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SCHOOL OF MEDICINE

Thesis

EFFECT OF WIRELESS GLUCOSE METER ON HYPERGLYCEMIA AND PRENATAL VISITS

by

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EFFECT OF WIRELESS GLUCOSE METER ON HYPERGLYCEMIA AND PRENATAL VISITS

CHENIN VERONICA POELS

ABSTRACT

Gestational diabetes mellitus can have devastating effects in the health of the mother and child. While pregnancy rates are decreasing, prevalence of GDM is increasing, and it is estimated that up to 9% of pregnancies are complicated by diabetes in the United States. Traditional treatment and monitoring of gestational diabetes mellitus relies on patient's compliance to document glycemic levels. This proposed study will evaluate the effectiveness of telemedicine using a wireless glucose meter that transmits information to the providers in real time. The prospective open cohort randomized clinical trial will take place in medical centers around Boston. Two hundred participants diagnosed with gestational diabetes will be recruited over a period of 24 months from these centers and randomly placed into two groups. One group will follow traditional treatment, and the intervention group will be asked to use iGlucose meter system. Glycemic levels and frequency of prenatal visits will be evaluated and analyzed. If telemedicine proves to be efficacious in treating GDM, this would give providers a new treatment plan to consider to effectively manage blood glucose levels and reduce poor perinatal outcomes related to gestational diabetes mellitus.

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LIST OF ABBREVIATIONS

ACOG .....American College of Obstetics and Gynecology

ADA.....American Diabetes Association

AJOG ..... American Journal of Obstetrics and Gynecology

BG..... Blood Glucose

BMI..... Body Mass Index

DM..... Diabetes Mellitus

EFW .....Estimated Fetal Weight

GDM .....Gestational Diabetes Mellitus

HA1c.....Hemoglobin A1c

HAPO.....Hyperglycemia and Adverse Pregnancy Outcomes

hPGH.....Human Placental Growth Hormone

hPL ..... Human Placetal Lactogen

IADPSG ..... International Association of the Diabetes and Pregnancy Study Groups

IGT.....Impaired Glucose Tolerance

IOM.....Institute of Medicine

IRB..... Institutional Review Board

IUFD .....Intrauterine Fetal Demise

LGA .....Large for Gestational Age

NDDG.....National Diabetes Data Group

NICU.....Neonatal Intensive Care Unit

NIH ..... National Institutes of Health

OGTT..... Oral Glucose Tolerance Test

SGA..... Small for Gestational Age

T2DM.....Type 2 Diabetes Mellitus

INTRODUCTION

Background

Gestational diabetes mellitus (GDM) is a condition that develops during pregnancy, in which the woman develops carbohydrate intolerance, similar to existing diabetes mellitus (DM). It is estimated that up to 9% of pregnancies are complicated by diabetes, with most of the glucose intolerance having been exacerbated during pregnancy. Women with GDM have a higher risk of complications prior to delivery and during, including preeclampsia and having to undergo a C-section. Maternal risks after delivery also include development of DM, while fetal risks include macrosomia (also risk for mother), neonatal hypoglycemia, hyperbilirubinemia, shoulder dystocia and birth trauma.

In 2014, the U.S. Preventive Services Task Force recommended that all pregnant patients be screened for GDM at 24 weeks of gestational age. Screening includes a 50mg oral glucose tolerance test (OGTT), and a 1-hour venous glucose determination for patients with low suspicion of pre-existing diabetes. If a patient is suspected of having pre-existing diabetes or metabolic syndrome (overweight with BMI >25 or 23 in Asian Americans, increased abdominal girth, family history of DM, previous GDM, hypertension, polycystic ovarian syndrome, cardiovascular disease), early pregnancy screening includes a fasting blood glucose followed by a 75mg glucose load 2-hr plasma glucose measurement. A more widely accepted approach, called the two-step approach, discards the use of a 75mg glucose solution and substitutes it with an initial oral glucose challenge test of 50mg followed by a 100mg oral glucose tolerance test where blood glucose levels are checked 1 hr, 2hrs and 3hrs after ingestion of oral solution. The oral

glucose tolerance test (OGTT) is only performed if the patient screened positive with the 50mg oral glucose solution, reducing the need to subject patients to this test. Screening thresholds differ by institutions, with special consideration regarding patient population and individual patient.

Treating GDM can significantly reduce the rate of newborn complications, mentioned earlier, and development of preeclampsia. The frequency of C-sections is also reduced when GDM is well controlled. Treatment is not limited to just medications, but dietary counseling and physical exercise encouragement are the primary treatments of GDM. Women who are diagnosed with GDM should be counseled about nutrition and exercise before prescribing them insulin or metformin.

There exist various different types of classification of GDM. Type A, which is diabetes that originated during pregnancy, is further divided into two subtypes. Type A1GDM individuals are patients whose GDM is diet-controlled and usually tend to have less pregnancy and delivery negative outcomes than A2GDM individuals. Type A2GDM is the class assigned to patients who are unable to control their glycemic levels with diet or exercise and require insulin treatment. Type B to T, are types of pre-gestational diabetes that existed prior to pregnancy.

Statement of the Problem

Recommended monitoring of GDM is much more intensive than for non-pregnant patients with DM; daily glucose monitoring four times a day, once after waking up (fasting) and the rest after each meal. Monitoring schedule and treatment might vary, depending if the patient has elevated blood sugars at a certain time of day but normal

throughout of the day. Clinics will prescribe or provide a glucometer which stores the last week's blood glucose values, and is reviewed on the next prenatal visit. Adjustments of the medication or monitoring can be made if needed, and the next visit is scheduled. However, having to present to the prenatal clinic frequently might be tedious to some patients, especially to patients who do not have access to transportation, have children at home to take care of, or cannot afford to take one day off work per week.

With new technology emerging, implementing technology in medicine is key in this time and age. Phone applications have evolved to transfer data and improve quality of life, either by setting reminders or easing communication with recipients who are across the city, state or country. Incorporating health phone applications will enable patients' access to providers and vice versa. Data entered into an app can be viewed by the health providers in real time, and through secure app messaging the providers/nurses can readjust medication or inform the patient to come in for their weekly visit.

Hypothesis

The use of telemedicine in gestational diabetes will improve control of hyperglycemia (pre-prandial blood glucose goal levels under 100 mg/dL and 1-hour post-prandial blood glucose goal under 150mg/dL) and reduce frequency of prenatal visits compared to traditional treatment.

Objectives and specific aims

As part of monitoring gestational diabetes mellitus in real time using telemedicine, patients will be able to receive instantaneous notifications about their glucose level. Providers will interact with the patient, and provide care early enough, therefore

hyperglycemia will be regulated and acted upon. The aim of the study is to determine the impact of iGlucose system meters to decrease blood sugar levels in pregnant women diagnosed with GDM and the impact on the frequency of prenatal visits related to glucose monitoring.

