Misoprostol **D**osing in BMI Greater Than **30**: A Randomized Controlled Trial (MD30 RCT)

Study Protocol and Statistical Analysis Plan

NCT05262738

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Version 1.1

Introduction

As of 2019, approximately 24.9% of women in the United States underwent induction of labor[1]; this number is likely to increase after the ARRIVE trial[2] demonstrated maternal benefit to elective 39-week inductions. Of these women, approximately 84% will require cervical ripening by various methods[3]. While several studies have examined the fastest and safest methods of cervical ripening, few studies have specifically examined the fastest and safest method of cervical ripening in obese women. Carbone et al in 2013 demonstrated that vaginal misoprostol with foley bulb cervical ripening resulted in shorter time to delivery when compared to vaginal misoprostol alone[4]. This finding was further supported by Levine and colleagues in 2016[5].This intervention did not reveal any difference in labor complications or adverse maternal/neonatal outcomes. Similar studies have been attempted in the obese population with mixed results[6-8]. Unfortunately, most guidelines to date regarding cervical ripening regimens have not made specific recommendations regarding the obese population.

Obesity in the United States is now a well-recognized epidemic with approximately 29% of pregnancies complicated with a BMI > 30 and increasing steadily[1]. A retrospective study found delivery costs to be significantly higher in obese women compared to their normal BMI cohort[9]. Obesity in pregnancy is characterized by increased rates of pre-gestational and gestational hypertensive disorders, diabetes, and growth abnormalities[10], leading to increases in medically indicated inductions. Intrapartum, obesity has been linked to increased rates of prolonged latent phase, which is associated with increased rates of cesarean and operative deliveries, hemorrhage, and chorioamnionitis[11-17]. In a NICHD funded MFMU network study in 2018 examining the length of the latent phase of labor in women undergoing induction, approximately 96.4% of women reached active phase by 15 hours. However, when comparing to non-obese women, the first stage of labor was noted to be significantly longer in duration with a slower progression for both nulliparous and multiparous obese women[18].

Misoprostol is a commonly used agent utilized for cervical ripening that may be administered orally, buccally, or vaginally. There exists a number of dosing and route combinations, however 25mcg vaginally is the most commonly used. ACOG also states that higher doses (such as 50mcg) may be appropriate in some clinical situations[19]. Thus, both 25mcg and 50mcg of vaginal misoprostol have been used as the standard of care across the United States. A meta-analysis by Sanchez-Ramos in 2002 pooled results from 5 RCTs comparing the safety and efficacy of 25mcg versus 50mcg of intravaginal misoprostol dosing[20]. This systematic review demonstrated a significantly greater efficacy with 50mcg dosing (shorter time to delivery, greater proportion of deliveries within 24 hours, and less frequent oxytocin use). While tachysystole occurred more frequently in the 50mcg dosing group, maternal/neonatal outcomes were similar between both groups. However, there was no examination of differences in dosing by BMI category.

Compared to normal weight women, obese women have lower rates of contractions after misoprostol administration than their normal BMI cohort[21]. This suggests a lower bioavailability of misoprostol in women with a large volume of distribution thereby impacting the efficacy of misoprostol. Therefore, obese women may reasonably need a higher dose of misoprostol compared to normal weight. Comparisons between vaginal and oral misoprostol regimens in obese women demonstrate a lower rate of cesarean deliveries[22-23]. In fact, Sherwin et al, described a retrospective cohort in 2016 of 483 obese women undergoing induction of labor with either 25mcg or 50mcg of vaginal misoprostol. Time to delivery was significantly shorter when 50mcg dosing was used compared to 25 mcg[24]. This comparison,

however, has not been studied in a randomized controlled fashion, and the most common dosage of misoprostol remains 25mcg vaginally regardless of maternal BMI. We aim to determine if 50mcg (compared to 25 mcg) of vaginal misoprostol reduces the time from induction start to delivery in obese women.

Obese women are known to have longer induction times, greater failed induction rates, and higher rates of cesarean deliveries, all of which are known to increase maternal and neonatal morbidity. Therefore, appropriate interventions aimed to reduce these consequences are warranted. If this study demonstrates a reduction in time from induction to delivery of three hours, this could potentially result in an estimated 3.1M hours saved on labor and delivery in the United States[1]. With the average cost of a vaginal delivery in the United States ranging from $5000-$11000[25-26], this could potentially translate to a savings of up to $1.89B in labor and delivery hours saved in the United States.

