Detemir versus NPH for type 2 diabetes mellitus in pregnancy: a comparative-effectiveness, open label, randomized controlled trial

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STUDY PROTOCOL

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1. Background

Pre-gestational diabetes affects 0.7-1.5% of pregnancies, while the prevalence continues to increase, with a reported increase of 27.7% from 1999 to 2005. [1-3]

Pre-gestational diabetes refers to type 1 and type 2 diabetes, while Type 2 diabetes mellitus is the common major form of diabetes and account for about 90% of all diabetic cases worldwide. Type 2 diabetes mellitus is associated with a decrease in insulin secretion and elevated insulin resistant and has several risk factors including: weight, race, inactivity and family history and the number of adults with diabetes is increasing from year to year globally.[4]

Women with diabetes mellitus remain at increased risk of adverse pregnancy outcomes during pregnancy and birth, with a higher risk for pregnancy loss, gestational hypertension, macrosomia and cesarean delivery compared to women without diabetes mellitus. [5] Glucose control during pregnancy decreases the risk of complications such as fetal demise, birth injuries and macrosomia.[6,7]

Insulin is the preferred agent for management of both type 1 diabetes and type 2 diabetes in pregnancy because it does not cross the placenta and oral agents are generally insufficient to overcome the insulin resistance in type 2 diabetes and are ineffective in type 1 diabetes.[8-10] **However, currently there is insufficient data to determine what type of insulin achieves the best glycemic control during pregnancy with minimum adverse events such as hypoglycemia.**[11]

Basal insulins suppress uncontrolled hepatic glucose production and therefore have to be relatively long acting, usually injected once or twice daily. Basal insulin includes neutral protamine hagedron (NPH, isophane insulin) and the modern insulin analogs- insulin glargine and insulin detemir.

The main difference between NPH and insulin analog is the pharmacodynamics; NPH will peak between 4-12 hours after injection with a duration of action around 14 hours. Whereas both glargine and detemir are characterized by a gentle rise and fall with a longer duration of action (18-20 hours) in most patients.[12] NPH is often the initial choice of insulin treatment in patients with diabetes mellitus during pregnancy but because of its duration of action fails to mimic the physiologic profile of insulin release, it may require multiple injections during the day and has been associated with increased risk for hypoglycemia.[13]

Outside of pregnancy, clinical trials comparing efficiency outcomes with basal insulin analogs found that insulin analogs are mostly non-inferior or better than other insulins, while reducing the incidence of hypoglycemia and weight gain- two main adverse effects that are of concern for the patient and the physician. [14-17] Switching patients with diabetes mellitus type 2, who were inadequately controlled on NPH, to basal insulin was associated with significant improvement of glycemic control and reduction of the hypoglycemic events during treatment with basal analogs.[18] A recent registry based study regarding the long term effect of basal insulin treatment on cardiovascular

mortality found substantially higher mortality rates among users of NPH insulin as compared to insulin analogs; detemir or glargine.[19]

Over the past years, there has been an increase in the use of long acting basal insulin in the treatment of patients with diabetes mellitus type 2. The American Diabetes Association (ADA) 2018 guidelines on pharmacological approaches to glycemic control [10] recommend that when basal insulin is added to anti hyperglycemic agents in patients with type 2 diabetes, long-acting basal analogs (U-100 glargine or detemir) can be used instead of NPH to reduce the risk of symptomatic and nocturnal hypoglycemia. According to the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2018 consensus statement on the management of patients with diabetes mellitus, basal insulin analogs are preferred over NPH because a single basal analog dose provides a relatively flat serum insulin concentration for 24 hours or longer. Basal insulin analogs and NPH were equally effective in reducing HBA1C in clinical trials; however, insulin analogs caused significantly less hypoglycemia. [20]

Basal insulin in pregnancy: NPH was the first basal insulin that have shown to be safe during pregnancy. In the past years, many doctors prefer to prescribe long acting basal insulin for different reasons including: patients that have difficulty controlling their blood glucose levels using NPH due to its shorter duration of action, use of insulin analogs prior to pregnancy and the higher risk for hypoglycemic events reported with NPH.

