Metabolic Analysis for Treatment Choice in Gestational Diabetes Mellitus (MATCh-GDM)

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I. Abstract:

Gestational diabetes (GDM) is a significant clinical and public health burden, affecting over 400,000 pregnant women in the United States each year. Without adequate treatment, women with GDM and their infants are at risk for substantial morbidity. Because of this, experts recommend treatment focused on normalization of hyperglycemia to improve outcomes. However, providers have limited capacity to predict which treatment will achieve glycemic goals. This results in a choice based on provider and patient preference and a trial and error approach, which can create delays in glycemic control within the short (8-10 weeks) window between diagnosis and delivery. Maternal and fetal morbidity may be related to a mismatch between glycemic pathophysiology and the mechanism of action of glucose lowering agents. In fact, GDM is heterogeneous, with predominant insulin resistance (IR) in 50%, insulin secretion deficit (ISD) in 30%, and a combination of both in 20% of women as underlying mechanisms of hyperglycemia. This variation in GDM pathophysiology and clinical outcomes supports the use of an individualized treatment approach. The overall goal of this project is to investigate an individualized treatment approach for GDM where treatment is based on each woman's GDM mechanism.

II. OBJECTIVES

The overall objective is to perform a pilot study using an individualized treatment approach for GDM where treatment is based on each woman's GDM mechanism.

Aim 1: Evaluate the feasibility of conducting a pilot RCT comparing individualized GDM treatment and usual care (treatment chosen by provider and patient without regard for pathophysiologic heterogeneity).

Sixty pregnant women with GDM will be randomized to individualized treatment based on GDM mechanism (determined at the time of a 3-hour oral glucose tolerance test (OGTT) vs. usual care. We will measure feasibility by the proportion of women who are eligible, who enroll, and who remain in the study.

Aim 2: Inform the design of a larger RCT comparing individualized GDM treatment and usual care.

We will assess the consistency of the GDM causal mechanisms with a repeat OGTT two weeks after treatment initiation, adherence to treatment assignment and dose titration, and the distribution of adipose-related metabolism covariates (e.g. obesity, lipid profile, free fatty acids). This data will be used to inform the study design, data collection procedures and outcomes measures of the large-scale RCT.

Aim 3. Assess participant and provider acceptability of an RCT comparing individualized GDM treatment and usual care.

We will conduct individual semi-structured interviews with 3 groups: (1) pilot participants (n=16), to determine acceptability and burden of the study; 2) prenatal care providers (n=15) to determine their satisfaction with study procedures, and 3) women who are approached but decline to participate in the pilot study (n=15) to determine barriers to participation.

III. PARTICIPANTS

***Inclusion criteria*:**
Pregnant women 18-45 years old, beyond 24 weeks of gestation, who are scheduled for a 3-hour oral glucose tolerance test.

Exclusion criteria:
- Preexisting type 1 or type 2 DM

- Multiple gestation

- GDM diagnosis without 3-hour OGTT

- Oral or IV corticosteroid use in the past 7 days

- Major congenital anomaly with anticipated preterm delivery

- Allergy to glyburide, metformin or sulfa

- History of severe pulmonary disease(pulmonary requirement for oxygen therapy or daily treatment for restrictive of obstructive pulmonary disease)

- History of hepatic disease (LFT's greater than two times of upper normal range)

- History of renal disease (serum creatinine higher than 1.2 mg/dL)

- History of heart failure or myocardial infarction

IV. Outcome Measures- The primary objective of the pilot study is to evaluate the feasibility of conducting a randomized trial comparing individualized treatment versus usual care for GDM. Our primary feasibility outcomes will be the number (proportion) of women who are eligible, screened, enrolled and remain in the study at each outcome assessment. As pregnant women are a difficult population to retain, we will identify any issues related to recruitment, enrollment and retention that will be necessary to account for when determining the sample size estimated for the future trial. Reasons for exclusion and subject refusal will be tracked at the time of screening by the research team. We will assess reasons for participant attrition through a follow-up call or e-mail at the time of withdrawal. We will determine the proportion of women who remain on the treatment assigned at the beginning of the pilot within each arm. We will review health records to determine the reason for changing treatments. We will measure trough levels at the time of the repeat OGTT. We will also review treatment titration to assess the proportion of participants who are titrated according to the protocol.

V. Analysis Plan – Demographic characteristics, such as race, age, parity, and insurance will be compared between study arms to assess balance and comparability. Descriptive summaries will include the mean and standard deviations (or medians and quartiles for skewed distributions) for continuous variables and frequencies and proportions for categorical variables. Due to the pilot nature of this RCT, hypothesis testing is not the primary focus, but rather estimation within each study arm.