REVIEW OF THE LITERATURE

Definition of Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is a condition defined as impaired glucose tolerance or hyperglycemia with onset during pregnancy.[1] During early gestation, metabolic changes stimulate adipose tissue accumulation, therefore insulin secretion increases and insulin sensitivity may change or remain the same. However, later in gestation, adipose tissue deposits decrease, while post-prandial free fatty acids increase, and glucose disposal mediated by insulin decreases by 40 to 60% compared to pre-gravid levels, inducing increased hepatic glucose production and severe insulin resistance.[2] [3] Insulin secretion increases up to 200% in order to maintain euglycemic levels in the normal pregnant mother [2] [4] and pre-metabolic syndrome may exacerbate these conditions. Elevated adiposity correlates with the secretion of adipokines, pro-inflammatory cytokines from adipose tissue. [5] These include leptin, TNF-alpha, adiponectin, interleukin-6 and others.[6]

Adiponectin, a protein involved in glucose regulation by stimulating skeletal muscle glucose uptake by reducing hepatic gluconeogenesis and FFA breakdown, has been shown to be decreased in patients with GDM vs non-GDM patients. [7] This protein is exclusively synthesized in adipocytes and follows an inverse relationship with higher body mass index (BMI), type 2 DM [8], fasting c-peptide concentrations (marker of insulin secretion) and progression of gestation- even in lean women.[7] [9] Adiponectin is further reduced by TNF-alpha and other pro-inflammatory mediators, by inhibition of adiponectin transcription in adipocytes.[10] Once a patient has been diagnosed with GDM,

she is at higher risk of developing GDM in her next pregnancy due to lower plasma adiponectin concentrations post pregnancy.[11] These patients are also at higher risk of developing peripheral vascular dysfunction and have lower stroke volume and cardiac output compared to non-GDM patients when adjusting for BMI.[12] Lipolysis is accelerated in pregnancy likely in response to placental growth hormone, and exaggerated in obese or GDM patients. Reduction in the transcription factor peroxisome proliferator-activated receptor (PPAR-γ1, expressed in all tissues- regulates fatty acid storage and glucose metabolism), due to TNF-alpha[13] and growth hormone[14], inhibits adipocyte differentiation leading to an excess response of lipolysis and adipose tissue insulin resistance in pregnancy.[15] Another mechanism associated with insulin resistance is related to human placental lactogen (hPL)[16] and human placental growth hormone (hPGH)[17]. In pregnancy both hormones are increased; hPL induces insulin secretion from the pancreas[18], and hPGH has been documented to cause severe peripheral insulin resistance when overexpressed in transgenic mice[19] and increase expression of the p85 subunit of phosphatidylinositol 3-kinase (PI3K, involved in metabolic actions of insulin) acting as an inhibitor of PI3K activity therefore triggering severe insulin resistance in skeletal muscle.[20 21]

Consequently, increased pro-inflammatory cytokines, decreased adiponectin, additional lipolysis, placental growth hormone among other metabolic changes trigger general insulin resistance and initiate GDM.

Epidemiology

Approximately 9% of all pregnancies in the United States are affected by GDM, which results in 200,000 cases annually.[1].A recent study showed that GDM prevalence varies depending on risk factors across different racial or ethnic groups. Advanced maternal age (older than 35 years), obesity, family history of type 2 diabetes (T2DM), and foreign-born status affect each ethnic group differently. Advanced maternal age has little impact on Asian Indians compared to Hispanics and non-Hispanic whites, but the Asian Indian group carries the highest prevalence out of nine ethnic groups observed.[22] The same study also showed that overweight or obesity is the most significant risk factor for non-Hispanic whites, Hispanics, Filipinos and Asian Indians. The percentage of GDM cases that are attributed to overweight and obesity among Hispanics is 39.1%, 41.2% for non-Hispanic whites, 50.45% for non-Hispanic blacks and up to 52.8% among American Indians while Asian Indians only have a 15.1% prevalence attributable to obesity.[23]

As in T2DM, Asians in general may be more susceptible to insulin resistance which may be due to a dissimilar distribution of lipid stores compared to other ethnicities and Asian's greater body fat percentages given lower BMI levels.[24] A study review concluded that the prevalence of GDM in a population echoes the prevalence of T2DM in the same population,[25] with the women of childbearing age belonging to a minority being disproportionately affected by obesity and T2DM.[26] [27]

Low maternal educational level has been associated with GDM as well, after adjusted for race, age, parity and family history of diabetes. This is likely due to higher proportions of overweight and obesity among this population. Bouthoorn *et al* found that

low educational level is associated with a threefold risk of developing GDM in comparison to a high education level.[28]

Risk factors

It is hypothesized that the majority of women with GDM have beta cell dysfunction even before pregnancy, and have a form of chronic insulin resistance post-pregnancy when compared to non-GDM women post-pregnancy,[29] although very little is known about the genetics in GDM women with chronic insulin resistance and its relation to T1DM.[30] However, studies have shown clustering of GDM instances in families, showing a familial tendency, and reoccurs in 30-91% women with a history of GDM depending on ethnicity and age.[31] Other established risk factors for GDM include a past delivery of a macrosomic newborn (greater than 4000g birth weight), high parity, family history of diabetes mellitus and maternal birth weight.[32,33]

Physical activity

In addition to ethnicity, genetic predisposition and maternal age, there are some modifiable risk factors for GDM. Physical activity appears to have a favorable effect in various insulin resistance syndromes. There is an acute improvement of insulin sensitivity even with mild physical activity and a long-term improvement with continued physical activity that results in reduction of adiposity and increase in lean muscle mass.[34] A 2015 meta-analysis described a 28% risk reduction of GDM in women who were placed in a physical activity regimen compared with those in control groups.[35] Another meta-analysis from 2011 analyzed observational studies and found a significant protective effect (pooled OR 0.76 [0.70-0.83]) for exercise in early pregnancy.[36] Knowler *et al* [37] reported

a decrease of insulin therapy for overweight women with GDM who participated in resistance exercise training during their pregnancy. Liu *et al* [38] showed that women who became physically active during early pregnancy had a lower rate of GDM than those who stayed inactive (1.6 vs 3.6%, p=0.004) and those who began physical activity and continued for 3 months had 59% lower unadjusted odds of GDM (OR 0.41, 95% CI [0.17-0.95]), even when adjusting for age, race/ethnicity, education, parity, pre-pregnancy BMI and smoking. The same study demonstrated a lower GDM rate in women who reported brisk walking as their most common physical activity (1.6 vs 3.7% p= 0.0167) compared to women who did not, and brisk walking was strongly associated with lower GDM risk when adjusting for the same co-variables mentioned earlier (OR 0.38, 95% CI [0.16-0.89]).

However, there have been some studies that have not been able to provide sufficient evidence to suggest that a regimen of physical activity benefits patients at risk for GDM compared to standard care, and that it is not cost-effective to perform weekly exercise for these patients.[39] Dietary factors also play an important component in the development of GDM. There has been extensive studies of risk reduction and risk-enhancing dietary components associations with T2DM, which suggest that total carbohydrate and fat intake are not necessarily risk-enhancing factors to T2DM, but specific kind of carbohydrates, such as whole grains[40 41 42], may be protective while trans fatty acids and polyunsaturated fats may increase risk of T2DM[43 44] in women and substitution of these fatty acids with nonhydrogenated polyunsaturated fatty acids will reduce T2DM risk.[43]

Diet

A low glycemic index diet combined with a high fiber intake and lowest amount of processed refined grains reduces glycemic and insulin secretion responses therefore lowering the risk of T2DM.[44] A 2004 prospective study demonstrated that higher intake of fat and minimized intake of carbohydrates (or substitution of carbohydrates with fat) may be associated with increased risk of GDM and impaired glucose tolerance (IGT).[45] However, GDM has not been studied extensively as IGT so the conclusion that dietary factors during pregnancy play a major role cannot be determined. Another large prospective study in 2006 by Zhang C. *et al*[46], indicated pre-pregnancy diet is associated with the risk of glucose intolerance in pregnancy. The study compared two pre-gravid dietary patterns and their respective associations with GDM risk. One diet, comically named the Western diet, was composed of high intake of red meat, processed meat, refined grain products, sweets and large fatty carbohydrate loads. The other diet, termed prudent dietary pattern, consisted of fruits, green leafy vegetables, fish and poultry. GDM risk was significantly higher in pre-gravid women with high intake of red/processed meats (six servings per week, association may be attributed to increased iron intake)[47], independently of BMI and adiposity percentage, compared to women who consumed two servings or less of red meat per week.

