Study Title: Induction of labor with Oral misoprostol alone versus Combined Oral misoprostol with Foley bulb: a Cluster Randomized Trial

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University of Texas Southwestern Medical Center Institutional Review Board Protocol

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Purpose:

We propose a prospective, cluster-randomized clinical trial to compare standard of care (oral misoprostol) with a combination method of oral misoprostol and transcervical foley bulb (study group) in patients requiring induction of labor. We hypothesize that the use of the combined method of oral misoprostol plus intracervical foley bulb for cervical ripening and induction of labor will reduce the rate of primary cesarean delivery when compared with oral misoprostol alone. We also aim to evaluate the time to delivery, intrapartum and postpartum infectious morbidities, fetal distress, blood loss at delivery, uterine activity, and neonatal outcomes including APGAR scores, umbilical cord blood pH, and neonatal intensive care unit (NICU) admission.

Background:

Induction of labor is associated with increased cesarean delivery rate, especially in those women with an unfavorable cervix.[1] Both pharmacologic and mechanical methods have been utilized for cervical ripening and labor induction. Evidence on the safety and effectiveness of various mechanical and pharmacologic methods of cervical ripening and labor induction is abundant, and yet the cost of these different methods of induction varies widely when taking into consideration medication storage, cost, and staffing requirements. Given the high immediate and long term costs of cesarean delivery, and the national priority to reduce the rate of primary cesarean delivery in the United States,[2] a randomized trial powered to detect a reduction in the rate of primary cesarean delivery has the potential benefit of changing obstetric practice both at Parkland Hospital and nationwide.

Beginning in the 1980s, the overall rate of induction of labor in the United States gradually increased, reaching a peak of 23.8% in 2010.[3] Likewise, the rate of cesarean

delivery in the United States has increased steadily to peak in 2009 above 32%.[4] There is increased maternal morbidity among women with primary cesarean delivery compared with vaginal delivery, including higher rates of transfusion, unplanned hysterectomy, and ICU admission.[5] Although the problem of reducing the rate of primary cesarean delivery is complex, there is a continued need to determine the most effective and safest way to promote cervical change in women with an unfavorable cervix who require labor induction.

A cervical ripening agent may be needed for women with an indication for induction of labor who have an unfavorable cervix.[6] Both pharmacologic and mechanical methods have been utilized for cervical ripening prior to labor induction. Among pharmacologic methods, prostaglandins have been recognized as more effective than intravenous oxytocin alone at both cervical ripening and induction of labor, achieving higher rates of vaginal delivery.[1] There is abundant clinical experience on the safety and efficacy of oral and vaginal misoprostol when used appropriately for cervical ripening and induction of labor, and both are supported by the American College of Obstetricians and Gynecologists.[6] Based on prior studies of various dosing and administration regimens,[7-10] oral misoprostol (100μg) given every four hours for a maximum of two doses is currently the standard of care at our institution for cervical ripening and labor induction in those women with gestations of 36 weeks or greater, without a prior uterine scar, who are not in labor and who otherwise meet strict criteria for fetal well-being.

Controversy exists on whether the accepted mechanical technique of cervical ripening and dilation with transcervical foley catheter used in combination with a pharmacologic method may be more effective than prostaglandins alone in achieving

cervical ripening and induction of labor. Most trials comparing combination foley and misoprostol are powered to detect a shortened time to delivery rather than the more clinically relevant outcome of reduced primary cesarean delivery rate.[7,9,11-17] Available evidence suggests that the combination of foley catheter with misoprostol for induction of labor reduces the time to vaginal delivery, but what remains unclear is whether this method also reduces the rate of primary cesarean delivery. Additionally, although the theoretical risk exists, evidence is conflicting regarding the risk of chorioamnionitis with the use of transcervical foley catheter in women with intact membranes.[14,17-19] There is no current evidence that the use of transcervical foley contributes to adverse neonatal outcomes. The largest published randomized trial comparing oral misoprostol alone to foley catheter alone, in which the primary outcome was a composite of neonatal morbidity and/or maternal hemorrhage, demonstrated similar safety and effectiveness of the two methods in induction of labor.[19] However, a comparison arm involving the combination of the two methods was not included in the study.