VI. Sample Size - We will introduce the pilot trial to all women undergoing an OGTT. We plan on screening 300 women to allow us to include ~60 women in the pilot study. This sample size

will allow us to have various GDM mechanisms represented. Assuming 30 women within each study arm and a 5% type I error rate, we will have the ability to estimate within-arm 95% confidence interval margin-of-errors of no more than 0.18 for each of our feasibility outcomes.

VII. Study Procedures:

Screening Visit
Participants are eligible to be screened if they have scheduled a 3-hour oral glucose tolerance test, as recommended by their primary physician. Her medical records will be reviewed and she will be asked questions about her medical history, physical examinations, laboratory tests, and medications to make sure she is eligible for the study. She will be instructed on procedures to follow for the upcoming study visits. This screening visit will be performed by a member of the research team at the time of the scheduled 3-hour oral glucose tolerance test. It is not expected to prolong the time of the clinical test.

The 3-hour oral glucose tolerance test is usually performed following an abnormal glucose screen during pregnancy. After completion of the consent form, subjects will undergo a standard oral glucose tolerance test in the outpatient laboratory unit. Samples will be collected at 0, 1, 2 and 3 hours after ingesting a 100g oral glucose load. A standard oral glucose tolerance test includes blood collection for glucose determination at 0, 1, 2, and 3 hour after ingestion of a 100g oral glucose load (3mL x4 = 12mL total). The study will include additional sample collection at the initial time point (0 hour) for lipid (6mL), and at 0, 1, 2 and 3 hour for insulin and c-peptide (3 mL x4 = 12 mL) determination.
Additionally, anthropometric measures including triceps, subscapular and suprailiac skin fold thickness will be performed.

Materials needed per participant
- **Four** red top tubes for plasma samples (Insulin, C-peptide, free fatty acids)
- **One** green top sodium heparin or lithium heparin tube for serum samples (lipid panel)
- Lange skinfold caliper

1. Blood Samples During screening visit (Table 1)

Time Intervals (in mins)	**Insulin; C-peptide, free fatty acids,**	**Lipids**
Tube top	**Red**	**Green**
0	X	X
60	X	
120	X	
180	X	

a. At time **0** (c-peptide, insulin, free fatty acids, and lipids)

- Fill a pre-prepared red top tube with 4 mL of blood (insulin, c-peptide, free fatty acids)
  1. Gently invert tube five times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

- Fill a pre-prepared light green top tube with 4 mL of blood (lipids)
  1. Gently invert tube five times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

b. At times **60**, **120 and 180** (c-peptide, and insulin)

- Fill a pre-prepared red top tube with 4 mL of blood (insulin, c-peptide, free fatty acids)
  1. Gently invert tube five times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

Sample processing:

1. Materials and equipment needed per participant

a. During study visit:

- 1.5mL cryovials **(fill each with 1mL)**
- Labels for cryovials which should include subject ID, visit number and sample time following the study's protocol. Please indicate light green (LG) or red (R) on the cryovials to help differentiate samples

Cryovial Label appearance

Feghali MATCh-GDM OGTT Subject (ID) Sample time (LG/R)

ated volume, please add any excess volume of blood to red ample according to protocol.

The blood specimens will be processed at the CTRC and vials will be transferred **WEEKLY** to the central lab for analysis as per Table 2. All remaining vials will be stored at the CTRC at least at -70.

Table 2. Number of microvials to be transferred to the central lab for analysis

Time Intervals (in mins)	**Insulin; C-peptide, free fatty acids,**	**Lipids**
Microvial	**Red**	**Green**
0	2	1
60	2	
120	2	
180	2	

Women who are diagnosed with gestational diabetes are eligible for the pilot study.

Study visit #1
Each woman will meet with a physician from the study team and be randomized to one of two study treatment groups: individualized therapy or usual care. A randomization sequence will be generated and incorporated into the database prior to recruitment. Permuted block randomization with randomly varying block sizes will be performed by a web-based data entry system.

All women diagnosed with GDM will be started with medical nutritional therapy as per clinical guidelines. The decision to start treatment is based on home glucose values after 1-2 weeks of medical nutritional therapy. Pharmacologic treatment is recommended if fasting values are greater than 95mg/dl or postprandial values are greater that 140mg/dL. Initiation of usual care vs/ individualized treatment will only occur once glucose values exceed these goals despite medical nutritional therapy. Following initiation of pharmacologic therapy, and throughout gestation, home blood glucose levels will be reviewed weekly and the doses of drugs will be adjusted in person during a clinic visit or via telephone per the email.

In women randomized to individualized treatment, women will be matched to therapy based on their GDM mechanism (metformin for predominant insulin resistance, glyburide or insulin for predominant insulin secretion deficiency, or a combination of metformin and glyburide or insulin for a mixed GDM mechanism). Women who are randomized to usual care will receive standard counseling about treatment options for gestational diabetes and be prescribed metformin, glyburide, or insulin. The medication will be prescribed and she will be instructed to take the study medications with food to decrease the side effects. Dosing will follow pre-specified strategies described in Appendix A and each woman will be given instructions regarding her dose upon weekly review of her home blood glucose values.