Methods

Study Design:

Double-blind, Randomized Controlled Trial

Study Site:

Ascension Seton Medical Center is a non-profit, private hospital with a level IV maternal care designation that experiences approximately 5000 deliveries a year. Ascension is the primary obstetrical teaching site for the University of Texas at Austin Dell Medical School. The Labor & Delivery ward is a mix of private obstetrical practices and an academic/public teaching component, thus representing a diverse patient population generalizable to the obstetric community as a whole. The academic service is primarily managed by the house staff, midwives, and faculty. This service is comprised of a patient population from the University of Texas at Austin Women's Health Department, CommUnity Care Health Centers, and Ascension Medical Group. The cervical ripening methods employed on labor and delivery consist of a mix of various misoprostol route administrations often times with co-administration of mechanical methods (Cook Balloon) as well. The most commonly employed cervical ripening method involves placement of 25mcg of vaginal misoprostol into the posterior fornix every 4 hours for up to 6 maximum doses. The decision to utilize mechanical ripening, transition to Oxytocin, artificial rupture of membranes, and route of misoprostol administration is at the discretion of the house-staff and faculty on service. However, at this time there does not exist any delineation of cervical ripening methods based on maternal BMI at admission.

Participants:

All patients admitted to Labor & Delivery at Ascension Seton Medical Center will be screened against the inclusion and exclusion criteria by research staff. Eligible patients will be approached by study staff. If interested, the patient will be consented for the study and randomized to either fifty micrograms of vaginal misoprostol dosing (intervention) or twenty-five micrograms of vaginal misoprostol dosing (control) for induction of labor.

Study Criteria:

<u>Inclusion Criteria:</u>

1. Singleton gestation
2. Age 18 years or older
3. Gestational age >= 36 weeks
4. BMI >= 30 kg/m^2 at time of labor induction
5. Cephalic presentation (including successful external cephalic version)
6. Cervical dilation <= 3cm
7. Intent to proceed with cervical ripening

Exclusion Criteria:

1. Contraindication to vaginal delivery (placenta previa, vasa previa, prior classical cesarean, non-vertex presentation, etc.)
2. Contraindication to prostaglandin administration (significant allergy, prior cesarean delivery, etc.)
3. Multiple gestations
4. Gestational age < 36 weeks
5. Non-reassuring fetal heart tracing
6. Evidence of clinical chorioamnionitis
7. Significant vaginal bleeding with concern for abruption
8. Prior cesarean delivery or uterine surgery
9. Major fetal anomaly or demise
10. Cervix >3cm
11. No intention to proceed with cervical ripening (not indicated, favorable bishop score, plan for Oxytocin administration, etc.)
12. Uterine tachysystole (defined as >= 5 contractions within a 10m period)
13. Fetal Growth Restriction (EFW <= 5% or elevated/absent/reversed Umbilical Artery dopplers)
14. Inability to give consent (inability to read/write in English or Spanish)

Safety Data

Prior Studies of Safety

1. Sanchez-Ramos 2002 meta-analysis reviewing RCTs to compare the safety and efficacy of 25mcg versus 50mcg of intravaginal misoprostol for cervical ripening and labor induction[20]. This study included a total of 933 women, of which tachysystole occurred in 41 versus 98 women receiving 25mcg versus 50mcg of misoprostol respectively (OR 0.36, CI 0.24-0.53). Cesarean for FHR abnormalities occurred in 25 versus 37 women (OR 0.66, CI 0.39-1.14). APGAR scores less than 7 at 5 min occurred in 8 versus 15 neonates (OR 0.54, CI 0.22-1.28). NICU admissions occurred in 22 versus 36 neonates (OR 0.60, CI 0.34-1.06).
2. Farah in 1997 performed an RCT to compare the safety and effectiveness of intravaginal misoprostol at 25mcg versus 50mcg dosing[27]. This study included 399 patients in total. Tachysystole occurred in 15.6% versus 32.8% of participants (p = 0.0001), however cesarean deliveries occurred in 12% versus 15.9% of women which was non-significant. Umbilical cord pH, APGAR scores < 7, and NICU admissions were also non-significant between the groups. Maternal complications such as hemorrhage and endometritis were non-significant between groups.

