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# Application and utility of full-term continuous glucose monitoring in gestational diabetes mellitus

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**APPLICATION AND UTILITY OF FULL-TERM CONTINUOUS GLUCOSE  
MONITORING IN GESTATIONAL DIABETES MELLITUS**

by

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B.S., Northeastern University, 2014  
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**ABSTRACT**

Gestational diabetes mellitus (GDM) is a common complication of pregnancy that results in chronic hyperglycemia during gestation. It is commonly the result of pre-existing impaired pancreatic beta cell function that is exacerbated due to the physiological demands of pregnancy. The International Diabetes Federation estimates that GDM affects approximately 14% of pregnancies worldwide. In the United States, the true prevalence of GDM is unknown but is estimated to that up to 14% of all pregnancies in the United States are diagnosed with GDM. Glycemic management is of the utmost importance in managing gestational diabetes, as it reduces adverse maternal and fetal outcomes. Historically, self-monitored blood glucose (SMBG) has been the universal way in which blood glucose is managed during pregnancy. However, SMBG does not provide a comprehensive glycemic profile. Continuous glucose monitoring is more comprehensive, as it allows for continuous measurement of interstitial glucose. The proposed study will evaluate the utility of long-term use of continuous glucose monitoring in pregnancy and potentially reduce poor maternal and fetal outcomes.

## TABLE OF CONTENTS

ACKNOWLEDGMENTS .....	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vi
LIST OF TABLES .....	viii
LIST OF ABBREVIATIONS.....	ix
INTRODUCTION .....	1
Background.....	1
Statement of the Problem.....	3
Hypothesis.....	4
Objectives and Specific Aims .....	4
REVIEW OF THE LITERATURE .....	5
Physiological Alterations During Pregnancy .....	5
Overview of Gestational Diabetes Mellitus .....	6
Pathophysiology of Gestational Diabetes Mellitus.....	7
Epidemiology of Gestational Diabetes Mellitus .....	10
Risk Factors for Gestational Diabetes Mellitus .....	11
Screening and Diagnostic Recommendations.....	14
Complications of Gestational Diabetes Mellitus .....	17
Gestational Diabetes Management .....	19

Existing Research on CGM Use in Pregnancy .....	24
METHODS .....	33
Study Design.....	33
Study Population and Sampling.....	33
Intervention.....	34
Study Variables and Measures.....	36
Recruitment.....	37
Data Collection .....	37
Data Analysis .....	38
Timeline and Resources.....	39
Institutional Review Board .....	39
CONCLUSION.....	41
Discussion.....	41
Summary.....	42
Clinical and/or Public Health Significance.....	43
REFERENCES .....	44
CURRICULUM VITAE.....	47

## LIST OF TABLES

Table	Title	Page
1	Diagnostic Criteria for Gestational Diabetes Mellitus	17
2	Inclusion and Exclusion Criteria	34
3	Blood Glucose Targets	36

## LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
FDA	U.S. Food and Drug Administration
GDM	Gestational Diabetes Mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
IADPSG	The International Association of Diabetes in Pregnancy Study Groups
OGTT	Oral Glucose Tolerance Test
GDM	Gestational Diabetes Mellitus
SMBG	Self-Monitoring Blood Glucose

## INTRODUCTION

### Background

In normal pregnancy, there are various physiological alterations that occur to support the increased physical and metabolic demands of pregnancy. Maternal physiology must continually adapt to allow for proper development of the fetus, as well as support the demands of childbirth. One of these adaptations occurs because of increased hepatic glucose production and reduced insulin sensitivity. In pregnant women with normal glucose metabolism, the pancreatic beta cells can compensate for this change. In pregnant women with abnormal glucose metabolism, the pancreatic beta cells are impaired and unable to compensate appropriately.

Gestational diabetes mellitus (GDM) is a metabolic condition that has been traditionally defined as carbohydrate intolerance with variable severity that occurs during pregnancy. In recent years, the definition of gestational diabetes has been refined to state that it is diabetes that is diagnosed in the second or third trimester of pregnancy. For women with GDM, the body is unable to overcome the normal insulin resistance that occurs during pregnancy because of pancreatic beta cell impairment. This in turns leads to chronic hyperglycemia during pregnancy. Gestational diabetes affects women worldwide with an estimated prevalence of 14% with a similar prevalence in the United States. While there are current prevention strategies in place, gestational diabetes continues to disproportionately burden many racial/ethnic groups including Native Americans, Hispanics, Asians, and African American women. In the United States, these groups have a higher risk of GDM compared to Caucasian women.

GDM is the most common metabolic complication that occurs during pregnancy, yet screening and diagnostic methods remain controversial. Routine screening for GDM during prenatal care is not yet a universal practice. There are only a few countries that implement GDM screening as a standard component of prenatal care. In the United States, the American College of Obstetricians and Gynecologists recommend that pregnant women be tested between 24 and 28 weeks of gestation if they have an average risk of developing GDM. Screening should be completed as soon as feasible if severe obesity, strong family history of type 2 diabetes, previous history of GDM, impaired glucose metabolism or glucosuria are present. Similar to screening recommendations, diagnostic methods are not universal. In the United States, there are two approaches to diagnosis of GDM. The most used approach is the two-step approach, which utilizes an initial one-hour screening 50-gram glucose challenge test. Once this step is completed, the test is terminated or testing is continued with a diagnostic evaluation.

Upon diagnosis of GDM, women should be educated about the importance of lifestyle management including nutritional modifications, physical activity, and weight management. Education pertaining to lifestyle changes are individualized according to current diet, level of physical activity, and pre-gestational weight. Nutrition and physical activity modifications are considered first line for treatment of gestational diabetes. When hyperglycemia persists in the presence of lifestyle modifications, multiple daily injection insulin is initiated. The efficacy of treatment is measured via observation of blood glucose. Self-monitoring of blood glucose is a mainstay of GDM treatment as it allows for insight into the glycemic profile of the individual. Women are encouraged to measure

fasting blood glucose and post-prandial blood glucose. Historically, compliance rates have not been high regarding self-monitoring blood glucose (SMBG). In addition, SMBG only provides limited insight into glucose excursions during pregnancy.

### **Statement of the Problem**

Gestational diabetes mellitus is the most common metabolic disorder that occurs during pregnancy. In the United States, GDM prevalence in several race/ethnicity groups has been increasing over the past 20 years. GDM results from pancreatic beta cell impairment, which leads to chronic hyperglycemia in pregnancy. Hyperglycemia has short term and long-term effects on both mother and fetus, which is why glycemic management is the focus of treatment for GDM. One component of the multi-disciplinary treatment plan is the use of self-monitoring blood glucose. This allows for insight into glycemic variability during pregnancy. However, research has shown that pregnant women are often non-adherent to SMBG and SMBG does not provide a comprehensive profile of glucose during pregnancy. With advances in diabetes technology, continuous glucose monitoring has become more and more advantageous for individuals with type 1 and type 2 diabetes. However, there is limited research on the utility and application of continuous glucose monitoring in gestational diabetes. Using continuous glucose monitoring for the entire duration of pregnancy will provide a comprehensive profile of glycemic variability during pregnancy. In addition, it will assist in clinical management of GDM and potentially improve maternal outcomes and fetal outcomes.

## **Hypothesis**

Current research shows that continuous glucose monitoring not only has similar accuracy to self-monitoring of blood glucose but also allows for a more comprehensive profile of glucose during diabetic pregnancy. There is limited research on the application and utility of long-term continuous glucose monitoring in pregnancy especially with gestational diabetes mellitus. Use of continuous glucose monitoring throughout the entire duration of pregnancy will improve periods of hyperglycemia and improve maternal and fetal outcomes related to hyperglycemia.

