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Randomized Study of Postpartum Metformin Use to Augment Breastmilk Supply

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RANDOMIZED STUDY OF POSTPARTUM METFORMIN USE TO AUGMENT BREASTMILK SUPPLY

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ABSTRACT

Gestational diabetes is defined as impaired glucose tolerance with onset during pregnancy and affects approximately 8.2% of pregnancies. Recently, it has been shown that insulin resistance is a predictor of poor milk supply in women attempting to breastfeed. Some mothers with gestational diabetes who used metformin for optimal glycemic control during pregnancy have found that metformin use has improved their ability to produce milk after delivery; however, the effects of continuing metformin postpartum have not yet been studied. It is theorized that continued metformin use in the postpartum period in women with gestational diabetes may improve postpartum milk production. **Using a randomized control trial, our objective is to determine if continuing the use of metformin for 8 weeks postpartum is an effective intervention in increasing milk supply in women who are diagnosed with gestational diabetes.** We hypothesize that we will see an increase in breast milk production in these women.

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 The Burden of Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy and has important health implications for both the mother and child even after pregnancy. In recent years, studies have shown that the rate of mothers being diagnosed with GDM has significantly increased therefore making it an important public health concern to address. In one study from 2016 it was estimated that the prevalence of GDM increased to 8.2% from 4.6% in 2010. [1]

Gestational diabetes mellitus is defined as impaired glucose tolerance with onset, or first recognition, during pregnancy. [2] Insulin resistance during pregnancy stems from a variety of factors, one being the secretion of human placental lactogen which is a hormone that is produced and secreted by the placenta. This hormone functions in breaking down fats from the mother in order to provide carbohydrates for the baby in the placenta.[3] Additionally, it creates a state of mild insulin resistance for the mother in order to benefit the fetus by increasing the availability of maternal glucose for fetal consumption.[4] Normally, the beta cells of the pancreas are able to make additional insulin to overcome this insulin resistance, but when the production of insulin is not enough to overcome the effects of the placental hormones, the result is gestational diabetes.

Routine screening for GDM is typically performed been 24 and 28 weeks of gestation and the diagnosis of GDM in the US is made using a series of tests, first a

screen and then a diagnostic test. The first test is known as the oral glucose challenge test (GCT).[5] This test involves drinking a solution containing 50g of glucose and drawing blood to measure glucose levels at one hour after consumption. If positive, women then are asked to complete a fasting 3-hour oral glucose challenge test (OGTT) with 100g of glucose in solution and have their glucose levels checked fasting and at 1, 2, and 3 hours after consumption of the drink. There are two subtypes of gestational diabetes that are classified using the White classification system, they are type A1 and type A2.[3] A patient is diagnosed with type A1 GDM if they are able to keep their blood sugars at goal with diet and exercise alone. A diagnosis of type A2 GDM is made when a patient has GDM and has blood glucose values above target for fasting and after meals. This type of GDM requires more aggressive treatment with insulin or other medications.[3]

Gestational diabetes increases the risk of complications in pregnancy and childbirth as well as long-term health for the mother and infant. GDM carries a long-term risk of obesity and glucose intolerance in the offspring. One of the best interventions proven to help reduce obesity in children is through breastfeeding, which is recommended for the first six months of life according to the American Academy of Pediatrics.[6] However, only about 19% of women who initiate breastfeeding do so for the entire six months.[7] One of the biggest reasons that is given as to why many women stop breastfeeding earlier than they intended to is because of a low milk supply. Other than encouraging mothers to increase the frequency and thoroughness of breast emptying, there are not any evidence-based strategies to help mothers increase their milk supply.[8]

Emerging evidence suggests that glucose intolerance and delayed lactogenesis are correlated and that diabetes during pregnancy may increase the risk of persistent low milk supply. In a case-control analysis, Riddle et al. 2016 showed that women who were diagnosed with a low milk supply were significantly more likely to also have been diagnosed with GDM and have problems with insulin metabolism compared to other mothers.[7] It has also been shown that lactation onset is delayed in obese women with poor glucose control.[9] The onset of lactation plays a crucial role in the duration of breastfeeding as seen in a recent study by Chapman et al.[10] This study additionally showed that on average women who experienced delayed onset of lactation breastfed for a much shorter duration.

Over time we have started to better understand that insulin plays a role in lactation and that impaired insulin and glucose metabolism is correlated with poor lactation in mothers. A recent study showed that insulin stimulates the expression of genes that are directly involved in milk protein synthesis.[11] Since proper insulin levels are necessary for lactation, good glycemic control can enhance milk production while decreasing the delay in lactation.[12] We hypothesize that by continuing metformin postpartum in women who were diagnosed with GDM and continuing to control glucose and insulin levels, we may see an increase in breast milk production as well as a more rapid onset of lactation.

1.1.2 Role of Metformin Use in Gestational Diabetes Mellitus

It has been shown that with proper treatment of GDM the incidence of many of the adverse complications associated with GDM can be reduced. Nutritional management and exercise are the foundations of treatment, but insulin or metformin are added in women who cannot achieve optimal glycemic control with diet and exercise changes

alone. Although insulin has been and still is considered the gold standard therapy of choice during pregnancy for many decades, oral hypoglycemic medications have recently been introduced as treatment for GDM as many women find the prospect of multiple injections a day intolerable.[13]

One specific oral antidiabetic medication is metformin. This drug has been used for decades in the treatment of type 2 diabetes as well as polycystic ovarian syndrome but its use in pregnancy has be limited.[14] Recently, several observational and randomized control trials compared metformin to insulin and have found that metformin does not increase adverse outcomes, and potentially even reduces maternal weight gain during pregnancy, which is key in this population as many enter pregnancy with elevated BMIs.[15] Metformin has several mechanisms of action which include, decreasing hepatic glucose production by suppressing gluconeogenesis, increasing insulin sensitivity, as well as enhancing peripheral glucose uptake.[14,16] All of these functions lead to lower blood glucose levels and improved glycemic control.[17] Since it is recently starting to be understood that insulin plays a role in lactation and that impaired insulin and glucose metabolism is correlated with poor lactation in mothers, we believe that by continuing metformin during the postpartum period and continuing to control glucose levels, we could see an increase in breast milk production as well as a more rapid onset of lactation.

In all of the studies that have addressed the different therapeutic options for diabetes during pregnancy several neonatal and maternal outcomes have been analyzed and studied but one factor that has not been studied in depth is the effect on breast milk production and lactogenesis. Breastfeeding is an important factor that is known to impact health outcomes in infancy and childhood making it an important factor to identify and

study, especially in correlation with metformin therapy. It has been shown that delayed onset of lactation and the perception of having a poor breastmilk supply is associated with a shorter breastfeeding duration.[10,18] Therefore, finding a way to increase the postpartum milk production in women diagnosed with GDM could aid in longer compliance with breastfeeding.

