Official Title: Glyburide vs Glucovance in the Treatment of GDM

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Abstract: This study will be a randomized open label trial of glyburide compared to glucovance in the management of gestational diabetes. We hypothesize that glucovance will provide improved glycemic control and a lower failure rate with no increase in neonatal adverse outcomes. Sixty-seven patients will be randomized by computer to each arm of the study. Outcomes will be glycemic control, failure rate of the drug to achieve glycemic goals, and neonatal outcomes.

Lay abstract: Two medications which can be taken by mouth are usually used to treat patient with gestational diabetes. The names of those medications are glyburide and metformin. Both of these medications have been shown to be safe for use in pregnancy. This study would like to compare the drug glyburide, to a drug that is a combination of glyburide and metformin to see which one is better at helping patients to keep their blood sugar at normal levels. Patients who participate in the study will be assigned to take one of the drugs being studied. As part of the study, the levels of blood sugar that is measured in the morning and after meals will be stored in a computer program as well as information about the babies weight at birth, amount of sugar in the babies blood at birth, and if there are any complications during the delivery .

OBJECTIVE: To compare glyburide to glucovance for treatment of gestational diabetes

SPECIFIC AIM #1: To compare glycemic control in patients treated with glucovance to glycemic control in patients treated with glyburide.

We hypothesize that glucovance will be superior to glyburide in achieving euglycemia.

SPECIFIC AIM #2: To compare the maternal outcomes of hypoglycemia and drug failure rate in patients treated with Glyburide to glycemic control in patients treated with glucovance.

We hypothesize that glucovance will have a similar rate of hypoglycemia and a lower rate of drug failure requiring initiation of insulin therapy.

SPECIFIC AIM #3: To compare the neonatal outcomes of gestational age at delivery, birthweight, fetal anomalies, neonatal hypoglycemia, APGAR scores and admission to the NICU in patients treated with glyburide to patients treated with glucovance.

We hypothesize that neonatal outcomes will be similar between the two groups

BACKGROUND

Gestational diabetes (GDM) is defined as carbohydrate intolerance with onset or first recognition during pregnancy. It is estimated that gestational diabetes affects 2-10% of all pregnancies. [1] The national and state

prevalence rates are estimated to be 9.2% and 3-10%, respectively .[2] It is estimated that border regions such as El Paso, Texas have a 10-15% prevalence rate. [3] A study performed by the Department of OB/GYN at Texas Tech University Health Sciences Center El Paso found that the prevalence of GDM in El Paso was 8.7%.[4]

Gestational diabetes is a problem worldwide and in El Paso, and is increasing. It is estimated that the prevalence of GDM is 1:50 to 1:20 pregnancies. It is more common Native Americans, Hispanics and Blacks. There has also been an increase in the incidence of GDM in the last decades.[5] This increase has been attributed to the increased obesity and type 2 diabetes rates.[5] Women who are diagnosed with GDM are at higher risk for complications during pregnancy and delivery, and also have an increased risk of developing type 2 diabetes after delivery. [2] Additionally, the fetus is at risk for macrosomia and neonatal hypoglycemia .[3]The rates of GDM vary depending on race. Pregnant Hispanic (5.4%) and African American (5.4%) females are at higher risk of developing GDM compared to non-Hispanic white. [3] Furthermore, Hispanic women who were born in Mexico and live in a border region have a prevalence rate of 10-15%.[3]

GDM is diagnosed by a two-step testing process. In step one the patient receives a 50g glucose load with determination of blood glucose levels one hour later. If the one hour value is ≥ 130mg/dl, patient receives a second glucose challenge of 100g. Blood glucose is checked prior to the 100g load, and at one hour, two hours and three hours. Expected values are 95mg/dl, 180mg/dl, 160mg/dl and 145mg/dl. Two values that meet or exceed these expected values are considered diagnostic of gestational diabetes.

The typical approach to the management of GDM is by proper diet and exercise. When blood sugar levels are not maintained within normal levels with diet and exercise, then a medication regimen is necessary. The American College of Obstetrics and Gynecology (ACOG) guidelines suggest that oral medications as well as insulin are suitable for the treatment of GDM.[6] Literature also, suggests that it is not necessary for patients to use insulin for the treatment of GDM prior to the use of oral medications.[6]

Pregnant women are no more or less compliant than other diabetics. It is well documented that the use of oral agents improves compliance and is easier to dose.[7] The failure rate of both glyburide and metformin during pregnancy has been studied. The failure rate of glyburide in pregnancy is 16-20%.[8] The failure rate of metformin in pregnancy is 34-40%.[9] The failure rates of glyburide and metformin have not been studied locally.