Study visit #2:
- If not performed within the past 8 weeks, then about a teaspoon (5ml) of blood will be drawn to check her hemoglobin level.
- The study visit will be performed by a member of the research team during a routine visit to her caregiver at Magee-Womens Hospital and should take no more than 10 minutes to complete.

Study visit #3:
This visit will take place two weeks after initiation of treatment for gestational diabetes. This visit will take about 3-4 hours to complete in the Clinical Translational Research Center (CTRC) of Magee Womens Hospital of UPMC.

Participants will come to the CTRC at MWH in the fasting state to complete their OGTT.

A. Prior to the testing written consent will be confirmed

B. Participants will receive the 100g glucose solution and have blood samples drawn at 0,60,120, and 180 minutes by the CTRC staff.

2. Materials needed per participant
    - **Four** red top tubes for plasma samples (Insulin, C-peptide, free fatty acids)
    - **Four** grey top tubes for plasma samples (glucose)
    - **One** green top sodium heparin or lithium heparin tube for serum samples (lipid panel)
    - Lange skinfold caliper

3. Blood Samples During study visit (Table 3)

Time Intervals (in mins)	**Glucose**	**Insulin; C-peptide, free fatty acids,**	**Lipids**
Tube top	**Grey**	**Red**	**Green**
0	X	X	X
60	X	X	
120	X	X	
180	X	X	

a. At time **0** (glucose, c-peptide, insulin, free fatty acids, and lipids)

- Fill a grey top tube with 4mL of blood (glucose)
  1. Gently invert tube 5 times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

- Fill a pre-prepared red top tube with 4 mL of blood (insulin, c-peptide, free fatty acids)
  1. Gently invert tube five times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

- Fill a pre-prepared light green top tube with 4 mL of blood (lipids)
  1. Gently invert tube five times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

b. At times **60**, **120 and 180** (glucose, c-peptide, and insulin)

- Fill a grey top tube with 4mL of blood (glucose)
  1. Gently invert tube 5 times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

- Fill a pre-prepared red top tube with 4 mL of blood (insulin, c-peptide, free fatty acids)
  1. Gently invert tube five times to avoid clotting
  2. Place sample on ice
  3. Centrifuge sample at 1200 RFG (approximately 3000rpm) at 4°C for 15 minutes

Sample processing:

2. Materials and equipment needed per participant

a. During study visit:

- 1.5mL cryovials **(fill each with 1mL)**

- Labels for cryovials which should include subject ID, visit number and sample time following the study's protocol. Please indicate light green (LG), red (R), or grey (G) on the cryovials to help differentiate samples

Cryovial Label appearance

Feghali MATCh-GDM
Visit#
Subject (ID)
Sample time LG/R/G

Notes:

1. **If blood draw exceeds indicated volume, please add any excess volume of blood to red top tubes and process the sample according to protocol.**
2. **Protocol allows for a volume up to 1ml of discarded blood for each blood draw**

C. Questionnaires: participants will complete a demographic sheet, and brief questionnaires assessing lifestyle factors such as physical activity, sleep quality and diet.

D. Height and weight will be measured using standard protocols. Maximum hip circumference and skinfold thickness over biceps, triceps, subscapular and supra iliac regions will be measured using previously published methods.

E. Once the OGTT is completed, the CTRC staff will assess for any problems with the testing and the participant will be discharged

F. The blood specimens will be processed at the CTRC and vials will be transferred to the central lab for analysis as per Table 4. All remaining vials will be stored at the CTRC at least at -70.

Table 4. Number of microvials to be transferred to the central lab for analysis

Time Intervals (in mins)	Glucose	Insulin; C-peptide, free fatty acids,	Lipids
Microvial	**Grey**	**Red**	**Green**
0	1	2	1
60	1	2	
120	1	2	
180	1	2	

Interviews will occur at the time of the second OGTT for women who are enrolled in the study and at the time of refusal for those who opt out. Interviews will focus on participant/provider perception of study/treatment and whether they experienced any burdens. 16 participants (8 in each group) will be interviewed along with 10 women who decline to enroll in the study but agree to an interview.

Additional study visits:
During a participant's routine prenatal visits (which typically occur every 1-2 weeks) with her provider that occur between 29 and 40 weeks of gestation, she will also meet with a member of the research team who will record information about her blood glucose measurements, pregnancy, weight, and any side effects she had since the last study visit. These study visits ill occur in her provider's office and will take no more than 10 minutes to complete.

At the time of labor and delivery
Delivery: At delivery, the hospital research nursing team we will measure infant birth weight and length at delivery. We will collect umbilical cord venous blood for assay of c-peptide. We will only collect these samples if it is safe to do so and possible to do so based on staffing.
Air displacement plethysmography will be used to measure body composition (PEA POD; Life Measurement Inc, Concord, CA) in the newborns within 72 hours post-delivery to provide an estimate of percent body fat and lean body mass.