## **Objectives and Specific Aims**

The objective of this study is to conduct a randomized controlled trial in women with GDM to further investigate glycemic variability during pregnancy using continuous glucose monitoring for the entire duration of pregnancy. In addition, this study will explore the therapeutic effect of continuous glucose monitoring for women with gestational diabetes mellitus and the impact on maternal and fetal outcomes. Specifically, this study aims to:

- Provide a comprehensive review of gestational glycemic profiles in gestational diabetes
- Determine if long term continuous glucose monitoring improves hyperglycemia
- Determine if long term continuous glucose monitoring improves maternal outcomes
- Determine if long term continuous glucose monitoring improves fetal outcomes

## **REVIEW OF THE LITERATURE**

### **Physiological Alterations During Pregnancy**

During normal pregnancy, there are numerous physiological alterations that occur to support the increased physical and metabolic demands of the pregnancy.<sup>1</sup> Continual adaptation of maternal physiology is necessary to allow development of the fetus and for mother and fetus to survive the demands associated with childbirth.<sup>1,2</sup> These adaptations occur within most body systems and are interlinked and affected by the hormonal influence of the placenta and the anatomical adaptations.<sup>3</sup> The cardiovascular, respiratory, hematological, renal, gastrointestinal, and endocrinological systems all undergo changes to support the mother and fetus.<sup>1,2,3,4</sup>

The metabolic adaptations that occur during pregnancy are influenced by environment, physical status, lifestyle behaviors, pre-pregnancy nutrition, and maternal and fetal genetic constitutions.<sup>3</sup> The endocrinological changes that occur during pregnancy can be attributed to the increased metabolic demands of the mother and fetus. This allows for adequate supply of nutrition, blood, and oxygen. As pregnancy progresses, most of the endocrine adaptations occur by means of the hypothalamus and its connection to endocrine glands throughout the body. It encompasses the anterior and posterior pituitary gland, thyroid gland, parathyroid glands, adrenal glands, ovaries, and uterus.<sup>4</sup> Carbohydrate and fat metabolism undergo changes, as well, to allow for fatty acid and glycerol utilization for maternal energy and glucose and amino acids for the fetus.<sup>1</sup> Despite these shifts in energy utilization, a euglycemic state is still maintained due to both compensation and proliferation within the maternal pancreas.<sup>2</sup> In pregnant women

with normal glucose metabolism, fasting blood glucose is lower than at baseline as a result of an estrogen mediated increase in insulin sensitivity and insulin production.<sup>5</sup> However, as the pregnancy continues to the second and third trimesters, blood glucose rises due to the combination of increased hepatic glucose production and decreased insulin sensitivity.<sup>5</sup> The placenta contributes to the rise in blood glucose by means of placental hormones, such as human placental lactogen and progesterone. These placental hormones influence glucose metabolism by increasing peripheral insulin resistance, which in turn elevates postprandial glucose.<sup>1,5</sup> However, in the setting of normal pancreatic function at baseline, normal blood glucose is maintained because of the pancreas' ability to overcome physiologic resistance by increasing insulin secretion.<sup>5</sup>

### **Overview of Gestational Diabetes Mellitus**

Gestational diabetes mellitus (GDM) is traditionally defined as carbohydrate intolerance with variable severity that begins during pregnancy or that is first observed during pregnancy.<sup>6</sup> This includes glucose intolerance that normalizes in the post-partum period, as well as diabetes mellitus that is diagnosed during pregnancy. Diabetes mellitus can be further divided into Type 1 diabetes, Type 2 diabetes, and monogenic diabetes.<sup>6,7</sup> In recent years, gestational diabetes mellitus has been defined as diabetes that is diagnosed in the second or third trimester of pregnancy. In addition, it must not be a form of diabetes that was not clearly overt diabetes prior to pregnancy.<sup>6</sup> The latter definition aims to provide clarity for gestational diabetes as this helps to identify normal physiologic alterations in pregnancy from abnormal alterations in pregnancy. Pregnancy is often

referred to a natural stress test for the body and a window to future health complications.<sup>8</sup> Given the stress produced by pregnancy, it is important to identify whether pregnancy is simply revealing prior underlying beta cell dysfunction or if the impaired glucose intolerance and impaired homeostasis is simply the result of pregnancy.<sup>8</sup>

### **Pathophysiology of Gestational Diabetes Mellitus**

Historically, there have been inconsistencies in both screening and diagnosis of gestational diabetes. Despite these inconsistencies, the molecular processes underlying the pathophysiology of gestational diabetes is consistent. During a normal pregnancy, there is a relative state of insulin resistance.<sup>1</sup> Normally, the body can overcome insulin resistance by means of beta cell hyperplasia. However, for patients with GDM, the body is unable to overcome the insulin resistance due to beta cell dysfunction. GDM typically manifests because of beta cell dysfunction coupled with insulin resistance.<sup>9</sup>

Beta cells are located in the pancreas and are responsible for insulin storage and insulin secretion in response to glucose load in the blood. Beta cell dysfunction is defined as the loss of the ability to adequately sense blood glucose concentration or the loss of ability to release sufficient insulin in response to increasing blood glucose concentration.<sup>9</sup> The mechanisms behind beta cell dysfunction are varied and complex and can occur at various stages. However, the susceptibility genes related to GDM are those that relate to beta cell function. In addition to susceptibility genes, beta cell dysfunction is further exacerbated by insulin resistance, which is always a manifestation of pregnancy. This in turn creates a cycle in which the patient has beta cell dysfunction, which leads to

hyperglycemia and insulin resistance, which in turn further exacerbates the already present beta cell dysfunction.<sup>9</sup>

Coupled with beta cell dysfunction is insulin resistance, which refers to the inability of cells to adequately respond to insulin secretion. The mechanisms that influence insulin resistance are also varied but are most often the result of a failure of insulin signaling.<sup>9</sup> From a molecular standpoint, the impairment in insulin signaling leads to inadequate plasma membrane translocation of glucose transporter 4, GLUT-4. GLUT-4 is the primary transporter for glucose uptake into the cell, which allows for its use as energy. For individuals with GDM, the rate of glucose uptake via GLUT-4 is reduced by as much as 54%.<sup>9</sup> This leads to reduced energy for cells, as well increased serum glucose levels. These molecular changes that occur during pregnancy often persist in the postpartum period and have negative maternal and fetal consequences.<sup>9</sup>

In addition to beta cell dysfunction and insulin resistance, neurohormonal dysfunction has also been implicated in the pathogenesis of diabetes mellitus including the GDM subtype.<sup>9</sup> Neurohormonal networks are responsible for the regulation of appetite, energy expenditure, and basal metabolic rate. These networks are intricate and include both central and peripheral systems. The central system is composed of the cortical centers that control cues related to cognition, vision, and rewards. The peripheral system includes signals that are affected by satiety and hunger hormones. This network is often affected in GDM due to tight regulation by the circadian rhythm, which can be affected in patients with GDM by influencing adiposity and glucose utilization.<sup>9</sup>

Two of the most important cell signaling proteins that are secreted by adipose tissue are leptin and adiponectin. These two proteins are strongly influenced by adipose tissue mass. Leptin, a satiety hormone, is secreted by adipocytes in response to adequate fuel stores and is also secreted by the placenta during pregnancy. During pregnancy, the placenta is responsible for most of the plasma leptin. Similar to insulin resistance, leptin resistance also manifests during pregnancy. In GDM, plasma leptin levels are further increased, as well as leptin resistance. While a small degree of leptin resistance is important to bolster fat stores during pregnancy, hyperleptinemia can contribute to fetal macrosomia.<sup>9</sup>