Glyburide is an antihyperglycemic agent in the sulfonylurea class. It is has been used in pregnancy since 2000 when a landmark paper was published demonstrating the efficacy and safety of its use in pregnancy.[10] Glyburide is FDA pregnancy category B indicating that it may safely be used in pregnancy. Glyburide works by activating the ATP-sensitive potassium channels in pancreatic beta cells which stimulates insulin release. The major side effect associated with glyburide is hypoglycemia. This problem is common to all antihyperglycemic agents and is not unique to glyburide. This effect can be ameliorated with close attention to correct caloric intake Glyburide should not be used in patients with sulfa allergies.

Metformin is FDA pregnancy category B indicating it is considered safe for use in pregnancy. Metformin is a biguanide antihyperglycemic agent which works by increasing sensitivity to the action of insulin. Metformin

has minimal risk of hypoglycemia. The most common side effect is gastrointestinal upset which usually resolves within one week of medication initiation.

Glucovance is a drug combination of glyburide and metformin (aka glucophage). Both glyburide and metformin have been studied individually in pregnancy and are often used together in pregnancy as separate doses of each drug.[8-10] The combined drug, glucovance, has not been studied in pregnancy. Glyburide and metformin have complementing mechanisms of action, so patients who take glucovance may have better glycemic control.

Oral antidiabetic drugs have been found suitable for the management of gestational diabetes because of their ability to provide good glycemic control when used properly. It is known that glyburide and metformin do cross the placenta, but there are no recorded long-term studies that have shown the implications of in utero exposure to these drugs.[8,11]

Current literature notes that glyburide has been associated with higher neonatal birth weight, neonatal hypoglycemia, increased macrosomia (Jiang et al., 2015). No studies indicated increased fetal death associated to the use of oral blood sugar medications. Glyburide and Metformin have been studied extensively for use in pregnancy; however there are no published studies on the use of the combination drug glucovance during pregnancy. The failure rate for metformin and glyburide used as single agents is relatively high. The purpose of this study is to see if the combination drug has a lower failure rate. The proposed study will compare glyburide and glucovance in the treatment of gestational diabetes.

STUDY DESIGN: A randomized open label study of patients with GDM not controlled with diet.

Patients will be randomized to either glucovance or glyburide. Sixty-Seven patients are required in each arm.

METHOD:

All patients presenting to the Diabetes in pregnancy clinic at Texas Tech HSC with a diagnosis of gestational diabetes who fail dietary management will be invited to participate in the study. Failure of dietary management is defined as 20% of values which exceed the expected goals of fasting ≤95mg/dl and 1hour postprandials ≤140mg/dl over a 2 week period. All patients of the OB/Gyn Diabetes clinic who fail dietary management are given the standard treatment for gestational diabetes, which consists of a regimen of oral antidiabetics (glyburide or metformin), unless contraindicated by patients' medical history or physicians assessment. If diabetes is not controlled with oral medication, defined as 20% of values which exceed the expected goals of fasting ≤95mg/dl and 1hour postprandials ≤140mg/dl over a 2 week period, then the patient is offered insulin as part of the treatment. See Figure 1 below for an outline of possible options for patients.