1.2 Statement of the Problem

For many years, it has been known that maternal obesity is associated with delayed lactogenesis and a shortened duration of breastfeeding.[19] Recently a study known as the Feeding Practices Study II showed that "insufficient milk" was the primary factor that mediated the association between maternal obesity and lower prevalence of exclusive breastfeeding.[20] We know that insulin resistance plays a huge role in obesity but for many years it was believed that insulin did not play a direct role in mammary gland function. Recently, studies have shown mammary glands to be sensitive to insulin during pregnancy and lactation.[21] This leads us to believe that mothers with insulin-resistant conditions, such as gestational diabetes, are at an increased risk for insufficient milk production.

Metformin is a first line drug for improving insulin sensitivity, and it is known to be safe for use during lactation through studies of women with Type 2 diabetes;[22] however, its efficacy in improving milk production has not yet been studied, specifically when continuing treatment with metformin into the postpartum period in women diagnosed with gestational diabetes and treated with metformin during pregnancy. This supports the need for a randomized control trial to investigate the effects of metformin on milk production. The results of this study could help shape best practices for

breastfeeding in mothers with gestational diabetes. It is relevant to medical practice, specifically physician assistant practices, because it would aid in understanding how to best treat mothers with gestational diabetes in the postpartum period and how to help them reach their breastfeeding goals, which could in turn improve long-term health outcomes for themselves as well as their children.

1.3 Goals and Objectives

This study aims to investigate the relationship between postpartum metformin use and breastmilk production in women who were diagnosed with A2 gestational diabetes and treated with metformin during pregnancy. We want to determine if metformin use has an effect on the mammary glands and therefore milk production.

Our primary outcome will be breastmilk production which will be measured using infant test weighs taken immediately before and after each feeding. This will be statistically analyzed as a continuous variable. Secondary outcomes that will be measured include the following: maternal fasting blood glucose levels, infant weight gain over the course of the study period at office visits, number of wet diapers per day, and need for supplementation with formula as prescribed by a pediatrician due to poor weight gain. We have chosen these secondary variables because they are significant, independent factors that may be predictors of how well our independent variable, metformin, is functioning and the effects that it is producing in addition to how it affects maternal glycemic control in the postpartum period. These outcomes will allow us to explore the potential beneficial effects of metformin as an intervention on low milk supply in mothers with gestational diabetes.

1.4 Hypothesis

We hypothesize that continuing metformin treatment for 8 weeks postpartum in women who are diagnosed with gestational diabetes mellitus will lead to an increase in breastmilk production through better glucose control.

1.5 Definitions

- *Blood Glucose Levels:* The concentration of glucose present in the blood. Measured with a sample of blood. A fasting blood glucose level under 100mg/dL is normal in non-pregnant individuals.
- *Gestational Diabetes Mellitus:* Gestational diabetes mellitus (GDM) occurs when a woman's pancreatic function is not sufficient to overcome the diabetogenic environment of pregnancy. GDM is defined as glucose intolerance that was not present or recognized prior to pregnancy.[3]
- *Insulin:* A hormone made by the pancreas that allows your body to use sugar (glucose) from carbohydrates in the food that you eat for energy or to store glucose for future use. Insulin helps to prevent blood sugar level from getting too high or too low.
- *Lactogenesis:* The onset of milk secretion and includes all of the changes in the mammary epithelium necessary to go from the undifferentiated mammary gland in early pregnancy to full lactation.[23]
- *Metformin:* Oral diabetes medication that helps control blood sugar levels.

- *Postpartum:* The period of time that begins immediately after the birth of a child as the mother's body returns to a non-pregnant state. In this study we refer to the postpartum period as the first 8 weeks following childbirth.

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

We conducted multiple searches of medical literature databases, including PubMed, Ovid, and Cochrane, starting in August 2019 through July 2020. In these searches, we used the MeSH terms [gestational diabetes] or [insulin resistance, pregnancy-induced] and [metformin] or [hypoglycemic drugs] and [breast feeding] or [lactation] or [human milk] or [milk supply]. We further reviewed the references of these studies to identify relevant studies not found in our searches. We included mostly systematic reviews, meta-analyses, and quantitative studies, including case-control studies, cohorts, and randomized controlled trials.

2.2 Review of Empirical Studies

2.2.1 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM), the most common metabolic disorder of pregnancy, is defined as "the type of glucose intolerance that develops in the second and third trimester of pregnancy, resulting in hyperglycemia of variable severity"[1]. Gestational diabetes mellitus affects approximately 8.2% of pregnancies in the United States, and it is increasing in prevalence as a consequence of increases in obesity prevalence and advanced maternal age.[2] Gestational diabetes mellitus occurs when a mother develops dysglycemia because of endocrine disruption that occurs during pregnancy. Insulin resistance during pregnancy stems from a variety of factors, one being the secretion of human placental lactogen which is a hormone that is produced and secreted by the placenta. This hormone functions in breaking down fats from the mother in order to provide glucose for the baby in the placenta.[3] Additionally, it creates a state of

mild insulin resistance for the mother in order to benefit the fetus by increasing the availability of maternal glucose for fetal consumption.[4] Normally, the beta cells of the pancreas are able to make additional insulin to overcome this insulin resistance, but when the production is insulin is not enough to overcome the effects of the placental hormones, the result is gestational diabetes.

There are two different subtypes of gestational diabetes based on the White Classification system; A1 and A2. They differ in the forms of treatment that they require. Type A1 is able to be adequately controlled with diet and exercise whereas type A2 requires more intensive treatment with medications.[5] Screening for GDM usually occurs between 24 and 28 weeks of gestation[6] and is typically done by utilizing the two step approach. The first is a screening involving a 50g oral glucose challenge test, where the mother drinks a beverage consisting of 50 grams of dissolved sugar and an hour later her blood is drawn to measure the glucose concentration.[6] If the value is less than 130-140 (depending on the lab and cut-off used) then the test is said to be normal, but if the blood sugar levels are elevated then further testing must be conducted to diagnose gestational diabetes.[7] The subsequent diagnostic test to be performed is the glucose tolerance test which must be done after the conclusion of an eight-hour fast by the patient. A fasting sample of blood is taken first, typically first thing in the morning, and then the patient drinks a beverage that contains 100 grams of glucose. Blood samples are then taken after 1, 2 and 3 hours.[6] If two of the four blood sugar values are elevated the mother is then diagnosed with GDM.[8]

Once the diagnosis is made it is important to determine the best treatment plan due to the risk of complications that are associated with it. The initial treatment of GDM consists of diet modifications, glucose monitoring, and exercise. [9] If these measures fail to adequately control blood sugar, medications such as insulin or metformin are used to achieve euglycemia.[6] Initiation of treatment in mothers with GDM is important because it has been shown to reduce the rate of serious neonatal outcomes such as death, large for gestational age infants, shoulder dystocia, bone fractures and nerve palsy.[10]

