Fasting Versus Fed: Effect of Oral Intake Prior to the Glucose Tolerance Test in Pregnancy

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1. PURPOSE OF THE STUDY

a. Brief Summary

Gestational diabetes (GDM) complicates approximately 400,000 pregnancies in the United States annually and is associated with significant adverse pregnancy outcomes, including increasing the lifetime risk of type 2 diabetes. The American College of Obstetrics and Gynecology (ACOG) recommends that all pregnant women undergo GDM screening between 24-28 weeks gestation utilizing a 1-hour oral glucose tolerance test that was designed to be administered without regard to the last meal or time of day. However, studies suggest that the timing of one's last meal prior to the 1-hour GDM screen may have a significant impact on GDM screening glucose levels. In addition, providers routinely alter the timing of the 1-hour GDM screen based on patients' self reported oral intake prior to the exam. We plan to conduct a prospective randomized trial comparing a 6-hour fast versus liberal oral intake within 2 hours prior to the glucose tolerance test in pregnancy in order to evaluate the effect of the fasting versus the fed state on routine GDM screening results.

b. Objectives

Gestational diabetes is associated with adverse maternal and neonatal outcomes such as hypertensive disorders of pregnancy, increased risk for cesarean delivery, macrosomia, neonatal hypoglycemia and hyperbilirubinemia, and birth trauma. Treatment of gestational diabetes has been shown to mitigate these outcomes. Therefore, ensuring that women are accurately screened for the disease will help ensure that they are diagnosed and treated appropriately. We aim to determine the effect of fasting versus a fed state on the result of the 1 hour 50-g oral GTT in pregnancy This study may have far-reaching implications for how patients should be counseled regarding how to prepare for this test in a standardized fashion.

c. Rationale for Research in Humans

This study will provide information to support evidence-based guidelines to help providers understand how the duration from last oral intake prior to the test will affect test results. As this study is aimed at studying gestational diabetes, pregnant women will be required to be study participants. Neonatal charts of pregnant women who consent to be in the study will also be reviewed in order to assess the corresponding neonatal outcomes for this group of women.

2. STUDY PROCEDURES

a. Procedures

Screening will be undertaken through the Lucile Packard Children's Hospital (LPCH) Stanford outpatient obstetrics clinic. At a new patient intake, a phone conversation is completed by the Obstetric RN where patients are asked if they are willing to participate in research studies run through our OB/Gyn department. Potential patients will be identified during this intake phone call. A member of the clinical care team can also ask the patient for permission to be contacted by the research staff. Patient will then be approached by the research staff for enrollment and provide informed consent for the study which the patient will sign either in person or through a remote/ electronic consenting process. After obtaining informed consent, the patient will be randomized to one of two groups: 1. fasting for at least 6 hours prior to the GDM screen. 2. liberal PO intake within 2 hours of the GDM screen. Patients will then undergo the 1 hour glucose tolerance screening test for gestational diabetes at the same gestational age they would normally take the test (after 24 weeks gestation) as per standard of care. Water intake is allowed in the fasting group. During the time of the glucose screening, patients will be required to complete a short online/phone survey detailing when their last oral intake was and what it consisted of. Women who screen positive with glucose results greater than or equal to 140 mg/dL will then be required to undergo a fasting 3 hour oral glucose tolerance test which is according to standard of care. ACOG currently endorses a positive screening result for the 1 hour glucose tolerance test that ranges from 130-140 mg/dL. LPCH Obstetrics outpatient clinic typically uses 140 mg/dL as the screen positive cutoff. A 140 mg/dL cutoff will be used for women enrolled in the study. A medical chart review will be performed for all patients and their neonates after delivery.

b. Procedure Risks

The blood draws and glucose testings that are being performed are part of the standard of care for any pregnant woman in the screening and diagnosis of gestational diabetes. Currently, the recommendation is that the 1 hour screening test be administered without regard to the time of day or last oral intake. This study will randomize women to a fasting vs fed group prior to the GDM screen. A 6 hour fast has not been shown to have any deleterious effects in pregnancy.

c. Alternative Procedures or Courses of Treatment

This study is following standard of care guidelines for the screening for gestational diabetes. Patients may elect not to participate in the study and therefore decide for

themselves when their last oral intake will be prior to the 1 hour oral glucose tolerance test.

d. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

All patients will be treated by their clinical providers according to their usual treatment protocols and standard of care. Clinical providers will determine the type of treatment the patient will receive during their pregnancy and postpartum.

e. Study Endpoint(s)

The protocol director and investigators who serve as the data and safety monitors will be responsible for addressing whether there are any safety concerns related to the study or if there is any need to terminate the study before target enrollments are completed. Unanticipated problems or adverse events will be reported to the IRB. The study will end after the target enrollment has been completed.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Gestational diabetes (GDM) is characterized by a state of insulin resistance in the second and third trimester, with the prevalence being estimated at up to 9% in the United States [1,2]. Women with gestational diabetes have a higher risk of large for gestational age (LGA) infants, neonatal hypoglycemia, hyperbilirubinemia, cesarean delivery, shoulder dystocia, preeclampsia, and birth trauma [2–5]. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) trial further demonstrated a continuous association between hyperglycemia and the risk of adverse maternal and neonatal outcomes [3], and treatment of gestational diabetes has been shown to significantly decrease the risk of maternal and neonatal morbidity[6]. Screening for gestational diabetes is routinely performed between 24- 28 weeks gestation in all pregnancies, with early screening being utilized for those with risk factors that would lead to a predisposition for GDM or pregestational diabetes [2]. In the United States, the two step approach is commonly employed which utilizes a 1-hr 50-g oral glucose tolerance test for screening followed by a 100-g 3-hr glucose tolerance test for those who screen positive on the screening test to confirm the diagnosis of GDM. Cutoff values for a positive screen range from 130 mg/dL – 140 mg/dL and vary by institution [2,7,8]. The 1-hour oral glucose tolerance test is traditionally obtained without regard to time of day or time of last meal [7,9–12]. There are no societal guidelines regarding appropriate oral intake prior to the test, and there appears to be discordant advice given to patients regarding whether or not they should fast prior to the test. Moreover, contrary to patients' and providers' intuition, small cohort studies suggest that fasting prior to the GDM screen may actually lead to an increase in the 1 hour result, and it has previously been suggested that different cutoff values may be considered when the test is administered in the fasting versus the fed state [7,9,13–16]. Coustan et al performed a prospective crossover study in 1986 that looked at 20 known gestational diabetics and 50 presumed normal patients. Patients were administered the 1 hour glucose tolerance test 1 hour after receiving a standardized meal and then a week later fasted and took the test. They found that fasting only made a significant difference

in the glucose levels for the known gestational diabetics but not for the presumed normal controls [13]. A more recent study by Hancerliogullari et al from Turkey in 2018 surveyed women prior to their 1 hour GDM screen to determine the effect of fasting on the GDM screen glucose levels [16]. They found a significant difference in GDM screen glucose values following a 6.5 hour fast, with fasting leading to a higher glucose level [16]. However, much of the data regarding the 1 hour glucose tolerance test is based upon cohorts from the 1960-1980s with few studies examining this screening test in a modern cohort. It is well recognized that pregnant women today are generally older, more diverse, and have higher BMIs than women 40 years ago; therefore determining optimal GDM screen strategies in a modern cohort is warranted. Our goal is to use evidence based methodology to determine the effect of a fasting vs fed state prior to the routine GDM screen in pregnancy.

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4. PARTICIPANT POPULATION

a. Planned Enrollment

We estimate a total sample size of 200 women (100 women in each study arm) is required for this study based on a power calculation at power = 0.8, alpha = 0.05, and a 20% difference in screen positive rate between the fed versus fasting group. Patients will be enrolled at Lucile Packard Children's Hospital (LPCH) Stanford. No other external sites will be involved in the study. All enrolled participants will be pregnant patients as this study aims to investigate the effect of oral intake prior to the 1 hour oral glucose challenge test for gestational diabetes.

b. Age, Gender, and Ethnic Background

The patient population is pregnant women of childbearing age (more than or equal to 18 years old) including their infants from the current pregnancy. Ethnic background will reflect the local and regional population.