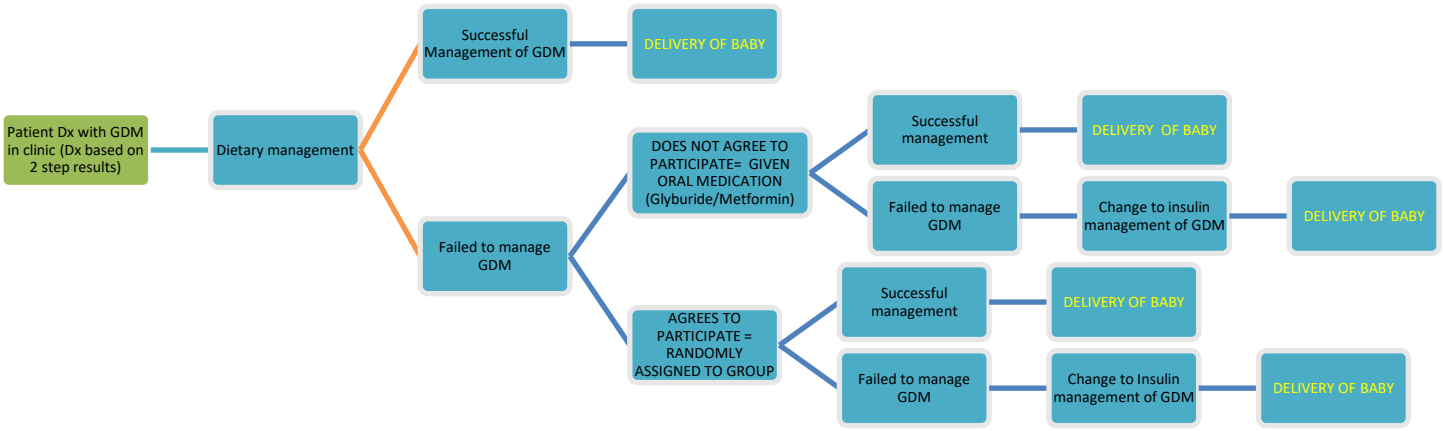

Figure 1. Possible options for treatment of GDM of patients in the OB/Gyn Diabetes clinic.

In this study patients will be invited to participate in a randomized open label trial of Glucovance and glyburide. Participants have to be above the age of 18, and be between 12-32 weeks pregnant. Participants will be asked to sign an informed consent and a HIPPA authorization for release of medical record information for the purpose of monitoring patient safety and medication effectiveness. The forms will be explained to the subject in their preferred language, and will be asked if they have any questions and if they understand the study. After informed consent is obtained, patients will be randomized to either a glyburide or glucovance group.

All patients will receive counseling on diet and exercise by a registered nurse (RN) in the clinic, as well as information on daily self-monitoring of blood glucose. The Department of OB/GYN does not employ a registered dietician (RD), but the RN in the GDM clinic has received education on nutrition and diet in diabetes and will work closely with the perinatologist. Any informational sheets that are provided to the patient will be given in their preferred language and will be thoroughly explained by the RN and physician, and will be given the opportunity to ask any questions that they may have.

Each patient will purchase their own blood monitoring devices, but will be shown how to perform proper self-monitoring of blood sugar at home. Patients are instructed to check their blood sugars following the steps below: (See patient information sheet)

1. Wash your hands with soap and warm water
2. Insert a test strip into your meter.
3. Use your lancing device on the side of your fingertip to get a drop of blood. (Gently squeezing and

massaging your finger before pricking can increase blood flow)

4. Touch and hold the edge of the test strip to the drop of blood, and wait for the result. (Do not remove the test strip until results appear on display screen).
5. Your blood glucose level will appear on the meter's display.
6. Compare your results to the glucose range.
    a. Fasting= 60-95 mg/dL
    b. 1 hour AFTER meals= 60-140 mg/dL
7. Any out of range blood sugar levels (high or low) should be reported to your MFM by calling the OB/Gyn clinic at 915-215-5000, or notifying the MFM at the next medical visit.

Subjects will be instructed to take medication as prescribed, and informed on the signs and symptoms of hypoglycemia (see sample GDM information guide). Furthermore, the subjects will be instructed to take a fast acting carbohydrate food (see list of foods) for blood sugars 60 mg/dL or below, and will be encouraged to seek emergency care for persistent blood sugars below 60 mg/dL after treatment with food. If hypoglycemia does occur, the participants will be instructed to call the OB/Gyn clinic and notify MFM at the time of their next appointment. Patient's blood sugar and meal journal/record will be reviewed to identify any persistent high or low blood sugars.

Prenatal care will be performed in the diabetes in pregnancy clinic staffed by a maternal-fetal medicine specialist and by residents in obstetrics and gynecology. Decisions regarding medication changes will be made by the attending maternal-fetal medicine specialist.

Participants will be in the study until they deliver. The estimated length of time in the study is between 6 and 26 weeks depending on gestational age at the time of enrollment. Study participants will be followed up during their normal clinic visits. The frequency of clinic visits will vary depending on the need of every subject, but there will be about 7-12 visits and each will be approximately 1 hour long.

The medications, glyburide or glucovance, will be provided to the participants at no cost during the time they are in the study or until they deliver. Medications will be dispensed by any of the UMC Outpatient Pharmacies. Participants will be given information about the pharmacies available and their hours of operations (see patient pharmacy information handout).