2.2.2 Treatment of Gestational Diabetes Mellitus

Insulin, for many years, has been the treatment of choice when lifestyle changes fail to maintain proper glycemic control during pregnancy. [9] Recently studies have suggested that oral hypoglycemic medications may be safe and acceptable alternatives, one specific medication being metformin.[11] Metformin was first approved for the treatment of diabetes in the United States by the FDA in 1995 and has been used for decades in the treatment of type 2 diabetes as well as polycystic ovarian syndrome but its use in pregnancy has be limited.[12] Metformin is a biguanide and has several mechanisms of action which include, decreasing hepatic glucose production by suppressing gluconeogenesis, increasing insulin sensitivity, as well as enhancing peripheral glucose uptake.[12] All of these functions lead to lower blood glucose levels and better glucose control. Studies has shown that metformin can achieve blood glucose control in women with GDM just as effectively as insulin but at a lower cost and with better adherence due to it being an oral medication rather than one that must be injected.[13] Additionally, one randomized control trial known as the Metformin in Gestational Diabetes Trial which was conducted by Rowan et al., compared the use of metformin to insulin in pregnant

women with GDM and found that metformin does not increase adverse outcomes and may even reduce maternal weight gain during pregnancy.[14] This was one of the largest studies that aided in introducing metformin as an alternative treatment for GDM. When treating women with gestational diabetes metformin can be initiated from the time of diagnosis and is typically discontinued with delivery.

Although the standard therapy for women with gestational diabetes requiring drug treatment has been insulin for many years, in some settings oral agents are now becoming the first option.[15] Metformin treatment is usually initiated with divided doses of 500mg twice a day and the dose can be increased up to 2000mg daily.[16] Oral agents are becoming an attractive alternative to insulin due to their lower cost, easier administration and better acceptance by patients compared to injections with insulin.

2.2.3 Benefits of Breastfeeding

Breastfeeding has many health benefits, both in the short term and long term for both infants and their mothers. Due to ethical considerations it is difficult to perform randomized control trials looking at the benefits of breastfeeding, but there have been many observational studies that have carefully analyzed the relationship between breastfeeding and maternal and infant outcomes. Research suggests there are particular benefits of breastfeeding for women with a history of GDM and their infants,[17] including improved short-term insulin sensitivity and glucose homeostasis,[18] improved long-term insulin sensitivity,[19] and reduced risk of type 2 diabetes[20] many years postpartum. Specifically, it was shown that women with GDM who breastfed for at least 3 months had the lowest risk of development of diabetes after pregnancy.[21] Some studies have

reported a protective association between breastfeeding and type 2 diabetes risk[22,23] and slower early weight gain[24] among offspring of women with GDM. A systemic review by the World Health Organization found that breastfed infants were 35% less likely to develop subsequent type 2 diabetes compared to their non-breastfed counterparts.[25]Despite established benefits of breastfeeding, there is evidence that breastfeeding initiation, duration, and exclusivity may be lower among women with GDM[26-28]

2.2.4 Relationship between Metabolic Disorders and Lactation

It is well established that obese women are at increased risk of delayed lactogenesis and short breastfeeding duration, but the underlying causal contributors remain unclear.[29] Maternal obesity is a strong risk factor for insulin resistance and prediabetes, but until recently a direct role for insulin in milk production had not been elucidated. Over the past six years, studies in both animal models and humans have shown insulin-sensitive gene expression to be dramatically upregulated specifically during the lactation cycle. Insulin is now considered to play a direct role in lactation, including essential roles in secretory differentiation, secretory activation, and mature milk production. At the same time, emerging clinical research suggests an important association between suboptimal glucose tolerance and lactation difficulty. To develop effective interventions to support lactation success in obese women further research is needed to identify how, when, and for whom maternal insulin secretion and sensitivity affect lactation ability.

Recently there has been emerging evidence that suggests that glucose intolerance and delayed lactogenesis are correlated and that diabetes during pregnancy may increase

the risk of persistent low milk supply. In a case-control analysis it was shown that women who were diagnosed with a low milk supply were significantly more likely to also have been diagnosed with GDM. Specifically, they were found to be 2.6 times more likely to have problems with insulin metabolism compared to other mothers.[30] It has also been shown that lactation onset is delayed in women with poor glucose control. The onset of lactation plays a crucial role in the duration of breastfeeding as seen in a recent study by Chapman et al.[31] This studied showed that on average women who experienced delayed onset of lactation, >72 hours after delivery, on average breastfed for 8 months less than mothers who experienced lactation within 72 hours of delivery.

Although it's been shown in studies that all women with GDM have lower exclusive breastfeeding rates compared to women without GDM, one study which looked at metformin versus placebo in postpartum women with GDM found that women who had been randomized to the metformin group had a higher exclusive breastfeeding rate compared to placebo, 22.2% versus 9.3%, p=0.055.[32] This same study also found that the frequency of breastfeeding cessation was lower in the metformin group compared to placebo, 21.9% vs. 36.8%, p=0.912. In numerous studies it is frequently cited that low milk supply is the reason why many mothers stop breastfeeding earlier than they had planned.[33] Riddle and Nommsen-Rivers (2016) conducted a case control study to better understand the relationship between maternal diabetes and low milk supply, this was the first study conducted to look at this relationship. The study found that the presence of diabetes during pregnancy increased the risk of persistent low milk supply. Mothers with a diagnosis of low milk supply but no other lactation problems, such as latching onto the breast, were compared to mothers with lactation problems but without low milk supply.

In the case group 14.9% of the women had a history of diabetes during pregnancy, while in the control group 6.2% of the women who had lactation problems but not low milk supply had maternal diabetes.[30]

Since low milk supply appears to be associated with gestational diabetes this could support the concept that interventions targeting insulin action and glycemic control may be a promising and novel strategy toward improving milk supply in vulnerable mothers.

2.2.5 Breastfeeding Outcomes and Gestational Diabetes Mellitus

Studies of gestational diabetes mellitus in relation to breastfeeding are limited in number but the majority suggest the same outcomes, that breastfeeding issues are higher in mothers with GDM compared to mothers without GDM. These studies cite problems such as delayed onset of lactation, lower breastmilk production and shorter breastfeeding duration as some of the adverse outcomes from having GDM.[30,31] Infants born to mothers with GDM are more likely to experience complications, such as cesarean delivery, preterm birth and macrosomia, and therefore require intensive care. All of these factors also result in lower breastfeeding rates.[34] In a U.S. study, women with GDM were about 40% less likely to be exclusively breastfeeding on hospital discharge compared women without diabetes.[27] In another study that covered 37 states in the United States, the initiation rates were similar between mothers with and without GDM, but the mothers with GDM tended to cease breastfeeding earlier: 65.7% vs 68.8% at 2 months postpartum, respectively.[35] Factors that may affect the disparity include physiologic and behavioral challenges like higher prevalence of delayed onset of lactation,[36,37] neonatal hypoglycemia,[38] breastfeeding problems at home, and inadequate breastfeeding.[39]

Identification of a lower breastfeeding rate in a population that benefits more from breastfeeding is what has motivated us to develop this research question to identify the barriers that contribute to decreased breastfeeding in women with GDM. We hope to use this study to determine proper methods and therapies to help combat these impediments to breastfeeding. Additionally, we recognize the need to perform this study in a racially and ethnically diverse population as these are populations with lower breastfeeding rates and with higher risk for GDM.