Adiponectin functions to enhance insulin signaling and fatty acid oxidation, as well as inhibit gluconeogenesis.<sup>9</sup> Similar to leptin, adiponectin is also secreted by adipocytes but, unlike leptin, concentrations are inversely proportional to adipose tissue mass. GDM is associated with increased leptin concentrations and decreased adiponectin.<sup>10</sup> Given that low concentrations of adiponectin are seen in obese individuals, the role of adiponectin in the pathogenesis of GDM is independent of obesity.<sup>10</sup> Adiponectin may also play a negative role in fetal growth, such that adiponectin may impair insulin signaling and amino acid transport across the placenta. Emerging evidence suggests that adiponectin gene methylation in the placenta may be associated with maternal glucose intolerance, as well as fetal macrosomia.<sup>11</sup>

## **Epidemiology of Gestational Diabetes Mellitus**

The International Diabetes Federation estimates that GDM affects approximately 14% of pregnancies worldwide, which is representative of approximately 18 million births.<sup>12, 13</sup>

The frequency of gestational diabetes typically follows the frequency of type 2 diabetes in the underlying population.<sup>9</sup> In the United States, the true prevalence of gestational diabetes is unknown. Historically, there have been several issues that have prevented a true snapshot of gestational diabetes in the United States. The first is the definition of gestational diabetes as carbohydrate intolerance during pregnancy. This definition encompasses more than one subtype of diabetes, which makes the diagnosis of gestational diabetes unclear since diabetes may have been undiagnosed prior to pregnancy.<sup>10</sup> In addition to the definition of GDM, the criteria used for diagnosis varies among health professionals. However, it is now that that of the International Association of Diabetes and Pregnancy Study Group (IADPSG) be used for the diagnosis of GDM.<sup>10</sup> The second issue in studying trends in GDM is the identification of unrecognized diabetes prior to pregnancy. Until recently, diabetes screening began at age 40 unless there were risk factors present. Therefore, women of childbearing age are often not screened prior to pregnancy. This presents an issue when hyperglycemia is identified during pregnancy. It raises the question of whether hyperglycemia is the result of normal physiological alterations that occur during pregnancy or underlying abnormal physiology.<sup>11,12,13,14</sup>

Despite the issues in studying trends, GDM prevalence has increased in several race/ethnicity groups during the past 20 years.<sup>10</sup> In the United States, Native Americans,

Hispanics, Asians, and African American women have a higher risk of GDM than Caucasian women.<sup>9,10</sup> Many studies have found this rise in GDM is reflected in or may contribute to the increasing prevalence of type 2 diabetes and obesity. There is a gap in the literature regarding epidemiological data pertaining to modifiable risk factors of GDM. In addition to obesity, it is likely that sedentary lifestyles, diets high in saturated fat, and smoking are contributors to GDM. While the burden of GDM lies heavily within minority populations, the relative contributions of risk factors differ by race/ethnicity. There is substantial variation of prevalence and risk factors among racial/ethnic groups but there are consistent significant contributors to GDM in these populations. Advanced maternal age, overweight/obesity, family history of type 2 diabetes and foreign borne status are all significant contributors.<sup>15</sup>

### **Risk Factors for Gestational Diabetes Mellitus**

It is known that pregnancy forces the body to undergo several physical and metabolic alterations to adapt for pregnancy. The known pathophysiology of GDM suggests that individuals who develop GDM have underlying beta cell impairment prior to pregnancy.<sup>1,2,3,4</sup> Beta cell impairment results in the inability to adapt to these alterations that accompany pregnancy which leads to hyperglycemia and GDM. GDM is often considered to be type 2 diabetes that is unmasked by the metabolic alterations that occur during pregnancy.<sup>16, 17</sup> As a result, these two diabetes subtypes share several of the same risk factors. Similar to other risk factors, there are both modifiable risk factors and non-modifiable risk factors.

### *Overweight and Obesity*

Maternal weight status is assessed using maternal pre-pregnancy body mass index (BMI), whereby a BMI that is greater than or equal to 25 kg/m<sup>2</sup> is considered overweight and greater than or equal to 30 kg/m<sup>2</sup> is considered obese.<sup>18</sup> Pre-pregnancy BMI alone is a risk factor for GDM and this is further complicated by expected weight gain during pregnancy. Pregnant mothers are expected to gain approximately 30% of gestational weight in body fat.<sup>18</sup> The combination of pre-pregnancy body fat and the additional gained during pregnancy leads to increased lipid production. Triglycerides are the main type of lipids that accumulate in adipose tissue and other organs, such as the liver. Accumulation in the liver results in hepatic insulin resistance. Insulin resistance is further exacerbated by pregnancy, which increases the risk of developing GDM during pregnancy. Obesity complicates almost all aspects of pregnancy. It can contribute to other metabolic disorders, such as metabolic syndrome, which serves as an additional driver of GDM. These can in turn result in adverse consequences such as hypertension, still-birth, and premature delivery.<sup>7,18</sup>

### *Metabolic Syndrome and Nutritional Diet*

Metabolic syndrome is a term used to describe the occurrence of multiple metabolic disorders. These include obesity, dyslipidemia, hypertension, and abnormal glucose metabolism. There are multiple drivers of metabolic syndrome but diet is consistently a significant driver of this cluster of disorders. Metabolic syndrome is often

accompanied by a western diet that is high in sweets, fats, and processed foods.<sup>17, 18</sup> Both metabolic syndrome and poor nutrition contribute to the abnormal pathophysiology that influences the development of GDM.

### *Maternal Age*

A universal definition of advanced reproductive age has not been established in women partially due to the fact that the effects of aging are additive rather than effects occurring once a threshold is reached (UTD). As maternal age increases, fertility decreases and risk of complications increases. Over the past four decades, there has been an increase in the average age of childbearing.<sup>19</sup> For example, 9% of births in the United States in 2014 were to women at least 35 years of age.<sup>19</sup> This is a 23% increase from the year 2000. Studies have found that the risk of GDM increases linearly with maternal age.<sup>19</sup> The relationship between maternal age and GDM has not been fully established but it is likely due to high levels of insulin resistance and high levels of circulating adipokines and inflammatory markers, as well as oxidative stress.<sup>19</sup>

### *Ethnicity, Family History, and Socioeconomic Status*

GDM complicates up to 9% of pregnancies in the United States with the highest burden on pregnant women of non-white race and lower socioeconomic status.<sup>20, 21</sup> Similar to type 2 diabetes, the development of GDM is associated with multiple ethnic and racial groups, such as Hispanic, African American, and Asian women.<sup>7, 15, 20, 21</sup> There

are multiple mechanisms surrounding this increased risk including health predisposition, family history, and socioeconomic status.

GDM is a multifactorial disease that is influenced by genetics and the environment. Given the similarities between GDM and type 2 diabetes, a family history of type 2 diabetes is a significant risk factor for the development of GDM. There are multiple risk gene polymorphisms associated with type 2 diabetes and, of these, at least five have also been identified in GDM.<sup>7, 15, 20, 21</sup> This is of importance due to the prevalence of type 2 diabetes in these ethnic and racial groups.

In addition to increased prevalence in these ethnic and racial groups, these groups are also more likely to be of a lower socioeconomic status. Low-income populations are often unaware of the risk factors of GDM, complications of their diagnosis, and other relevant information. This can be attributed to lack of affordable and dependable access to healthcare.