Data abstraction: Once written consent if provided and participant completes the first study visit, a member of the research team will conduct at least two prenatal and two postnatal EHR data abstraction from the prenatal and delivery records: type of delivery, prenatal and delivery complications. We will also collect information regarding any treatment for gestational diabetes as well as the number of ultrasounds and tests for assessment of fetal well-being (biophysical profiles, non-stress tests).

VIII. Participant withdrawal:

Participants may withdraw from the study at any time.

Participants will be removed from the study if they eat at unscheduled times during/preparing for their study visit. This will also interrupt their oral glucose tolerance test. Since subjects will not be able to eat prior to breakfast on the day of the study visit, the research team will be monitoring subjects for signs and symptoms of the hypoglycemia, which include, heart palpitations, sweating, hunger, confusion, abnormal behavior, and visual disturbances. If subjects develop any of these symptoms, standard hospital protocols will be followed. Risks will be evaluated at the study visit through observation of the subject and by eliciting a verbal description of the subject’s comfort level.

The principal investigator will terminate the involvement of a given subject in the research study if said subject develops a condition that precludes her from having blood draws or upon meeting any of the exclusion criteria during study participation. This study will be terminated if the risk-to-benefit ratio changes (i.e. risk outweighing benefits is identified during the study).

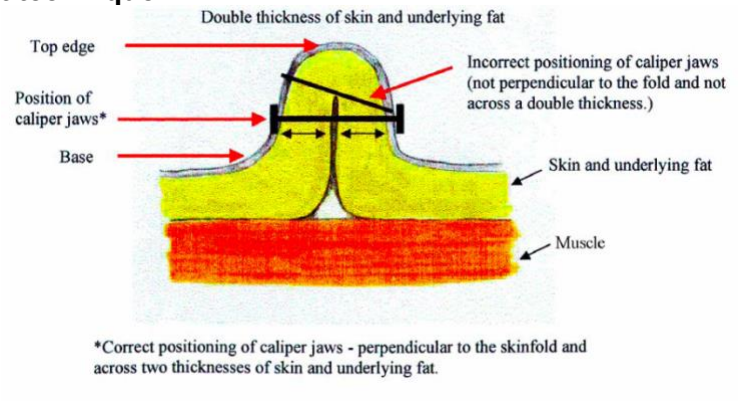
IX. Compensation:
Participants will receive $25 for completing the screening procedures, $75 for completing the repeat 3-hour oral glucose tolerance testing, and $50 for completing the cord blood and

neonatal body composition assessment. She will be paid a total of $150 for completing all study procedures.
All payments will be made in the form of a UPMC WePay debit card.
No cash or money orders shall be exchanged between research staff and study participants.
No compensation will be provided for partial completion of the research study.
No cash or money orders shall be exchanged between research staff and study participants.

