2018

Recurrent gestational diabetes mellitus: the effect of a lifestyle intervention

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

RECURRENT GESTATIONAL DIABETES MELLITUS: THE EFFECT OF A LIFESTYLE INTERVENTION

by

AUDREY CROCKER

B.A., Occidental College, 2012

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2018

Approved by

First Reader _____

Aviva Lee-Parritz, M.D.
Associate Professor of Medicine

Second Reader _____

John Weinstein, Ph.D.
Assistant Professor of Medicine

ACKNOWLEDGMENTS

I would like to thank my thesis advisor, Dr. Lee-Parritz, and Myrita Craig, MS HPE, DrPH candidate, for the knowledge, expertise, and guidance they have provided throughout this process. I would also like to thank my family, friends, and fellow classmates for their constant love and support.

RECURRENT GESTATIONAL DIABETES MELLITUS: THE EFFECT OF A LIFESTYLE INTERVENTION

AUDREY CROCKER

ABSTRACT

Gestational diabetes mellitus (GDM) is the most common complication of pregnancy that affects 1-14% of all pregnancies. If not properly managed, GDM can be a devastating disease, leading to birth complications such as shoulder dystocia and neonatal hypoglycemia. GDM has many long-term implications as well, such as increased risk of obesity and type 2 diabetes mellitus (T2DM) in both the mother and the offspring. Additionally, women with a history of GDM are at increased risk of recurrent GDM in a subsequent pregnancy and multiple episodes of GDM further increases a woman's risk for these short and long-term consequences. For this reason, a diagnosis of GDM provides an opportunity to target GDM and T2DM risk factors to prevent recurrence of GDM and halt the diabetes disease course. Research has shown that diet and physical activity interventions provided after a pregnancy complicated by GDM can delay or prevent the onset of T2DM yet literature on prevention of recurrent GDM is lacking.

This thesis will propose a new intervention applied to the inter-pregnancy interval (IPI), designed to reduce incidence of recurrent GDM. The study will examine the effect of a diet and physical activity intervention for women with a recent pregnancy complicated by GDM on recurrence in a subsequent pregnancy and weight gain in the IPI. We hypothesize that our intervention will reduce incidence of GDM recurrence compared to the control group and that women in the intervention group will lose more

weight compared to women in the control group. The results of this study will provide a background for further study on the prevention of GDM recurrence with the hope that prevention of recurrent GDM will prevent the short and long-term sequela of GDM.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ACOG ..... American College of Obstetrics and Gynecologists

ADA ..... American Diabetes Association

BMI ..... Body Mass Index

BU ..... Boston University

C&C ..... Carpenter and Coustan

Cesarean section ..... C-section

DPP ..... Diabetes Prevention Program

GDM ..... Gestational diabetes mellitus

HAPO ..... Hyperglycemia and Adverse Pregnancy Outcomes

IADPSG ..... International Association of Diabetes in Pregnancy Study Groups

IPI ..... Inter-pregnancy Interval

NDDG ..... National Diabetes Data Group

NPH ..... Neutral Protamine Hagedorn

OGTT ..... Oral glucose tolerance test

PIPOD ..... Pioglitazone in Prevention of Diabetes

T2DM ..... Type 2 diabetes mellitus

TRIPOD ..... Troglitazone in the Prevention of Diabetes

INTRODUCTION

Background

As one of the most common complications of pregnancy in the United States, the diagnosis, management, and prevention of gestational diabetes mellitus (GDM) is a priority for affected individuals, healthcare providers and the healthcare system in the United States. The prevalence of GDM varies between 1-14% depending on the population studied and the diagnostic criteria used making it the most common complication of pregnancy in the United States.[1]

GDM refers to any degree of glucose intolerance with the onset or first recognition during pregnancy and is a result of the acquired insulin resistance of pregnancy paired with underlying ß-cell dysfunction in the pancreas.[2] In these women, the pancreas is unable to secrete adequate amounts of insulin to maintain euglycemia during pregnancy, leading to hyperglycemia and, thus, GDM.[2] There are many long and short-term consequences associated with GDM. These include shoulder dystocia, neonatal hypoglycemia and an elevated risk to both the mother and fetus of becoming overweight or obese and of developing type 2 diabetes mellitus (T2DM).[3,4,5,]

The prevalence of GDM tends to mirror the prevalence of T2DM in a given population due to overlapping pathophysiology and risk factors. Therefore, due to increased prevalence of risk factors such as overweight and obesity, rates of T2DM as well as rates of GDM are increasing in the United States. A diagnosis of GDM is an early indicator of an increased risk of T2DM, providing an early opportunity to target risk factors to prevent the short-term consequences of a recurrent episode of GDM and the

long-term consequences of recurrent GDM such as increased risk of T2DM.[6,7,8]

Due to the significant adverse consequences of GDM, adequate screening and diagnosis is critical. While there are many screening and diagnostic criteria, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the American Diabetes Association (ADA) maintain the most accepted guidelines. The IADPSG recommends screening all women at the first prenatal visit while the ADA only recommends screening with risk factors present at the first prenatal visit.[3,9]

First line treatment of GDM includes diet and exercise. Second line treatment includes pharmacologic treatment with oral hypoglycemic agents such as metformin and glyburide or insulin therapy.[3] Management of GDM using any of these methods is reliant on home glucose monitoring.[10]

Understanding the pathophysiology, prevalence, and risk factors for GDM are integral to prevention of GDM. Common risk factors for GDM include older age, overweight or obesity, high parity, excessive weight gain in pregnancy, and a prior history of GDM.[2,11, 12] By targeting the modifiable risk factors, the diabetes disease course may be delayed or prevented.

Statement of the Problem

Women with a history of GDM are at increased risk of recurrent GDM.[12] With each episode of GDM, a woman's risk of adverse short term outcomes and of T2DM increases.[13,14,15] Therefore, preventing recurrence of GDM by targeting risk factors in the inter-pregnancy interval (IPI), the time between two consecutive live births minus the

second infant's gestational age, can potentially decrease these adverse consequences.[16] There are modifiable and non-modifiable risk factors in the IPI that affect a woman's risk of recurrent GDM. Modifiable risk factors include the length of the IPI and weight gain during the IPI.[12] Existing research examining the effect of the length of the IPI on incidence of GDM recurrence is contradictory, however studies have consistently shown that weight gain during the IPI increases a woman's risk of recurrent GDM.[17,18] Therefore, weight gain during the IPI is a risk factor that may be effectively targeted in order to prevent GDM recurrence.

Previous studies have shown that lifestyle interventions targeting weight loss during the subsequent pregnancy after a GDM index pregnancy decrease incidence of recurrent GDM.[19] Additionally, the literature demonstrates that diet and exercise interventions decrease incidence of T2DM after a GDM pregnancy. However, there are no studies that have examined a lifestyle intervention targeting weight loss during the IPI.

Because diet and exercise interventions have been shown to be effective under other circumstances, this study targets weight gain between pregnancies with a diet and exercise intervention after a pregnancy complicated by GDM. The recurrence of GDM will be examined in order to determine if lifestyle intervention decreases recurrence of GDM. The prevention of recurrent GDM is important in preventing adverse outcomes of a GDM pregnancy and ultimately decreasing the risk of developing T2DM.

Hypothesis

A diet and exercise intervention provided to overweight women for one year immediately following a pregnancy complicated by GDM will decrease the incidence of recurrent GDM in a subsequent pregnancy.

Objectives and specific aims

Due to the immense health implications of GDM, prevention of recurrent GDM is integral in improving health outcomes for women with a history of GDM. A diagnosis of GDM offers a unique opportunity to identify women at high risk for recurrent GDM or at high risk for future T2DM. Therefore, interventions to modify risk factors are integral in modifying the disease course. This study will seek to provide a lifestyle intervention in the IPI in overweight women with a recent pregnancy complicated by GDM in order to prevent recurrence of GDM in a subsequent pregnancy. There are three specific aims of this study:

- To determine if incidence of recurrent GDM can be decreased with a lifestyle intervention in overweight women.
- To determine the effectiveness of a lifestyle intervention on weight loss in the IPI.
- To determine if weight lost or weight gained during the IPI is associated with recurrent GDM.