While some doctors believe that detemir is safe and effective in women with type 2 diabetes during pregnancy, the American College of Obstetricians and Gynecologists (ACOG) acknowledge that women with type 2 diabetes in pregnancy should be treated with basal insulin but do not specify which type of insulin is recommended.[21]

A few studies evaluated the use of long acting insulin analog in pregnancy. In a meta-analyses of 8 studies evaluating glargine, which included only observational and retrospective studies, a total of 702 women with pre-gestational or gestational diabetes treated with either glargine or NPH, there were no significant differences in the maternal and neonatal outcomes between NPH and glargine [22] . One prospective study examined maternal and neonatal outcomes in 138 women with preexisting diabetes and gestational diabetes treated with glargine or NPH and found that maternal outcomes were significantly worse in the pre-gestational group receiving NPH insulin compared to insulin glargine [23]. Maternal hypoglycemia occurred significantly more likely in the NPH insulin group compared to insulin glargine.

In recent years, insulin detemir has become a preferred agent of treatment of diabetes in pregnancy. In contrast to insulin glargine, in 2012, insulin detemir received US Food and Drug Administration approval for reclassification to pregnancy category B from pregnancy category C. This was based on a randomized control trial comparing insulin detemir and NPH in 310 pregnant women with diabetes mellitus type 1[24]. Results demonstrated that detemir was non-inferior to NPH in both glycemic control and hypoglycemia events.

Since then, there have been a few studies evaluating the use of detemir in pregnancy (Table 1). In all of them, detemir was comparable to NPH in achieving glucose control as well as maternal and neonatal outcomes. Only one randomized controlled study,[25] has investigated detemir in the setting of pregnant women with gestational diabetes and diabetes mellitus type 2. In this study, only 7 (17%) patients that received detemir and 7 (16%) patients that received NPH, had diabetes mellitus type 2 and all the other patients in the study had gestational diabetes. The result of this study indicated that detemir was not inferior to NPH for the treatment of GDM and T2DM in pregnancy. Of note, there were more hypoglycemic events per patient in the NPH group.

The recent Cochrane review (2017)[11] regarding different insulin types and regimens for pregnant women with pre-existing diabetes concluded that at present, insufficient data exists to allow the review authors to make any substantial or concrete conclusions about the effectiveness of one insulin type or regimen over another in pregnant women with pre-existing type 1 or type 2 diabetes.

Until now, no study has compared neonatal and maternal outcomes in patients with diabetes mellitus type 2 treated with detemir versus NPH. We hypothesize that treatment with detemir in patients with diabetes mellitus type 2 during pregnancy will reduce adverse neonatal outcome and reduce the number of hypoglycemic events during pregnancy compared to patients treated with NPH. To prove this hypothesis, we propose a comparative- effectiveness, open label, randomized controlled trial for treatment of Type 2 diabetes in pregnancy with long acting insulin detemir versus NPH.

Table 1: Human studies on the use of insulin detemir in pregnancy

Author Year	Design	Insulin	N	Type of diabetes	Primary outcome	Difference in the mean basal glucose	Difference in the mean fasting glucose
Lapolla et al. 2009	Report	Detemir	10	T1DM	Glycemic control		
Shenov et al. 2012	Retrospective	Detemir	18	T1DM +T2DM	Maternal and neonatal outcome		
Mathiesen et al. 2012	RCT	Detemir vs NPH	310	T1DM	HBA1C at 36 weeks of gestation	125.1 vs 132.8 mg/dL (P=0.003)	96.8 vs 113.8 mg/dL (P=0.012)
Callesen et al. 2013	Retrospective	Detemir vs glargine	113	T1DM	Glycemic control estimated by HBA1C		
Hod et al. 2014	RCT	Detemir vs NPH	313	T1DM	HBA1C at 36 weeks of gestation		
Herrera et al. 2015	RCT	Detemir vs NPH	87	GDM and T2DM	Overall mean blood glucose	2.1 mg/dL (P=.293)	
Koren et al. 2016	Retrospective	Detemir vs Glyburide	91	GDM	Good glycemic control		91.8 vs 91.8 (P=0.91)

2. Methods

2.1 Study objectives

2.1.1 Objective

To determine whether use of detemir compared to NPH decreases rates of composite neonatal outcome and maternal hypoglycemia events in women with T2DM

2.1.2 Rationale

Treatment with Basal insulin analogs improve glycemic control in patients with uncontrolled diabetes. They have been associated with fewer events of hypoglycemia in non-pregnant and pregnant women. Many women of childbearing age are now receiving insulin analogs and would prefer to continue using them during pregnancy and their efficiency in pregnancy requires further study.