The funds to purchase these medications come from the department of OB/GYN, and no funding will be provided by any pharmaceutical company. The Prescriptions will be identified on the prescription with a unique study identifier. During the study duration, monthly reports will be generated to identify those prescriptions pertaining to the study and monthly bills will be generated, for those identified prescriptions. (For details on pricing and dosage please refer to attached email)

Participants who withdrawal from the study or who are no longer taking the study medication (such as other oral medications or insulin), will be responsible for the cost of their medications.

Subjects may have potential side effects or allergy to medication. Each patient will be given a generic information sheet from the pharmacy that indicates the side effects and signs and symptoms of an allergic

reaction to the medication. Also, the potential side effects will be discussed with the patient by the MFM at the time the medications are being prescribed. (See attached information sheet for glucovance and glyburide)Patients will be encouraged to notify PI of any side effects noted while taking the medication. Any side effects reported by the patient or noted through medical records will be documented and reviewed promptly and reported as required to IRB and/or FDA.

Participant medical charts (Texas Tech and UMC) will be reviewed to obtain information on fetal and maternal complications, outcomes, drug dosages, side effects, and gravida and para will be collected for analysis. (See data collection sheets for detailed variable list) Only infant information available in the mother's chart will be abstracted.

Medication Side Effects (per pharmacy patient information sheet, the information sheet may be revised by the pharmacy at any time)

Glucovance

What are some side effects that I need to call my doctor about right away?

- **WARNING/CAUTION:** Even though it may be rare, some people may have very bad and sometimes deadly side effects when taking a drug. Tell your doctor or get medical help right away if you have any of the following signs or symptoms that may be related to a very bad side effect:
- Signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat.
- Signs of liver problems like dark urine, feeling tired, not hungry, upset stomach or stomach pain, light-colored stools, throwing up, or yellow skin or eyes.
- Change in eyesight.
- Low blood sugar may occur. Signs may be dizziness, headache, feeling sleepy, feeling weak, shaking, a fast heartbeat, confusion, hunger, or sweating. Keep glucose tablets or liquid glucose on hand for low blood sugar.
- It is common to have stomach problems like upset stomach, throwing up, or loose stools (diarrhea) when you start taking this drug. If you have stomach problems later during care, call your doctor right away. This may be a sign of an acid health problem in the blood (lactic acidosis).

What are some other side effects of this drug?

- All drugs may cause side effects. However, many people have no side effects or only have minor side effects. Call your doctor or get medical help if any of these side effects or any other side effects bother you or do not go away:
- Headache.
- Belly pain.

- Upset stomach or throwing up.
- Loose stools (diarrhea).
- Dizziness.
- These are not all of the side effects that may occur. If you have questions about side effects, call your doctor. Call your doctor for medical advice about side effects.
- You may report side effects to your national health agency.

Glyburide

What are some side effects that I need to call my doctor about right away?

- **WARNING/CAUTION:** Even though it may be rare, some people may have very bad and sometimes deadly side effects when taking a drug. Tell your doctor or get medical help right away if you have any of the following signs or symptoms that may be related to a very bad side effect:
- Signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat.
- Signs of liver problems like dark urine, feeling tired, not hungry, upset stomach or stomach pain, light-colored stools, throwing up, or yellow skin or eyes.
- A heartbeat that does not feel normal.
- Very bad dizziness or passing out.
- Change in eyesight.
- Any bruising or bleeding.
- Low blood sugar may occur. Signs may be dizziness, headache, feeling sleepy, feeling weak, shaking, a fast heartbeat, confusion, hunger, or sweating. Keep glucose tablets or liquid glucose on hand for low blood sugar.

What are some other side effects of this drug?

- All drugs may cause side effects. However, many people have no side effects or only have minor side effects. Call your doctor or get medical help if any of these side effects or any other side effects bother you or do not go away:
- Upset stomach.
- Heartburn.
- Bloating.
- These are not all of the side effects that may occur. If you have questions about side effects, call your doctor. Call your doctor for medical advice about side effects.
- You may report side effects to your national health agency.

Compared to insulin, glyburide may cause the baby to have higher birth weight (9 pounds or above), and hypoglycemia after birth, and metformin may cause the mother to gain less weight during pregnancy, have a shorter pregnancy (average 1 day shorter) and may be associated with a higher risk of having a premature baby.[12]

All the participants will be encouraged to notify the doctor of any side effects they may have while taking the medication or any concerns.