2.3 Confounding Variables

It is difficult to isolate the effect of metformin on breastmilk production due to a multitude of potential confounding variables. These include maternal age, maternal ethnicity, maternal marital status, pre-pregnancy BMI, family history of GDM or type 2 diabetes, diagnosis of GDM in previous pregnancies, other signs of insulin resistance such as polycystic ovarian syndrome or metabolic syndrome, number of previous breastfed infants, vaginal versus cesarean delivery, gestational age at delivery, previous breast surgery, maternal education level, maternal socioeconomic status and parity. The majority of these will be discussed in this section.

Pre-pregnancy BMI is often controlled for in statistical analyses as a covariate in studies that analyze the effect of GDM on breastfeeding.[29] Most of these studies have even found that pre-pregnancy BMI significantly affect their results.[21,29]. In a study conducted by Pinhero et al, it was found that women who had a higher pre-pregnancy BMI in addition to GDM had a much higher likelihood of having delayed breastfeeding initiation compared to those mothers who had a normal pre-pregnancy BMI and GDM. Additionally, a study by Haile et al looking at the relationship between GDM and

exclusive breastfeeding at time of discharge found that women with a higher pre-pregnancy BMI compared to women with a normal pre-pregnancy BMI had lower odds of exclusively breastfeeding at the time of discharge.[27] This study also showed us that the presence of GDM was negatively associated with higher a BMI.[27] Together, these two previous studies show that pre-pregnancy BMI should be considered as a potential confounder in the present study.

Several studies have identified maternal characteristics such as younger maternal age, low income, ethnicity, less maternal education, and unmarried status to be associated with lower breastfeeding prevalence among women so these will all be taken into consideration as confounders as well.[40,41] Additionally, research studies conducted by Ahluwalia et al indicated that women who had induced labor or cesarean sections were less likely to initiate and continue breastfeeding compared to women who had spontaneous vaginal deliveries.[42,43] Due to this information we will also consider the different types of delivery, vaginal vs cesarean, to be a confounders in our proposed study.

In the proposed study, randomization will act to minimize any statistically significant differences in baseline characteristics between the control and intervention groups, which will serve to minimize the effects of confounding on the results. Furthermore, we plan to collect and report these characteristics and will note any significant differences in baseline characteristics between groups.

2.4 Safety

Metformin is a first-line, FDA approved drug for treating Type 2 diabetes.[44] In addition, it has been shown to be safe when used in women with polycystic ovary

syndrome to improve insulin action.[45] More recently studies have been conducted showing that it is safe to use during lactation with milk concentrations being very low and serum concentrations in breastfed infants being nearly undetectable.[46] A large prospective study by Glueck et al found that there were no adverse effects or differences in growth and development between infants who were breastfed vs formula fed of mothers that were taking metformin for 6 months postpartum.[47] One of the most concerning side effects of metformin is lactic acidosis. However, in a review of 18 clinical studies that looked at the use of metformin for treatment of polycystic ovary syndrome there were not any reports of lactic acidosis occurring.[45] All of this supports the safety of metformin use in our study in both women with GDM and their infants and we do not expect to see any negative effects on neonatal or maternal outcomes.

2.5 Review of Relevant Methodology

The purpose of this section is to review methodology in previous studies as they pertain to the proposed study. A detailed description of the proposed study's methods will be discussed in Chapter 3.

2.5.1 Study Design

Most previous studies examining the effect of gestational diabetes on breastmilk supply and lactation have been retrospective cohort studies, prospective cohort studies or case-control studies.[29,30,48] These designs of studies are limited since they can only establish an association between GDM and low breastmilk supply, they can't explain the mechanism behind the outcome or establish direct correlation between metformin use postpartum and breastfeeding in women with A2GDM during pregnancy. Thus, the proposed study design is a randomized controlled trial, which allows us to determine a

causal relationship between the intervention and the primary outcome while minimizing the effect of bias and confounding variables.

Due to the nature of the intervention we will be able to blind the participants to the group they are randomized to by giving the control group a placebo. In the randomized controlled trial conducted by Nommsen-Rivers et al, the authors blinded the members of the research team, as well as the statistician who reviewed the data that was collected, to the allocation.[49] We will similarly blind the research team members who review the medical charts and data in order to reduce bias effect on the investigators' interpretation of the results.

2.5.2 Selection Criteria

In order to select the inclusion and exclusion criteria for the proposed study, we analyzed several previous studies' selection criteria and chose the most applicable and relevant to our study population.

First, our study will include only women with a diagnosis of GDM type A2 treated with metformin during pregnancy as this is the intended study population. We differentiated type A1 from A2 because our study participants will have received treated with metformin to control their blood glucose levels during the antenatal period. This means that the participants will have GDM that didn't respond to diet and exercise changes alone and therefore need additional treatment with metformin. The gestational age at time of recruitment in a previous randomized controlled trial was more than or equal to 37 weeks' gestation but in that study the intervention was started after birth.[49] For the sake of our proposed study, we will only include term deliveries which means any women who are over 37 weeks' gestation and have a diagnosis of A2GDM on metformin

will be recruited. The study will be introduced at the time of their diagnosis of GDM requiring metformin for glycemic control during pregnancy, which could occur as early as 24 weeks gestation. Consent and randomization will occur at the clinic once women have reached 37 weeks' gestation to ensure they were maintained on metformin for glycemic control with their A2GDM diagnosis.

For our study, it is important to ensure that our group of women doesn't have any complicating comorbidities or prior diagnosis of diabetes that could alter our outcome data. For similar reasons, Nommsen-Rivers et al excluded women who were diagnosed pre-gestational Type 1 or Type 2 diabetes as well as those who had a history of breast surgery and we will do the same in our study.[49] Multiple gestation is defined as a high-risk pregnancy that increases the likelihood of GDM. Because of this, Nommsen-Rivers et al excluded women with multiple gestation and we will also exclude women with multiple gestations.

Furthermore, it is important to our study that participants are able to engage in frequent and exclusive breastfeeding regardless of which group they are randomized to. When conducting their study with breast pumping and breast emptying, Nommsen-Rivers et al excluded women who would have insufficient frequency of completing both pumping and emptying.[49] In the proposed study, we will exclude women who do not plan to exclusively breastfeed.