2.1.3 Primary outcome

Composite adverse neonatal outcome:

- Neonatal intensive care unit (NICU) admission or
- Neonatal hypoglycemia (<40 mg/dL in the first 24 hours of life and less than 50 mg/dL after) or requiring medical therapy or
- Respiratory distress (need for at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure or ventilation at the first 24 hours of life or
- Shoulder dystocia - defined as the need for any extra maneuvers, other than gentle downward traction of the fetal head in order to deliver the fetal body after the fetal head has been delivered or
- Large for gestational age (LGA) -weight over 90th percentile of the expected value according to gestational age or
- Macrosomia- Fetal weight above 4000g

2.1.4 Secondary outcome measures; Maternal

- Mean fasting glucose
- Mean post prandial glucose
- Hypoglycemia events (<60 mg/dl)
- Maternal weight gain
- Gestational hypertension
- Preeclampsia
- Cesarean delivery
- Operative vaginal delivery

2.1.5 Secondary outcome measures; Neonatal

- Gestational age at delivery
- Small for gestational age (SGA)
- Neonatal intensive care unit (NICU) length of stay
- 5-minute Apgar score ≤ 5
- Neonatal jaundice requiring therapy

2.1.6 Ancillary Studies

2.1.6.1 Medication adherence survey: Medication non- adherence is an important public health issue that clinicians encounter. Approximately 78% of e-prescriptions are actually filled; only 72% of new prescriptions are filled.[26] Non-compliance is most common among new prescriptions for chronic conditions including diabetes (31.4%). Diabetes is a common chronic condition. Adherence to medications can be affected by a variety of factors in patients with diabetes; perception that medications are only needed when glucose levels are high, concerns regarding adverse effects and lack of self-confidence in their self-treatment.[27] Medications are commonly used in pregnancy with at least 81.2-96.9% of women using at least one medication, either prescribed or over-the-counter.[28,29] The attitudes regarding drug use in pregnancy and ability to obtain drug information plays an important role in medication adherence[30,31]. The MMAS-8 validated survey (attached as Figure 1) will be given to women to complete during their routine prenatal visit if they meet study criteria and agree to the study. This is a copyrighted survey and for this particular study, we have permission to use the MMAS-8. This survey will be supplemented with other questions collecting information on demographics and challenges with prescription error and pick up problems. It takes approximately 10 minutes to complete. The answers will not be available to the managing health care provider, but will be kept in the locked research office until after the delivery of subject. Based on the scores of the survey, the subject will be divided into groups based on high, medium and low adherence. Maternal demographics, antepartum course, pregnancy outcomes and neonatal outcomes will be collected from prenatal/office and hospital chart. Outcomes between groups will be compared.[31-34]

2.1.6.2 Social determinants of health (SDH) Survey (SDH)- while our approach to clinical care is rooted in biology, an increasingly interdisciplinary approach is being employed that acknowledges SDH, i.e the social and structural aspects of a patient's life that can influence health. Social determinants of health (SDH) include but are not limited to basic resources, educational opportunities and economic stability, access to health care, community resources, literacy, socioeconomics, and safety.[35] By understanding SDH, interventions can be pursued that can improve individual and population health. For patients living with diabetes, there is a correlation between social determinants of health and glycemic control.[36] Many obstetrical conditions are also impacted by SDH. [37] Using this broader context to understand patients' health care decision-making and health literacy facilitates recognizes the intersections of social identity and their associated patterns of structural oppression, and fosters a creative approach to overcoming potential barriers. The PRAPARE Assessment (The Protocol for Responding to and Assessing Patients'

Assets, Risks, and Experiences) is an established tool to briefly assess SDH. Core measures of this tool include race, ethnicity, education, employment, insurance, income, material security, transportation, social integration and support, stress and migrant, veteran and housing status. It will provide insight by which we can understand correlations between SDH and health care outcomes in our population as a springboard to improving both the outcomes and the pathways leading to them. The brevity of questions covering numerous social domains can help target particular social features that may be correlated with glycemic control as well as target resource referrals and utilization, thereby translating into actionable items.

2.1.6.3 Physician empathy survey- Physician empathy represents understanding of patient concerns, experiences, and perspectives that is communicated to the patient, which within a therapeutic relationship, includes an intention to help. (8) Regardless of intention, empathy must be conveyed and therefore perceived by the patient.[38] The perception of empathy has been associated with patient compliance with physician recommendations, thereby linking outcomes to to physician engagement and empathetic care. [39] The Jefferson scale of patient perception (JSPPE) of physician empathy has 5-items rated on a 7-point scale that can be answered to assess the patient's perception physician empathy.[40,41] Patients will be will be instructed to fill the scale and to hand them back to the researcher in a closed envelope. All forms will be anonymized. The questionnaires will be returned directly to the researchers in closed envelopes and the results will be inserted into a data system by a designated person. Empathy score will be the total score of JSPPPE and we will use this information to correlate perceptions of empathy with compliance as well as maternal and neonatal outcomes.