The purpose of this study is to determine whether the use of a transcervical foley catheter, in combination with the standard oral misoprostol regimen will result in a decreased primary cesarean delivery rate among women with a cervical dilation of 2 centimeters of less who require induction of labor at term. This study is not an FDA-regulated study: there is no intent to test the foley bulb under an FDA-regulated protocol. Likewise, there is no intent to submit the results of this study for a change in the labeling of the foley used for this study.

Concise Summary of Project:

This will be a prospective, cluster-randomized trial comparing two methods of induction of labor at term among women who present for delivery at Parkland Hospital. Eligible participants will include nulliparous and multiparous women at 37 weeks gestation or greater, with a living, singleton fetus and no major fetal malformations, in cephalic presentation, with intact membranes, no prior uterine scar, who qualify for prostaglandin administration and who have a cervical dilation of 2 centimeters or less, measured at the level of the internal os. Patients with non-reassuring fetal status, HIV, active herpes outbreak, a prior uterine scar, or any contraindication to prostaglandins (including 4 or more painful contractions per 10 minutes prior to prostaglandin administration) will be excluded from participation in the study. Computer-generated cluster randomization will occur on a weekly basis for all study participants, to either the combination method of foley bulb plus oral misoprostol regimen (study group/standard of care plus foley bulb) or to oral misoprostol alone regimen (control/standard of care).

According to the randomization protocol each week, participants will be randomized to either the standard of care (oral misoprostol/control group) or standard of care plus foley bulb (study group). The study group will undergo placement of a 30 French foley catheter filled with 30-35cc sterile saline into the cervix in addition to the standard regimen of oral misoprostol 100 micrograms given every 4 hours for a maximum of 2 doses, for patients who meet criteria for fetal well-being, and do not had more than 4 painful contractions in 10 minutes. Misoprostol will not be administered to patients who have progressed to active labor, defined as 4 centimeters cervical dilation. The control group will undergo induction with the standard of care misoprostol protocol alone.

The primary outcome will be the rate of vaginal delivery. Secondary outcomes will include obstetric outcomes, maternal outcomes, and neonatal outcomes. Obstetric outcomes will include indication for induction, need for oxytocin, indication for cesarean delivery, time to active labor, time to delivery, labor analgesia, presence of chorioamnionitis, meconium-stained amniotic fluid, terbutaline use, tachysystole (defined as 6 or more contractions in 10 minutes or tetanic contraction of 120 seconds or longer) or hyperstimulation syndrome (defined as tachysystole accompanied by fetal heart rate decelerations). Maternal outcomes will include estimated blood loss, transfusion requirement, postpartum fever, uterine rupture, and unplanned hysterectomy. Neonatal outcomes will include umbilical cord blood pH, 5-minute APGAR score, intubation or ventilation in the delivery room, neonatal sepsis, and admission to Neonatal Intensive Care Unit (NICU) admission.

Data from these pregnancies will be obtained using several methods: data entry encounter forms completed by research nurses from the electronic medical record; and from the Parkland Hospital Obstetric Database. This database is maintained for operations, including quality assurance, and is able to be accessed only by the epidemiologist within the Obstetrics Department (Don McIntire, listed as co-investigator). The database uses a secure file server that is password protected and encrypted. Specific variables queried will include the date and gestational age at delivery, age, race, parity, singleton or multiple gestation, mode of delivery, the maternal weight and body mass index at initial prenatal visit, perineal laceration, labor induction and/or augmentation, intrapartum complications such as chorioamnionitis, infant condition at birth including APGAR score (Appearance, Pulse, Grimace, Activity, and Respiration),

infant cord gas (arterial pH), Neonatal Intensive Care Unit (NICU) admissions, and infant complications such as intraventricular hemorrhage and ventilator requirement.