3. Diro in 1999 randomized women to either 25mcg versus 50mcg of intravaginal misoprostol to compare the efficacy and safety for cervical ripening and labor induction[28]. This study included 251 participants of which hyperstimulation was significantly higher in the 50mcg regimen (19 versus 7.2%, p = 0.005), however cesarean delivery was non-significant between both groups. Fetal APGAR scores were non-significant between both groups (8.5 versus 8.4). No other maternal or fetal complications were recorded in the study.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be formed and consist of three individuals: a Maternal Fetal Medicine specialist with expertise in biostatistics (Dr. Radek Bukowski), Obstetrician & Gynecologist (Dr. Lauren Thaxton), and Pediatrician/Neonatologist (Dr. Alan Groves). These individuals are not involved with the study design nor have potential authorship of the manuscript. The primary purpose of the DSMB will be to monitor patient safety. Additionally, they will have the opportunity to review data collected to monitor the feasibility of the study.

Medication

The patient will be consented for the study and randomized to either fifty micrograms of vaginal misoprostol dosing (intervention) or twenty-five micrograms of vaginal misoprostol dosing (control) for induction of labor. Misoprostol, or Cytotec®, is a synthetic prostaglandin E_1 analog utilized for labor induction purposes and is considered the standard of care in the United States and endorsed by the American College of Obstetrics and Gynecologists[19]. A number of different routes and doses exist for misoprostol administration[6], however 25mcg and 50mcg vaginally are both considered the standard of care for labor induction in the United States.

Consent

Patients who meet inclusion criteria will be identified upon admission to Labor & Delivery at Ascension Seton Medical Center. Study staff will identify qualifying subjects and introduce the study in addition to confirming eligibility. If interested, the patient will be consented for the study by the research nurse or co-investigator. Patients will be randomized to either fifty micrograms of vaginal misoprostol dosing (intervention) or twenty-five micrograms of vaginal misoprostol dosing (control) for induction of labor. If the patient is randomized to the intervention, house staff or a co-investigator will place the vaginal misoprostol per the detailed plan below.

Blinding

Blinding will be achieved by providing misoprostol dosing in prepackaged, numbered envelopes. At randomization, a study number will be assigned and the matching envelope used for misoprostol doses. Misoprostol will be provided as quarters of a whole tablet, using 100 mcg quarters to provide 25 mcg dosing and 200 mcg tablet quarters to provide 50 mcg dosing. When quartered, the 100 and 200 mcg tablets are virtually identical with no distinguishing markings.

Design Protocol

<u>Prior to Randomization</u>

1. Documentation of digital cervical exam prior to randomization.

2. Standing weight and height obtained upon admission by standardized designated study scale.
3. Review eligibility criteria and confirm patient remains eligible for the intervention.
4. Obtain patient questionnaire regarding factors influencing decision to enroll or not enroll in study.
5. Consent patient.

Randomization Procedure

After consents are signed, patient will be entered into RedCAP database and randomized. RedCAP will generate a study number. Study team will pull matching envelope from Pyxis with study drug in appropriate blinded dosing.

At Time of Randomization

1. Placement of misoprostol dose by House Staff in posterior fornix with documentation of time
2. Continuous fetal monitoring and tocodynamometry as per usual care after misoprostol placement.
3. Repeat digital cervical exam 4 hours after initial dose
4. If the cervical exam remains <= 3cm and the intent remains to continue with cervical ripening
    a. Proceed with next dose of misoprostol if fetal heart tracings remain Category I, no evidence of continued uterine tachysystole with administration, no significant vaginal bleeding, etc.
    b. Do not proceed with subsequent dose if fetal heart rate tracings are Category II/III, continued uterine tachysystole is observed, significant vaginal bleeding with concern for abruption is witnessed, new contraindications to vaginal delivery arise.
    c. If unable to proceed with misoprostol given the above criteria has been met, proceed with usual labor management protocols at the discretion of the provider.
    d. The provider may choose to initiate resuscitative measures (oxygen, maternal re-positioning, IV fluid bolus, etc.) and wait up to 60 minutes to attempt to give a subsequent dose. However, no other dosage or forms (buccal, oral, etc.) of misoprostol should be given other than the randomized allocation.
5. Review of fetal heart rate tracings and uterine activity with documentation every hour.
6. Repeat steps 1-4 every 4 hours for either a maximum of 6 doses or a maximum of 24 hours has elapsed since the initiation of the first dose, whichever is first.
7. If unable to further proceed with misoprostol, usual labor management protocols should be followed at the discretion of the provider.
8. Administration of mechanical induction methods (foley balloon, cook balloon, etc.) at the discretion of the provider.
9. Usual labor and delivery management protocols should be followed by the provider. Usual indications for failure of induction, failure to progress, and second stage arrest should be followed. Although not mandated, it is suggested to providers that women should be allowed at least 18 hours in the latent phase after completion of any ripening, rupture of membranes, and use of oxytocin before considering the induction “failed” and proceeding to cesarean delivery absent any acute maternal or fetal indications.