REVIEW OF THE LITERATURE

Overview of gestational diabetes mellitus

GDM is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy.[20] This definition of GDM includes women who may have had unrecognized or undiagnosed glucose intolerance before their pregnancy and those with an onset during pregnancy which continued after pregnancy.[1] GDM is the most common complication of pregnancy in the United States with a prevalence between 1-14% depending on the population studied and the diagnostic criteria used.[1]

The implications of gestational diabetes are immense with short and long-term adverse effects for both the mother and the fetus. Short term consequences for the fetus include fetal macrosomia (birthweight > 4000g) and neonatal hypoglycemia.[5,21] Because glucose easily crosses the placenta, maternal hyperglycemia leads directly to fetal hyperglycemia. The pancreas of the fetus then responds by increasing its own insulin production and release. The resulting fetal hyperinsulinemia causes the majority of adverse fetal consequences of GDM.[3] Fetal macrosomia is a direct result of GDM. The hyperinsulinemic state of the fetus promotes excessive and disproportionate growth including excessive subcutaneous fat and broad shoulders, leading to should dystocia,[4] a complication of labor where the anterior shoulder of the infant is unable to pass below the pubic symphysis after delivery of the head. [4,22] The delivery of an infant with shoulder dystocia can often result in birth trauma, such as clavicle fracture or nerve injury to the brachial plexus, which can lead to long term complications such as Erb's palsy.[3]

Hypoglycemia in the neonatal period is another adverse effect of fetal

hyperinsulinemia. After birth, the infant is no longer exposed to the maternal source of glucose yet still has elevated circulating insulin levels, leading to hypoglycemia in the early neonatal period.[3,5] Neonatal hypoglycemia must be addressed rapidly to minimize the risk of serious adverse consequences such as seizures, brain injury, and long term neurodevelopmental impairment.[3,23] Other adverse outcomes include hyperbilirubinemia and hypocalcemia, both of which may require close monitoring in the NICU.[3] Additionally, the hyperglycemic intrauterine environment predisposes the fetus to early onset diabetes, in adolescence or early adulthood, even in populations with a relatively low incidence of T2DM.[24,25] T2DM is a metabolic disease that is characterized by dysfunction in insulin secretion, insulin action, or both. This dysfunction leads to chronic insulin resistance and resulting chronic hyperglycemia. Typically, T2DM has an onset in adulthood however, with increasing prevalence of risk factors, early onset T2DM is becoming more common.[26]

The maternal consequences of GDM include preeclampsia and cesarean section in the short term and increased risk of T2DM in the long term. If GDM remains untreated, mothers are at a higher risk of preeclampsia and cesarean section.[27,5] While GDM itself is not an indication for cesarean section, the complications associated with GDM, such as preeclampsia and macrosomia, may be an indication for cesarean section (c-section). If the mother is diagnosed with preeclampsia that necessitates early delivery and the mother's cervix has not sufficiently ripened for delivery, a c-section is indicated. C-section is indicated for macrosomia if the estimated fetal weight exceeds 4500 g in order to prevent shoulder dystocia and birth trauma during vaginal delivery.[3]

The pathophysiology of GDM originates from normal acquired insulin resistance of pregnancy. Throughout pregnancy, the placenta stimulates changes in maternal insulin resistance and metabolism of carbohydrates, lipids, and amino acids in order to provide a continuous and adequate supply of nutrients to the fetus for growth.[2] Insulin resistance is achieved with pregnancy-induced factors, such as placental growth hormone and tumor necrosis factor-alpha which stimulate a reduction in peripheral insulin uptake at the level of the skeletal muscle, a common site for whole-body glucose storage.[28] This leads to the acquired insulin resistance of late pregnancy and a more robust glucose supply to the fetus. Insulin resistance increases until the 24th week of pregnancy when elevated maternal glucose levels plateau and are maintained until delivery. Typically, the maternal pancreas is able to increase secretion of insulin to keep up with increased insulin resistance and maintain euglycemia.[2] However, in some cases the pancreas is unable to secrete adequate amounts of insulin, leading to maternal hyperglycemia and GDM.[2] The acquired insulin resistance of pregnancy typically returns to normal soon after delivery and resolves completely within one year.[28] All women with GDM require post-partum glucose testing to determine if blood glucose levels have returned to baseline or if the patient has persistent impaired glucose tolerance or T2DM.[29]

In order to manage the potential adverse outcomes of GDM, a mother's blood glucose must be controlled throughout her pregnancy. In all women with GDM, self-monitoring of blood glucose is recommended with the following goals based on American Obstetrics and Gynecology Guidelines (ACOG) — Fasting value: <95 mg/dL, 1 hour postprandial: <120-130 mg/dL, 2 hour postprandial: <120 mg/dL.[10] When a

woman presents with GDM, first line treatment to achieve euglycemia includes diet and exercise. Ideally, patients will meet with registered dieticians who can help patients to control blood glucose levels and manage appropriate weight gain during pregnancy.[3] If blood glucose levels remain uncontrolled with diet and exercise, pharmacologic treatment, such as insulin or oral hypoglycemic agents are used. Although oral hypoglycemic agents such as glyburide and metformin are commonly used as first-line pharmacologic therapy, they have not been approved by the U.S. Food and Drug Administration for GDM.[3,30] Glyburide works by stimulating insulin production and release from the pancreas and is effective in lowering HgbA1c concentrations, decreasing rates of macrosomia, and decreasing rates of neonatal hypoglycemia.[3] Metformin is an insulin sensitizer in the liver and in the periphery and has been shown to be effective in decreasing adverse pregnancy outcomes.[3] GDM can also be effectively managed with a combination of intermediate acting insulin preparations, such as Neutral Protamine Hagedorn (NPH), and short-acting insulin analogs, such as Insulin Lispro and Insulin Aspart.[3]

There are multiple proposed screening and diagnostic guidelines for GDM globally, leading to variable rates of GDM based on the diagnostic criteria used.[31] O'Sullivan and Mahan developed the first screening and diagnostic guidelines for GDM in the 1960s, based on a 3-hour 100-gram oral glucose tolerance test (OGTT).[32] The thresholds developed from the Sullivan criteria were based on the blood glucose thresholds that predicted subsequent diabetes in the mother after her pregnancy.[32] These thresholds were based on venous blood samples and were subsequently altered by the

National Diabetes Data Group (NDDG) and Carpenter and Coustan to account for laboratories' use of plasma measurements compared to whole blood measurements.[3] The American Diabetes Association (ADA) endorsed the Carpenter and Coustan (C&C) criteria due to improved accuracy in determining glucose levels from plasma. The C&C criteria then became the recommended diagnostic threshold validated by ACOG. Because of the known adverse perinatal outcomes of GDM, it became clear that diagnostic criteria must be able to predict adverse pregnancy outcomes. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed a direct relationship between the GTT values at 24-32 weeks gestation and adverse pregnancy outcomes, particularly fetal hypoglycemia and macrosomia.[5] Based on data from the HAPO study, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) developed thresholds for the use of a 75-g 2-h OGTT for diagnosis (Table 1). Due to the lower threshold glucose values, the IADPSG criteria increased the prevalence of GDM nearly two-fold.[33] The IADPSG recommends screening all women at the first prenatal visit with a fasting plasma glucose or a random plasma glucose while the ADA only recommends screening women with risk factors present at the first prenatal visit.[3] In the United States, ACOG recommends women at risk for GDM typically undergo testing as soon as possible in pregnancy, while all other women are universally screened at 24-28 weeks gestation. ACOG recommends a two-step screening approach involving a 50-g glucose challenge test followed by a 100-g 3-h OGTT if results of the initial screen are abnormal. [26,30] Most other countries do not universally screen for GDM and recommend a one-step approach with 75-g 2-h OGTT, fasting plasma glucose, or random plasma glucose.[26,30] Presently,

both the IADPSG and the ADA recommend the 75-g, 2-h OGTT for GDM at 24-28 weeks gestation in those who have not already been diagnosed with GDM.[3, 9] The commonly used screening and diagnostic guidelines for GDM among different groups are presented in Table 1.