Glyburide arm:

- Patients will check and record blood glucose fasting and 1 hour after each meal each day. Patients will also keep a diary of all meals. A copy of their diaries will be kept.
- The starting dose of glyburide may be 1.25mg to 5mg QD or BID depending on the degree of hyperglycemia.
- The dose of glyburide will be increased as needed to a maximum of 20mg /day.
- Antenatal testing will be initiated at 28 weeks
- Patients will receive monthly growth scans
- Participants will be asked to fill out a demographic sheet and emergency contact form during their initial enrollment

Glucovance arm:

- Patients will check and record blood glucose fasting and 1 hour after each meal each day. Patients will also keep a diary of all meals. A copy of their diaries will be kept.
- The starting dose of glucovance may be 1.25mg/250mg QD or BID increased to a maximum of 20mg/2000 as needed.
- Patients will receive monthly growth scans
- Antenatal testing will be initiated at 28 weeks.
- Participants will be asked to fill out a demographic sheet and emergency contact form during their initial enrollment

Although subjects will be reminded of the importance of following the procedures indicated in the consent form, there will be subjects who write their blood sugar on paper and some who fail to check according to the protocol, and we expect that this is going to happen frequently. This occurrence will not affect the study nor will it have any risk on the subject. Notes-to-file will be documented when these occur

Severe Adverse Events:
Severe Adverse Events (SAE) are internal events and include: death, Life-threatening experience, Hospitalization (for a person not already hospitalized), Prolongation of hospitalization (for a person already hospitalized), Persistent of significant disability or incapacity, Congenital anomaly and/or birth defects, Any event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes. As the research staff becomes aware of SAE's they will be reported to the Institutional review board. However, since eligibility criteria states a

participant must be pregnant and have gestational diabetes, all participants are expected to be admitted to the hospital to deliver their baby; therefore, this will not be considered an unanticipated event.

Compensation

No monetary compensation will be provided to participants.

INCLUSION CRITERIA

- Gestational diabetes
- Pregnancy > 12 weeks gestation
- 18 years of age or older
- Ability to give consent
- Women with gestational diabetes who fail dietary management of diabetes

EXCLUSION CRITERIA

- Inability to consent to the study
- Pre-existing diabetes
- G6PD deficiency
- Serum creatinine >1
- Liver disease
- Allergy to sulfa
- Allergy to glyburide (Patients will be assessed for any past medical history to include allergies to this medication)
- Allergy to metformin (Patients will be assessed for any past medical history to include allergies to this medication)
- Fetal anomalies
- Women who will not monitor their blood glucose

DATA MANAGEMENT

Consent forms and HIPPA release of information forms will be stored in locked cabinets in the Department of OB/GYN. Participants who wish to withdraw must notify the PI, in which a note will be made to their study file. All data collected on participants who withdraw will be de-identified in the database and will be used in the data analyses.

STATISTICAL ANALYSIS

Data will be analyzed using SAS 9.3 software (SAS Institute, Inc., Cary, North Carolina). The distribution of potential confounders across the two arms of the study will be examined.

Sample size calculations

Sample size calculations were performed using SAS software and OpenEpi (Open Source Epidemiologic Statistics for Public Health, www.openepi.com, Version 3.03a). The method of Fleiss with continuity correction was used. The sample size calculation was performed assuming a failure rate associated with glyburide of 31% and the failure rate of glucovance at 10%, to provide an 80% chance of detecting a 5% difference in the rate of failure between the two drugs. Drug failure is defined as 20% of values over two consecutive weeks (i.e. each week 20% of the measured values) fail to meet the glycemic goals of fasting ≤95mg/dl and 1 hour postprandial ≤140mg/dl. Sixty- seven patients are required in each arm.

Data analysis

Patient outcomes will be compared between groups. The initial analysis of the dichotomous outcome (oral medication failure) will involve the creation of a 2 x2 contingency table and the use of a chi-square or Fisher's exact test as appropriate. A risk ratio (RR) for the outcome of drug failure comparing the two medications will be calculated from a log-binomial regression models using the GENMOD Procedure. The RR will be reported along with a 95% confidence interval and P value. If confounding is detected then an adjusted RR will be calculated. Additionally, glucose and dietary diaries will be analyzed.

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