1.1 Design summary

This is a comparative-effectiveness, open label, randomized controlled trial for the treatment of pregnant women with diabetes mellitus type 2 with insulin detemir versus NPH

1.2 Inclusion criteria

- Preexisting type 2 diabetes mellitus requiring medical treatment or
- overt diabetes diagnosed prior to 20 weeks of gestation using either HBA1C ≥ 6.5 or fasting glucose ≥126 mg/dl or random blood glucose ≥ 200 mg/dl or two step method (50g GCT >135 mg/dl followed by 100 GCT with at least 2 values above thresholds: FBG >90, 1 hr >180, 2 hr > 155, 3 hr > 140 mg/dl).
- Gestational age ≤20 weeks
- Willing to start insulin therapy or to continue insulin treatment during pregnancy
- Singleton or twin pregnancy

1.3 Exclusion criteria

- Known allergy/prior adverse reaction to NPH/detemir
- Patients <18y
- Known major fetal anomalies
- Diabetic nephropathy (Cr≥1.5)
- Diabetic proliferative retinopathy
- Patients with Type 1 diabetes or gestational diabetes

1.4 Recruitment and feasibility

Recruitment will occur at the outpatient obstetric clinics at:

1. UT MFM clinic at Texas Medical center
2. UT Women center at Bellaire
3. Memorial Hermann Memorial city MFM clinic
4. Memorial Hermann Sugar land MFM clinic
5. Memorial Hermann Greater Heights MFM clinic
6. LBJ MFM clinic
7. St. Joseph MFM clinic
8. Memorial Hermann Katy MFM clinic
9. Cypress Fairbanks MFM clinic
10. Memorial Hermann Pearland MFM clinic
11. Women's Hospital of Texas MFM clinic
12. Memorial Hermann Cypress Hospital

1.5 Randomization

Randomization will be achieved by computer-generated random sequences that will be created by a non-clinical member of the research team. A permuted block randomization with a random fashion will be used to prevent imbalances between groups. The medication based on the computer-generated list will be typed out on a piece of paper with the medication regimen according to the below regimens. The piece of paper will be placed in an opaque envelope and numbered according to the computer-generated list. Envelopes will be kept secured at the outpatient obstetrics clinic and will be managed by the research team.

Intervention and procedures

Women that meet the inclusion and exclusion criteria will be approached by the research staff/MFM physician at their first outpatient visit. An informed consent will be obtained and a copy will be given to the subject**.** Women will be randomized to insulin detemir or insulin NPH as the basal insulin treatment during pregnancy. Group 1 will be composed of women allocated to detemir treatment. Group 2 will be composed of women allocated to NPH treatment. Detemir and NPH will be administrated subcutaneously at the same time. In both groups short acting Insulin (aspart/lispro/regular) will be administered as needed before each meal (0-30 minutes) according to the physician preference. Current weight will be obtained at the visit and the initial daily total insulin dose will be determined based on the patient weight and trimester according to the recommended guidelines for treatment during pregnancy. In the first trimester the patient weight will be multiplied by 0.7, in the second trimester by 0.8, and in the third trimester by 0.9 for the total daily units of insulin. [42,43]

In-group 1 the total daily dose of insulin will be divided into 50% detemir insulin and 50% short acting insulin. Detemir dose can be divided in half, injected in the morning and in the evening, 12 hours apart. Short acting insulin will be divided with one third each being injected with breakfast, lunch and dinner meals. In-group 2, approximately 60% of the daily insulin NPH dose is given in the morning and 40% in the evening. Of the morning dose, two third will be the NPH and one-third the short acting insulin. The evening insulin dose will be divided in 2: half will be short acting insulin the other half will be NPH at bed-time.