### **Screening and Diagnostic Recommendations**

GDM has become one of the most common complications of pregnancy but screening and diagnostic methods remain controversial.<sup>6</sup> Routine screening for GDM during prenatal care is necessary and should be a universal practice. There are two methods of screening: universal and selective screening.<sup>16, 17</sup> However, there are only a few countries that implement universal GDM screening as a component of prenatal care. Other countries utilize testing based on a risk assessment that is completed by the obstetrician-gynecologist. In the United States, the American College of Obstetricians and

Gynecologists (ACOG) recommends that pregnant women be tested between 24 and 28 weeks of gestation if they have an average risk of developing GDM. Average risk individuals would be women with normal pre-pregnancy weight, no known family history of diabetes, no history of abnormal glucose tolerance, and members of an ethnic group with low prevalence of diabetes.<sup>8</sup> Screening should be completed early in pregnancy if any of the following are present: severe obesity, strong family history of type 2 diabetes, previous history of GDM, impaired glucose metabolism, or glucosuria.<sup>8</sup>

Similar to screening recommendations, diagnostic thresholds are not universal and continue to remain a source of active discussion.<sup>6</sup> The first diagnostic criteria was published over 50 years ago using the results of a 100 gram oral glucose tolerance test (OGTT). Using the results of the OGTT, glucose concentrations were extrapolated from whole blood values to approximate blood glucose values. Since the establishment of these values, other detection strategies and diagnostic criteria have been developed.<sup>21</sup> The HAPO study has been a crucial part of the drive to create universal diagnostic criteria for GDM.<sup>21</sup>

The HAPO study was a multicenter, multinational, multiethnic group observational study that assessed the results of a 75-gram 2-hour OGTT at 24 to 32 weeks for 25,000 pregnant women at 15 centers in 9 countries.<sup>21</sup> Based on the findings from this study, the IADPSG updated the diagnostic criteria for GDM. In addition to this, the results indicated that there was a continuous risk of adverse maternal and fetal outcomes with glucose levels even below the threshold for GDM.<sup>9</sup> Since the update, the criteria has been widely accepted by national and international organizations.<sup>6</sup> The ADA,

the World Health Organization (WHO), the International Federation of Gynecology and Obstetrics, and the Endocrine Society all advise use of the IADPSG criteria in the diagnosis of GDM.<sup>9</sup>

The oral glucose tolerance test is an assessment of maternal response to glucose. There are two approaches to identifying whether GDM is present during pregnancy. The most commonly used approach is the two-step approach, which utilizes an initial one-hour screening 50-gram glucose challenge test.<sup>2</sup> Once this step is completed, the test is either terminated or testing is continued with a diagnostic evaluation as seen in Table 1. The diagnostic evaluation consists of a 100-gram 3-hour oral glucose tolerance test. The one step approach utilizes a singular 75-gram 2-hour glucose tolerance test.<sup>2</sup> Studies have been performed to compare the outcomes using both approaches. There is no clear evidence of a significant difference in performance, however, the one-step approach results in a higher prevalence of GDM.<sup>8</sup> Overall, there are advantages and disadvantages to both approaches. The one-step approach has a lower economic burden, as well as a lower threshold, which allows for earlier diagnosis and treatment. The two-step approach has a higher economic burden and requires more time but also provides diagnostic efficacy.<sup>8</sup>

**Table 1. Diagnostic Criteria for Gestational Diabetes Mellitus**

Fasting Plasma Glucose	≥ 105 mg/dl
1 hour Glucose	≥ 190 mg/dl
2-hour Glucose	≥ 165 mg/dl
3-hour Glucose	≥ 145 mg/dl

### **Complications of Gestational Diabetes Mellitus**

GDM is recognized as a common complication during pregnancy but is often a severe and neglected threat to maternal and fetal health. Hyperglycemia has a well-documented effect on both short term and long-term outcomes in mother and fetus. GDM has the potential to influence generations of outcomes.

#### *Maternal Complications*

Hyperglycemia has the potential to result in perinatal complications, as well as postnatal complications. For individuals with GDM, risks include gestational hypertension, pre-eclampsia, polyhydramnios, Caesarean section, and shoulder dystocia. Damage to endothelial cells as a result of high plasma glucose leads to vascular dysfunction and in turn, hypertension.<sup>21-24</sup> This is seen during the perinatal period and into the postpartum period. Both hypertension and diabetes are risk factors for pre-eclampsia, which can be life-threatening. Pre-eclampsia is a complication of pregnancy that results in high blood pressure, swelling of the upper and lower extremities, and proteinuria.<sup>1-3, 21-24</sup>

In normal pregnancies, hyperglycemia improves in the postpartum period. However, individuals diagnosed with GDM may observe insulin resistance and beta cell impairment that persists into the post-partum period. This is often due to the presence of these in the antepartum period. These abnormalities contribute to an increased risk of developing type 2 diabetes later in life. GDM can increase the risk of type 2 diabetes up to 50%.<sup>9, 10</sup> In addition, the risk of GDM reoccurring in future pregnancies is higher for women that have previously developed GDM.

### *Fetal Complications*

There are specific periods in which tissues and organs are increasingly sensitive to their external environment, which can later impact their susceptibility to disease. These periods include the perinatal period and the intrauterine environment for the fetus. With regards to GDM in the mother, there are immediate complications and long-term complications for the fetus. Maternal glucose can be transported across the placenta, while maternal insulin cannot. The fetus receives most of its glucose from maternal blood as the fetus only has limited availability to produce glucose.<sup>1,2</sup> While the fetus requires glucose for proper development, high levels of glucose transported from maternal blood are not required. When maternal plasma glucose is elevated, more glucose crosses the placenta, which stimulates insulin production by the fetus. Consequences of this abnormality include hypoglycemia at birth, which results from the sudden absence of maternal glucose in the continued presence of fetal insulin. Elevated glucose and insulin also contribute to fetal adiposity and increase in neonatal size at birth. Macrosomia

increases risk of shoulder dystocia, birth injury, and Caesarean section.<sup>11, 13, 16</sup> Fetal hyperinsulinemia not only affects birth size but also contributes to fetal hypoxia. Fetal hyperinsulinemia alters the synthesis of lung surfactant, thus increasing the risk of acute respiratory distress syndrome (ARDS).<sup>1-10</sup>

### *Childhood and Adult Complications*

The long-term impact of GDM exposure in utero has not been fully established. Studies have found that exposure to GDM can lead to adverse cardiovascular phenotypes, which includes increased adiposity, insulin resistance, increased systolic blood pressure, and risk of circulatory disease. Another relationship that has been investigated is that between GDM exposure and increased risk of prediabetes, diabetes, metabolic syndrome, and a higher BMI.<sup>13, 16</sup>

## **Gestational Diabetes Management**

### *Lifestyle Management*

Upon diagnosis of GDM, pregnant women should be educated about the importance of lifestyle management including nutritional modifications, physical activity, and weight management. Education pertaining to lifestyle changes should be individualized per patient according to current diet, level of physical activity, and pre-gestational weight. General guidance in pregnancy is for women to consume three meals and two snacks per day. The ADA recommends a balanced diet consisting of portion control, healthy fats, complex carbohydrates and approximately 20% protein. The DRI recommends a

minimum of 175 grams of carbohydrate, a minimum of 71 grams of protein, and 28 grams of fiber.<sup>23</sup> All diets should limit saturated fats and promote monounsaturated and polyunsaturated fats. Trans fats should be completely avoided. In addition, women are encouraged to limit simple carbohydrates as these contribute to higher post prandial glucose excursions compared to complex carbohydrates. Meal and snack components are further tailored to fit the individual's preferences, allergies, and other relevant factors. Women should keep a log of their meals and snacks, as well as post prandial glucose readings.<sup>23</sup>

Physical activity is encouraged during pregnancy with attention to pre-existing injuries and comorbidities. Current recommendations support 30 minutes of moderate intensity exercise approximately five days per week. Moderate exercise during pregnancy has been shown to lower the risk of GDM development, hypertensive disorders, and preterm birth. The potential benefits of exercise during pregnancy extend beyond the perinatal period and into the postnatal period with a strong contribution to lowering the risk of post-partum depression.<sup>24</sup> Light exercises are an alternative for pregnant women that cannot engage in moderate intensity exercise. High impact exercises should be avoided as they can contribute to abdominal trauma.

