pregnancy physical activity was associated with 30% reduced odds of GDM and early pregnancy physical activity was associated with a 21% reduction.

Breastfeeding also may have benefits in reducing the risk of recurrent GDM. In a retrospective cohort study of 229 women with prior GDM, the group who breastfed exclusively for > 1 month, was compared to a control group of women who either did not breastfeed or added formula at < 1 month postpartum. In the study group only 34.5% of women developed GDM in a subsequent pregnancy versus 45.6% in the control group[58].

6.4. Reducing Cardiometabolic Risk in Offspring

Maternal hyperglycemia and resulting alterations in umbilical–placental circulation and the other direct consequences such as fetal hyperglycemia, hyperinsulinemia and hypoxia have been implicated in development of endothelial dysfunction, insulin resistance, oxidative stress, inflammation, which collectively contribute to the structural and functional abnormalities of the cardiovascular system [59] in the offspring.

The Hyperglycemia and Adverse Pregnancy outcomes (HAPO) study [60] was a landmark study that demonstrated a strong linear association between higher maternal blood glucose levels (measured fasting, 1 hour and 2 hour postprandial) and risks for adverse pregnancy outcomes, macrosomia and newborn hyperinsulinemia. HAPO data helped establish diagnostic thresholds at which the odds for birth weight > 90th percentile, cord C-Peptide > 90th percentile and percent body fat > 90th percentile reached 1.75 times the estimated odds of these outcomes at mean glucose values [61].

In the large HAPO cohort of >25,000 women and an average BMI >27, the mean fasting, 1-hour, and 2-hour plasma glucose levels were 80.9 mg per deciliter (4.5 mmol per liter), 134.1 mg per deciliter (7.4 mmol per liter), and 111.0 mg per deciliter (6.2 mmol per liter), respectively. These values, in part, helped develop the guidelines for tight glycemic control in pregnancy. The ADA [62] and ACOG [63] recommend that fasting blood glucose values be below 95 mg/dL and postprandial blood glucose values be below 140 mg/dL at 1 hour or 120 mg/dL at 2 hours to reduce the risk of macrosomia. However, glucose concentrations during normal pregnancy in the absence of obesity are lower than the current suggested normal therapeutic targets [64]. The current therapeutic target thresholds for glucose are 2 SD above mean post meal values of glucose in normal pregnancies. The authors in this paper suggest lower targets for glycemic control, 122 and 110 mg/dL at 1 and 2 h postprandially, in the hopes of minimizing both LGA and small for gestational age (SGA) infants (infants <10th percentile for gestational age), by mimicking patterns of normal glycemia in pregnancy, in women without obesity.

However, tighter glycemic control in women with GDM has not shown lower LGA rates in either prospective [65] or retrospective trials [66], albeit improvements in rates of perinatal death, birth trauma, shoulder dystocia, and neonatal hypoglycemia were noted. This might suggest that achieving lower glycemic targets has the potential of affecting maternal and fetal pathophysiology that has been implicated in the development of long term cardiometabolic effects in the offspring.

7. Conclusions

There is ample evidence that development of gestational diabetes during pregnancy has far reaching consequences for future health of both mothers and offspring. Early recognition of risk factors, and timely intervention in terms of managing postpartum weight gain, breastfeeding, lifestyle and pharmacologic interventions, and appropriate screening can help mitigate the long-term

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risk cardiometabolic derangements in the future in affected individuals. Improvement in glycemic control during GDM pregnancy has decreased perinatal mortality and morbidity, however long-term data for future health of offspring with tighter versus less tight glucose targets is lacking. Effective interventions and health education for women with gestational diabetes, at a time when they are highly motivated to make lasting lifestyle changes, can significantly impact future population health.

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