Additionally, total fiber, cereal and fruit fiber consumption before pregnancy showed an inverse association with GDM risk.[48] Total glycemic load was measured likewise, and calculated by multiplying the carbohydrate content of each food by the glycemic index value of the particular food type (number associated with the food's effect

on a person's blood level, a value of 100 represents the standard, an equivalent amount of pure glucose), then multiplied by its consumption frequency and finally all values were added to obtain a final total glycemic load. The prospective study validated that the combination of high glycemic load and low fiber was associated with a 2.15-fold increased risk of GDM compared with a glucose-fiber balanced diet.[46 49]

Smoking

Smoking has been associated with an increased risk in T2DM in women,[50] but it has not been associated with increased maternal GDM. Nevertheless, there have been studies which have demonstrated a link between maternal smoking and gestational diabetes in the daughter,[51,52] but more studies are needed to confirm a direct association. Maternal obesity has been linked to increased risk of GDM, with a positive correlation of increasing BMI, especially with increased visceral adiposity, as mentioned earlier. [53] Alcohol consumption has been found to be associated with T2DM,[54] and in another study seemed to contribute to increased GDM risk in low-educated populations.[28] Male fetus has been associated with a worse beta-cell function, postprandial hyperglycemia and elevated risk of GDM in the mother.[55]

Weight gain

In 2009, the Institute of Medicine (IOM) issued new guidelines for pregnancy weight gain.[56] For singleton patients with a prepregnancy BMI of 25 to 29.9 kg/m^2, it is recommended to add 15 to 25 lbs, while obese patients (BMI of 30 kg/m^2 or more) should aim for 11 to 20 lbs. Women with a BMI greater than 25 kg/m^2 or greater than 23 kg/m^2 in Asian Americans should be screened for Pre-gestational diabetes or early

GDM.[57] In addition to being a risk factor for GDM, maternal obesity may cause cardio metabolic dysfunction and develop preeclampsia and obstructive sleep apnea.[58]

ACOG does not recommend to gain under the recommended value due to increased risk of neonates who are small for gestational age.[58] Other studies have found that limiting gestational weight gain will not prevent development of GDM[59], although the risk of undesirable outcomes does increase when gestational weight gain exceeds the range set by the IOM guidelines.[60]

Complications and outcomes of GDM

While GDM is described as a temporary condition that is resolved after delivery, it is associated with increased cardiovascular disease due to peripheral vascular dysfunction and metabolic abnormalities persisting after delivery. Peripheral vascular dysfunction may be caused by impaired endothelial function [61], rigidity of arterial walls (carotids and aorta) and impaired acetylcholine-induced vasodilation in extremities.[62]

More immediate risks are related to delivery complications. The risk of preterm delivery is increased in women with GDM due to preeclampsia and hypertension disorders, which accounts for a little less of half of preterm deliveries.[63] Preterm delivery is classified as a delivery, either induced or spontaneous, before 37 weeks of gestation.

Even though a large case-control study in 1998 [63] demonstrated no significant relationship between GDM and preeclampsia (OR 1.27, 95% CI 0.52-3.15), the HAPO observational study (Hyperglycemia and Adverse Pregnancy Outcomes), published by the New England Journal of Medicine in 2008,[64] found a significant association between hyperglycemia and preeclampsia. There was a small significant positive relationship

between elevated 1 hour and 2 hour OGTT levels and preterm delivery, although there was no differentiation between induced and spontaneous deliveries in this study. In fact, a retrospective study by *Yogev et al.* with 1,526 patients diagnosed with GDM showed that the rate of spontaneous preterm deliveries among GDM mothers (10.7%) was almost equivalent to the rate of spontaneous preterm deliveries among non-GDM mothers (11.3%), [65] while a cohort study of 46,230 pregnancies showed a significant higher risk of spontaneous preterm deliveries in patients with GDM vs patients with normal screening (6.7% vs 4%).[66]

However, GDM patients with spontaneous preterm deliveries in *Yogev et al.* were categorized by higher OGTT glucose values and higher mean blood glucose than patients with GDM with non-spontaneous preterm deliveries and well controlled glycemic levels. Spontaneous preterm delivery was more frequent in patients with poorly controlled GDM. Consequently, monitoring and controlling blood glucose levels will most likely decrease the risk of a spontaneous preterm delivery.[65] Of note, the same large case-control study in 1998 showed strong association with pregnancy-induced hypertension among women who received less prenatal care and African American women.[67]

In patients with pre-gestational diabetes, there is a risk of stillbirth if the fetus is delivered past term. Therefore, these patients are induced to prevent intrauterine fetal demise (IUFD). Patients with T1DM or T2DM were unlikely to have a successful pregnancy before the discovery of insulin, and perinatal mortality rate was close to 65% and maternal mortality approximately 30%.[68] After the discovery of insulin and the understanding of diabetes mellitus, perinatal mortality rate dropped dramatically, even

though the risk of fetal death was and is still dependent on race (primarily non-Hispanic black women), young maternal age under 19, old maternal age and multiple gestations.[69] A study published in 2000[70] reported the risk of IUFD was greater in T2DM than T1DM, due to less stringent glucose control in T2DM patients (34/1000 stillbirths in T2DM vs 12/1000 stillbirths in T1DM). The prognosis was worse if the patient had been newly diagnosed with T2DM. O'Sullivan et al[71] found a perinatal mortality rate of 64 births per 1000 in patients with GDM in the 1970s.

Beischer et al[72] found that screening routinely for GDM improved significantly the perinatal outcome, and that similar to diabetes mellitus in the total population, the prevalence of GDM had increased over time. Several studies have shown that women diagnosed with GDM had a higher incidence of stillbirth in prior pregnancies[73] and that women with metabolic syndrome (aka pre-diabetes) had a higher risk of stillbirth compared to nondiabetic women (rate of 19.7 intrauterine fetal demise (IUFD) vs 5.5 per 1000).[74] Still other studies have argued that there is no association between GDM and fetal death,[75] especially in populations where fetal death is common like Mozambique. This is important to consider, since there are multiple causes of stillbirth as mentioned above, that are not complicated by hyperglycemia alone, and women with GDM tend to have other cofactors that promote risks of stillbirth, like advanced maternal age and Hispanic ethnicity.[76]

The American Diabetes Association recommends inducing delivery at 38 weeks of gestation while ACOG opposes delivery before 39 weeks unless patient has failed in-hospital attempts of glycemic control and this surpasses risks to neonate.[57] Less fetal

macrosomia births and shoulder dystocia events have been observed in deliveries at 38 weeks,[77] but the outcomes of delivering before 39 weeks GA have been associated with NICU admissions[78] and excess morbidities seen in neonates.[79] The risk of expectant management carries a higher risk (but in itself is low) of stillbirth than the risk of delivering between 39 weeks to 40 weeks of gestation in women with GDM, although caution should be taken when making clinical recommendations if gestational age is not accurate or reliable. [76]

Delivering a fetus electively in the early term period given the elevated risk of IUFD has critical complications including respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN). Lung maturation in fetuses of diabetic mothers is often delayed and has been linked to hyperinsulinemia and hyperglycemia.[80 81] After 38 weeks' gestation, The Fifth International Workshop Conference on GDM does not recommend testing lung maturity if delivery is indicated.[82] Evidence has shown that elective induction or cesarean section if attempted before 38 weeks of gestation can increase the risk of requiring supplemental oxygen or needing ventilator assistance.[80 81] Infants born at 37 weeks were twice as likely to need ventilator assistance compared to babies with GA of 38 to 40 weeks, while infants born at 36 weeks were five times as likely, and 35 week gestation births were nine times as likely.[83] Approximately 8% of newborns born (in the United States) between 35 and 36 weeks require supplemental oxygenation, and are more likely to be re-hospitalized within 182 days after discharge.[83] Administration of corticosteroids for enhancement of fetal lung maturity is not

contraindicated with a diagnosis of GDM, however a more strict maternal glucose monitoring and additional insulin doses may be necessary.[82]