Table 1: Commonly used screening and diagnostic criteria for GDM[3]

Time of glucose measurement	**Original values (O' Sullivan and Mahan)[32], venous whole blood**	**NDDG modification (NDDG)[21], plasma**	**C&C modification (Carpenter and Coustan)[34] – ADA criteria**	**IADPSG[33] 2010**	**WHO[31] 2013**
Approach	100-g OGTT	100-g OGTT	100-g OGTT	75-g OGTT	75-g OGTT
Number of abnormal values required for diagnosis	2	2	2	1	1
Fasting mmol/L (mg/dL)	90 (5.00)	105 (5.83)	95 (5.27)	92 (5.1)	126 (≥ 7.0)
1 h mmol/L (mg/dL)	165 (9.16)	190 (10.55)	180 (9.99)	180 (10.0)	-
2 h mmol/L (mg/dL)	143 (7.94)	165 (9.16)	155 (8.60)	153 (8.5)	200 (≥ 11.1)
3 h mmol/L (mg/dL)	127 (7.05)	145 (8.05)	140 (7.77)	-	-

OGTT: oral glucose tolerance test
Adapted from Alfadhli *et al*[31] and Coustan *et al*[3]

When screening a woman for GDM, risk factors for GDM must be closely examined. Risk factors for GDM include older age, overweight or obesity, high parity, excessive weight gain in pregnancy, short stature, polycystic ovarian syndrome, history of diabetes mellitus in first degree relatives, macrosomia in previous and/or index pregnancy, and a past history of poor pregnancy outcomes.[2,11] Because the ADA recommends screening at the first antepartum visit for women with a risk of developing

GDM, the patient must be identified as high, average, or low risk based on her risk factors and screened accordingly as detailed in Table 2.[35]

Table 2: Clinical risk assessment and screening for GDM[35]

Risk category	**Clinical characteristics**	**Recommended screening**
High risk (presence of any is sufficient)	-Marked obesity -Diabetes in first degree relative (s) -Personal history of glucose intolerance -Prior delivery of macrosomic infant -Current glycosuria	Blood glucose screening at initial antepartum visit or as soon as possible thereafter; repeat at 24-28 weeks if not already diagnosed with GDM by that time
Average risk	Fits neither low- nor high-risk profile	Blood glucose screening between 24-28 week gestation
Low risk (all required)	-Age <25 -Low-risk ethnicity -No diabetes in first-degree relatives -Normal prepregnancy weight and pregnancy weight gain -No personal history of abnormal glucose levels -No prior poor obstetrical outcomes	Blood glucose screening not required
Adapted from Buchanan *et al*[35] based on recommendations of the American Diabetes Associations		

Proper screening and diagnostic criteria are important to avert the societal and economic costs of GDM. As discussed above, women with GDM are at an elevated risk of developing T2DM. According to England *et al*,[36] T2DM, a major sequela of GDM, is emerging as a leading cause of death and disability in the United States.[37] Up to 70% of women develop T2DM within the first 10 years after a GDM pregnancy.[7] People with T2DM are at increased risk for developing renal, cardiovascular, and retinal diseases

which poses a significant economic burden, $91.8 billion per year in the United States.[6] For this reason, prevention of T2DM is critical in improving individual and societal health. Because GDM has been shown to increase risk of developing T2DM, a diagnosis of GDM can be used as an early identifiable risk factor for T2DM and an early opportunity to alter the diabetes disease course. Thus, an understanding of the pathophysiology, prevalence, and risk factors for developing T2DM after GDM is important in order to develop interventions that can prevent the GDM to T2DM disease course.

Gestational diabetes mellitus is a risk factor for type 2 diabetes mellitus

GDM increases a woman's risk of developing T2DM later in life due to shared risk factors and pathophysiology. A personal history of GDM has been found to be the most significant risk factor for developing T2DM and women with a history of GDM have a 7 fold risk of developing T2DM.[6,8] A meta-analysis done by Kim *et al.*[7] reported the risk of developing T2DM after GDM increases sharply within the first 5 years postpartum and that women with higher glucose levels during pregnancy were at increased risk for developing T2DM. Additionally, GDM and T2DM share many of the same risk factors including family history of diabetes, increased age, increased BMI, and Asian and black ethnicity.[7] Other risk factors for the development of T2DM after GDM include an elevated pre-pregnancy BMI, insulin requirement during pregnancy, and diagnosis of GDM early in pregnancy.[38,39,40]

GDM and T2DM share two main pathophysiological defects: target cell insulin

resistance and insufficient secretion of insulin from the pancreatic beta cells.[35] Acquired insulin resistance of pregnancy typically occurs by the 24th week of gestation as a method to elevate circulating blood glucose levels and increase glucose supply to the fetus. Typically, a mother's pancreatic beta cells are able to increase insulin production and secretion to maintain euglycemia. However, when the mother's beta cells are unable to produce and secrete sufficient insulin to maintain euglycemia during acquired insulin resistance, maternal hyperglycemia and GDM occurs.[2] Insufficient beta cell function during pregnancy stems from maternal chronic insulin resistance. Thus, women with GDM typically exhibit two form of insulin resistance: the normal acquired insulin resistance of pregnancy in addition to an underlying chronic insulin resistance.[41] Chronic insulin resistance is associated with risk factors such as overweight, obesity, excessive weight gain during pregnancy, PCOS, IGT, or metabolic syndrome.[2] Women with chronic insulin resistance tend to become insulin resistant earlier in pregnancy and are more likely to be remain glucose intolerant post-partum.[41] With the onset of acquired insulin resistance of pregnancy, beta cells, already stressed from chronic insulin resistance, are unable to fulfill the need for increased insulin secretion.[42] The additional secretory demands put on beta cells during pregnancy further depletes the body's beta cell reserve, predisposing women with a history of GDM to developing T2DM in the future.[42]

The risk of developing T2DM after GDM is increasing, reflecting an increasing prevalence of T2DM in women globally.[43] The incidence of overweight and obesity in women of childbearing age is also increasing, putting more women at risk for developing

GDM. Rates of GDM tend to mirror rates of T2DM in a given population; as the prevalence of common risk factors, such as obesity, begin to increase so does the prevalence of GDM and T2DM. Similarly, metabolic syndrome is an indicator of future risk of T2DM. A study by Retnakaran *et al.*[44] found that women with glucose intolerance in pregnancy have an increased risk of developing metabolic syndrome postpartum.[44] Metabolic syndrome is characterized by central obesity, dysglycemia, hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol and increases lifetime risk for T2DM and cardiovascular disease.[45] Therefore, targeting characteristics of metabolic syndrome after GDM, such as obesity, may resolve the metabolic changes after pregnancy, delaying or preventing the onset of T2DM.[44]

Gestational diabetes mellitus recurrence and the inter-pregnancy interval

A recent meta-analysis by Schwartz *et al.*[12] reported a pooled GDM recurrence rate of 48%.[12] Schwartz *et al*. identified risk factors for recurrence of GDM. Multiparous women had a higher recurrence rate (73%) compared to primiparous women (40%). Additionally, ethnicity was a risk factor for GDM recurrence; non-Hispanic whites had a rate of 38% while all other ethnicities had a recurrence rate of 56% Although the meta-analysis found ethnicity to be a significant risk factor, family history of diabetes was not. Thus, the difference in recurrence rate among ethnic groups may not originate from genetic factors but most likely originates from non-genetic factors, such as socioeconomic status, nutrition, lifestyle, and education status. Other risk factors include age, insulin use in previous pregnancy, large for gestational age infant, and hypertension in the first or

second pregnancy.[12,15] Additionally, the risk of recurrent GDM increases with each episode of GDM.[46] As a woman's beta cells are stressed to produce adequate insulin to maintain euglycemia, cellular function is further depleted. Thus, insulin resistance during a subsequent pregnancy after GDM increases risk of recurrent GDM because of the previously impaired beta cell function.[12]

The literature about the effect of a subsequent pregnancy after GDM on the risk of T2DM is contradictory. A study by Peters *et al.*[13] reported that an episode of insulin resistance in a subsequent pregnancy, regardless of whether it was complicated by GDM, progresses beta cell dysfunction and may increase risk of T2DM.[13] However, recent studies have reported that recurrent GDM may increase a lifetime risk of T2DM 2-fold while a subsequent pregnancy without GDM does not increase risk.[14,15] Despite the acquired insulin resistance of pregnancy, a normal pregnancy may not contribute to the depletion of beta cell reserves to the same extent as a GDM pregnancy.[14] In fact, a subsequent pregnancy without GDM may be indicative of a reduced risk of developing T2DM; in a previously identified high-risk population, the outcomes of a subsequent pregnancy can offer an updated risk assessment of future T2DM. [44] Because studies have shown that a subsequent pregnancy that is not complicated by GDM may be protective against T2DM, prevention of recurrent GDM is key in reducing risk of T2DM.