2.5.3 Intervention

In the previous RCT conducted by Nommsen-Rivers et al participants were randomized 2:1 metformin:placebo allocation for the purpose of gathering more insight into the tolerance and safety of metformin. For the purposes of our study we will be

allocating participants in a 1:1 scheme. As was done in previous studies, we will be encapsulating the metformin and the placebo into matching capsules and packages for the purpose of maintaining blinding as best as we can. Unlike previous studies where the intervention was started at the time of birth and given in accordance with a titration schedule,[49] our study will allow participants to remain on the same dose postpartum as they were on in the antenatal period. To collect the data needed for the secondary outcomes, participants will be given journals with specific forms to be filled out daily over the course of the study.

2.5.4 Primary and Secondary Outcome Measures

A common problem encountered in studies on breastfeeding is how to quantify the amount of breastmilk produced. The primary outcome for relevant studies is milk output and this has been measured through weighing all milk that has been expressed and collected over a 24 hour period.[49] We felt that this data collection method was not feasible for new mothers since it required extensive time and effort and therefore we wouldn't have good compliance among study participants. Instead, we plan to collect our data using test weighs in which the participants will weight their infant on a specialized scale provided to them immediately before and after each feeding. There have been many studies conducted in the past that have concluded that test weighing is a reliable method for assessing milk intake in infants [50-53] so we feel as though this will still provide us with accurate data while making it as feasible as possible for our study participants.

Maternal fasting blood glucose levels and neonatal weights are often secondary outcomes in previous studies examining the effect of metformin treatment in women with GDM.[13,16] Since metformin is known to adequately control blood glucose levels we will

examine the mother's glucose levels as a secondary outcome as well as trend the infant's weight over the course of the study. Additionally, since we are aiming to see an increase in milk production with the use of metformin, we will monitor the number of wet diapers produced daily by each infant as well as keep track of how much feeding supplementation with formula is needed if the infant is unable to meet feeding requirements with breastmilk alone.

2.5.5 Sample Size and Statistical Significance

Previous studies have estimated a post-intervention increase of 30% vs 0% in the metformin vs placebo groups.[49] The study conducted by Nommsen-Rivers et al is the only randomized controlled trial we know of that has used metformin as an intervention to increase breastmilk production but since their study was considered a pilot study this affected their sample size parameters. They selected 79% power with an alpha of 0.10 to detect a difference of 30% in the volume of breastmilk produced from women taking metformin vs women taking the placebo.[49] Additionally, they allocated participants 2:1 (metformin:placebo) and in our study we will be allocating 1:1. We will take this study's sample size calculation and estimation of effect size into consideration but due to the nature of our study we will select a power of 80% with an alpha of 0.05.

2.6 Conclusion

The literature review supports the need for a well-designed randomized controlled trial to determine the effect of metformin use during the postpartum period on breastmilk supply in women diagnosed with GDM. There are very limited existing studies that look at this relationship, especially with metformin use that continues from the third trimester into the postpartum period. Existing studies have focused on the safety of metformin use

as well as its efficacy in improving insulin sensitivity but its efficacy in improving milk production has not been sufficiently studied and is still unknown. The results of a randomized controlled trial could help to guide providers' recommendations to women diagnosed with GDM who are having difficulty with breastmilk supply and breastfeeding.

2.7 References

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CHAPTER 3: STUDY METHODS

3.1 Study Design

We propose a two arm, double-blinded, parallel design, randomized controlled trial analyzing the effect of metformin use during the first eight weeks of the post-partum period on lactation in women who have been diagnosed with class A2 gestational diabetes mellitus (GDM).

In this study, we plan to analyze the effects of metformin between two groups: the experimental group of women who will take the prescribed dose of metformin daily and the control group who will be receiving a placebo. Both groups will have received the standard of care management for pregnant women diagnosed with A2 GDM during pregnancy, including regular prenatal visits and metformin treatment which had been started during their third trimester after failed management of gestational diabetes with diet changes and exercise. The treatment with metformin will be continued for the experimental group and will be substituted for a placebo at the time of delivery for the control group. Patients and providers will be blinded as to which pill (placebo versus metformin) they are receiving. We will use the Prenatal Breastfeeding Self-Efficacy Scale (P-BSES) as an intake survey to characterize baseline breastfeeding confidence between both groups of participants prior to being discharged from the hospital (Appendix A). During the study, we will employ daily breastfeeding and pumping logs amongst both groups as well as have mothers record their infants pre and post feeding weights.

3.2 Study Population and Sampling

The study population under investigation is women with singleton pregnancies in the third trimester who are diagnosed with gestational diabetes mellitus. The study population will be seeking prenatal care at the Yale New Haven Health System (YNHHS), with selection for the study population derived from the pregnant women who were diagnosed with GDM. The study population will include pregnant women over 18 years of age who were diagnosed with GDM and are being treated with metformin during the antenatal period. We will recruit participants from Yale Maternal Fetal Medicine Diabetes in Pregnancy Program at Long Wharf Medical Center which provides services for pregnant women diagnosed with GDM.

Participants will be pregnant women who are (1) ≥18 years of age, (2) at 24–36 weeks of gestation, (3) have a singleton pregnancy, (4) are planning to exclusively breastfeed their infant, (5) were able to read the information sheet and sign the consent form and (6) are planning to deliver within the Yale New Haven Health System. Prior to the study, women will be excluded from the study based on the following: (1) any of the following pre-existing health conditions as indicated in medical records: pre-gestational diabetes, chronic kidney disease, chronic liver disease including hepatitis, chronic hypertension on medication other than aspirin, and lupus (2) those who have had breast surgery (including single or double mastectomy and/or breast implants) (3) mothers with pre-gestational diabetes and (4) mothers diagnosed with gestational diabetes prior to 24 weeks' gestation.

Inclusion Criteria	***Exclusion Criteria***
• Age ≥18 years old	• Maternal health complications:

• At 24-36 weeks of gestation • Singleton pregnancy • Will exclusively breastfeed infant • Will deliver within the Yale New Haven Health System	1. Pre-gestational diabetes 2. Chronic kidney disease 3. Chronic liver disease including hepatitis 4. Chronic hypertension 5. Lupus • Not planning on exclusively breastfeeding • Previous single or double mastectomy and/or breast implants • Gestational diabetes diagnosis before 24 weeks' gestation

Table 1: Inclusion and Exclusion Criteria

3.3 Recruitment

Women who visit the Yale Maternal Fetal Medicine Diabetes in Pregnancy Program and are diagnosed with GDM and initiating treatment with metformin during the third trimester will be recruited for our study. We will exclude women who do not plan to deliver at YNHHS, as we will not have access to their delivery records. We plan to recruit women at their routine prenatal care visits occurring during the third trimester. If the woman has GDM at a prenatal visit and satisfies the remaining inclusion criteria, the patient will be informed of the study and consented by the research coordinator.