### *Pharmacologic Therapy*

Nutrition and physical activity modifications are considered first line therapy for treatment of gestational diabetes. If nutritional and physical activity modifications are not sufficient to achieve glucose control, pharmacologic therapy should be initiated.

Currently, there are no widely accepted protocols that have defined the threshold for pharmacologic intervention. Typically, pregnant women should follow dietary and exercise recommendations for a period of 10 to 14 days to evaluate euglycemia. Euglycemia failure is defined as failure of more than 50% of glycemic measures above target ranges.<sup>23, 24</sup>

Insulin and oral medications have been studied for management of diabetes mellitus in pregnancy. Insulin is considered the first line agent for treatment of GDM in the United States. Oral agents, such as metformin and glyburide, may be used as an alternative for a subset of women but they should be informed of the limited research and efficacy, as well as long-term consequences for the fetus.<sup>2, 23, 24</sup> Insulin dosing is titrated using the individual's body weight, gestational age, and glycemic profile. Insulin can be administered as a long-acting dose, a short acting dose or a combination of both depending on when the individual is experiencing hyperglycemia. In either case, self-monitoring of blood glucose is important to assess the efficacy of the insulin regimen, including periods of hypoglycemia.

### *Self-Monitoring Blood Glucose (SMBG)*

Management of GDM requires a multi-disciplinary approach including gestational diabetes education, dietary modifications, nutrition monitoring, physical activity, and pharmacological management. Self-monitoring of blood glucose via glucometer is an important component of this multi-disciplinary approach as it allows insight as to how effective each of the components are and whether modifications are required.

Independent of subtype, diabetes mellitus has better outcomes when tight glycemic control is achieved. In GDM, glycemic control is at the forefront given its potential to have adverse consequences on both mother and fetus.<sup>2, 23, 24, 25</sup>

Blood glucose measurements can be evaluated by obtaining a hemoglobin A1c, which refers to the average blood glucose over 3 months or self-monitored blood glucose. A1c provides insight into overall glycemic control, whereas self-monitoring blood glucose allows for insight into the day-to-day glycemic variability. The ADA recommends pregnant women achieve an A1c of less than 6% without significant hypoglycemia. If hypoglycemia persists, the A1c target can be increased to no more than 7%. Self-monitored blood glucose is the process by which an individual performs a fingerstick using an FDA approved glucometer.<sup>23</sup> The ADA recommends fasting and postprandial self-monitoring of blood glucose for individuals with gestational diabetes and those with pre-existing diabetes. Additional monitoring may be recommended for individuals who exercise, among other things. However, fasting and post-prandial glucose measurements provide insight into glucose control and allows for optimal glucose management. Fasting blood glucose measurements are important because they allow clinicians to monitor how well the patient's body can manage glucose in the absence of food. Post-prandial glucose readings are important because they allow clinicians to see monitor well the patient's body responds to food from a glycemic standpoint. Current recommendations indicate a fasting glucose of less than 95 mg/dL and either a one-hour post-prandial glucose of less than 140 mg/dL or a two-hour post-prandial glucose of less than 120 mg/dL.<sup>2, 23, 24</sup>

A1c measurements are independent of the instrument and the user, while SMBG accuracy and resulting treatment is entirely dependent on the user and the glucometer used. Glucose meters that meet FDA requirements are considered to provide the most reliable data for diabetes management. Despite FDA clearance, substantial variation among glucose meters remains. Therefore, it is encouraged that individuals use one meter to ensure reproducibility. While this can influence SMBG, this is not the major driver for the problems that exist for patients with diabetes and blood glucose monitoring. SMBG has and continues to be a mainstay of GDM treatment to achieve tight glucose control. However, SMBG continues to have poor reliability and poor adherence for patients with gestational diabetes. Both of which influences glycemic variability and maternal and fetal outcomes. An alternative to SMBG is the use of continuous glucose monitoring (CGM).

### *Continuous Glucose Monitoring*

Continuous glucose monitoring (CGM) refers to a type of diabetes technology that allows constant real-time monitoring of blood glucose. CGM measures interstitial glucose, which correlates with plasma glucose until glucose is rapidly rising or falling. CGM devices are typically worn on the upper extremity of the user and require site changes every 7-14 days. CGM provides an abundance of data compared to SMBG, which should allow for better analysis of glycemic profiles in gestational diabetes.<sup>25, 26, 27, 28, 29</sup>

### **Existing Research on CGM Use in Pregnancy**

Blood glucose monitoring during pregnancy is a crucial component of the multidisciplinary treatment plan for pregnant women with gestational diabetes. Blood glucose monitoring provides insight into the effectiveness of treatment intervention and the glycemic profile of the individual. However, glucose monitoring is commonly performed via SMBG, which requires adherence from the individual. In addition, SMBG only provides glucose measurements at specific time points. Due to the need to fully evaluate an individual's glycemic profile, newer devices have been developed that provide more frequent glucose measurement, improve patient compliance, and improve accuracy in glucose measurements. CGM technology is very promising as it allows for a continuous measure of interstitial glucose. CGM has been used extensively with individuals with Type 1 diabetes and Type 2 diabetes but the use of CGM technology has not been extensively studied in pregnant women with gestational diabetes.<sup>23,24,25,26,27,28,29</sup>

In a 2003 study, Yogev et. al. investigated the efficacy of a continuous glucose monitoring system for treatment adjustment in patients with diabetic pregnancy treated with insulin.<sup>28</sup> This pilot study consisted of eight consecutive women with diabetic pregnancies who were recruited via routine clinical visits. Each of the eight women had a gestational age that ranged from 24 to 32 weeks. Six of the eight patients had a prior diagnosis of Type 1 diabetes and the remaining two patients were diagnosed with gestational diabetes during pregnancy. In addition, all the women were treated with multiple daily insulin injections and received dietary education, as well as individual counseling. Baseline data included demographic, gravidity, parity, A1c, fructosamine,

and plasma glucose. All patients were educated and instructed on how to use the MiniMed CGM and placement of the CGM was performed by the same nurse for each of the eight women. During CGM wear, the women were blinded to CGM measurements and were instructed to perform six to eight capillary glucose measurements daily. CGM devices were worn for a total of 72 hours, reviewed by a physician who made appropriate insulin adjustments, and then worn again for additional 72 hours two to four weeks after insulin adjustments were made.<sup>28</sup> Using a Chi-square test to compare categorical variables and a paired t-test to determine the statistical significance ( $p < .05$ ), statistical analysis for the eight women was performed. There were a total of 267 simultaneous paired glucose measurements by SMBG and CGM for the two periods of the study. The absolute mean difference between the two was unremarkable with a value of  $0.72 \pm 0.32$  mmol/L (range 0-2.1 mmol/L).<sup>28</sup> For 82% of the paired measurements, the absolute difference did not exceed 0.55 mmol/L.<sup>28</sup> The average correlation coefficient between glucose measurements by CGM and by SMBG was  $0.94 \pm 0.02$  with a slope of 0.933. In each of the eight patients, insulin adjustments that were first made using SMBG data was further adjusted after review of CGM data.<sup>28</sup> The additional adjustment was warranted due to the presence of nocturnal hypoglycemia and post-prandial hyperglycemia. The most common insulin adjustments were a reduction in basal insulin to reduce nocturnal hypoglycemia and an increase in nutritional insulin to account for post-prandial hyperglycemia. The additional glucose measurements provided by CGM revealed prolonged hyperglycemia throughout the day, which is often missed using SMBG. In addition, numerous hypoglycemic events were observed via CGM that were