Therefore, the time between pregnancies, or the inter-pregnancy interval (IPI), may be an integral time to target modifiable risk factors in the prevention of recurrent GDM. Modifiable risk factors of GDM recurrence include the length of the IPI and weight gain between pregnancies.[12]

The association between the length of the IPI and risk of GDM recurrence is unclear. Two studies have been completed that found that a shorter IPI is a risk factor for recurrent GDM[17,47] and three studies found that a longer IPI is a risk factor for recurrent GDM.[16,47,48] With shorter IPIs, women who become pregnant soon after a pregnancy complicated by GDM are less likely to have lost excess weight gained during their pregnancy which could increase their risk of GDM.[17] This suggests that rather than length of IPI, risk of GDM may be dependent on weight gain or loss between pregnancies. The studies supporting short IPI as a risk factor were limited by small sample sizes (N=78 for Major *et al.* and N=32 for Nohira *et al.*). Additionally, the study by Nohira *et al.* did not include multivariate analysis and included only women with diet-treated GDM. The studies supporting longer IPI as a risk factor[16,49,48] include large sample sizes and multivariate analysis to account for all variables.

Evidence on the relationship between weight gain between pregnancies and GDM recurrence is stronger. Previous studies have identified weight gain between pregnancies as a risk factor with a weight gain greater than or equal to 15 pounds during the IPI associated with recurrent GDM.[17] A study by Ehrlich *et al*., similarily, found that women who increase their BMI units between pregnancies are at a higher risk for recurrent GDM. [50] A reduction in BMI units between pregnancies significantly reduced risk in women who were overweight or obese while BMI gains between pregnancies increased risk for women of normal weight.[18] These results demonstrate the important role of postpartum weight retention and weight gain in the risk of recurrent GDM.

Because GDM recurrence is a predictor of T2DM, interventions that decrease recurrence rates may eventually delay or prevent the onset of T2DM.[12] Literature on the optimal length of the IPI is contradictory and, thus, future observational studies will be needed to understand the IPI length as a risk factor. However, gains in BMI units between pregnancies have been shown to increase recurrence of GDM, indicating that this risk factor may be successfully targeted with interventions to reduce the incidence of recurrent GDM.

Existing research on prevention of GDM recurrence

The IPI is an integral time for lifestyle or pharmacological interventions that can potentially alter the diabetes disease course by either preventing recurrence of GDM or preventing or delaying the onset of T2DM. While there are few studies that have examined prevention of recurrent GDM, many studies have examined interventions to prevent T2DM after a diagnosis of GDM. Many of these interventions can be feasibly applied to the IPI to reduce incidence of recurrent GDM. Three different types of interventions have been studied to date: lifestyle (diet and physical activity), pharmacologic, and breastfeeding.

A study by Hu *et al.*[51] examined the effect of dietary intervention in women with a history of GDM. The two-year long intervention involved eight meetings with study dietitians: six meetings in person during the first year and two telephone meetings during the second year. Participants who received the intervention lost more weight within the first year than those in the control groups. Women demonstrated healthier behaviors

including increased leisure time physical activity and dietary fiber intake with decreased sedentary time and fat consumption. Women in the intervention group showed decreased BMI, waist circumference, and plasma insulin levels.

The Diabetes Prevention Program (DPP) Research Group demonstrated that an intensive lifestyle-modification program significantly decreased the risk of developing T2DM in people with impaired glucose tolerance. The research group reported a 58% reduction in the incidence of T2DM and a mean weight loss of 5.6 kg among the lifestyle modification group compared to placebo.[52] In a follow-up study, the effect of a lifestyle intervention on development of T2DM was examined in women with a history of GDM. 350 women from the DPP self-reported a history of GDM and were compared to1416 women in the study who reported a prior live birth but no history of GDM. Women were assigned to a life-style intervention group, metformin group, or placebo group. Women with a history of GDM had a 53.4% reduced risk of developing T2DM compared to placebo after the intensive life-style intervention and a reduction of 50.4% after the metformin treatment.[53] In a study done on women with a history a GDM who were warned of the high risk of T2DM and informed of the importance of healthy lifestyle modification, few women changed their lifestyle or lost weight after their pregnancy; 33% of the women gained weight after pregnancy and only 18% lost at least 5 kg.[54] The difference in outcomes between these two studies show that a more intensive, scheduled lifestyle intervention is more effective compared to counseling.

While the studies by Hu *et al.*[51] and Ratner *et al.*[53] examined lifestyle interventions in women with a history of GDM, they did not examine women in the

postpartum period. A study by O' Toole *et al*.[55] enrolled overweight, postpartum women into an intervention group to receive diet and activity recommendations, participate in group sessions, and record progress in a diet and activity journal. The intervention group lost significantly more weight (7.3 kg) within 1 year postpartum compared to the control group (1.4 kg). Although this study did not measure glucose levels, it shows that structured diet and exercise interventions in the postpartum period are effective in modifying risk factors for GDM recurrence and T2DM.

Breastfeeding has been associated with lower blood glucose levels postpartum as well as a reduced incidence of T2DM in women with a history of GDM.[56] A study by Stuebe *et al.*[57] showed that with each year of lifetime lactation, there was a 15% reduction in the risk of T2DM. A review by Keller *et al*.[58] examined the relationship between diet and exercise interventions in women who are breastfeeding and weight loss in the postpartum period. The review revealed that women receiving the diet and physical activity interventions lost more weight while breastfeeding than those who were not breastfeeding. This shows that a combination of lifestyle interventions and breastfeeding can help high-risk women manage weight postpartum to prevent or delay T2DM.

Randomized clinical trials have been completed studying pharmacologic interventions to decrease risk of T2DM after GDM. Drugs that have been studied include troglitazone and pioglitazone which decrease insulin resistance and metformin which decreases hepatic glucose production and improves insulin sensitivity. The Troglitazone in the Prevention of Diabetes (TRIPOD) study[59] performed a randomized clinical trial using troglitazone or placebo in obese Hispanic women with a history of GDM. The

study found a 55% decrease in the incidence of T2DM, which was explained by preservation of the pancreatic ß-cells during the intervention period. Women who did not develop T2DM during the TRIPOD study were enrolled into the Pioglitazone in Prevention of Diabetes (PIPOD) study[60] and received pioglitazone or placebo for 3 years. Results showed a significantly lower incidence of T2DM in the intervention group (4.6% yearly incidence rate) compared to placebo group (12.1% yearly incidence rate). Additionally, the DPP study showed a 50% reduction in T2DM incidence after treatment with metformin.[53] Although troglitzone, pioglitazone, and metformin showed significant reduction in T2DM incidence, none are currently approved by the FDA for prevention of T2DM.

While the above trials discuss prevention of T2DM, a trial by Koivusalo *et al.* administered a lifestyle intervention to prevent recurrent GDM. This trial assessed the effect of a moderate diet and exercise intervention on the incidence of GDM in pregnant women with either a history of GDM or a BMI >30 kg/m^2. [19] The intervention included 3 visits with a study nurse and one group visit to the group dietitian during pregnancy. There was a 39% decrease in incidence of GDM among these high-risk pregnant women despite a minority of women in the intervention groups reaching physical activity goals and only minor differences in weight gain between the intervention and control groups (7.6 kg vs. 7.7 kg, respectively). Thus, only small changes in lifestyle during pregnancy are necessary to prevent GDM. This lifestyle intervention is significant because it is generalizable and can be implemented by primary care providers.[19]

The above studies show that interventions exist that are effective in preventing or

delaying onset of T2DM in high-risk women. However, the efficacy of these interventions applied to the interconception period in preventing GDM recurrence is unclear. The Koisulavo *et al.* study showed a reduction in recurrent GDM, however, the intervention was only applied after conception of a woman's subsequent pregnancy. Literature on management of risk factors during the IPI and interventions during the IPI to reduce recurrence of GDM is lacking. However, literature in this area is needed because, as discussed above, recurrence of GDM is a risk factor for developing T2DM. As a first diagnosis of GDM is an early identifier of those at higher risk for T2DM, women with GDM are an easily targeted group at high risk for T2DM. It is therefore important to manage risk factors early in order to prevent recurrent GDM. In this study, investigators will test a lifestyle intervention applied after an index pregnancy complicated by GDM in an effort to reduce the incidence of recurrent GDM.

METHODS

Study design

This is a randomized controlled intervention trial targeting women with GDM. Participants will be overweight women with an index pregnancy complicated by GDM. The goal of this study will be to implement a lifestyle intervention that allows women to lose BMI units during the IPI with the goal of lowering the incidence of recurrent GDM.