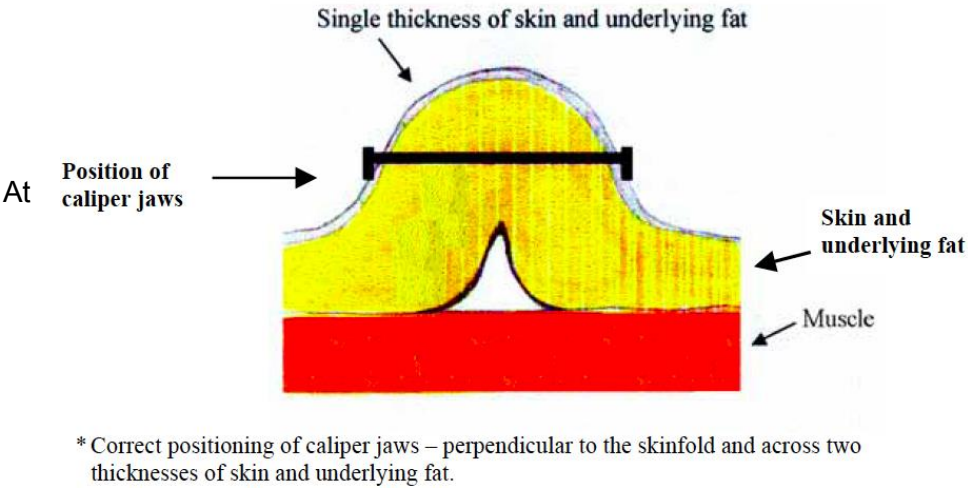
Skinfold Measurements

- Take skinfold measurements directly on skin-not through clothing
- Pick up and hold skinfold with thumb and forefinger of one hand (usually left). Apply the jaws of the caliper to the skinfold about ¼ to ½ an inch from the fingers holding the fold.
- Measure all skinfold measurements on the **right side**. Do not release the fingers holding the fold. The caliper should only be used to measure the thickness of the fold, not to hold the skin folded. Any pressure placed on the caliper jaws as a result of their holding the skinfold in a folded state will result in an incorrect higher reading.
- **Record skinfold measurements to the nearest tenth of a millimeter (0.1 mm)**
- **The protocol mandates that the skinfold consist of a double thickness of skin and underlying adipose (fat) tissue**
- **Do not take a skinfold measurement reading if you cannot construct a fold that has two thicknesses of skin and underlying fat.** Exhibits below depict examples of a correct and incorrect skinfold, respectively.
- If you are unsure if you have pinched only skin and no underlying muscle tissue, ask the subject to flex the muscle while you have a pinch.

Correct technique



Incorrect technique



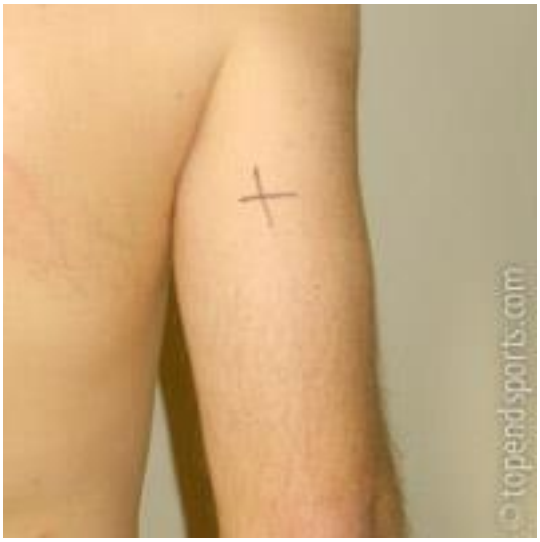
Triceps fold

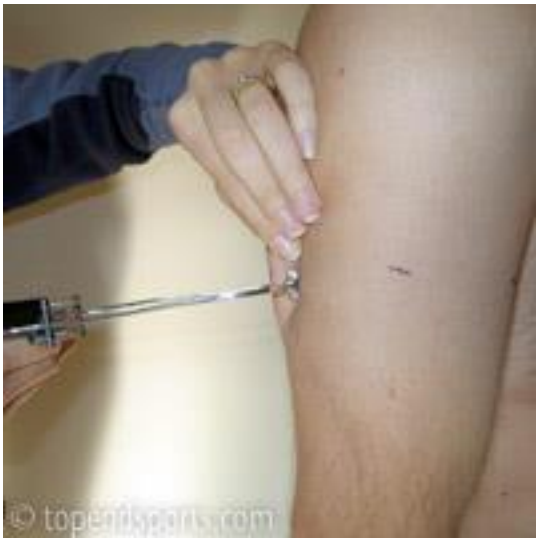
At the level of the mid-point between the acromiale (lateral edge of the acromion process, e.g. bony tip of shoulder) and the radial (proximal and lateral border of the radius bone, approximately the elbow joint), on the mid-line of the posterior (back) surface of the arm (over the triceps

muscle).

The arm should be relaxed with the palm of the hand facing forwards (supinated).

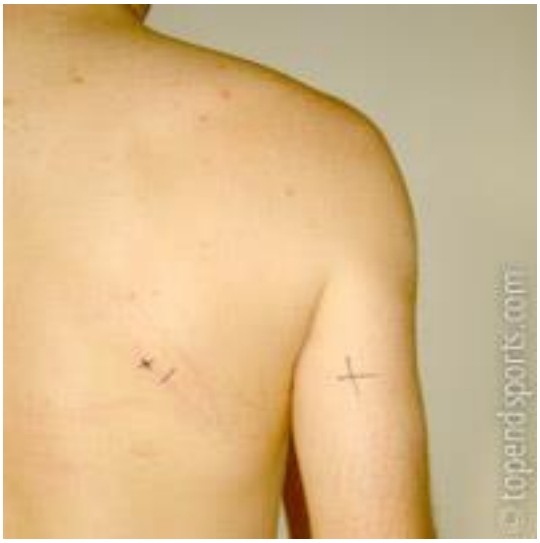
A vertical pinch, parallel to the long axis of the arm, is made at the landmark.