not observed via SMBG. These findings, while on opposite ends of the spectrum, both have negative consequences for mother and fetus. While this study was the first to evaluate the relationship between CGM use and insulin adjustments, there were a few limitations in this study. Pilot studies such as this are small-scale studies, whereas a randomized controlled trial would allow for a control group and an intervention group to better compare CGM to traditional SMBG and resulting insulin adjustments. In addition, the study sample was very small, which in turn creates a limitation for the power of the study. Furthermore, this study did not solely investigate the use of CGM with patients with gestational diabetes. Individuals with pre-existing diabetes compared to their GDM counterparts may have different requirements and attitudes towards CGM and SMBG, which is an important component. Finally, CGM use was limited to two 72-hour periods, which does not provide insight into the glycemic variability that exists throughout a pregnancy course.

Like Yogev et. al., McLachlan et. al. investigated the usefulness of CGM in diabetic pregnancies for insulin adjustments.<sup>30</sup> However, advanced the study further to also evaluate patient tolerability and the perception of usefulness from a physician standpoint. A total of 55 women with either type 1, type 2, or gestational diabetes were recruited into the study for use of CGM at times during their pregnancy in which glucose excursions were most likely to occur.<sup>30</sup> Study participants wore CGM for 72 continuous hours, during which time they also continued with SMBG at least four times per day and multiple daily insulin injections. Participants continued to follow their usual diet and lifestyle routine. A total of 68 CGM tracings were obtained from the 55 women included

in the study.<sup>30</sup> Of the 55 CGM tracings, 42 were assessed as providing additional information when compared to using SMBG readings alone for interpretation of glucose control.<sup>30</sup> The CGM tracings revealed postprandial hyperglycemia that was not identified using SMBG readings. Regarding tolerability of CGM, 37 of 48 (77%) women reported that the benefits of CGM use outweighed the inconvenience.<sup>30</sup> Nearly all, 44 of 48 women (92%), reported CGM use as easy or very easy to use.<sup>30</sup> Finally, 43 of 48 women (90%) reported their understanding of glucose control was either better or clearly better after 72 hour use of CGM.<sup>30</sup> In this study, CGM use resulted in additional information independent of diabetes type but generated the most information for individuals with type 1 diabetes. This can be attributed to the pathophysiology of type 1 diabetes and the resulting glucose variability. However, CGM use revealed overnight hypoglycemia and hyperglycemia and postprandial hyperglycemia. A comparison of SMBG to CGM measurements resulted in absolute mean difference of 12%, which indicates no significant differences between the two glucose measurement options.<sup>30</sup> During this study, CGM and SMBG data was reviewed by the study endocrinologist to determine whether CGM provides additional information that alters clinical management. In contrast to the 2003 study, the data was not blinded.<sup>30</sup> It may have provided some benefit to have the glucose assessment performed by a third blinded party. An additional limitation of this study is that, while the study population consists mostly of patients with gestational diabetes, it also includes other subtypes as well. Use of CGM was chosen for patients during the times in which glucose excursions are likely, which can potentially have an impact on the results. It also does not provide the level of insight needed to better

understand the glycemic profile of a pregnant women. From the study, it is not clear as to whether all the patients enrolled required insulin during the study which is another consideration.

Contrary to most studies performed using CGM technology, Kestila et. al. investigated the effects of CGM and SMBG use and initiation of anti-hyperglycemic medications in pregnant women with gestational diabetes.<sup>31</sup> The aim of the study was to investigate whether SMBG was an adequate means to determine the need for anti-hyperglycemic medications compared to CGM. A total of 73 pregnant women with GDM were enrolled into the study and randomized to either the CGM group or the SMBG group. Medtronic MiniMed CGM was used for the CGM group and Ascensia Elite meter and Super Glucocard II meter were used for the SMBG group.<sup>31</sup> All women enrolled in the study received dietary counseling and education on how to measure glucose. Treatment decisions were based on measurements obtained via CGM or SMBG. In addition to glucose observation, hospital records of mother and fetus were evaluated after pregnancy to identify pregnancy outcome variables, such as pregnancy induced hypertension, pre-eclampsia, premature rupture of membranes, still birth, birth weight, and height. A total of 36 women were randomized to the CGM group and 37 women were randomized to the SMBG group.<sup>31</sup> At baseline, there were no statistically significant differences between the two groups. This includes parity, maternal age, and pre-pregnancy BMI. With respect to indications for medical treatment, 16 of 36 patients in the CGM group had indications for initiation of anti-hyperglycemic medications based on CGM data.<sup>31</sup> However, if these same patients only used SMBG, only five of the 36

patients would have indications for initiation of anti-hyperglycemic medications. Among both groups, 31% of patients in the CGM were started on anti-hyperglycemic medications compared to 8% in the SMBG group.<sup>31</sup> CGM use in this patient population provided more glucose values for evaluation, which was better for the detection of hyperglycemia, especially post-prandial hyperglycemia. In addition to providing evidence to support the use of CGM, this study also provided insight into optimal timing for measurement of blood glucose via glucometer. Like prior studies, the use of CGM in this study was very limited.

As CGM technology expands, research continues to expand to investigate CGM utilization in pregnancy. Wei et. al. conducted a prospective, observational, open label randomized controlled trial to determine whether CGM use during pregnancy reduced gestational weight gain (GWG).<sup>32</sup> Pregnant women diagnosed with gestational diabetes diagnosed after 24 weeks of gestation were recruited into the study. Pregnant women were excluded if they had a diagnosis of diabetes mellitus, previous treatment for GDM, infection, or severe metabolic, endocrinological, or psychological comorbidities. Participants enrolled in the study were randomized into one of two groups: CGM or SMBG. The CGM group was further divided into early and late subgroups, which refers to either the second or third trimester. All participants were provided with nutrition counseling and education pertaining to blood glucose measurements. Pre-pregnancy BMI, gestational weight gain, and A1c were evaluated among other factors. After randomization, there were 51 participants in the CGM group and 55 participants in the SMBG groups. The groups did not differ in age, education, family history, and pre-

pregnancy BMI.<sup>32</sup> Analysis of the data consisted of Fisher's exact test, Pearson's  $\chi^2$  test, and student's t-test when appropriate.<sup>32</sup> Several outcomes were observed in this study with an emphasis on gestational weight gain. Results indicated that the CGM group had a lower proportion of patients that experienced excessive weight gain and a higher proportion of patients with appropriate weight gain. There were fewer patients in the CGM group that gained an inadequate amount of gestational weight.<sup>32</sup> Finally, women that wore CGM in the early stage gained less weight than women that wore CGM in the later stage of pregnancy.<sup>32</sup> Other outcomes observed include maternal glycemic variability, medication initiation, and maternal and fetal outcomes. The data supports the use of CGM use in pregnancy to reduce gestational weight gain. While HbA1c was lower in the CGM group, it was not statistically significant. However, insulin initiation was higher in the CGM group compared to the SMBG group. In addition, the initiation of insulin resulted in reduced periods of hyperglycemia without causing an increase in hypoglycemia. It is unclear as to whether CGM had a significant impact on maternal and fetal outcomes. This was the first study to examine the relationship between CGM use and GWG. This study provided new insight into use of CGM and the outcomes of diabetic pregnancy. However, the sample size of this study is rather small, which limits statistical power. As with earlier studies, this study captured a very small period of glycemia during pregnancy.