Participants will be recruited to the study by their participating obstetrician during their index pregnancy. All enrolled women will be planning a subsequent pregnancy within the next 2 years and are willing to use contraception during the study period. Women will be randomized into a life-style intervention group or a control group. The lifestyle intervention group will receive diet and physical activity counseling and will keep a weekly diet and physical activity journal. Physical activity goals will include 150 minutes of leisure time physical activity per week and improved diet (within 11 different diet components) with the goal of losing 5% of their pre-pregnancy weight. The intervention will be given for 1 year and all women will be followed through their second pregnancy. The goal of this study is to determine whether a life-style intervention for overweight women in the interconception period after a pregnancy complicated by GDM will decrease the incidence of GDM in a subsequent pregnancy.

Study population and sampling

Participants will be overweight, primiparous women enrolled after a pregnancy complicated by GDM. After delivery, eligible women will receive their 6-week postpartum glucose testing. Women with normal results will be enrolled in the study,

randomized, and a lifestyle intervention will be provided for one year. Women will be planning a second pregnancy within the next 1-2 years.

Study sample: Eligible participants will be overweight (BMI between25-30 kg/m^2), primiparous, planning a pregnancy within the next 1-5 years, willing to use birth control for the intervention period, have a negative pregnancy test at enrollment, and be English or Spanish speaking (Table 3). Researchers will restrict enrollment to an overweight population of women in order to restrict heterogeneity of the sample. Overweight women make up a large portion of the women who develop GDM and are at risk for developing T2DM. Additionally, a prior study by Ehrlich *et al.*[50] showed that women who were previously overweight and lost BMI units before the second pregnancy had a lower incidence of recurrent GDM. Therefore, overweight women may most benefit from a life-style intervention. Women will only be enrolled if their first pregnancy was complicated by GDM. Because parity is a risk factor for GDM, isolating primiparous women will remove confounding factors. Because women over 35 are at higher risk for GDM and T2DM outside of pregnancy, enrolled women will be less than 35. Women will only be enrolled in the study if the postpartum OGTT is normal in order to isolate glucose intolerance during pregnancy as a risk factor for recurrent GDM. Investigators will include breastfeeding and non-breastfeeding mothers in order to maintain an adequate sample size.

Exclusion criteria: Exclusion criteria include women who are pregnant at enrollment or planning to become pregnant during the intervention period, women with type 1 or type 2 diabetes, women who use of any medication that influences glucose

metabolism such as continuous corticosteroids or metformin, and women with substance abuse or with physical disability (Table 3). Additionally, women will be excluded if they have a history of acute or chronic pancreatitis, obesity induced by drug treatment, MDD or suicide attempt, or uncontrolled hypertension, if they have used any approved weight loss pharmacotherapy or have a history of surgical treatment of obesity, or if they are unable to give written or informed consent.

Table 3: Project inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
• Overweight (BMI 25-30 kg/m$^{2)}$ • Primiparous • Prior history of GDM (first documented episode of glucose intolerance during first pregnancy) • Age 18-35 years old • Normal 6 week postpartum OGTT after pregnancy with GDM • Planning a pregnancy within the next 1-2 years • Willing to use birth control for intervention period • Negative pregnancy test at enrollment • English or Spanish speaking	• Pregnant at enrollment or planning to become pregnant during intervention period • Diagnosis of type 1 or type 2 diabetes mellitus • Use of medication that influences glucose metabolism: e.g. corticosteroids or metformin • Substance use disorder • Physical disability • Medical history of: acute or chronic pancreatitis, obesity induced by drug treatment, MDD or suicide attempt, or uncontrolled hypertension • History of weight loss pharmacotherapy • History of surgical treatment of obesity • Unable to give written or informed consent

Randomization: Randomization will be done by a study nurse by dispensing the next sequentially numbered code envelope containing the intervention arm to be assigned to the participant. The intervention and control arms will be balanced equally.

Size of study population and power calculation: Based on data on GDM recurrence, the pooled GDM recurrence rate is 48%.[12] Because the women participating in this study are all primiparous, the estimated recurrence rate for this cohort will be lower, due to previous findings that recurrence is lower in primiparous vs multiparous women. Thus, the estimated recurrence rate used will be 40% as reported by Schwartz *et al.*[12] A 40% risk reduction will be used based a study by Koivusalo *et al.* of women who participated in a lifestyle intervention during a subsequent pregnancy after a GDM pregnancy.[19] Using an alpha of 0.05, power of 80%, probability of control exposure is 40% and probability of exposure in the intervention group in 29.28% (based on a 40% risk reduction after the intervention), and m value of 1, the sample size for each arm will need to be 105 subjects, (total = 210) to detect a significant difference by the chi-square test. Assuming 40% of participants drop out or are lost to follow up, 294 women will be enrolled.

Intervention

The intervention will include a visit with a study nurse and/or a nutritionist in an outpatient setting once every 3 months for one year, beginning at enrollment. With each meeting, the patient will receive diet and physical activity counseling. The ultimate goal will be for the patient to lose 5% of her pre-pregnancy weight. All participants randomized to the control arm will receive the usual postnatal care, care similar to usual primary care including leaflets containing information of healthy diet and exercise habits.

The dietary intervention: The participants in the intervention arm will be encouraged to increase their intake of vegetables, legumes, fruits, berries, whole grains,

fiber, low-fat dairy, and vegetable fats. The goal will be to meet a specified diet modification that will allow the patient to lose weight. Diet modification goals include: saturated fat intake <10% of energy consumed, total fat intake 40% of energy consumed, carbohydrate intake 40% of energy consumed, protein intake 20% of energy consumed and fiber intake 20-30 g/day.[30,51] During the first meeting, the study nurse and nutritionist will work with the patient to create a sample menu for 5 days (including 5 breakfasts, 5 lunches, and 5 dinners). Counseling on all of the following 11 topics will be discussed during the meeting: snacks, sugar-sweetened beverages, vegetables, fruits and berries, low-fat cheese, cooking fat, spread fat, fast food, high-fiber, bread and cereal, fish, and low-fat milk. Specific caloric intake will not be recorded. However, because women who are breastfeeding have different caloric needs compared to those who are not, this will be discussed during nutrition counseling. Recommended energy intake for breastfeeding women in the first 6 months postpartum ranges from 2130-2730 kcal/day and 2200-2800 kcal/day after 7 months of lactation.[61] During the postpartum period, information on breastfeeding and infant nutrition will also be given. At each 3-month visit, a dietary journal will be collected and reviewed. This will be used as motivation for participants as well as data collection. Patients in the control group will also keep dietary journals, which will be collected at each 3-month visit.

The physical activity intervention: The goal of physical activity counseling will be to achieve 150 minutes of leisure time physical activity per week (e.g. 30 minutes of moderate intensity physical activity 5 times per week). During the study visits every three months, participants will work with study nurses to develop an exercise plan that can be

modified every three months as needed. Physical activity log books will be used as motivation and used for data collection. Patients will wear a pedometer and heart rate monitor during exercise that will be used to determine physical activity intensity. Patients in the control group will also keep physical activity journals, which will be collected at each 3-month visit.

Study variables and measures

Primary outcome: The primary outcome will be the incidence of GDM in the subsequent pregnancy after the index pregnancy. GDM in the subsequent pregnancy will be diagnosed on the IADPSG protocol as described in Table 4.[33]

Table 4: IADPSG Recommendations for diagnosis of hyperglycemia in pregnancy

At first visit, assign diagnosis of preexisting diabetes if any of the following are present:
1) Fasting plasma glucose ≥ 126 mg/dL (≥6.99 mmol/L)
2) Hb A_{1C} ≥6.5% (≥48 mmol/mol)
3) Random plasma glucose ≥200 mg/dL (≥11.1 mmol/L) (confirmed by FPG or Hb A_{1C})
At first visit, assign diagnosis of gestational diabetes if present:
1) Fasting plasma glucose ≥92 mg/dL (≥5.11 mmol/L) and < 126 mg/dL (<6.99 mmol/L)
At 24-28 weeks gestation, perform 75-g, 2-h OGTT. Assign diagnosis of gestational diabetes if one or more of the following plasma glucose values is met or exceeded:
1) Fasting 92 mg/dL (5.11 mmol/L)
2) 1 h 180 mg/dL (9.99 mmol/L)
3) 2 h 153 mg/dL (8.49 mmol/L)
Adapted from the International Association of Diabetes and Pregnancy Study Groups Consensus Panel[33] and Coustan *et al*[3]

Secondary outcomes: Secondary outcomes include gestational weight gain and change in pre-pregnancy BMI units from the index pregnancy to the subsequent pregnancy, whether dietary and physical activity goals are met, and fasting plasma glucose concentrations taken at the visit every 3 months. Demographic data such as age, ethnicity, parity, length of the IPI, previous management of GDM (diet-treated, oral hypoglycemic agent, or insulin), socioeconomic status, and family history of diabetes, will also be collected to analyze confounding factors. Birth control method used during the IPI will also be recorded and adjusted for due to metabolic changes that occur as the result of hormonal birth control methods.