Women who would like to complete the study will read and sign the consent form (appendix B) to provide their informed, written consent to study participation. Once informed consent is obtained, women will be randomized in a 1:1 enrollment ratio to either the metformin group or the placebo group using an online randomization software and a block randomization scheme. Randomization will take place at the end of their third trimester (>37 weeks' gestation) in order to ensure medication continuation immediately after delivery and to ensure women did not get changed to another

medication from metformin during their prenatal care to help control their gestational diabetes.

After delivery all women in the trial will receive their medication through the investigational pharmacy, which will dispense metformin or a placebo pill designed to appear like metformin. The women will be instructed to not take any remaining pills of their own metformin following delivery. Both groups will take the pills for 8 weeks following delivery. The dosage of metformin will be 500mg daily.

The total recruitment period will be 12 months, from August 1, 2020 to August 1, 2021. The follow-up period will extend 8 weeks after each woman's date of delivery.

3.4 Subject Protection and Confidentiality

The Yale Institutional Review Board policy on research involving pregnant women and neonates is referenced in the consent form in Appendix B. The study will be conducted pending ethical review by the Human Investigation Committee (HIC) of Yale University School of Medicine and YNHHS. Written informed consent will be obtained from all participants prior to entry into the study at the patient's prenatal visit during the third trimester (see Appendix B). Subjects under the age of 18 years-old will not be included in this study. Additionally, all research staff will be trained in HIPAA. Upon entry into the study, participants will receive a de-identified number for data collection and statistical analysis. All protected health information will be de-identified for the purposes of blinding and confidentiality in the data analysis phase of the study. A Yale-encrypted computer with a password-protected Excel-based database will be used to maintain confidentiality and security of the data. Only co-investigators will have the password and access to the database. All backup drives will be password-protected. The

database will only be accessed on hospital property or through secure VPN access. All associated paperwork will be stored in a locked file in a locked office.

3.5 Study Variables and Measures

3.5.1 Independent Variable

The independent variable in this study is metformin use during the postpartum period, which is operationalized in the experimental group by having participants receive metformin from the investigational drug pharmacy after delivery. The control group will be given a placebo tablet from the same pharmacy to take once daily starting at the time of delivery. The pills will be identical in appearance so patients and their providers are blinded to which group they are in. Participants will be asked to maintain a log of their medication compliance as well as make note of any side effects they might be experiencing. Participants will be given all doses of their medication upon discharge from the hospital (56 total pills). Will contact participants once per week to review their logs, discuss any questions and obtain a pill count to monitor compliance.

3.5.2 Study Outcomes

The primary outcome of this study is breastmilk production. This will be measured using infant test weighs taken immediately before and after each feeding. We will ask participants to log these results in their breastfeeding logs which will be provided to them (Appendix C). Specialized scales will be provided for each participant to take home and use for the duration of the study to weight their infants. Prior to discharge from the hospital each mother will have the opportunity to meet with a lactation specialist to ensure that she is prepared and feels confident in her abilities to breastfeed once she returns home. Additionally, we will instruct the participants on how to get accurate

weights and observe them conducting practice test weighs prior to discharge. Should they get home and have any questions we will provide them with a link to an instructional video of how to conduct these weighs. Each participant will receive a follow up calls once a week throughout the duration of the study in which they can ask any questions or concerns they might have, and we will ensure that they are properly conducting the test weighs.

There are five secondary outcomes of interest that we will analyze: (1) onset of lactogenesis (2) infant weights at their routine pediatrician visits, (3) the need for feeding supplementation with formula, (4) number of wet diapers per day, and (5) maternal fasting glucose levels tested daily. Infant weights will also be checked at each follow up appointment which will occur at weeks 1,2, 4, and 8 of the study. We will ask each study participant to record the number of wet diapers and times that supplementation with formula was needed daily in the same log that they will be using to record their breast feedings (Appendix C). Participants will be instructed to take their own fasting blood glucose levels once daily upon waking in the morning for the day, prior to their first meal and keep a log of their results which will then be collected at the conclusion of the study. (Appendix D)

Primary Outcome	***Secondary Outcomes***
• Breastmilk production as measured by pre and post feeding infant weights.	• Time of onset of lactogenesis • Infant weights at their pediatrician visits • Frequency of feeding supplementation with formula • Number of wet diapers daily • Maternal fasting glucose levels

Table 2: Outcomes

3.5.3 Potential Confounding and Explanatory Variables

Development of GDM and subsequent low breastmilk supply is influenced by several covariates. Potential confounders include maternal age, maternal ethnicity, maternal education level achieved, maternal marital status, pre-pregnancy BMI, family history of GDM or type 2 diabetes, diagnosis of GDM in previous pregnancies, other signs of insulin resistance such as polycystic ovarian syndrome, number of previous breastfed infants, vaginal versus cesarean delivery, and parity. As participants will be randomized to their assigned group, we hope to minimize the effect of cofounding variables on the main outcome. We will also obtain this demographic and medical history data via an intake survey upon entry into the study (Appendix E) and through the participants' charts and will compare these characteristics of the participants between assigned groups for any significant differences.

3.6 Data Collection

Upon entry into the study, each participant will complete a Prenatal Breastfeeding Self-Efficacy Scale (P-BSES) to characterize their baseline breastfeeding confidence prior to being discharged from the hospital. Those who score less than 60 points on the scale or those who do not feel confident or adequately prepared will have an additional lactation consultation prior to discharge. The P-BSES is a 20-item scale designed to measure pregnant women's self-efficacy for breastfeeding. The four factors comprising the scale assess confidence regarding 1) skills and demands for breastfeeding or pumping, 2) gathering information about breastfeeding, 3) breastfeeding around other people, and 4) social pressure when breastfeeding. There is evidence that the P-BSES has good content validity and internal consistency[1] (Refer to Appendix A). We will obtain

previous breastfeeding information and maternal education level from each participant using a questionnaire (Appendix E). Information on baseline characteristics, including maternal age, maternal ethnicity, pre-pregnancy weight, height, and BMI will all be obtained from participant's electronic medical records.

In both groups, we will have participants log their daily feedings in a journal that will be given to them (Refer to Appendix C). This journal will also be used to input the test weighs before and after each feeding. We will ask participants to record the time of feeding, the duration of the feed, the type of feeding and if supplementation with formula was used. Additionally, we will have participants log the number of wet diapers per day. We will be evaluating the mother's fasting blood glucose levels daily so we will ask the participants to take a fasting blood glucose every morning and to record these results (Appendix D).

After discharge from delivery, we will ask to have the participants follow up at the Yale Pediatrics office at weeks 1, 2, 4, and 8. During these appointments we will perform all standard neonatal care as well as review the participant's journal entries and record the infant's weight.