The risk of shoulder dystocia and birth trauma increases with increased birth weight, and the rate of shoulder dystocia is higher in diabetic women vs nondiabetic women for each 0.25 kg increase in fetal weight. Shoulder dystocia, when the anterior shoulder of the newborn is wedged under the maternal pubic symphysis during pushing, complicates 35% to 45% of assisted deliveries of nondiabetic mothers.[84] This difference in risk of shoulder dystocia in newborns has been attributed to truncal obesity, wide shoulder diameter,[85] and the maternal obesity. Birth trauma includes fracture of the humerus and/or clavicle, injury to the brachial plexus, and facial palsy. Birth trauma results from shoulder dystocia complications, with brachial plexus being the most critical.[84] In 1993, Combs et al[86] stated elective induction of labor (IOL) increased the cesarean rate compared to spontaneous labor (57% vs 31% rate, $p<0.01$). Notwithstanding, a recent study showed that induction of labor at 38 weeks reduced the risk of shoulder dystocia (8/407; 2 % compared with expectant management 25/411; 6 %) when fetal macrosomia was suspected, and did not affect the risk of a cesarean section.[87] The American Journal of Obstetrics and Gynecology (AJOG) published a 2016 study that found a decreased risk of cesarean delivery in patients with GDM who had undergone IOL at 38 or 39 weeks of gestation compared to expectant management. However, the study also found an association of induction at 38 weeks with an increased risk of neonatal intensive care admission.[88] ACOG[57] endorses expectant management in women with A1GDM up to 40 +6 weeks of gestation if antepartum testing is suitable.

For women with well controlled Type 2 GDM (A2GDM), time of delivery should be from 39 weeks to 39+6 weeks of gestation, and if GDM is poorly controlled, risks of prematurity and stillbirth should be taken into consideration. ACOG also recommends cesarean section if the estimated fetal weight (EFW) is greater than 5000g in women without diabetes and greater than 4500g in women with GDM, or preGDM. However, sensitivity when screening for macrosomia is low, indicating inaccuracy therefore it cannot be diagnosed or predicted,[89] despite new sonographic methods to estimate birthweight or fetal hemodynamic indices.[86 87]

Existing research on GDM delivery outcomes

The HAPO[64] study in 2008 which reviewed adverse pregnancy outcomes of hyperglycemia, found that neonates born to hyperglycemic women were large for gestational age (LGA) above the 90th percentile, had greater frequency of cesarean section, most likely to be hypoglycemic, and greater than the 90th percentile of cord-blood serum C peptide (meaning insulin secretion was elevated). The frequency of these events had a positive correlation with the glucose category which were characterized by the measure of fasting plasma glucose, 1 and 2-hour plasma measure of hyperglycemia. The higher the category, the higher the maternal glucose levels were. Clinical neonatal hypoglycemia had a less apparent correlation with maternal hyperglycemia compared to other outcomes, in which 2.1% neonates born to the lowest maternal glucose category had clinical hypoglycemia, while the frequency of neonatal hypoglycemia for neonates born to the mothers with the most elevated hyperglycemia was 4.6%. Compared to the more substantial differences that were seen in the other outcomes, (for example the

frequency difference between the lowest and highest categories; were 5.3% vs 26.3% for birth weight above the 90th percentile, 13.3% vs 27.9% for primary cesarean section, and 3.7% vs 32.4% for hyperinsulinemia above the 90th percentile) the clinical neonatal hypoglycemia had the smallest difference when accounting maternal glucose levels. When confounding for other factors, the secondary outcomes revealed positive strong associations between preeclampsia, shoulder dystocia and/or birth injury. Intensive neonatal care and hyperbilirubinemia were associated with the 1-hour and 2-hour plasma glucose levels, but fasting glucose levels were not accurate predictors. There was no association seen between LGA or birth weight below the 10th percentile and maternal hyperglycemia. It is important to state that the women in this study did not have GDM or pre-GDM. However, two primary outcomes that are known to complicate pregnancies in mothers with GDM/pre-GDM were also seen in non-GDM patients with hyperglycemia. The study further supports that maternal hyperglycemia, even less severe than what is observed in diabetes mellitus, is associated with similar clinical prenatal conditions as GDM, therefore treating hyperglycemia without the diagnosis of GDM based on previous criteria, may reduce these effects.

The 2005 Australian Carbohydrate Intolerance Study in Pregnant Women trial[78], assessed if the treatment of gestational diabetes would reduce perinatal complications and analyzed the effects of treatment on maternal outcome, mood, and quality of life. Through randomization, patients in the intervention group received a diagnosis of glucose intolerance and were assigned the plan for intervention. Patients randomized in the routine-care group were informed they did not have GDM (after agreeing to participate in

the study). The treatment for the intervention group consisted of ongoing care by the obstetrical team including individualized dietary advice from a certified dietician taking into account the patients pre-gravid weight, diet, lifestyle and pregnancy weight gain. The patients were instructed to self-monitor their glucose levels four times a day, insulin therapy adjusted on basis of glucose levels. The study found the rate of fetal death, shoulder dystocia, clavicular fracture and nerve palsy were significantly lower in the intervention group compared to the routine-care group; 1% vs 4%, p=0.01, with adjustments of maternal age and race/ethnicity. Interestingly, the percentage of infants requiring admission to the neonatal nursery was higher in the intervention group (71%) compared to the routine-care group (61%), although there were no differences of fetal hypoglycemia and length of admission between these groups. The study attributed the increase of NICU admission to the knowledge of the diagnosis by the physicians. Treatment reduced the percentage of LGA from 22% to 13%, macrosomia from 21% to 10%, however other findings (SGA, 5-min Apgar score, IV therapy for hypoglycemia, neonatal convulsions and respiratory distress syndrome) remained similar despite treatment. There was no difference between the rates of cesarean delivery, however, the frequency of induction was higher in the intervention group (39% vs 29%) due to the knowledge of diagnosis.

In 2009[92] randomized controlled trial evaluated whether treatment of women with mild GDM reduces obstetrical complications and perinatal morbidities. They found comparable results to the 2005 Australian Carbohydrate Intolerance Study in Pregnant Women trial. In both of the studies, the rates of hypoglycemia and hyperbilirubinemia did

not differ between the groups, and antenatal preeclampsia, shoulder dystocia, LGA and fetal macrosomia were reduced in the treatment group. However, the treatment group in this study had a lower rate of cesarean sections (26.9% vs 33.8%, p=0.02) when adjusting for abnormal presentations and other obstetrical complications unrelated to GDM. Induction of labor remained the same in both groups. One limitation of the study was inability to monitor glucose levels in the control group, therefore it was not known if rigorous treatment of GDM reduced glycemic levels relative to regular obstetrical care.