Recruitment and enrollment

Participants will be recruited either by their participating obstetrician at Boston Medical Center during their index pregnancy which has been complicated by GDM or through advertisements in the local media (newspapers and television) in Boston. Eligible women will meet with a study nurse and provider 6-weeks post-partum. The visit will include a detailed explanation of the study, informed consent, and completion of a medical questionnaire to determine eligibility based on inclusion/exclusion criteria. The patient will undergo OGTT and a physical exam will be performed. The women will then undergo informed consent and be enrolled.

Incentives for participation include $30 cash upon enrollment and $10 at each visit with the study nurse.

Data collection

At enrollment, the following data will be collected for intervention and control groups: blood pressure, heart rate, weight, height, BMI, waist and hip circumference, self-reported pregnancy BMI ($Kg/m^{2)}$, treatment of GDM in index pregnancy (diet-treated, oral hypoglycemic agent, insulin), perinatal outcomes of the index pregnancy (birth weight and length, gestational age, sex of the infant, Apgar score, perinatal complications).

At each 3-month visit the following data will be collected for the intervention and control groups: physical exam findings (blood pressure, heart rate, respiratory rate, O2 saturation), anthropometric measurements (weight, height, BMI, waist and hip circumference), food frequency questionnaire collected from diet logs kept by the subjects, diet index, and physical activity index. Diet index will be a composite of consumption of each of the following 11 categories of food discussed above scored from 0-2 (2 is healthy, 0 is unhealthy): snacks, sugar-sweetened beverages, vegetables, fruits and berries, low-fat cheese, cooking fat, spread fat, fast food, high-fiber, bread and cereal, fish, and low-fat milk. Whether the subject met or did not meet the diet modification goals will be recorded. Physical activity will be recorded by number of minutes spent doing leisure time activity. Physical activity index will be a composite of number of minutes per week (0; <100, 1; 100-150, 2; 150-200; 3: >200) and intensity of exercise based on results of pedometer and heart rate monitor.

Data analysis

The difference in incidence of recurrent GDM among the intervention and control groups will be analyzed for significance using a chi-square analysis. The secondary outcomes will be tested for significance using a t-test for continuous variables that are normally distributed, Mann-Whitney U test for continuous variables that are not normally distributed, or chi-square test for categorical variables. Multiple regression analysis will be used to adjust for confounding variables. The level of significance will be set at $p=0.05$.

Timeline and resources

During summer 2018, the study will be submitted to IRB for approval, providers and study nurses will be recruited and trained, and advertisements or brochures advertising participation in the study will be developed. Recruitment and enrollment will begin in fall 2018. Participants will begin the study as they are enrolled. Enrollment will continue until sample size is reached (estimated one year of enrollment). After completion of enrollment, women will continue with the year-long intervention. Women who participated will be followed for a diagnosis of GDM in their second pregnancy. The timeline is outlined below in Table 5:

Table 5: Project timeline

Summer 2018
1) IRB submission and approval 2) Recruitment of participating study sites, nurses, providers 3) Development of participant recruitment tools: advertisements/brochures
Fall 2018-Fall 2019
1) Enroll subjects o Recruit women with current GDM o Set up 6-week post-partum appointment with eligible women o Sign consent forms 2) Begin intervention o Begin intervention
Fall 2019-Fall 2020
1) Stop enrollment 2) Continue intervention 3) Begin follow-up period for women completing intervention o Follow for subsequent pregnancy o Record if GDM is diagnosed in subsequent pregnancy

Project oversight, data collection, and data entry will all be completed by the primary investigator. Study nurses and nutritionists will see patients at each 3-month follow-up for vitals, physical exam, blood tests, and diet and exercise counseling (intervention only). Data analysis will be completed with the help of a statistician.

Institutional Review Board

This study will be submitted to review to the Boston University Medical Campus IRB for full review. This study is submitted for full review because an intervention will be applied to human subjects which does not fall within one of the 9 categories needed to qualify for expedited review.

CONCLUSION

Discussion

GDM significantly impacts a woman's life and carries a large health and economic burden. Although guidelines are established for screening, diagnosis, and management during a pregnancy complicated by GDM, post-partum follow up is lacking. A diagnosis of GDM has many long-term sequelae including risk of recurrent GDM, overweight/obesity, and development of T2DM. Therefore, follow-up post-partum after GDM is critical in preventing these consequences. While many studies have examined interventions that prevent T2DM, few studies have examined interventions that specifically prevent recurrent GDM. Prevention of recurrent GDM is important because a recurrent episode of GDM involves increased medical care during pregnancy, risk of adverse pregnancy outcomes, and elevated long-term maternal and fetal risk of obesity and T2DM.

This study will examine a lifestyle intervention, which ultimately may reduce incidence of recurrent GDM. However, there are limitations, which must be highlighted. First, this study is relatively long (1-year follow-up) which may lead to a larger group of women lost to follow-up larger than expected. Secondly, recruitment may take longer than expected because women who have GDM in a current pregnancy must be planning to have a subsequent pregnancy and be willing to use one form of contraception in the interconception period to prevent pregnancy during the intervention period. Lastly, due to potential complications, burden of management, and risk of recurrence, the diagnosis of

GDM in the index pregnancy may affect a woman's desire to have a second pregnancy. This may affect recruitment of participants.

If found to be effective, the findings of the study are generalizable as it only requires the participant to visit with a nurse or provider one time every three months. In general, the intervention is not difficult to implement from the provider's perspective. However, lifestyle changes such as increased leisure time physical activity and healthy diet changes can be particularly difficult for mothers with a newborn as they can be time consuming. For this reason, if motivation is lacking, the intervention may not function with all mothers. Despite these obstacles, this intervention will give women the tools to begin a healthy lifestyle.

Summary

Management and prevention of GDM is incredibly important in ensuring a healthy pregnancy and preventing long-term health complications. As more Americans are affected by GDM and T2DM, it is becoming more important to manage risk factors for these diseases early. Because GDM and T2DM share similar risk factors, GDM is an early indicator for T2DM in the long term. This provides an ideal opportunity to target a patient's risk factors and halt the diabetes disease course before any adverse health events take place. Although many studies have focused on the prevention of T2DM after GDM, there is literature lacking on targeting the IPI to prevent recurrent GDM.

Prevention of recurrent GDM is important for many reasons. By preventing a recurrent episode of GDM, a patient's risk of short-term consequences from GDM is reduced. Additionally, recurrent GDM increases a patient's risk of developing T2DM

while a subsequent pregnancy not complicated by GDM may be protective against T2DM. For this reason, an intervention that can prevent a recurrent episode of GDM may provide the perfect opportunity to alter the diabetes disease course.

Clinical and/or public health significance

The public health implications of GDM are immense and prevention will lead to improved maternal and fetal outcomes. T2DM, a major sequela of GDM, is emerging as a leading cause of death and disability in the United States. People with T2DM are at increased risk for developing renal, cardiovascular, and retinal diseases which poses a significant economic burden, $91.8 billion per year in the United States.[6] Because many women with a history of GDM develop T2DM, preventing GDM may decrease incidence of T2DM, relieving its public health burden.