The data entry encounter forms will include data regarding presenting cervical examination, time of induction, and cervical examinations (see attached Data Encounter Form). The data obtained from the data encounter forms will be entered into a computerized database operated by the departmental biostatistician (Don McIntire, co-investigator). This data will be supplemented with information obtained from review of the medical record. Maternal and neonatal outcome data from the existing obstetric operations database will be linked to the labor subset database created from the encounter forms and prenatal record. All data collected will be de-identified with a link maintained between research data and identifiable information using a key. The key to the coding system will be located in an electronic file that is password protected and encrypted and able to be accessed only by the departmental biostatistician listed (Don McIntire, co-investigator). Following publication, the key to the coding system will be destroyed by purging the file so that there is no direct or indirect link to subject identifiers or other information.

In summary, the research team will not have direct contact with the patient. All information will be obtained either using the Obstetric database or data entry forms with information obtained from the electronic medical record. These indices are routinely recorded by labor and delivery unit staff for labor induction (eg. Time of misoprostol given, etc.).

Calculations for statistical analysis will be conducted with the departmental biostatistician (Don McIntire, co-investigator). This is prospective study will be submitted

under the full review status of the University of Texas Southwestern Institutional Review Board (IRB).

Study Procedures:

Management of labor will proceed according to the standard induction protocols in place at Parkland Hospital. The number of misoprostol doses (up to 2 doses for a single induction event) will be recorded. The need for oxytocin following misoprostol will be determined according to routine obstetric management currently used at Parkland Hospital. All women meeting inclusion criteria as described above who require induction of labor will be included in the study. According to the cluster randomization protocol, either a combination method of standard of care plus foley bulb, or standard of care (oral misoprostol) alone will be implemented each week on the Labor and Delivery unit. During weeks randomized to the standard of care plus foley bulb, all eligible women undergoing induction of labor will receive prostaglandin using the current labor stimulation regimen as well as transcervical placement of a 30 French foley catheter with a 30cc balloon, filled with 30 to 35 cc of 0.9% sodium chloride solution, according to FDA guidelines for filling the foley bulb. Induction start time and foley bulb placement time will be recorded. Success of foley bulb placement and time to successful placement will be recorded. Complications of induction will be recorded, such as vaginal bleeding, fetal distress, rupture of membranes, or emergent delivery within 30 minutes of foley bulb placement. Failed foley bulb placement will be determined ultimately by the faculty on Labor and Delivery as per management practices. Analgesia requirement during labor will be recorded. Transcervical foley bulb will remain in place until expelled spontaneously, or for up to 12 hours during induction. The need for removal of foley bulb prior to being

spontaneously expelled at less than 12 hours will be left up to the discretion of the faculty on Labor and Delivery, and the time of removal and reason for removal will be documented. Maternal complications and will be documented, and neonatal complications will be recorded as previously described. Postpartum infectious morbidities and readmission to the hospital will be recorded, with review of the patient's medical record at least 2 weeks after hospital discharge to determine readmission for wound morbidity. The patient's participation the study will be concluded after this final review of the medical record. Neonatal outcomes will be abstracted from the infant's medical record at discharge.

Sub-Study Procedures: N/A

Criteria for Inclusion of Subjects:

Nulliparous and multiparous pregnant women at 37 weeks gestation or greater, with a living, singleton fetus and no major fetal malformations, in cephalic presentation, no prior uterine scar, with intact fetal membranes, who qualify for prostaglandin administration and who have a cervical dilation of 2 centimeters or less, measured at the level of the internal os, requiring induction at Parkland Health and Hospital System.

Criteria for Exclusion of Subjects:

Any patient not meeting above inclusion criteria will be deemed ineligible for the study. Patients with latex allergy, non-reassuring fetal status, HIV, active herpes outbreak, a prior uterine scar, or any contraindication to prostaglandins (including 4 or more painful contractions per 10 minutes prior to prostaglandin administration) or to vaginal delivery will be excluded from participation in the study. Because of the potential risk of vertical transmission in the case of inadvertent rupture of fetal membranes during placement of

foley bulb and the lack of data regarding the use of foley bulb in this population, patients with HIV will be excluded from the study.