Patients that have been treated with previous diabetic medications will continue treatment with the new insulin after randomization as suggested by our department protocol and is determined by the medications half time (Table 2, Table 3):

1. Patients treated with metformin will continue metformin or stop it depends on the physician decision. They will start insulin on the same day without need for washout.
2. Patients treated with Glyburide or a combination of glyburide and metformin, according to our standard of care and due to the risk of hypoglycemia will stop the glyburide and will only start insulin on the next day. Metformin will be prescribed at the discretion of treating physician.
3. Patients treated with Glargine (Lantus) prior to randomization, will start NPH/detemir 24 hours after stopping glargine due to his longer half time.
4. Patients treated with NPH/Detemir that are randomized to the same medication can continue the new treatment on the same day in the next scheduled injection (am/pm).
5. Patients treated with NPH/detemir that are randomized to a different type of insulin can also continue the new treatment on the same day in the next scheduled injection (am/pm).

Table 2: Action profile of the commonly used oral diabetic medications in pregnancy

Type	Time to Peak of plasma concentration (hours)	Elimination half time in plasma (hours)	Undetectable in blood plasma
Metformin	1-3 hours	6.2 hours	24 hours
Glyburide	2-3 hours	4 hours	24 hours

Modified from the medication insert information sheet.

TABLE 3: Action profile of the commonly used insulin in pregnancy

Type	Onset of action	Peak of action (Hours)	Duration of action (Hours)
Insulin NPH	2-4 hours	4-10 hours	10-18 hours
Insulin Detemir	2-3 hours	6-8 hours	6-23.2
Insulin Glargine	4-6 hours	none	24 hours

Modified from the medication insert information sheet.

Follow up: Patient will be asked to continue follow up as standard and to check glucose levels at fasting, 1 hour pre-prandial and/or 1 or 2 hours postprandial, as recommended by their treating physician. Each patient will have a meeting with a registered nurse and diabetic educator in order to learn how to self-administer insulin. Patient will be followed every 1-2 weeks, as necessary, determined by their glucose control, until delivery. Of note, these visits do not constitute an extra burden for the patient, as this is the regular interval that patients with diabetes mellitus type 2 would have been followed even if they were not enrolled in the study.

A release of records form will be signed at randomization, so that in case that the patient delivers at another center, we can still obtain records from her delivery.

The research team will collect participant data including demographic characteristics, medical history, obstetric history, labor course and outcomes. At each visit, patient weight, blood pressure, compliance, side effects and fetal ultrasound parameters will be evaluated. Glucose levels will be recorded at each visit to determine the mean overall glucose, mean fasting glucose, mean postprandial glucose, percentage of values below, within and above target values.
The treating physician will adjust insulin dose to maintain good glucose control based on targets:

- fasting glucose <95 mg/dl
- 2-hour postprandial values < 120 mg/dl, overall mean glucose < 100 mg/dl

Subjects that fail the therapy assigned by randomization will continued to be followed until delivery, regardless of the regimen that their provider chooses for glycemic control.

- Every participant will be invited to answer a 10 min Medication adherence survey once during pregnancy.

- Every participant will be invited to answer a 10 min PRAPARE Assessment survey (The Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences) once during pregnancy.
- Every participant will be invited to answer a 5 min JSPPE empathy survey (The Jefferson scale of patient perception of physician empathy) at 3 clinical visits during pregnancy: at the first visit, in the second trimester and in the third trimester of pregnancy.

1.6 Safety assessment

1.6.1 Risk associated with NPH/Detemir

Insulin treatment including detemir and NPH has reported possible risks and discomfort including:

1. Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including detemir and NPH. The rates of hypoglycemia in the detemir clinical trials (32%) were mostly comparable between detemir-treated patients and NPH-treated patients. Some studies have shown a lower risk for hypoglycemic events with detemir compared to NPH. Severe hypoglycemia is defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with blood glucose below 50 mg/dL has been reported to occur in 0.4 of patients treated with detemir and 1.5% in patients treated with NPH.
2. Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including detemir and NPH. Local allergy in the injection site reported in 0.25% of patients with detemir and 0.12% of patients with NPH.
3. Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin adsorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy.
4. Weight gain can occur with insulin therapy and has been associated to detemir and NPH, it has been attributed to the anabolic effects of insulin and the decrease in glycosuria.
5. Insulin, including detemir and NPH, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

NPH and detemir have been used in pregnancy and is not believed to cause birth defects or any problem in the developing fetus or newborn. REPROTOX®, an information system developed by the Reproductive Toxicology Center, is a database on the reproductive effects of chemical, medications, physical agents, and biologics. REPROTOX® lists insulin detemir use during pregnancy has been associated with outcomes similar to those with NPH insulin. The FDA lists detemir as a category B drug. REPROTOX® information regarding NPH is that poorly controlled diabetes mellitus during pregnancy is a cause of fetal

complications, including congenital anomalies. Insulin therapy can reduce the risk of those complications. The FDA lists NPH as a category B drug.