LIST OF JOURNAL ABBREVIATIONS

Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Am J Perinatol	American Journal of Perinatology
BJOG An Int J Obstet Gynaecol	BJOG: An International Journal of Obstetrics and Gynecology
Can Med Assoc J	Canadian Medical Association Journal
Clin Chem	Clinical Chemistry
Cochrane Database Syst Rev	Cochrane Database Systematic Review
Diabet Med	Diabetic Medicine
Diabetes Res Clin Pract	Diabetes Research and Clinical Practice
Endocr Care	Endocrine Care
Int J Gynecol Obstet	International Journal of Gynecology and Obstetrics
J Clin Endocrinol Metab	The Journal of Clinical Endocrinology and Metabolism
J Clin Invest	The Journal of Clinical Investigation
J Obstet Gynaecol Can	The Journal of Obstetrics and Gynecology Canada
J Obstet Gynecol Neonatal Nurs	The Journal of Obstetric, Gynecologic, and Neonatal Nursing
J Perinatol	The Journal of Perinatology
J Women's heal	The Journal of Women's Health

JAMA	The Journal of the American Medical Association
Matern Child Health J	Maternal and Child Health Journal
N Engl J Med	New England Journal of Medicine
Nat Clin Pr Endocrinol Metab	Nature Clinical Practice Endocrinology and Metabolism
Obstet Gynecol	Obstetrics and Gynecology
Saudi Med J	Saudi Medical Journal

REFERENCES

1. American Diabetes Association. Gestational Diabetes Mellitus. *Diabetes Care*. 2004;27(1):S88-90. http://care.diabetesjournals.org.ezproxy.bu.edu/content/diacare/27/suppl_1/s88.full.pdf. Accessed October 9, 2017.

2. Duan T, Yang H, Van Assche A, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care#. *Int J Gynecol Obstet*. 2015;131(S3):S173-S211. doi:10.1016/S0020-7292(15)30033-3.

3. Coustan DR. Gestational diabetes mellitus. *Clin Chem*. 2013;59(9):1310-1321. doi:10.1373/clinchem.2013.203331.

4. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. 2016. doi:10.1007/s11892-015-0699-x.

5. Group THSCR. Hyperglycemia and Adverse Pregnancy Outcomes. *N Engl J Med*. 2008;358(19):1991-2002. doi:10.1056/NEJMoa0707943.

6. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009;373:1773-1779. doi:10.1016/S0140-6736(09)60731-5.

7. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002;25(10):1862-1868. doi:10.2337/DIACARE.25.10.1862.

8. Feig DS, Msc M, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *Can Med Assoc J*. 2008;179(3):229-234. doi:10.1503/cmaj.080012.

9. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in

Pregnancy INTERNATIONAL ASSOCIATION OF DIABETES AND PREGNANCY STUDY GROUPS CONSENSUS PANEL*. *Diabetes Care*. 2010;33:676-682. doi:10.2337/dc09-1848.

10. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 60, March 2005. Pregestational diabetes mellitus. *Obstet Gynecol*. 2005;105(3):675-685. http://www.ncbi.nlm.nih.gov/pubmed/15738045. Accessed December 21, 2017.

11. Berger H, Crane J, Farine D, et al. Screening for gestational diabetes mellitus. *J Obstet Gynaecol Can*. 2002;24(11):894-912. http://www.ncbi.nlm.nih.gov/pubmed/12417905. Accessed December 20, 2017.

12. Schwartz N, Nachum Z, Green MS. The prevalence of gestational diabetes mellitus recurrence—effect of ethnicity and parity: a metaanalysis. *Am J Obstet Gynecol*. 2015;213:310-317. doi:10.1016/j.ajog.2015.03.011.

13. Peters RK, Kjos SL, Xiang A, Buchanan TA. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. *Lancet*. 1996;347(8996):227-230. https://ac-els-cdn-com.ezproxy.bu.edu/S0140673696904055/1-s2.0-S0140673696904055-main.pdf?_tid=e2c5f9ce-a45b-11e7-a395-00000aab0f01&acdnat=1506610209_e26b52b3eb16a9163673a51efdb60311. Accessed September 28, 2017.

14. Russell C, Dodds L, Armson B, Kephart G, Joseph K. Diabetes mellitus following gestational diabetes: role of subsequent pregnancy. *BJOG An Int J Obstet Gynaecol*. 2007;115(2):253-260. doi:10.1111/j.1471-0528.2007.01459.x.

15. Retnakaran R, Austin PC, Shah BR. Effect of subsequent pregnancies on the risk of developing diabetes following a first pregnancy complicated by gestational diabetes: a population-based study. *Diabet Med*. 2010;28(3):no-no. doi:10.1111/j.1464-5491.2010.03179.x.

16. Khambalia AZ, Ford JB, Nassar N, Shand AW, McElduff A, Roberts CL. Occurrence and recurrence of diabetes in pregnancy. *Diabet Med*. 2013;30(4). doi:10.1111/dme.12124.

17. Major CA. Recurrence of gestational diabetes: who is at risk? *Am J Obstet Gynecol*. 1998;179(5):1038-1042. http://ac.els-cdn.com.ezproxy.bu.edu/S000293789870211X/1-s2.0-S000293789870211X-main.pdf?_tid=b18f7864-981a-11e7-bb32-00000aacb35d&acdnat=1505262787_164cecffdb5aa25f9d525c6c5c0ae1ea. Accessed September 12, 2017.

18. Ehrlich SF, Hedderson MM, Feng J, Davenport ER, Gunderson EP, Ferrara A. Change in Body Mass Index Between Pregnancies and the Risk of Gestational Diabetes in a Second Pregnancy. *Obstet Gynecol*. 2011;117(6):1323-1330. doi:10.1097/AOG.0b013e31821aa358.

19. Koivusalo S, Rono K, Klemetti M, et al. Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL). *Diabetes Care*. 2016;39:24-30. doi:10.2337/dc15-0511.

20. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. *Diabetes Care*. 1998;21 Suppl 2:B161-7. http://www.ncbi.nlm.nih.gov/pubmed/9704245. Accessed December 28, 2017.

21. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes*. 1979;28(12):1039-1057. http://www.ncbi.nlm.nih.gov/pubmed/510803. Accessed December 20, 2017.

22. Acker D, Sachs B, Friedman E. Risk Factors for Shoulder Dystocia. Obstetrics and Gynecology. http://ovidsp.tx.ovid.com.ezproxy.bu.edu/sp-3.27.2b/ovidweb.cgi?WebLinkFrameset=1&S=MHJLFPLMCMDDKLLMNCFKLBGCFDBDAA00&returnUrl=ovidweb.cgi%3FMain%2BSearch%2BPage%3D1%26S%3DMHJLFPLMCMDDKLLMNCFKLBGCFDBDAA00&directlink=http%3A%2F%2Fovidsp.tx.ovid.com%2Fovftp. Published 1985. Accessed December 28, 2017.

23. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics*. 2008;122(1):65-74. doi:10.1542/peds.2007-2822.

24. Damm P. Future risk of diabetes in mother and child after gestational diabetes mellitus. *Int J Gynecol Obstet*. 2009;104(Supplement):S25-S26. doi:10.1016/j.ijgo.2008.11.025.

25. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes*. 2000;49(12):2208-2211. doi:10.2337/DIABETES.49.12.2208.

26. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26 Suppl 1(suppl 1):S5-20. doi:10.2337/DIACARE.26.2007.S5.

27. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes. *N Engl J Med*. 2005;352(24):2477-2486. doi:10.1056/NEJMoa042973.

28. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007;30 Suppl 2(Supplement 2):S251-60. doi:10.2337/dc07-s225.

29. Kjos SL, Buchanan TA, Greenspoon JS, Montoro M, Bernstein GS, Mestman JH. Gestational diabetes mellitus: The prevalence of glucose intolerance and diabetes mellitus in the first two months post partum. *Am J Obstet Gynecol*. 1990;163(1):93-98. doi:10.1016/S0002-9378(11)90676-0.

30. Practice Bulletin No. 180: Gestational Diabetes Mellitus. *Obstet Gynecol*. 2017;130(1):e17-e37. http://ovidsp.tx.ovid.com.ezproxy.bu.edu/sp-3.27.2b/ovidweb.cgi?WebLinkFrameset=1&S=GGLCFPGFNKDDELBFNCFKGEMCKAPOAA00&returnUrl=ovidweb.cgi%3F%26Full%2BText%3DL%257cS.sh.22.23%257c0%257c00006250-201707000-00051%26S%3DGGLCFPGFNKDDELBFNCFKGEMCKAPOAA00&direct. Accessed January 2, 2018.

31. Alfadhli EM. Gestational diabetes mellitus. *Saudi Med J*. 2015;36(4):399-406.

https://www.smj.org.sa/index.php/smj/article/view/smj.2015.4.10307/7156. Accessed September 11, 2017.