3.7 Sample Size Calculation

The main goal of the proposed study is to test the two-sided null hypothesis that metformin use during the postpartum period does not change the amount of breastmilk production. Sample size calculation is based on the primary outcome of breastmilk production. The aim is to observe an increase in the amount of breastmilk produced in the experimental group compared to the control group. Our calculation is based on previous studies which found there to be a median increase of 8mL/24hr. For a two-sided

hypothesis with a type 1 error of 1% and a power of 80%, a total sample size of 56 is required, or 28 in each arm. Due to the nature of the study and comparing median values versus means, we will add 15% to each group to compensate. Additionally, we must account for 10% attrition rate. Therefore, our final sample size of will be 72 participants used in this study. Please see Appendix F for the full sample size calculation.

3.8 Statistical Analysis

Demographic information will be obtained for all participating women and will be analyzed for any statistically significant differences between groups (Refer to Table 3). Characteristics of interest that will be analyzed include maternal age, maternal ethnicity, maternal education level achieved, maternal marital status, pre-pregnancy BMI, family history of GDM or type 2 diabetes, diagnosis of GDM in previous pregnancies, other signs of insulin resistance such as polycystic ovarian syndrome, number of previous breastfed infants, vaginal versus cesarean delivery, and parity. Student t-test will be used for analysis of maternal age, as a continuous, parametric variable. Wilcoxon rank sum will be used to analyze ordinal variables such as maternal ethnicity, maternal marital status, and maternal BMI, as well as non-parametric continuous variables such as parity. A chi square test will be used to analyze proportions between groups for ethnicity and previous diagnosis of GDM. Lastly, we will analyze educational level (measured by mean years) with ANOVA. Multivariate analysis using logistic regression will be utilized for any statistically significant differences between groups in these baseline characteristics.

Baseline Characteristics	Metformin Group %	Placebo group %	P-value (P<0.05)
Maternal Age			
18-24 years			
25-30 years			
30-35 years			
≥35 years			
Ethnicity			
Non-Hispanic White			
Black			
Hispanic			
Asian			
Other			
Marital Status			
Married			
Single			
Other Forms of Insulin Resistance			
Yes			
No			
Family History of GDM			
Yes			
No			
Family History of Type 2 DM			
Yes			
No			
Diagnosis of GDM in Previous Pregnancy			
Yes			
No			
Parity			
0			
1			
2			
>3			
Number of Previous Breastfed Infants			
0			
1			
2			
>3			
Type of Delivery			
Vaginal			
Cesarean			

Pre-pregnancy BMI 19.8-25.9 26.0-28.9 29.0-34.9 ≥35.0			
	Mean (SD)	Mean (SD)	
Education (years)			

Table 3: Baseline Characteristics of Study Population

3.9 Timeline and Resources

Pending Institutional Review Board (IRB) approval, we will begin recruiting pregnant women for 12 months; all mothers must deliver within the first 18 months and follow up will last for 2 months following time of delivery. All data will be collected within a 2-year timespan. We will then require one month to run and interpret results and an additional month to write and report our findings. Proposed study personnel include: one principal investigator to oversee all operations, one physician trained in obstetrics to assess participant's charts for diagnosis of A2GDM, one Physician Assistant student for data organization, statistical analysis and writing, and one trained research assistant for recruitment and intake.

3.10 References

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CHAPTER 4: CONCLUSION

4.1 Advantages and Disadvantages

It is well documented that women who are diagnosed with gestational diabetes mellitus have worse breastfeeding outcomes than their counterparts. Specifically, women with GDM have much lower exclusive breastfeeding rates and shorter durations of breastfeeding.[1,2] Unfortunately, up to this point there have not been any studies looking at effective interventions to improve breastfeeding rates in this population. Therefore, there is a need for a large randomized controlled trial to examine the use of an existing therapeutic agent used in treating gestational diabetes and determine if there is a causal relationship between metformin use during the postpartum period and increased breastmilk supply. This study addresses the paucity in the current literature and has the potential to change current practice guidelines.

The proposed study has both its strengths and limitations. A major strength of our study is its feasibility and practicality. The intervention requires little time commitment from participants and is easy to implement. Metformin, in comparison to insulin, has been found to be viewed favorably by patients due to its oral route of administration, low cost, easy dose titration, and low risk of hypoglycemia.[3] Also, study participants will have been on metformin prior to delivery so they will already be used to the medication and will be less likely to experience side effects throughout the duration of the study. All of these are factors that will aid in achieving high medication compliance with participants. Additionally, the intervention is low-cost since all required medications and devices will be supplied to each participant. We will be able to closely monitor adherence

as follow-up visits will be completed at set time intervals and phone call follow-ups will be implemented weekly throughout the duration of the study to answer any questions or concerns participants might have. Therefore, we anticipate strong internal validity and minimal response bias in this study. However, by limiting our study to the Yale New Haven Health System we may limit our external validity and generalizability. Despite limiting recruitment to the Yale New Haven Health System, we will strive to recruit a diverse group of participants.

The main advantage of this study is its randomized, prospective design that allows for the observation of a causal relationship between metformin treatment and breastmilk production in women diagnosed with GDM. It is the only randomized controlled trial that tests the effect of continuing metformin treatment into the postpartum period on the production of breastmilk in women with a diagnosis of GDM. By conducting an RCT and randomizing patients 1:1 to the intervention and control groups, we hope to decrease selection bias and confounders. Furthermore, our proposed study will be double blinded which we hope will aid in limiting outcome reporting bias.

When considering the timeline for the study we realize that an eight-weeklong duration may limit our understanding of long-term effects of metformin on breast milk production. However, we feel that a longer intervention duration would decrease patient adherence. Since we know that metformin typically begins to improve blood sugar control within a week[3,4] we feel as though eight weeks is a sufficient amount of time to get an understanding of what effects metformin might have. We know that studies similar to ours that have been done in the past have concluded after about four weeks[5] so we

hope that continuing our study for an additional four weeks will be an advantage and give additional insight into our research question and place emphasis on the importance of continued breastfeeding beyond the initial postpartum period.

4.2 Clinical and Public Health Significance

In all of the previous studies addressing the different therapeutic options for diabetes during pregnancy, several neonatal and maternal outcomes have been analyzed and studied but one factor that hasn't been studied in depth is the effect on breast milk production and lactogenesis. This is a long-term factor that can have an impact on infancy and childhood for many neonates and it is an important factor to identify and study in correlation with metformin therapy.