Recommendations based on research

The American Diabetes Association recommends screening for GDM at 24-28 weeks of gestation. Women with T1DM or T2DM should be counseled about preconception, and about the risk of development of diabetic retinopathy during pregnancy, and advised to maintain glycemic levels in reference range (HA1c < 6.5%) to minimize the possibility of fetal congenital anomalies. Due to risk of retinopathy, trimestral eye examination is recommended if initial eye exam was abnormal.[93]

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) states that women who are high risk and are found to have diabetes in their initial prenatal visit receive a diagnosis of diabetes mellitus, not GDM. This was done after consideration from the American Diabetes Association and multiple obstetrical organizations of the increased incidence of type 2 diabetes in women of childbearing age, which ended in pregnant women with undiagnosed type 2 diabetes.[1] A study of 4507 women showed that for the 302 compliant patients who were diagnosed with GDM by the end of the study (using OGTT) , only 4% were identified at their first prenatal visit –

before 24 weeks- using fasting plasma glucose. Therefore, fasting plasma glucose screening test at the first prenatal appointment has poor specificity which makes it inefficient screening for GDM.[94]

Initially, GDM diagnosis criteria was established by O'Sullivan in 1964, but the criteria was changed by the National Diabetes Data Group (NDDG) in 1979. In 1982, Carpenter and Coustan (C&C) proposed to modify the plasma glucose parameters, which was adopted shortly by the ADA and ACOG.[94] The C&C criteria follows a two-step process and is the approach most commonly and currently used in the United States. [95] The initial screening test is composed of a 50g oral glucose solution ingestion followed by a 1 hour venous glucose measurement. The patient does not need to fast for this part of the test. If the value is elevated (greater than 130-140 mg/dL, depending on the provider's preferences), the patient screened positive therefore a 100 g OGTT is performed.[96]

In the HAPO study, diagnostic parameters for GDM were a fasting plasma glucose less than 105 mg/dL and a 2-hour plasma glucose level less than 200 mg/dL after a 75 gram OGTT between 28 weeks to 32 weeks of gestation.[64] Due to the outcomes found in the HAPO study, the IADPSG and ADA[1] now recommend the guidelines shown on Table 1 for the diagnosis of GDM. A single elevated value on any of the categories of plasma glucose would be diagnostic of GDM after a 75 gram glucose load. [93]

Table 1. Diagnostic Criteria for GDM

	NDDG (in mg/dL)	*C&C (50g followed by 100g OGTT)*	*IADPSG based on HAPO study (75g OGTT)*
Fasting plasma glucose	≥105	≥95	≥ 92
1-hour	≥190	≥180	≥180
2-hour	≥165	≥154	≥153
3-hour	≥145	≥140	≥140

The IADPSG also recommends that women with a fasting plasma glucose in the range of 92 mg/dL and 126 mg/dL during the first trimester be diagnosed with GDM. A fasting glucose value greater than 126 mg/dL might be indicative of overt T2DM, if not assessed in the initial prenatal visit.[93]

The National Institute of Health (NIH) recommended continuation of the two-step approach of GDM screening after much deliberation. NIH concluded that the adoption of the one-step process would increase the prevalence of GDM from 5-9% to 15-20%, therefore increasing direct and indirect health cost with insufficient evidence of improved health outcomes.[1] NIH also stated concern that the new diagnosis of GDM in women with low range hyperglycemia may have unintentional consequences, such as increase in cesarean deliveries[78], life disruptions and psychosocial burdens.[97] Potential benefits in adopting the two-step process include an international diagnostic standard that would allow better standardization of best patient care practices and unification of research outcomes.[98] The concerns for negative implications of the increased rate of diagnosis were tested in a retrospective cohort study comparing different parameters for two step

testing.[94] The 2016 study compared outcomes of 952 women screened using the IADPSG criteria, and 888 women by C&C criteria. The results showed that the prevalence of GDM was substantially higher in the IADPSG group (13.44% vs 2.59%), the risk of primary cesarean section was reduced in the IADPSG group (21.7% vs 24.7%). The IADPSH group also had reduced fetal outcomes for birthweight under 90th percentile, jaundice, admission to NICU, birth trauma and neonatal hypoglycemia. When individually analyzed, the fetal outcomes were not significantly different in both groups.[94] Other studies have shown a reduction in risk of gestational hypertension, prematurity, cesarean section, LGA, low 1-minute Apgar score, NICU admissions,[99] polyhydramnios and pre-eclampsia using IADPSG criteria compared to Carpenter and Coustan criteria.[100] Another study in 2014 comparing the 1-step approach vs the 2-step approach in high risk pregnancies found there were no disparities between the groups for the mode of delivery, birth weight or Apgar score. However, they found significant differences in the compliance of screening, and attributed it to the longer interval it takes to complete the 2-step approach.[101] Further research needs to be done in order to resolve the uncertainty of which approach would be the best to implement in the fullness of time. Also, it is important to consider the population's ethnicity since it may be reasonable to vary the screening threshold to equilibrate sensitivities and specificities among different ethnic groups and reduce false positive results, but more research needs to be completed in order to determine the ideal thresholds. [102]

Glycemic levels in non-obese, non-diabetic without evidence of congenital malformations related to hyperglycemia were reviewed in two studies. Parretti *et al* [103]

selected 51 from 66 Caucasian pregnant women with a normal 1-hour GTT (mean 115.8 mg/dL) who delivered to term without congenital malformation. Subjects were taught to monitor their blood glucose from 28-38 weeks without lifestyle modifications or dietary restrictions. The results showed a daily mean glucose reading of 71.9 mg/dL (SD 5.7 mg/dL) at the beginning of 28 weeks and a daily mean glucose reading of 78.3 mg/dL (SD 5.4 mg/dL) reaching 38 weeks of gestation. The increase of glucose levels from 28 weeks to 38 weeks is explained by the decrease in insulin sensitivity as pregnancy advances. [3] [4] The study found that the 1-hour postprandial glucose values positively correlated with fetal abdominal growth as early as 28 weeks, and was preserved throughout the third trimester, which indicates that 1-hour postprandial glucose readings are good predictors of infant birth weight and supports The National Institute of Child Health and Human Development—Diabetes in Early Pregnancy Study.[104] However, the study is limited by lack of generalizability due to its non-diverse subject population. In Yogev *et al*'s study [105], obese and non-obese women without a diagnosis of diabetes mellitus were evaluated for 72 consecutive hours. The mean fasting blood glucose level for the study group was 75 mg/dL (SD 12 mg/dL), and mean blood glucose level was 83.7 mg/dL (SD 18 mg/dL). The average time needed to reach a postprandial peak glucose value of 110 mg/dL (SD 16 mg/dL), which was the mean postprandial peak glucose reading, was 70 minutes (SD 13 minutes). Obese women were characterized by elevated postprandial glucose values—for 1, 2 hour postprandial and postprandial peak values—and had a significantly lower mean blood glucose value at night. Interestingly,

there was no difference between obese and non-obese patients in fasting and mean blood glucose values.

The Fifth International Workshop Conference[82] and ADA[93] recommend the following values as targets for maternal capillary glucose concentrations:

- Pre-prandial glucose value less than or equal to 95 mg/dL
- One-hour post-prandial glucose value less than or equal to 140 mg/dL
- Two-hour post-prandial glucose value less than or equal to 120 mg/dL

These values are for newly diagnosed diabetes in pregnancy. For pregnant women with overt T1DM or T2DM, the glycemic goals for fasting, pre-prandial and overnight glucose are between 60-99 mg/dL. Peak post-prandial glucose levels should remain between 100-129 mg/dL and HbgA1c under 6.0%. [106]

Nonpharmacological treatments

Lifestyle interventions should be the primary therapeutic strategy for patients with GDM. A 2017 meta-analysis that evaluated the effects of lifestyle interventions with and without pharmacotherapy in the treatment of GDM reviewed 15 trials (total of 4501 women) and found that more women in the intervention group had met their desired postpartum weight within one year versus the control group.[107] [108] Postpartum depression was also decreased compared to the control group.[78] [108] Fetal adverse outcomes were also decreased in the experimental group; LGA risk was reduced as well as birthweight, macrosomia, and neonatal fat mass. [78] [108] [109] Lifestyle interventions should include diet, physical activity, education about GDM, education about self-monitoring and other types of interventions the provider believes is appropriate for an individual patient.