32. O'SULLIVAN JB, MAHAN CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes*. 1964;13:278-285. http://www.ncbi.nlm.nih.gov/pubmed/14166677. Accessed December 20, 2017.

33. Shang M, Lin L. IADPSG criteria for diagnosing gestational diabetes mellitus and predicting adverse pregnancy outcomes. *J Perinatol*. 2014;34(2):100-104. doi:10.1038/jp.2013.143.

34. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768-773. http://www.ncbi.nlm.nih.gov/pubmed/7148898. Accessed December 20, 2017.

35. Buchanan TA, Xiang AH. Gestational diabetes mellitus. *J Clin Invest*. 2005;115(3):485-491. doi:10.1172/JCI200524531.

36. England L, Milton Kotelchuck B, Hoyt Wilson BG, Cui X, Carrie Shapiro-Mendoza BK, Kotelchuck M. Estimating the Recurrence Rate of Gestational Diabetes Mellitus (GDM) in Massachusetts 1998–2007: Methods and Findings. *Matern Child Health J*. 2001;19. doi:10.1007/s10995-015-1750-x.

37. England LJ, Dietz PM, Njoroge T, et al. Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus. *Am J Obstet Gynecol*. 2009;200:365.e1-365.e8. doi:10.1016/j.ajog.2008.06.031.

38. Albareda ME, Caballero A, Badell G, et al. Diabetes and Abnormal Glucose Tolerance in Women With Previous Gestational Diabetes. *Diabetes Care*. 2003;26(4):1199-1205. http://care.diabetesjournals.org.ezproxy.bu.edu/content/diacare/26/4/1199.full.pdf. Accessed September 27, 2017.

39. Lö K, Knopff A, Baumgarten A, et al. Predictors of Postpartum Diabetes in Women With Gestational Diabetes Mellitus. *Diabetes*. 2006;55:792-797. http://diabetes.diabetesjournals.org.ezproxy.bu.edu/content/diabetes/55/3/792.full.

pdf. Accessed September 27, 2017.

40. Valizadeh M, Alavi N, Mazloomzadeh S, Piri Z, Amirmoghadami H. The Risk Factors and Incidence of Type 2 Diabetes Mellitus and Metabolic Syndrome in Women With Previous Gestational Diabetes. *Int J Endocrinol Metab*. 2015;13(2). doi:10.5812/ijem.21696.

41. Buchanan TA, Xiang A, Kjos SL, et al. Gestational Diabetes: Antepartum Characteristics That Predict Postpartum Glucose Intolerance and T^pe 2 Diabetes in Latino Women turn IGT with weight gain and an early gestational age at diagnosis of GDM suggests a role for chronic insulin resistance in m. *Diabetes*. 1998;47:1302-1310. http://diabetes.diabetesjournals.org.ezproxy.bu.edu/content/diabetes/47/8/1302.full.pdf. Accessed September 27, 2017.

42. Buchanan TA. Pancreatic B-Cell Defects in Gestational Diabetes: Implications for the Pathogenesis and Prevention of Type 2 Diabetes. *J Clin Endocrinol Metab*. 2001;86(3):989-993. doi:10.1210/jcem.86.3.7339.

43. Lauenborg J, Hansen T, Møller Jensen D, et al. Increasing Incidence of Diabetes After Gestational Diabetes A long-term follow-up in a Danish population. *Diabetes Care*. 2004;27(5):1194-1199. http://care.diabetesjournals.org.ezproxy.bu.edu/content/diacare/27/5/1194.full.pdf. Accessed September 27, 2017.

44. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJG. Glucose Intolerance in Pregnancy and Postpartum Risk of Metabolic Syndrome in Young Women. *Endocr Care*. 2010;95(2):670-677. doi:10.1210/jc.2009-1990.

45. Bentley-Lewis R. The metabolic syndrome in women. *Nat Clin Pr Endocrinol Metab*. 2007;3(10):696-704. doi:10.1038/ncpendmet0616.

46. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. *YMOB*. 203:467.e1-467.e6. doi:10.1016/j.ajog.2010.05.032.

47. Nohira T, Kim S, Nakai H, Okabe K, Nohira T, Yoneyama K. Recurrence of gestational diabetes mellitus: Rates and risk factors from initial GDM and one abnormal GTT value. *Diabetes Res Clin Pract*. 2005;71(1):75-81. doi:10.1016/j.diabres.2005.05.011.

48. Schwartz N, Green MS, Yefet E, Nachum ● Zohar. Modifiable risk factors for gestational diabetes recurrence. *Endocrine*. 2016;54:714-722. doi:10.1007/s12020-016-1087-2.

49. Holmes HJ, Lo JY, Mcintire DD, Casey BM. Prediction of Diabetes Recurrence in Women with Class A 1 (Diet-Treated) Gestational Diabetes. *Am J Perinatol*. 2010;27(1):047-052. doi:10.1055/s-0029-1241733.

50. Ehrlich SF, Hedderson MM, Feng J, Davenport ER, Gunderson EP, Ferrara A. Change in Body Mass Index Between Pregnancies and the Risk of Gestational Diabetes in a Second Pregnancy. *Obstet Gynecol*. 2011;117(6):1323-1330. doi:10.1097/AOG.0b013e31821aa358.

51. Hu G, Tian H, Zhang F, et al. Tianjin Gestational Diabetes Mellitus Prevention Program: Study design, methods, and 1-year interim report on the feasibility of lifestyle intervention program. 2012;5:0-8. doi:10.1016/j.diabres.2012.09.015.

52. Knowler W, Barrett-Connor E, Fowler S. REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN. *N Engl J Med*. 2002;346:393-403. https://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pmc/articles/PMC1370926/pdf/nihms-5217.pdf. Accessed September 27, 2017.

53. Ratner RE, Christophi CA, Metzger BE, et al. Prevention of Diabetes in Women with a History of Gestational Diabetes: Effects of Metformin and Lifestyle Interventions. *J Clin Endocrinol Metab*. 2008;93(12):4774-4779. doi:10.1210/jc.2008-0772.

54. Stage E, Ronneby H, Damm P. Lifestyle change after gestational diabetes. *Diabetes Res Clin Pract*. 2004;63:67-72. doi:10.1016/j.diabres.2003.08.009.

55. O 'toole ML, Sawicki MA, Artal R. Structured Diet and Physical Activity Prevent Postpartum Weight Retention. *J WOMEN'S Heal*. 2003;12(10):991-998. http://online.liebertpub.com.ezproxy.bu.edu/doi/pdf/10.1089/154099903322643910. Accessed October 10, 2017.

56. Kjos S, O Henry RM, BUchanan TA, MIshell DR. The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. *Obstet Gynecol*. 1993;82(3):451-455. http://buprimo.hosted.exlibrisgroup.com/primo-explore/openurl?sid=Entrez:PubMed&rft_id=pmid:8355952&vid=BU&institution=BOSU&url_ctx_val=&url_ctx_fmt=null&isSerivcesPage=true&lang=en_US. Accessed October 13, 2017.

57. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of Lactation and Incidence of Type 2 Diabetes. *JAMA*. 2005;294(20):2601. doi:10.1001/jama.294.20.2601.

58. Keller C, Records K, Ainsworth B, Permana P, Coonrod D V. I N R E V I E W Interventions for Weight Management in Postpartum Women. *J Obstet Gynecol neonatal Nurs*. 2008;37(1):71-79. doi:10.1111/J.1552-6909.2007.00202.x.

59. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of Pancreatic ℕ-Cell Function and Prevention of Type 2 Diabetes by Pharmacological Treatment of Insulin Resistance in High-Risk Hispanic Women. *Diabetes*. 2002;51(9):2796-2803. http://diabetes.diabetesjournals.org.ezproxy.bu.edu/content/diabetes/51/9/2796.full.pdf. Accessed September 28, 2017.

60. Xiang AH, Peters RK, Kjos SL, et al. Effect of Pioglitazone on Pancreatic β-Cell Function and Diabetes Risk in Hispanic Women With Prior Gestational Diabetes. *Diabetes*. 2006;55(2):517-522. https://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pmc/articles/PMC1389697/pdf/nihms8227.pdf. Accessed September 28, 2017.

61. Zello GA. Dietary Reference Intakes for the macronutrients and energy: considerations for physical activity. *Appl Physiol Nutr Metab*. 2006;31(1):74-79. doi:10.1139/h05-022.

CURRICULUM VITAE