This is an important problem to find a solution to because currently 23% of reproductive aged women in the United States are prediabetic and 8.2% of women are diagnosed with gestational diabetes; therefore, this could be an unrealized impediment to raising breastfeeding rates and breastfeeding duration in the US.[6] Finding a way to increase the postpartum milk production in women diagnosed with GDM could aid in longer compliance with breastfeeding. This is important because it has been proven that continued breastfeeding for more than six months lowers the chances of childhood and adult illnesses and, if the child does get ill, can help the child in recovering more quickly.[7] It has also been shown that longer breastfeeding duration lessens the child's chances of developing type 1 and type 2 diabetes as well as obesity.[8] Breastfeeding is not only beneficial for infants but also for mothers, by continuing breastfeeding beyond six months, it can lower the lifelong risk of developing heart disease,[9] type 2 diabetes[10] and cancers of the breast, ovaries and uterus in women.[11] It is clear that it is important to try

to find a targeted therapy that can support lactation success in women who have glucose intolerance.

Our hope is that this proposed study would address an important question that has not yet been addressed in the literature. The findings of this study will provide insight into breastfeeding rates and success in women with A2GDM.

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Appendices

Appendix A: Infant Feeding Intentions Scale

Please read the following statements and answer circling the number closest to your feelings. It is important to know (remember) that there is no right or wrong answer in answering these questions. We are interested in how much you are relyed of yourself about your breastfeeding.

1: I am definitely not confident 2: I am not quite confident 3: I am confident4: I am very confident 5: I am completely confident

1. I can find the answers to problems I may encounter while breastfeeding my baby.	1	2	3	4	5
2. I can find the information I need about breastfeeding my baby.	1	2	3	4	5
3. If I have questions about breastfeeding my baby, I know whom I can ask.	1	2	3	4	5
4. I can talk about the importance of breastfeeding my baby with my husband.	1	2	3	4	5
5. I can talk about breastfeeding my baby with health workers.	1	2	3	4	5
6. I can organize my day according to the times I need to breastfeed my baby.	1	2	3	4	5
7. I can find time for breastfeeding my baby even if I am busy.	1	2	3	4	5
8. I can breastfeed my baby even when I am tired.	1	2	3	4	5
9. I can breastfeed my baby even when I am feeling depressed.	1	2	3	4	5
10. I can draw milk manually or through use of a breast pump.	1	2	3	4	5
11. I can milk my breast and prepare my milk for someone else to feed my baby.	1	2	3	4	5
12. I can breastfeed my baby even if it causes a little discomfort.	1	2	3	4	5
13. I can breastfeed my baby without any feelings of shame.	1	2	3	4	5
14. I can breastfeed my baby while my husband is present.	1	2	3	4	5
15. I can breastfeed my baby while my family or friends are present.	1	2	3	4	5
16. I can breastfeed my baby even when people I do not know are present.	1	2	3	4	5
17. I can call a breastfeeding consultant when I have problems with breastfeeding.	1	2	3	4	5
18. I would breastfeed my baby even if my husband did not want me to do it.	1	2	3	4	5
19. I would breastfeed my baby even my family did not want me to do it.	1	2	3	4	5
20. I can breastfeed my baby for two years.	1	2	3	4	5

Appendix B: Human Investigations Committee Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: *Randomized Study of Postpartum Metformin Use to Augment Breastmilk Supply*
Principal Investigator: *Audrey Merriam, MD*
Co-Principal Investigator: *Meghan Sowers, PA-SII*

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the effects of continuing metformin treatment into the postpartum period and its effects on breastmilk supply in women with gestational diabetes. If you are reading this consent form, you have been selected for recruitment in this study during your pregnancy. You were selected for potential recruitment in this study, because you are currently pregnant and have gestational diabetes mellitus which is currently being treated with metformin. Gestational diabetes is a condition that only affects pregnant women and causes high blood sugar levels. This condition can have many effects on mothers and babies, one of them being delayed lactogenesis, when milk production starts, as well as decreased milk production resulting in lower breastfeeding rates. This study will take place within the Yale New Haven Health System over the next two years.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, you will be randomly assigned to one of two groups, either the metformin group or the placebo group. An online software will be used to assign all participants randomly into one of the two groups.

If you are assigned to the metformin group, you will be instructed to take metformin daily. This will start at the time of delivery and will continue for eight weeks postpartum. You will also be given a journal to record your feedings as well as other variables that we would like to collect data on. Additionally, we will ask participants to check their blood sugar levels daily and record these findings.

If you are assigned to the placebo group, you will be instructed to take one placebo tablet daily. This will start at the time of delivery and will continue for eight weeks postpartum. You will also be given a journal to record your feedings as well as other variables that we would like to collect data on. Additionally, we will ask participants to check their blood sugar levels daily and record these findings.

After you give birth, our research team will contact you and give you instructions as to what to do going forward. We will additionally gather data from your medical chart such as demographic information (i.e. age, race), past medical history (e.g. number of previous pregnancies, health complications) weight, gestational age at delivery, whether or not you had a Cesarean section (and if so, why), assessment of your baby, and any complications that may have occurred during labor or birth. This information will help us determine if there is any difference in outcomes between the groups.

You will be told of any significant new findings that develop during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your healthcare outside of the study, the payment for your healthcare, or your healthcare benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study. If you do become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. The researchers may withdraw you from

participating in the research if necessary. This may occur if your obstetrician feels it is medically unsafe to proceed with the intervention to which you have been allocated.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

You do not give up any of your legal rights by signing this form.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

Relationship:_____

Date:_____

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Audrey Merriam. If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix C: Breastfeeding Log

Date	Start Time	Stop Time	Weight before feeding (in g)	Weight after feeding (in g)	Breast (Left or Right)	Was a bottle used? Y or N	Supplementation with Formula? How much?	Number of Wet Diapers	Notes

Appendix D: Maternal Blood Glucose Monitoring Log

Day/Date	Time	Fasting? Y or N	Blood Sugar Reading	Did you take your medication today? Y or N	Notes

Appendix E: Baseline Intake Form

Patient Information Form

Please fill out this form to the best of your ability.

1. What is your marital status? (Circle one)

   Married Single

2. Do you have a family history of gestational diabetes mellitus? Yes No
3. Do you have a family history of type 2 diabetes? Yes No
4. Have you ever been pregnant before? Yes No
   a. If "yes" how many times? _____
   b. If "yes" were you ever diagnosed with gestational diabetes during any of your previous pregnancies? Yes No
   c. If "yes" did you breastfeed? Yes No
5. Approximately how many years did you attend school (including high school, college, graduate school, or an additional education)? _____

Appendix F: Sample Size Calculation

Input: Tail(s): Two
Power, 1 - β = 0.80
Type I error rate, α = 1%
Median increase in primary outcome, 8mL/24hr
Sample Size: 56 (28 per group)

Compensation for comparing medians, 15% to each group, 56 x 1.15=64.4 participants
Estimated attrition rate, 10%, 65 x 1.10= 71.5 participants

Adjusted Sample Size = **72 participants (36 per group)**

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