c. Vulnerable Populations

All participants in this trial will be pregnant women as we are studying gestational diabetes which is a unique disease state that occurs in pregnancy. However, we are following standard of care in terms of the timing of the blood draw in pregnancy and also in the quantity of the blood draw. Pregnant women identified as eligible for the study will be counseled by members of the team regarding benefits and risks with participation. A written informed consent form will be obtained from all participants. If at any time participants wish to withdraw, they will be allowed to do so. All pregnant women obtaining prenatal care at the outpatient obstetrics clinics of LPCH may be eligible for the study. Some of these may be homeless women, economically and educationally disadvantaged women, employees, and/or students, though specific cohorts will not be targeted. Neonates of women enrolled in the study will not have any blood draws or any other interventions performed as part of the study but neonates will have information abstracted from their charts to correlate neonatal outcomes with maternal findings. There will be no changes to neonatal care from this study.

d. Rationale for Exclusion of Certain Populations

This study will not be offered to pregnant minors (age < 18 years old) because we anticipate to reach our enrollment goal in the pregnant population that is greater than or equal to 18 years old.

e. Stanford Populations

Laboratory personnel, employees, and students may be recruited if they meet inclusion criteria, using the same informed consent and treatment protocol as other participants. It is not possible to estimate the number of such participants, but they will likely represent a small minority of the total subjects recruited.

f. Healthy Volunteers

Only pregnant women will be included.

g. Recruitment Details

Women potentially eligible for the study will be identified by preliminary screening of LPCH outpatient obstetric clinic medical records. A member of the care team will notify the potential participant about their eligibility for the research study and will obtain the patient's permission before the research team can approach. The medical record review will also determine the inclusion/exclusion criteria for the study. If eligible, the study will be discussed and reviewed with the patient. We will also address questions or concerns. If the patient is interested, she will be consented and enrolled in the study. A description of the study will also be listed on the Maternal Fetal Medicine Research (MFM) Studies flyer. This flyer is included in the New OB packet, which is given to every pregnant women during their initial OB visit at the LPCH OB Clinic. If the patient is interested, she can reach out to our team, and we will discuss the study and any questions or concerns. If still interested, she will be consented and enrolled in the study. Recruitment materials will be submitted to IRB prior to use. The study will be registered on ClinicalTrials.gov and the Stanford school of medicine website

h. Eligibility Criteria

i. Inclusion Criteria

1) Pregnant patients 18 years and older
2) Planned delivery to occur at LCPH Labor and Delivery unit
3) Pregnancy being followed by LPCH outpatient obstetrics clinic
4) Singleton pregnancy

ii. Exclusion Criteria

1) Pregestational diabetes
2) Gestational diabetes diagnosed in the 1st trimester
3) Diabetes medication use prior to pregnancy
4) Inability to give informed consent
5) Chronic steroid use in pregnancy
6) Less than 24 weeks of gestation at the time of the 1 hour oral glucose tolerance test
7) Prior history of bariatric surgery

i. Screening Procedures

Women receiving prenatal care at the LPCH Obstetric clinic will be screened if eligible for the study. Potential participants will be identified by review of electronic medical records which will include the collection of personal health information. If eligible, the

participant will be approached to review the study and have questions answered. If the patient provides consent, she will be enrolled in the study.

j. Participation in Multiple Protocols

Patients will be asked if they are participating in any other research protocols during the consenting process. If the patient is already participating in other research studies, she will not be enrolled if the study procedures involved will conflict with what is required in the protocol.

k. Payments to Participants

Patients participating in the study will receive a token gift of a $15 gift card to demonstrate appreciation for their participation in the study. This level of compensation is within the category of token level of appreciation and will not constitute undue pressure on participants to participate in this study.

l. Costs to Participants

No additional costs will be charged to the patient.

m. Planned Duration of the Study

The estimated length of time for the study is approximately 18 months with 15 months of enrollment and 3 months of data analysis and summarization of findings.

10/2020-12/2021: Patient recruitment and enrollment. We anticipate that all 200 patients will be enrolled during this timeline. All patients enrolled will ensure delivery is by the end of 02/2022.
02/2022-04/2022: Data analysis
04/2022-06/2022: Manuscript development and submission

The total time per participant includes: (i) enrollment activities (30 minutes) via remote process or at LPCH obstetrics clinic, (ii) active participation to include a universal 1 hour oral glucose challenge test at 24 weeks of gestation or greater to screen for gestational diabetes which is standard in all pregnancies. Non active participation will include chart review of the patient's medical records and the associated neonatal medical records (iii) Analysis of data - 3 months.