Cost of GDM

The cost of gestational diabetes imposes a significant financial burden. Few studies have analyzed the cost implication GDM can contribute to health care costs. In 2007, there were approximately 180,000 cases of GDM in the United States. GDM is associated with a significant increase in ambulatory visits due to pregnancy complications, both maternal and fetal. The total national cost attributable to GDM in that year was $596 million increase for maternal care, roughly $3,305 per mother diagnosed with GDM. Ambulatory visits due to complications caused by GDM amounted to $130 million, while total ambulatory visits by mothers with GDM incurred $418 million.[110] [111] Eight percent, ($51 million) of the costs attributed to GDM are paid by the patient.[110] In 2012, the cost of an uncomplicated vaginal delivery was $9,775, compared to $15,041 for an uncomplicated cesarean delivery.[112] In a pre-term delivery, cost of delivery increases dramatically to $45,000 per delivery, costing $26.2 billion nationwide.[113]

In the past 3 decades, 84% of pregnant patients between the ages of 25 and 34 received care in the first trimester, compared to patients under 20 years of age (34%).[114] A 1997 study evaluated the effectiveness of encouragements for improving compliance with the first prenatal visit. The study found that women receiving a transportation voucher had a compliance rate of 82% vs 60% of the control group.[115]

Telemedicine

Telemedicine incorporates the diagnosis and treatment of patients with telecommunications technology. Telemedicine systems have been used in diabetes care, and have been shown to have potential benefits by improving communication between

patient and provider, allowing providers to assess the condition of the patient weekly, helping to manage diabetes and by educating the patient in making the right decisions in regard to their condition.[116] When telemedicine has been integrated into the treatment of women with gestational diabetes, studies have shown that the number of check-ups or outpatient clinic visits are reduced in interventional groups compared to control groups. One study showed improvement in 3rd trimester metabolic control and a reduction in cesarean sections and macrosomia rates,[117] while another study showed no significant differences regarding metabolic control and birth complications but supported the decreased need of outpatient clinic visits.[118] It is important, however, to educate the patient on the frequent use of telemedicine system to appreciate a potential benefit in metabolic control, which can be a possibility when treating GDM in underserved women.[119]

Telemedicine and Preexisting DM

An application called Few Touch was developed for people with T2DM aged 44-70. To determine if such tools could support lifestyle changes in patients with T2DM, user feedback for a 6-month intervention was analyzed and was found to support good usability of the system. The design of the Few Touch Application included three functionalities for the study: blood-glucose sensor system (connected via Bluetooth), a nutrition habit registration system (manual input choosing food type) and physical activity sensor system (step counter). Diet recording required manual input, which some users found laborious, however, there was an improvement in the increase of fruit and vegetable daily intake. The physical activity sensor included a pedometer connected via

Bluetooth to the mobile device. Users transferred data by tapping on a button of the app an average of 0.9 times a day. On average, users checked their physical activity graph once per day. While this system sounds promising, there was some difficulty implementing this system due to battery life of pedometer, troubleshooting and transferring of information or other problems concerning the lack of versatility when wearing the pedometer, as it was required to use a belt in order to carry the pedometer correctly. However, 8 out of 12 users were satisfied, and increased their physical activity (20% increase in the number of steps) The users received automatic feedback from the application, depending on their status of their goals in regards to diet and physical activity, which they seemed to appreciate, especially the food-related texts.[120] The limitation of this study were the small sample of patients who tested the Few Touch application, and involvement of the users in the design of the application, therefore the feedback might have been not as positive with an unbiased cohort.

Other functionalities, such as health care professional control in the therapy and real-time communication would allow distant interaction with the patient's insulin pump (if needed), glucometer or continuous glucose monitor through a secure network. This secure network can be achieved by establishing a connection between the medical devices and a mobile device (Bluetooth or wireless internet), and then using the patients personal network for data transferring.[121]

A recent article released in 2014 described the process on clinical practice guidelines using a telemedicine system called MobiGuide for patient guidance. They provided a methodology that encompassed the components of a smartphone application,

the formalization of the guideline into workflows and patient-friendly advice to be created in MobiGuide. The main elements of the Mobiguide system included a decision support system, meant for the representation computer-interpretable guidelines, a body area network that provides instant monitoring of signals supported by a mobile application that connects with the back-end server and operates communications between different sections of the mobile application, a secured personal health record that is accessible and merges user's information from the body area network to the user's data in the hospital EMR. Finally, a knowledge base containing computer-interpretable guidelines. The internal structure of the smartphone user interface is composed of various components (data controller, secure storage controller, messaging, etc.) which facilitate the efficiency and ease of use for the patient. [122]

iGlucose system by Smart Meter provides another way of conveying blood glucose information to the healthcare team. It uses cell-technology to transmit blood glucose results, information is available to the patient through a personal web portal in which the patient can log in to access information and modify settings. The patient's data is uploaded with an assigned unidentifiable number corresponding for the respective patient, and then downloaded to a portal for the healthcare team to see immediately. The system also counts with virtual care coaching, enabling text communication between patient and provider, test reminders, notifications and alerts (for hypoglycemia or hyperglycemia). This system can actually provide an efficient and effortless way to deliver information without the need of recording it the traditional way or verifying that the wireless Bluetooth glucose meter is connected to a smartphone.[123]

Existing Research on GDM using Telemedicine

Given *et al.* [124] conducted a feasibility study for a randomized controlled trial that explored the potential for telemedicine in the treatment of GDM. The control group was given usual care (blood glucose monitoring and attend a specialist diabetes clinic at least every 2 weeks) while the intervention group was given the usual care plus the use of a device that allowed weekly transmission of data to the medical team. In addition to a glucose meter, patients in the intervention group also received a set of scales, blood pressure monitor, and a telemedicine hub installed in the patient's home. The telemedicine hub asked for compliance of insulin, hypoglycemic events and recent illnesses. Information was reviewed a day or two after it was finalized. IF there were any problems derived by the telemedicine data, health care providers contacted the patient to discuss readjustment of treatment or to arrange an appointment to reassess in person. Patient satisfaction was measured by completing a questionnaire at 36-38 weeks of gestation. Participants from both groups were satisfied, but participants in the intervention group identified several potential benefits including convenience of skipping appointments, reassurance, and avoiding travel time. 89.4% of the participants in the intervention group strongly agreed that they were satisfied with the system and would use it again. However, while participants found the telemedicine equipment straightforward, many found that the transmission of data was delayed (more than 20 minutes) and that caused inconvenience for one of the participants. Limitations in this study included restriction to access of patient data, as the data was presented in a long list that was difficult to interpret. Participants also felt that the opportunity to ask questions was lost in

the intervention group, given that they felt more comfortable discussing small topics in a private office setting versus a phone call. Another limitation was that this sample was a self-selected group, and any patients with aversion towards technology would have declined to be part of the study.