10. Route of delivery and indication for cesarean up to the discretion of the provider.
11. Following delivery, universal cord gas collection (arterial, and/or venous) will be collected for all participants
12. Postpartum patients will be asked to complete a survey regarding their satisfaction with their cervical ripening method, prior to discharge from the hospital.

Outcomes

Primary Outcomes

1. Interval time from labor induction initiation to delivery (vaginal or cesarean)

Secondary Outcomes

1. Interval time from labor induction initiation to complete cervical dilation
2. Interval time from labor induction to vaginal delivery
3. Vaginal Deliveries
4. Cesarean Deliveries
5. Indication for Cesarean Delivery (if applicable)
6. Operative Deliveries
7. Number of Participants exhibiting Uterine Tachysystole (after 4 hours post-misoprostol)
8. Number of Participants exhibiting Uterine Tachysystole with Fetal Decelerations
9. Number of Participants receiving Terbutaline
10. Number of Participants exhibiting Non-Reassuring Fetal Heart Tracings
11. Number of Participants diagnosed with Clinical Chorioamnionitis
12. Number of Participants diagnosed with Postpartum hemorrhage
13. Composite Maternal Morbidity (ICU admission, Sepsis, Need for Transfusion, Death)
14. Composite Neonatal Morbidity (ICU admission, APGAR <=7 at 5 minutes, Sepsis, Acidemia identified upon cord collection (pH < 7.15, Base Deficit >12.0 mmol), Induced Hypothermia, Perinatal Death)
15. Patient satisfaction of cervical ripening method as measured by the Six Simple Questions and Visual Analog Pain Scale surveys[29-30].

Baseline Characteristics

1. Maternal Age
2. Maternal BMI
3. Gestational Age
4. Parity
5. Race
6. Admission Cervical Dilation
7. Indication for Labor Induction
8. Number of Participants receiving a mechanical method of dilation (foley bulb, cook, etc.)
9. COVID vaccination status

Outcome Evaluation

The outcomes will be assessed during the course of the inpatient admission through chart review. The timing of misoprostol placement will be accurately recorded by the nursing staff. Admission, fetal heart

rate tracing review, and delivery times will be recorded by the nursing staff. Adverse outcomes and maternal/fetal complications rates will be recorded prior to hospital discharge by chart review. Given that all outcomes will be evaluated at the time of inpatient admission, there will be no anticipated loss to follow-up.

Randomization

Randomization will occur according to a predetermined computer-generated stratified randomization scheme prepared by a study statistician. This method will be used to achieve balance among the intervention and control groups in terms of patients' characteristics including BMI >= 40 kg/m^2, parity, and intent to proceed with mechanical dilation at initiation of misoprostol placement. These three variables will be dichotomous such that there will exist a pre-stratified BMI >=40 kg/m^2 group, BMI <40 kg/m^2 group, multiparous group, nulliparous group, proceeding with mechanical dilation, and not proceeding with mechanical dilation. A separate block will be generated for each combination of covariates, and patients will be assigned to the appropriate block of covariates. When subjects have been identified and assigned into blocks, simple randomization will be performed within each block to assign subjects to one of the groups (control versus intervention).