Using of Insulin during pregnancy does not appear to affect your chances of breastfeeding, or the length of time the participate can breastfeed. Insulin is transported into human milk at comparable concentrations to serum insulin. Mothers using insulin to treat diabetes may nurse their infants.

1.6.2 Specification of safety parametersbe

Both of the intervention proposed are done in routine clinical care and have been tested in previous studies. The medications are not new in pregnancy, they do not cross the placenta and not associated with congenital anomalies. Therefore, the establishment of safety data monitoring board is not necessary. The principal investigator and mentor will monitor the progress of study and determine the safety parameters.

1.6.3 Management of adverse events

Any adverse event will be reported to the committee for the Protection of Human Subjects (CPHS). Due to the use of medications that have been used in pregnancy in the past, there is no increased anticipation of severe adverse events.

1.6.4 Procedures in the event of abnormal clinical finding

In the event of an abnormal clinical finding, the health care provider caring for the participant will be notified to allow treatment in the usual clinical manner.

1.7 Statistical considerations

1.7.1 Sample size

Retrospective data collected from Memorial Hermann Hospital showed that 43.6% of women with type 2 diabetes would have composite adverse neonatal outcome. [44]

In order to detect a 40% reduction in this rate between the groups with 80% power and a Bayesian posterior probability of 75% (of any reduction),108 (54 per group) women need to be randomized.

A total of 216 women would need to be approached for consent, to accommodate an expected enrollment rate of 50%.

Based on our ICD-10 consult code, there were approximately 200 type 2 diabetic consults across the sites from March 2017 - March 2018. If we anticipate a 50% enrollment rate, we should be able to complete this study in 1.5 years. After one year, we are going to assess the feasibility for a period of 12 month. If recruitment was less than 40 women, we will conclude that the study is not feasible.

Interim analysis after 50% enrollment will be performed in order to assess the frequency of the primary and secondary outcomes. At that point, a decision will be made to see if there is a need to adjust the sample size.

1.7.2 Statistical tests

An intent-to-treat analysis will be conducted. Composite primary outcome will be evaluated with a Bayesian binomial model using a neutral informative prior (excluding treatment effects outside the range of 0.3-3 in the relative risk [RR] scale). We will report RR and 95% credible intervals as well as probability of reduced adverse neonatal outcome. Secondary outcome measures will be compared using the independent t-test for continuous variables and the x^2 or fisher's exact test for categorical variables as appropriate. Mann-Whitney U test will be used for non-parametric comparisons.

1.8 Ethical considerations

1.8.1 Informed consent

A copy of the informed consent document in both English and Spanish will be submitted by the PI to the Institutional Review board (IRB) for review and approval prior to the start of the study. A properly executed written informed consent shall be obtained from each patient prior to entering the study. All prospective study candidates will be given a full explanation of the consent form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the investigator is assured that the individual understands the requirements of the study, the subject will be asked to sign the consent. The investigator shall provide a copy of the signed and dated informed consent to the patient and the original shall be maintained in the patient's study files. Patients who do not sign the consent form will not be permitted to participate in the study.

1.8.2 Institutional review board

Before initiation of the study, the PI will obtain approval of the research protocol from the IRB. The study will be registered in www.clinicaltrials.gov as required by the US law for public access.

1.8.3 Subject confidentially

Each study's subject anonymity will be maintained throughout the study, prior to collection of the data a unique study number will be assigned to each case thus de-identifying the individual subject. In the study site, there will be a log of the study subject to the assigned study number. Research assistants are in compliance with required CITI training. When results of this research study are reported in medical journals or at scientific meetings, the subjects who take part will not be named or identified. The Federal Privacy Act protects the confidentiality of medical records and any private health information collected. Access to personal information will be limited to the investigators only. However, these individuals are required to keep all information confidential.

1.8.4 Data handling and record keeping

Access to source documents:
Research personal will perform data collection manually from patient charts at the different sites. Please refer to attached data collection sheet

for detail on variables to be collected. Data will be collected from randomization until 6 weeks post partum.

1.8.5 Records retention: Data will be digitally encrypted and stored in the UTHealth Redcap system. At the conclusion of the study, the principal investigator will retain copies of the approved protocol and all other supporting documentation related to the project. De-identified patient information may be used for future research projects.

1.86 **Quality control Assurance:** the principal investigator and co-investigators

Go through all the files to assure that data is reliable and complete. The verification will be by self assessment.

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