Current research supports the use of CGM during pregnancy for women with gestational diabetes. A 2018 study by Paramasivam et. al. sought to further support this with an open-label randomized controlled trial to evaluate the therapeutic effect of CGM

use in women specifically with insulin-treated GDM.<sup>26</sup> A total of 57 women were enrolled in the study in Malaysia.<sup>26</sup> Women with type 1 diabetes, type 2 diabetes, or newly diagnosed overt diabetes were excluded from the study.<sup>26</sup> The women enrolled were randomized into one of two groups: CGM use at 28, 32, and 36 weeks gestation or standard antenatal care with SMBG.<sup>26</sup> In contrast to other studies which utilized CGM for 72-hour time periods, this study obtained CGM data for 7 days at three different time points during pregnancy, which allowed more data and insight into glycemic variability during pregnancy. Compared to standard antenatal care, the additional use of CGM improved glycemic control. Changes in A1c were compared in both groups and was significantly lower in the group which used CGM.<sup>26</sup> In addition, the use of CGM resulted in reduced hyperglycemia without increasing hypoglycemia. The improvements observed are not solely due to CGM use but the response to data obtained from CGM. Responses include more aggressive insulin therapy to reduce hyperglycemia, as well as maternal lifestyle changes secondary to observing prolonged hyperglycemia.

A more recent study by Zaharieva et. al. sought to expand the current knowledge of hyperglycemia by exploring the patterns of hyperglycemia in pregnant women with gestational diabetes.<sup>33</sup> In addition, they also explored whether CGM was more effective than OGTT at predicting the subsequent demands associated with pregnancy. This was an observational study with a study population of women diagnosed with GDM between 24- and 28-weeks gestation.<sup>33</sup> All participants received education on nutrition and lifestyle interventions as well as SMBG. Participants wore Medtronic CGMs for a period of seven days, in addition to SMBG four times daily. Data from 90 participants was evaluated and

revealed nocturnal hyperglycemia in patients not currently on insulin therapy. Over half (60%) of the participants had nocturnal hyperglycemia for more than 10% of the time.<sup>33</sup> This is an important finding given the relationship between maternal hyperglycemia and fetal outcomes.<sup>33</sup> While prior studies have used CGM data to make treatment decisions, this study did not allow access to CGM data. The study team made clinical decisions solely based on SMBG data. This can be seen as a strength or limitation of the study. As a strength, it allows for the evaluation of blood glucose trends without intervention. A true limitation of this study is the small sample size.

Based on existing research, CGM technology is promising in clinical practice for women with gestational diabetes. CGM has allowed for more insight into the glycemic profile of a woman with gestational diabetes. However, many of the studies performed have small sample sizes, which does not provide a true reflection of GDM. In addition to the small sample sizes, the participants are not reflective of the racial and ethnic groups that are more commonly burdened by this disease. Finally, the existing research has not demonstrated the impact of CGM use during the entire pregnancy and its impact on maternal and fetal outcomes.

## **METHODS**

### **Study Design**

The study will be a prospective, open label randomized controlled trial in women with gestational diabetes to investigate the application and utility of continuous glucose monitoring for the entire duration of pregnancy by comparing continuous glucose monitoring to traditional self-monitored blood glucose monitoring during pregnancy.

Patients will be recruited from local health centers after diagnosis of gestational diabetes mellitus. Once enrolled, patients will be randomized to either monitor glucose via fingersticks or wear a continuous glucose monitor. Data will be compiled during pregnancy to evaluate post prandial glucose differences.

### **Study Population and Sampling**

The study population will consist of pregnant women who are patients of Boston Medical Center and affiliated community health centers. All women will be recruited during routine clinic visits. Women over the age of 18 with a gestational age of 24 to 28 weeks and diagnosis of GDM will be eligible for participation in this study. The study will recruit approximately 384 women that meet the inclusion criteria for this study. The estimation of sample size for this study is based on the percentage of pregnancies per year with a GDM diagnosis, a 5% margin of error and a 95% confidence interval. The CDC approximately an average number of births at 6, 369,000 births per year.

Approximately 7% of pregnancies in the United States will carry a diagnosis of

gestational diabetes. The GDM diagnosis must be made using the ACOG guidelines.

Inclusion and exclusion criteria for participation in the study is as listed in Table 2.

**Table 2. Inclusion and Exclusion Criteria**

<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<ol style="list-style-type: none"><li>1. Patient must be over age 18 at time of recruitment.</li><li>2. Patient must have diagnosis of gestational diabetes mellitus at &gt;24 weeks gestation.</li><li>3. Gestational diabetes mellitus diagnosis must be done using appropriate diagnostics.</li></ol>	<ol style="list-style-type: none"><li>1. Patient with history of Type 1 diabetes.</li><li>2. Patient with history of Type 2 diabetes.</li><li>3. Patient with a history of preterm delivery, macrosomia, respiratory distress syndrome, or congenital defects.</li><li>4. Patient with significant history of tobacco use or recreational drug use.</li></ol>

### **Intervention**

All study participants, independent of study arm, will receive gestational diabetes management education at the start of the study. This includes general information about gestational diabetes, as well as pharmacological and non-pharmacological management of gestational diabetes. Non-pharmacological management will include nutrition

counseling and general exercise recommendations. Each study participant will also be provided education on how to measure plasma glucose with instructions on when to measure glucose and how to record the data. The eligible study participants will then be randomly assigned into either the control group or the intervention group. The control group will receive the current standard of care for gestational diabetes. This includes blood glucose monitoring four times daily. This will consist of daily monitoring of fasting blood glucose and one to two hours after meals. There is insufficient data to determine whether checking one hour or two hours postprandial is superior. Therefore, study participants will have the option of checking at either time point. Whether it is one or two hours post prandial, both measures are very predictive of glucose control and provide insight about the potential for maternal and fetal complications.<sup>20,21</sup> In addition to the initial dietary counseling, the participants will also have ongoing appointments with registered dietitians for carbohydrate adjustments, as needed throughout pregnancy. Women with GDM are encouraged to participate in exercise as this is known to decrease peripheral insulin resistance. Exercise recommendations should be individualized based on each patient profile. If the patient is unable to achieve glycemic control with non-pharmacologic treatment, insulin will be initiated and titrated by their primary care provider. Finally, these patients will have access to both their obstetrician, as well as access to the study coordinators if any assistance is needed.

The participants that are randomly assigned to the intervention group will have the same recommendations with the exception of blood glucose monitoring. For patients in the intervention group, rather than manually checking their blood glucose, they will be

using a continuous glucose monitor to check their blood glucose at the same time points. However, patients will be required to perform finger sticks for CGM calibration and during times at which they feel as if they may be hypoglycemic and hyperglycemic. These patients are still expected to record blood glucose values in a journal as this will provide immediate feedback regarding whether the respective blood glucose is within the target range. Table 3 reflects blood glucose targets that have been widely accepted for patients with gestational diabetes.

**Table 3. Blood Glucose Targets**

Time of Day	Glucose Target
Fasting plasma glucose; before first meal of the day	<95 mg/dL
1-hour Postprandial Glucose	<140 mg/dL
2 hours Postprandial Glucose	<120 mg/dL

**Study Variables and Measures**

The primary outcome of this study will be postprandial glucose readings as this is a strong indicator of glycemic control in gestational diabetes compared with hemoglobin A1C. At entry of the study, demographic data, gravidity, parity, and body mass index (BMI) will be recorded. Hemoglobin A1C, fructosamine and plasma glucose will be measured as well. Demographic data will include race, age, primary language, and education level. In addition, data will be collected on nutrition, exercise, and use of

insulin during pregnancy. Finally, we will include data pertaining to ED visits and hospitalizations pertaining to pregnancy.