Statistical Analysis

Descriptive statistics will characterize the group of individuals recruited to assess comparability of the treatment and control groups. Chi-Square test or Fisher's exact test will be used for categorical variables. Continuous variables will be examined for normality using the Shapiro-Wilk test; normally distributed continuous variables will be compared using the Student's t-test and those non-normally distributed will be compared using the Mann-Whitney U test. Analysis of the primary outcome will consist of a simple comparison of time from labor induction to delivery between the treatment and control group using generalized linear models. Stratified analyses will be used to identify potentially confounding effects. All tests will be two-tailed and use a significant level of <0.05. Data will be analyzed with the intention-to-treat principle.

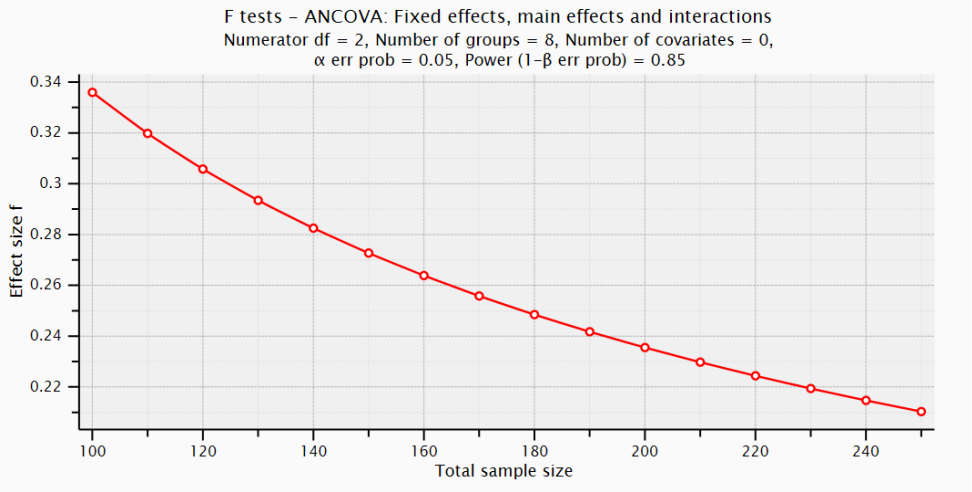
Blinding

This study will be double blinded with the research participants and providers/nursing masked to the interventions. A study statistician will create a randomization scheme as described above which will be utilized by the research pharmacy to distribute pre-packaged masked intervention packets.

Power Analysis

Sample size estimations were conducted using G*Power. Our analyses estimated a medium effect based on a 3-hour difference (SD=6) between our treatment (M=15 hours) and control (M=18 hours) groups[4]. These estimations were derived from the work of Carbone et al, Obstet Gynecol. 2013. We computed the required sample size to detect a medium effect with the specified parameters: strata = 8, power = 0.85, α=.05, *f*=0.25. This yielded a total sample size of approximately 180 participants total, 90 per group. Figure 1 depicts the relationship between sample size and effect size the study proposed. As effect size decreases, sample size increases.

Figure 1. Relationship between effect size and sample size for MD 30 RCT.



Future Plans

If our results demonstrate that 50mcg of vaginal misoprostol provides shorter interval time to delivery, is safe and well-tolerated, and has similar vaginal delivery rates compared to current induction methods, we will plan to seek funding for a multi-center trial to alter current induction methods for obese patients. This will provide a larger and thus more generalizable patient population to provide guideline recommendation changes.

Budget

To achieve a double-blind study, misoprostol doses will be provided as pre-quartered tablets of either 100 mcg tabs (to achieve 25 mcg) or 200 mcg tabs (50 mcg). These tablets are virtually indistinguishable in size. Ascension Hospital Research Pharmacy has provided significantly discounted rates to provide prepackaged blinded doses of misoprostol to this study. Their estimates include:

- Start-up fees $1125
- Quarterly Maintenance $100/month - 100% = Agreed to discount for Fellow research project
- Combined Enrollment/Dispensing Fees $150/subject - 50% = $75 x 180 subjects = $13,500
- Misoprostol tablets 100mcg x 180 subjects = $100
- Misoprostol tablets 200mcg x 180 subjects = $100
- Close-out fees $200
- Total Estimated Research Pharmacy Fees: $15,025
- Document Translation Fees: $500
- Standard medical grade weight scale: $150 (approximate)
- Participant compensation: $10 x 180 subjects = $1800

Projected Total Costs: $17,475

Research RN Support - Provided by University of Texas Department of Women's Health
Statistical Support - Provided by University of Texas Department of Women's Health

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