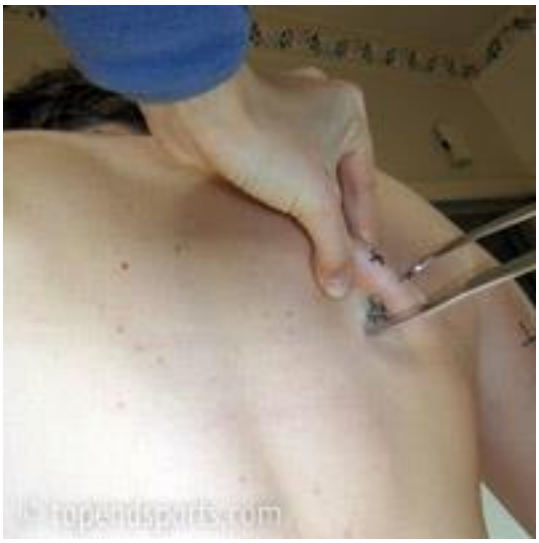




Subscapular fold

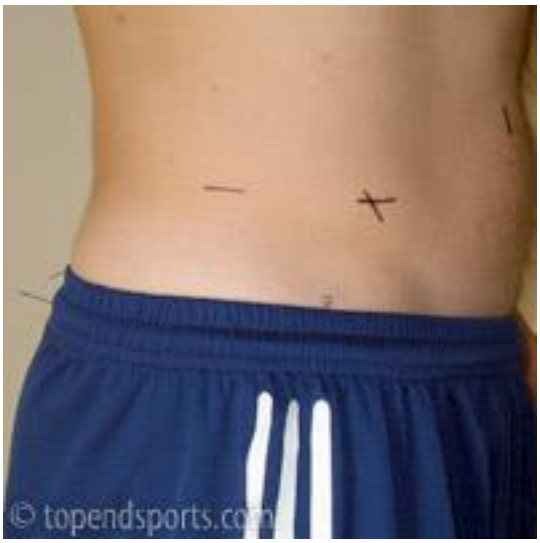
- Landmark: the lower angle of the scapula (bottom point of shoulder blade)
- If there is difficulty finding this landmark, get the subject to reach behind their back with their right arm, while feeling for the movement of the scapula
- The pinch is made following the natural fold of the skin, approximately on a line running laterally (away from the body) and downwards (at about 45 degrees).





Suprailiac fold

- Landmark: immediately above the iliac crest (top of hip bone), on the most lateral aspect (side).
- The fold is directed anteriorly and downward in line with the natural fold of the skin. The right arm should be held across the body to keep it away from the measurement area.



Metabolic Analysis for Treatment Choice for Gestational Diabetes Mellitus (MATCH-GDM)

Screening Phone Script

Thank you for calling to find out more about this research study. My name is _____ and I will be telling you more about the study.

The purpose of this research study is to determine the best way to choose medications to treat pregnancy-induced diabetes (called gestational diabetes). In usual care, medications to treat gestational diabetes include insulin, metformin and glyburide. They are used for treatment of diabetes in pregnant and non-pregnant patients. Each of these medications targets a pathway of diabetes and recent studies suggest that women have different pathways for gestational diabetes. We are proposing to match medications to treat gestational diabetes with a woman's unique pathway. You may be eligible to take part in this study because you are being tested for gestational diabetes and may be expected to need medications.

This study includes one screening visit, a study visit and measurements after delivery and to be done here at Magee. The screening visit includes additional blood draws at the time of your 3-hour oral glucose test that was requested by your physician. If you are diagnosed with diabetes then you are eligible to continue in the study. During the course of the study, we will perform research tests and procedures such as drawing blood samples from a vein in your arm, performing brief physical exams, recording your medical history and other research measurements, and asking you to complete a repeat 3-hour oral glucose test 2 weeks after starting treatment. We also will collect blood samples at the time of your labor and delivery of your baby and assess the fat content of your newborn before you leave the hospital.

You will be compensated for your participation in this research study and could receive up to $150 for completing all portions of the study.

Does this sound like something you would be interested in participating in?
(If No): Thank you very much for calling.

(If Yes): Before enrolling people in this study, we need to determine if you meet the eligibility criteria. If it is alright with you, I would like to ask you a series of questions. You do not have to answer these questions, and you need to know the purpose of these questions is only to determine whether you are eligible for this study. All information that I receive from you, including your name and any other identifying information, will be strictly confidential and kept under lock and key. Please keep in mind that these are only a sampling of the inclusion and exclusion criteria. There are other criteria, including the results of the screening blood work, that may make you ineligible for participation.

Do I have your permission to ask you these questions?

(If No): Thank you very much for calling.

(If Yes, ask the following questions):

(Date and time permission granted: _____; Interviewer signature: _____)

How old are you?
Must be between 18-45 years of age

The answers of these questions must be answered "Yes":

Are you pregnant with one baby at this time?

Are you beyond 24 weeks' of pregnancy?

Has your doctor recommended a 3-hour glucose test to check for diabetes during this pregnancy?

This question must be answered "No": Are you taking any medications for the gestational diabetes yet?

Was everything normal on your baby's ultrasound?

Do you have a history of diabetes outside of pregnancy?

Have you taken any steroids by mouth or through injection in the past 7 days?

Do you have an allergy to Glyburide, Metformin or Sulfa?

Do you have any significant hepatic disease?