### **Recruitment**

All women will be recruited from Boston Medical Center and affiliated community health centers, including Mattapan Community Health Center. Participants will be recruited by obstetric clinicians during their visits. Obstetric clinicians will be educated on this study once approved so they are aware of those patients that may potentially enroll into the study. All clinicians will be provided a checklist that will alert them to suggest enrollment into the study. They will then review the patient's medical history and obstetric history to determine whether the patient satisfies the inclusion criteria for the study. At each site, there will be study coordinators available to meet with the patient to provide additional information, answer questions, and obtain written and signed consent from the patient. Communication with study participants throughout the duration of the study will be based on the patient's preference. They will have the option for phone calls and/or secured messaging.

### **Data Collection**

All patients enrolled in the study will have baseline data recorded. This data includes pressure, heart rate, body weight, height, BMI, waist and hips circumference, self-reported pregnancy BMI, treatment of gestational diabetes and index pregnancy, perinatal outcomes of the index pregnancy, and A1c. For the weekly logs of blood glucose,

nutrition, and activity, patients will have the option of using a physical logbook or an electronic logbook based on patient preference. The electronic logbooks will sync directly to the data cloud, whereas the physical logbooks will require manual input upon receiving them at the clinic visits. The intervention group will be wearing a continuous glucose monitor which has the ability to store and sync information to a data cloud. Relevant data from clinic visits will be recorded as well.

Data will be entered into the REDCap data management system. REDCap is a secure web application that is commonly used to capture data for clinical research and allow for the creation of databases. All data will be fully encrypted. Data will then be transferred to an Excel sheet as needed for analysis.

### **Data Analysis**

The primary outcome for this study will be to assess glucose variability among the intervention and the control groups. Glucose variability will be based on the total time at which the subjects' blood glucose values are either below, within, or above targets.

Using the data obtained from the continuous glucose monitors, analysis will be performed to determine whether there is a statistically significant difference between the two study arms. To analyze this, a t-test will be used.

In addition, demographic information will be summarized as well. Summary statistics will be performed using the data obtained from the control group and the data from the intervention group. For each of these parameters, the mean values will be compared. The results will be presented as the mean  $\pm$  SD. Maternal and fetal outcomes will be

measured but will not have full analysis since all outcomes may not be present at the time of birth.

### **Timeline and Resources**

The study will take approximately three years to complete. This includes the time to get approval for the study, recruitment, and data analysis. It is anticipated that IRB approval will take approximately one month as this will be submitted under an expedited review. Patients will be recruited as they are diagnosed and recruitment will continue until a sufficient number of patients are enrolled as determined by sample size. This study will require a principal investigator, study coordinators, dietitians, and statistician. In addition to personnel, this study will also require continuous glucose monitoring kits, glucometers, lancets, and testing strips.

### **Institutional Review Board**

This study protocol will be submitted to the Boston University Medical Center Institutional Review Board for expedited review under the 45 CFR 46.110 criteria. Categories of research that may be reviewed through an expedited review procedure included those in which the research activities do not present more than minimal risk to human subjects. Areas for expedited approval include not putting subjects at risk of criminal or civil liability, damaging their financial standings, viability, insurance, reputation, or breach of confidentiality. Continuous glucose monitoring is a minimally invasive way to monitor blood glucose and has been well-established as another means of

glucose monitoring during pregnancy. Historically, there have been only minor local adverse events reported with use of continuous glucose monitoring. These include hypersensitivity, itching, pain, redness, burning, and subcutaneous hemorrhage. Additionally, sleep disturbances, attention deficits, problems related to the CGMS monitor, and adhesive tape irritability. None of which resulted in sensor withdrawal.

## CONCLUSION

### Discussion

Continuous glucose monitoring provides significant insight into glycemia during pregnancy compared to self-monitored blood glucose via fingersticks. The primary objective of this study is to determine whether continuous glucose monitoring during pregnancy influences glycemic control. The findings of this study will likely support the idea that continuous glucose monitoring is superior to self-monitored blood glucose readings due to the ability to capture nearly constant blood glucose levels compared to the readings captured by fingersticks. The accessibility to blood glucose via CGM will likely have a positive influence on maternal behavior during pregnancy. Post-prandial glucose excursions will likely be lower in the CGM population compared to controls.

The present study has several limitations. Adherence to self-monitored blood glucose monitoring has been a long-standing problem and continues especially in the control population. Patients enrolled in the study will be educated on the importance of monitoring but there are limitations in enforcing monitoring for patients outside of the clinical environment. Another limitation of the study is having a fingerstick matched to CGM readings for individuals in the CGM group. Third, all enrolled participants will be provided with education on non-pharmacological treatments for GDM including nutritional changes and the incorporation of physical activity, both of which have been established as effective treatments for gestational diabetes. However, it is difficult to determine how much these lifestyle interventions impact glycemic variability during pregnancy. Lifestyle interventions can have varying levels of individual effects. The

patient's physiology, comorbidities, medications among other factors must be considered. Finally, while this study will primarily recruit from health centers with a diverse population, there are pregnant women that would be ideal participants that refuse to give informed consent. Gestational diabetes disproportionately affects minority individuals, however, there is no way to control which pregnant women choose to participate in the study.

While there are limitations for a study of this nature, there are also considerable strengths. This study is the first to evaluate the contribution of continuous glucose monitoring throughout the entire duration of pregnancy once diagnosed with gestational diabetes. Previous studies have only examined the use of CGM for three to seven days during pregnancy. This study provides a significant amount of data and various profiles of gestational diabetes that can be further studied and potentially used to adjust treatment approaches in the future. Second, this study is also the first of its kind with a study population that is more representative of the individuals upon which GDM has the highest burden which is pregnant women on non-white race and of lower socioeconomic status. Finally, use of CGM in turn leads to higher glycemic control thus reducing the risk of detrimental fetal and maternal outcomes.

## **Summary**

Continuous glucose monitoring is a valuable tool to study maternal glycemic profiles during pregnancy especially those diagnosed with gestational diabetes. Continuous glucose monitoring measures plasma glucose continuously, which allows for the

detection of hyperglycemia over the entire postprandial period. This is an important detection as the post prandial period and glycemia during this time is highly indicative of overall glycemic control and the risk of adverse maternal and fetal outcomes. In addition to the detection of hyperglycemia, it is also more effective at the detection of hypoglycemia and overall glycemic variability. Research has also shown that CGM data is more comprehensive and is convenient for patients. This is the first study to utilize CGM technology for the duration of pregnancy. In addition, this study will also provide more insight into pregnant users' acceptability especially in the minority population. Further research with larger sample sizes should be performed, as well as longitudinal studies that follow mother and fetus, to evaluate the development of adverse outcomes.

### **Clinical and/or Public Health Significance**

There is sufficient evidence that CGM technology is superior to SMBG and effectively captures gestational glucose profiles and improves maternal glycemia with an emphasis on the post-prandial period. This is likely multi-factorial with contributions from lifestyle interventions and medication adjustments, all of which contributes to improved glycemic control, which can have significant impact on maternal and fetal outcomes. For example, approximately 50% of individuals diagnosed with gestational diabetes go on to develop type 2 diabetes. This also has implications for the fetus. This data supports the use of CGM as standard of care for pregnant women diagnosed with gestational diabetes and those of higher risk to develop gestational diabetes.

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## CURRICULUM VITAE