In a Spanish study, a web-based telemedicine platform was designed to evaluate patients remotely by viewing their input data transmitted from their glucose meter directly to the cloud and presented in an electronic logbook for the physician. The system prioritized the physician's view according to patient's metabolic condition. Using decision support tools, the platform made diet recommendations automatically, while insulin recommendations were notified to the physician to approve. The goal of the study was to evaluate effectives of the system and observe the impact in the time required to assess or see a patient, frequency of face-to-face visits, patients' compliance to self-monitoring and patients' satisfaction. The study revealed that the time devoted by physicians for patients' evaluation was reduced by 27% and ambulatory visits were reduced by 89%. Monitoring frequency was not decreased, as patients' average number of blood glucose measurements averaged 3.89 times a day and sent data every 3.477 days. There were some discordances between the medical team and the system's recommendations (20 out of 75 therapy adjustments made by clinicians), nutritionists accepted 27 out of the 60 initial diet therapies proposed by the system, but rectified only 3 out of the 29 diet adjustments that were suggested by the system. However, the number of visits in the intervention group was less (0.367 ± 0.901 visits) compared to the control group (3.207 ± 2.846 visits), which the majority of the physicians found favorable.[125]

A proposed trial was published in 2016 to compare the efficacy of a smartphone-based blood glucose management system with standard clinic care in GDM. The primary outcome is mean BG with corrections for number of measurements, percentage of pre-prandial and postprandial reading and length of care. The secondary objective of the proposed study is to compare the control and intervention group for compliance to the allocated blood glucose regime, maternal and neonatal outcomes, glycemic control (using HbA1c) and patient attitudes. The strength of this study is that the study will take place within the maternity diabetes service of a National Health Service hospital in London, thus obtaining data in real-life scenario. Limitations include population sample that is uniform and similar, where the study will be conducted in a single tertiary center where women have low levels of social deprivation and high rates of literacy. Another limitation is that outcomes related to GDM, such as shoulder dystocia, birth trauma or stillbirth, will not be measured, which are risks highly associated with GDM. [126]

METHODS

Study design

The prospective study will be a multicenter, open cohort randomized clinical trial of wireless glucometer with smartphone device vs. traditional glucose monitoring in patients with gestational diabetes mellitus.

Study population and sampling

The patients will be recruited over a period of 24 months from outpatient antenatal clinics at 5 major academic institutions in Boston, including Boston Medical Center, Brigham and Women's Hospital, St. Elizabeth's Medical Center, Beth Israel Deaconess Medical Center and Massachusetts General Hospital.

Expected estimated sample size is 400 patients currently pregnant and with a new diagnosis of GDM. Estimation of sample size is based on 5% margin of error for a population size of approximately half a million patients (women diagnosed with GDM in the United States at a given year)[127] and a 95% confidence interval. Eligible participants in the study include patients over the age of 18 who are diagnosed with GDM at the standard screening of GDM, between the gestational age of 24 weeks to 28 weeks. The diagnostic criteria will be based on the ACOG guidelines using the two-step process.[96] If non-fasting, initial oral glucose challenge test consists of consuming a 50mg oral glucose solution, and blood glucose levels will be checked 1 hour after. If the value falls above 135 mg/dL, the patient screened positive. If the value is greater than 180 mg/dL, the patient is diagnosed with GDM and does not need to transition to the second step. For values between 135 and 180 mg/dL, the patient will transition to the oral glucose

tolerance test, in which the patient will be asked to fast before coming into the next appointment. Fasting blood glucose values should fall under 95 mg/dL to be considered normal. The patient then will be given a 100g oral glucose solution as the tolerance test. Venous blood glucose measurement will be checked 1hr, 2hrs and 3 hours after ingestion. Any value above thresholds will confirm the diagnosis of GDM. Threshold values and inclusion criteria were resumed on Table 2.

Table 2. Inclusion and Exclusion Criteria for Patients

Inclusion	**Exclusion**
1. Patients over the age of 18. 2. Patients will have a diagnosis of Gestational diabetes at 24 weeks to 30 weeks of gestation. 3. Required thresholds for GDM diagnosis following ACOG, after a positive oral glucose challenge test: • Fasting glucose greater or equal to 95 mg/dL • 1 hr 100g OGCT greater or equal to 180 mg/dL • 2 hr 100g OGCT greater or equal to 154 mg/dL	1. Patients with diagnosis of gestational diabetes prior to 24 weeks of gestation. 2. Patients with obstetric history of preterm delivery, macrosomia, respiratory distress syndrome or congenital defects. 3. Patients with Type 2 or Type 1 diabetes mellitus. 4. Patients who smoke tobacco, cannabis, drug users, or uses alcohol during pregnancy.

• 3 hr 100g OGTT greater or equal to 140 mg/dL • If patient's initial OGCT was greater than 180 mg/dL, confirmation of GDM diagnosis does not need OGTT. 4. Patients should have access to a mobile device to receive notifications. 5. Patients should have reliable access to transportation for prenatal visits.	5. Patients who have been recently treated with systemic corticosteroids or will be treated. 6. Patients who speak a language that is not available on iGlucose system.

Intervention

The eligible study population will be randomized into two groups based on a complete list of patients from the selected medical centers. The subject will be randomized after initial prescription of insulin, metformin or non-pharmacological treatment based on patient's needs and risk factors. The control group will receive traditional treatment for gestational diabetes. Patients will be asked to check their blood glucose levels (finger stick) four times a day: first when waking up before eating breakfast, second before lunch, third before dinner and lastly before going to bed. They will be taught how to

adjust their insulin (if taking it) depending on the BG measurement. The BG values will be recorded on a small, portable booklet. At each prenatal visit, the BG values will be evaluated and the patient assessed for continuation or adjustment of treatment. Prenatal visits will be scheduled once a week.

The intervention group will follow similar recommendations as the control group, however, they will not annotate their BG readings in the booklet. Patients in this group will receive an iGlucose glucometer. This glucometer will be ready to use when given to the patient, and will contain patient's information and decode it when sending information to the cloud. In addition, the patient will be taught to use the Personal Web Portal to access her information and be able to contact an obstetrics nurse if needed. The patient will also have her mobile device linked to the device, and receive virtual message coaching in regards to her care. Patients in this group will be assessed real time and if adjustments need to be done to her medication, a nurse will contact the patient to inform her of the change in dosage or medication. If the patient feels the medication is working, without side effects or any concerning symptoms, she may opt out of her next scheduled appointment. If the medication is not working, or the patient is complaining of concerning symptoms, she will have the option to schedule an appointment within less than a week.

Image 1. iGlucose system layout[123]

Study variables and measures

The primary outcome will be postprandial capillary glucose readings within the controlled range in the intervention group. Glucose targets have been established by ADA and ACOG as a fasting glucose of less than 95 mg/dL, one-hour postprandial blood glucose concentration less than 140 mg/dL or a two-hour postprandial glucose concentration less than 120 mg/dL. Another primary outcome that will be observed is decreased frequency of scheduled prenatal visits in the intervention group compared with the control group. Number of missed appointments in both groups will count as prenatal visits, but will be compared as a secondary outcome, where the intervention group will have less missed appointments.

Additional secondary variables to be collected include type of treatment (non-pharmacological, insulin or oral medication (glyburide, metformin), race, age, parity,

BMI, primary language, education level, maternal obstetric complications (pre-eclampsia, hypertension) and location of obstetrics care.

Recruitment

Subjects will be referred to the study from 5 antenatal clinics from medical centers in Boston. These are Boston Medical Center, Brigham and Women's Hospital, St. Elizabeth's Medical Center, Beth Israel Deaconess Medical Center and Massachusetts General Hospital. Participants will be recruited by obstetric nurses and specialists. Obstetric nurses and providers will review the patient's obstetric history with them to determine eligibility and ask if the patient will be willing to participate in a study to obtain informed consent after the diagnosis of GDM is confirmed.

Data collection

Participants who agree to take part in the study will have undergone a complete medical and obstetrics history. For the intervention group, blood glucose data will be obtained from the iGlucose system. Information will travel from the wireless device to the cloud. Patient information is uploaded to the cloud encrypted, then decoded when downloaded to the Population Management Portable that can be viewed by the provider. Frequency of scheduled visits will be noted by the obstetrics team.