Do you have congestive heart failure or a history of an MI?

Do you have any severe pulmonary disease?

Please check:

___Volunteer is NOT ELIGIBLE to be screened for this study.

(If NOT ELIGIBLE): Thank you for your interest, but you are not eligible for this study. The information that I collected from you will be destroyed.

___Volunteer is ELIGIBLE to be screened for this study.

(If ELIGIBLE): You are eligible to participate in the study. Would you like to schedule your first study visit?
(If No): Thank you for calling.

(If Yes): (Schedule the Volunteer)

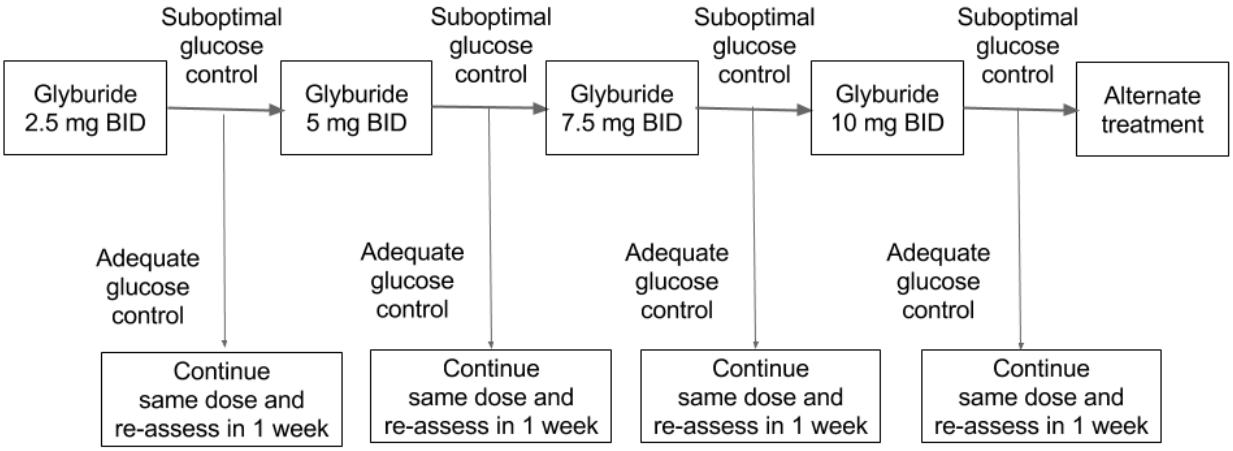
Do you have any questions at this time?

Subject's Name:_____ Phone:_____

Date Scheduled:_____ Time of Appointment:_____
Phone Script reviewed by:_____

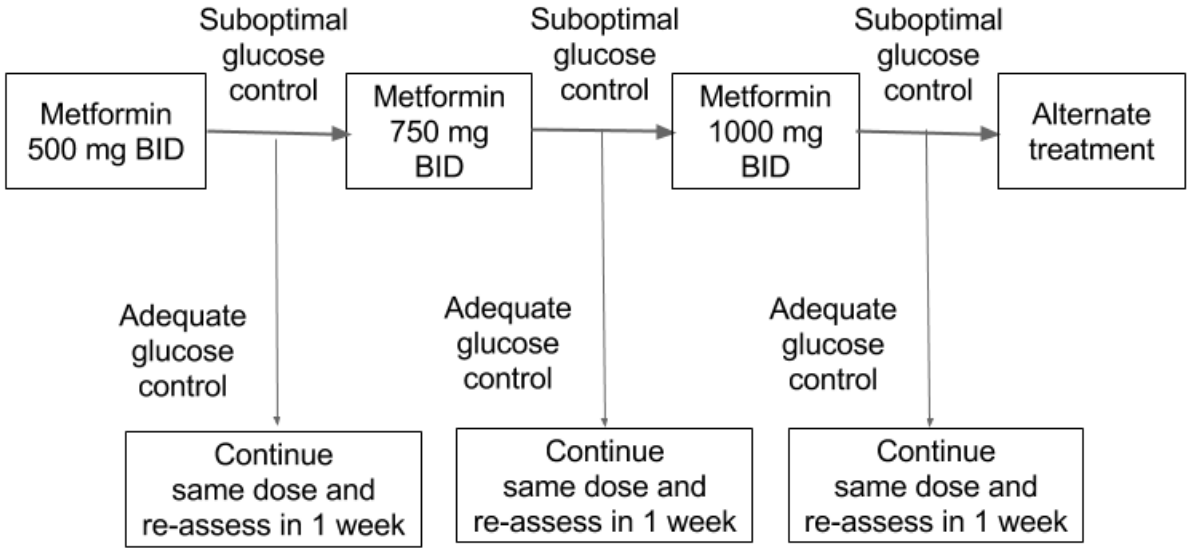
APPENDIX A
Study Protocol – Treatment Algorithms