5. RISKS

a. Potential Risks

i. Commercially available drugs, biologics, reagents or chemicals

Every pregnant woman (irrespective of participation in the study) undergoes a routine gestational diabetes screen using a 50 g glucose drink. Side effect of the drink includes nausea, vomiting, abdominal bloating, and/or headache. Women participating in the study

will have a GDM screen using a 50 g glucose drink that is identical to those not participating in the study.

ii. Procedures

Every pregnant woman (irrespective of participation in the study) has a blood draw that is a part of the GDM screen. Women participating in the study will also have a blood draw as a part of the GDM screen. The risks of a blood draw includes discomfort at the site of puncture, possible bruising, redness, and swelling around the site, bleeding at the site, feeling lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw.

iii. Overall evaluation of risk

The protocol is no more than minimal risk (i.e., "not greater than those ordinarily encountered in daily life") AND only involve human subjects as described below:

- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
  a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
  b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
- Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

b. International Research Risk Procedures

Not Applicable.

c. Procedures to Minimize Risk

Standard safety procedures will be followed to minimize risk associated with blood draw including the use of gloves and cleansing of area where venipuncture is to be performed with alcohol. In addition, the 1 hour glucose tolerance test will be administered during the standard time of pregnancy at 24 weeks of gestation or greater. With regards to protecting patient confidentiality, we will assign each participant a study code that will be based on

the order of their enrollment and will have no reference to any personal identifying information. We will keep an electronic list that connects patient names with study codes during the data collection period. This list will be kept on a password-protected document, on a password-protected/ encrypted computer in a locked office in the administrative offices of the Department of Obstetrics and Gynecology, or entered into a secure server such as RedCap, Encore and Box. Access to the databases will only be granted to the research team included under the IRB protocol.

d. Study Conclusion

The study will terminate once enrollment goal is achieved. If the patient experiences a rare adverse reaction to a blood draw or from the glucose drink, the obstetrician will be notified and will treat the event per usual standard practice (e.g. monitor vital signs, treat with ice packs, antibiotics, etc if needed).

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

For women who are participating in the study, neonatal charts will be reviewed to correlate maternal findings with neonatal outcomes. This study poses no risk to neonates as they will continue to receive routine care as provided by their care team and will not undergo any blood draws or interventions due to the study. Only neonates (0-28 days of life) of women who consent to participate in this study will be included and thus neonates will not be able to give assent. Consent for chart review of the neonates will be obtained from the mother when gives consent for HIPPA authorization.

ii. Person(s) responsible for Data and Safety Monitoring

N/A

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

N/A

v. DSMB Reporting

N/A

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

N/A

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

f. Risks to Special Populations

Children's Findings OHRP: 46.404 Research not involving greater than minimal risk. The research must present no greater than minimal risk to children and adequate provisions must be made for soliciting the assent of the children and the permission of their parents or guardians. For women who are participating in the study, neonatal charts will be reviewed to correlate maternal findings with neonatal outcomes. This study poses no risk to neonates as they will continue to receive routine care as provided by their care team and will not undergo any blood draws or interventions due to the study. Only neonates (0-28 days of life) of women who consent to participate in this study will be included and thus neonates will not be able to give assent. Consent for chart review of the neonates will be obtained from the mother when gives consent for HIPPA authorization.

Pregnant Women or Fetuses: All of the following conditions are met:

Met a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data assessing potential risks to pregnant women and fetuses;

Met b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

Met c) Any risk is the least possible for achieving the objectives of the research;

Met d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means , her consent is obtained in accord with the informed consent provisions of subpart A of this part;

N/A e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of` unavailability , incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

Met f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

N/A g) For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

Met h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

Met i) Individual engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;

Met j) Individual engaged in the research will have no part in determining the viability of a neonate.

6. BENEFITS

The participants will not benefit directly by participating in this study, as they would receive equally appropriate treatment should they choose not to participate. The knowledge gained in this study will be important in establishing the effect of oral intake prior to the routine GDM screening test.

7. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.