For the control group, weekly blood glucose data will be collected at every follow up visit. If more than 90% of FS readings are within range, patient may return in two weeks instead of one. Number of scheduled visits and appearances will be quantified. Information will be de-identified in both groups and later analyzed.

Data analysis

We will be fitting two regression models, one for each outcome of interest. We expect that the first primary outcome, pre-prandial capillary glucose, follows a normal distribution. Thus, we will use a linear regression to predict the mean capillary glucose with the following covariates: group assignment (control or intervention), type of treatment (non-pharmacological, insulin or metformin), race, age, parity, BMI, hypertension, and location of obstetrics care. After fitting model, a 2-sided t-test will be performed on the coefficient belonging to group assignment with the null hypothesis that the coefficient is equal to zero.

Next, the second primary outcome, number of prenatal visits, is continuous data; therefore, we will use a Poisson regression with the same covariates listed above. Afterwards, we perform a one-sided t-test on the coefficient belonging to group assignments with the null hypothesis that the coefficient is equal or greater than zero, since we are interested in observing a significantly lower frequency of visits in the intervention group. If over-dispersion (data displays larger variance than expected under Poisson regression), we can use a negative-binomial regression, however, the effect of group assignment should be easier to interpret when using the Poisson regression. All of the inferences from these models will be made after adjusting for possible confounders.

Timeline and resources

The study will be completed three years after initiation. A principal investigator will manage and work with study coordinators in each medical center. Study coordinators will be required to collect information, and provide the equipment necessary depending on

facility. Assuming a patient was diagnosed at 24 weeks and was recommended to check her capillary glucose levels four times a day until 40 weeks of gestation, she would require 448 test strips, or 3 purchases of 150 test strips. She would need only 336 if she was diagnosed at 28 weeks, which approximates to 3 purchases of 150 test strips as well. Therefore, if we are to obtain an iGlucose meter with 150 test strips and purchase 300 test strips for the remainder of the pregnancy, the total cost approaches $137.20 per patient at co-pay pricing.[123] The price of a standard glucose meter ranges from $10-40, and cost of test strips vary widely depending on manufacturer and storehouse, and is dependent on the Insurance. The expected price range for the control group per patient is between $100.00 and $200.00. The cost of a principal investigator and a minimum of 5 research coordinators will span from $300,000 per year to $400,000, with an additional $80,000 for a statistician.

Institutional Review Board

This study protocol will be submitted to the IRB for expedited review under 45 CFR 46.110 criteria. This study will involve the minimally invasive collection of patient records along with patient identification in order to ask patient specific questions important for study outcomes. Additionally, information on minors will not be collected in this study. It is low risk to the study population, and does not require personal patient information.

CONCLUSION

Discussion

This study has significant limitations. First, the study does not address the cofounders of diet and exercise. GDM can be treated with other methods besides controlling with medication. Research has shown that exercise and diet are important components in the treatment of diabetes mellitus. Lifestyle intervention is the first line treatment in GDM, and in most cases, it is enough to control hyperglycemia in pregnant women. Second, this study requires a large sample group of patients diagnosed with gestational diabetes that meet the inclusion criteria. Also, this study does not evaluate patient satisfaction, which could indicate compliance in the future. Finally, the recruited participants will likely be from the Northeast region of the United States. Although the study is located in Boston, where there will be a varied population, there is still a risk of having a population that lacks diversity.

This study has considerable strengths as well. The additional cost of the glucose meter and strips is approximately $137.20 per patient, amounting to $27,440 for a maximum of 200 subjects in the intervention group. This makes the study feasible. The estimated number of pregnancies in the United States in 2009 was 6.369 million. [127] If we use this number and estimate that 9% of these pregnancies have GDM, we would have approximately Ho3,210 pregnancies in the US with GDM at a given year. If the number of prenatal visits is reduced to at least 50% using telemedicine ($137.20 per person adds up to $78 million) with improved glycemic control, the cost savings would be approximately $200 million.

Summary

GDM is the development of insulin sensitivity during pregnancy. The risks of GDM are not only detrimental to the mother, but can affect the fetus during pregnancy and after birth. It takes a multidisciplinary team to treat patients and to reduce the risks and prevent postnatal complications. To diligently monitor glycemic levels, close follow up is recommended, but this can bring major inconvenience to the mother and a heavy burden on the clinical schedule. The former is particularly important if the mother has other children, works full time, or commuting takes a long time. Telemedicine allows immediate assessment of glycemic levels by the providers and instant communication with the patient if required.

The proposed study will evaluate glycemic levels between two groups. One group will follow the traditional treatment of GDM, while the other group will be given a glucose meter with ability to transmit information to a safe portal and be treated accordingly. The study will also observe the impact of wireless glucose meters on the frequency of prenatal visits.

Clinical and/or public health significance

While not observed in this study, research has shown that the majority of patients are satisfied with telemedicine incorporated into their treatment of diabetes. If the goals of this study are met, patients will benefit from less frequent trips to the doctor's office and receive adequate treatment instantaneously without having to wait for their next prenatal visit.

Patients with GDM may consider it a temporary disease that does not require close observation and management. However, the impact can be life changing to the fetus. If by making close management of GDM more feasible using telemedicine, benefits may not only be seen in individuals but also in the general cost of this disorder. Ultimately, this can reduce the complications associated with GDM and the financial burden it conveys.

LIST OF JOURNAL ABBREVIATIONS

Acta Diabetol	Acta Diabetologica
Am J Clin Nutr	The American Journal of Clinical Nutrition
Am J Epidemiol	American Journal of Epidemiology
Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Am J Public Health	American Journal of Public Health
Arch Gynecol Obstet	Archives Gynecology Obstetrics
Br J Obstet Gynaecol	International Journal of Obstetrics and Gynaecology
Chin Med J	Chinese Medical Journal
Clin Diabetes	Clinical Diabetes
Clin Endocrinol Metab	The Journal of Clinical Endocrinology & Metabolism
Curr Opin Clin Nutr Metab Care	Current Opinion in Clinical Nutrition & Metabolic Care
Curr Opin Obstet Gynecol	Current Opinion in Obstetrics and Gynecology
Diabet Med	Diabetic Medicine
Int J Endocrinol	International Journal of Endocrinology
Int J Epidemiol	International Journal of Epidemiology
Int J Med Inform	International Journal of Medical Informatics
J Biol Chem	Journal of Biological Chemistry
J Clin Endocrinol Metab	Journal of Clinical Endocrinology and Metabolism
J Clin Invest	Journal of Clinical Investigation

J Diabetes Sci Technol	Journal of Diabetes Science and Technology
J Gerontol A Bil Sci	Journals of Gerontology. Series A, Biological Sciences and Medical Sciences
J Gynecol Obstet Biol Reprod	Journal of Gynecology Obstetrics & Human Reproduction
J Matern Fetal Neonatal Med	Journal of Maternal-Fetal and Neonatal Medicine
J Perinat Med	Journal of Perinatal Medicine
J Telemed Telecare	Journal of Telemedicine and Telecare
J Ultrasound Med	Journal of Ultrasound in Medicine
JAMA	Journal of the American Medical Association
Med Inform	Medical Informatics
Mol Endocrinol	Molecular Endocrinology
NIH Consens State Sci Statement	NIH Consensus & State of the Science Statements
Obstet Gynecol	Obstetrics & Gynecology
Obstet Gynecol Clin North Am	Obstetrics & Gynecology Clinics of North America
Paediatr Perinat Epidemiol	Paediatric & Perinatal Epidemiology
Pediatr Endocrinol Metab	Journal of Pediatric Endocrinology & Metabolism
Prev Chronic Dis	Preventing Chronic Disease
Proc Nutr Soc	Proceedings of the Nutrition Society

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