Glyburide Dosing Algorithm



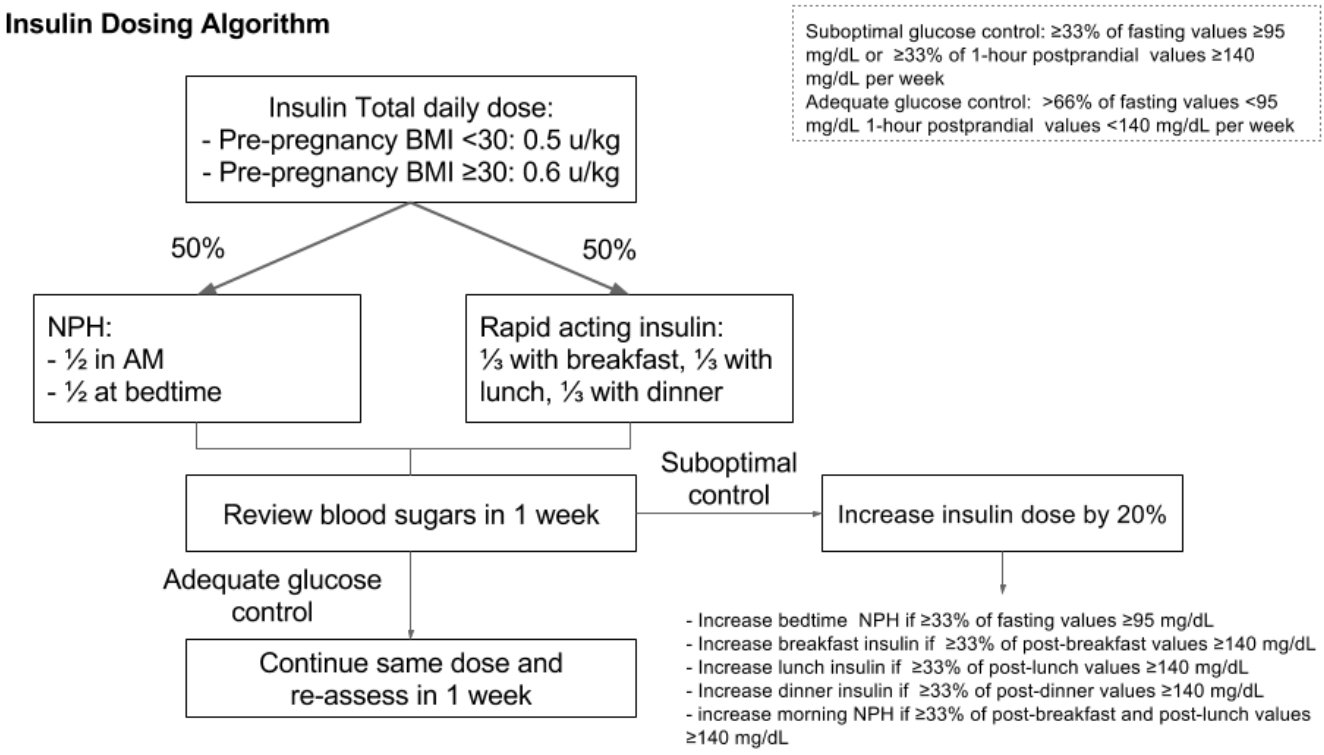
Suboptimal glucose control: ≥33% of fasting values ≥95 mg/dL or ≥33% of 1-hour postprandial values ≥140 mg/dL per week
Adequate glucose control: >66% of fasting values <95 mg/dL 1-hour postprandial values <140 mg/dL per week

Metformin Dosing Algorithm



Suboptimal glucose control: ≥33% of fasting values ≥95 mg/dL or ≥33% of 1-hour postprandial values ≥140 mg/dL per week
Adequate glucose control: >66% of fasting values <95 mg/dL 1-hour postprandial values <140 mg/dL per week

Insulin Dosing Algorithm



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Metabolic Analysis for Treatment Choice in Gestational Diabetes Mellitus (MATCh-GDM)

PI:_Maisa Feghali (412-270-1058, feghalim@upmc.edu)

MATCh-GDM_ Form 1: Sample data

Participant ID: _____

Date: _____

Research staff collecting data (initials):

	Time of blood draw	**Time of specimen processing**	**Number of cryovials**
0			
60			
120			
180			

Metabolic Analysis for Treatment Choice in Gestational Diabetes Mellitus (MATCh-GDM)

PI:_Maisa Feghali (412-270-1058, feghalim@upmc.edu)

MATCh-GDM _ Form 2: Anthropometric data

Participant ID:_ _____

Date: _____

Research staff collecting data (initials):

Weight: _____kg

Height: _____cm

Skinfold thickness:

Triceps fold: _____mm

Subscapular fold: _____ mm

Suprailiac fold: _____ mm