Sources of Research Material:

Data from these pregnancies will be obtained using two methods: data entry encounter forms completed by research nurses from the electronic medical record; and the Parkland Hospital Obstetric Database. This database is maintained for operations, including quality assurance, and is able to be accessed only by the epidemiologist within the Obstetrics Department (Don McIntire, listed as co-investigator). The database uses a secure file server that is password protected and encrypted. Specific variables queried will include the date and gestational age at delivery, age, race, parity, singleton or multiple gestation, mode of delivery, the maternal weight and body mass index at initial prenatal visit, perineal laceration, labor induction and/or augmentation, infant condition at birth including APGAR score (Appearance, Pulse, Grimace, Activity, and Respiration), infant cord gas (arterial pH), Neonatal Intensive Care Unit (NICU) admissions, and infant complications such as intraventricular hemorrhage and ventilator requirement.

The data entry encounter forms will include data regarding presenting cervical examination, time of induction, and cervical examinations (see attached Data Encounter Form). The data obtained from the data encounter forms will be entered into a computerized database operated by the departmental biostatistician (Don McIntire, co-investigator). This data will be supplemented with information obtained from review of the medical record. Maternal and neonatal outcome data from the existing obstetric operations database will be linked to the labor subset database created from the encounter forms and prenatal record. All data collected will be de-identified with a link

maintained between research data and identifiable information using a key. The key to the coding system will be located in an electronic file that is password protected and encrypted and able to be accessed only by the departmental biostatistician listed (Don McIntire, co-investigator). Following publication, the key to the coding system will be destroyed by purging the file so that there is no direct or indirect link to subject identifiers or other information.

In summary, the research team will not have direct contact with the patient. All information will be obtained either using the Obstetric database or data entry forms with information obtained from the electronic medical record. These indices are routinely recorded by labor and delivery unit staff for labor induction (eg. Time of misoprostol given, etc.).

Recruitment methods and consenting process:

All subjects will be women who deliver at Parkland Health and Hospital System. The cluster randomized trial design is such that each week, the chosen method of induction of labor in patients meeting inclusion criteria is randomized to either standard of care (oral misoprostol) or standard of care plus foley bulb. The weekly cluster randomization method is chosen because randomizing on an individualized basis would create risk on a busy labor an delivery unit where nurses administer medications to more than one patient during a shift. All patients who would meet criteria for induction of labor will be participants in the study. A waiver of consent will be requested for this study, as the two methods of induction being compared are both widely accepted and practiced methods used for women with an unfavorable cervix who require induction of labor. The risks and benefits of induction of labor will be discussed with each patient prior to

administration and consent for delivery obtained, consistent with the current standard of care on Labor and Delivery at Parkland Hospital. Patients will be fully informed about the agents used for induction of labor (i.e., misoprostol alone or foley bulb and misoprostol, as well as oxytocin) and verbal consent as standard of care for induction will be obtained. The risk of transcervical foley bulb is minimal, and the primary risk of participation in the study is breach of confidentiality. The waiver of consent is appropriate because all patients will receive the same standard of care, and all methods of induction utilized are approved by the American College of Obstetricians and Gynecologists. Furthermore, obtaining consent from individual patients is impractical on a busy labor and delivery unit that would require research staffing for 24 hours a day, 7 days per week.

Data will abstracted from the medical record as described above and all patient identifiers removed prior to data analysis. Therefore, patients who meet inclusion criteria and who require induction of labor will be automatically enrolled in the study and data from induction and delivery will be abstracted without direct contact with any research personnel.

Potential Risks:

Potential risks of participation in the study include the risks associated with induction of labor with any standard pharmacologic or mechanical method. Additional risks include breach of confidentiality. However, as stated below, every effort will be made to reduce the risk of loss of confidentiality.

Risks of mechanical induction of labor include the same risks as pharmacologic induction of labor, except for the potential risk of inadvertent rupture of the foley balloon (0.5%). Benefits to foley bulb placement include potential shortened time to vaginal

delivery and fewer fetal heart rate changes when compared with prostaglandins alone, and potentially reduced risk of cesarean delivery. Induction of labor is carried out only when the benefit to mother and fetus outweigh the potential risk, and the current standards of care at Parkland Hospital regarding induction of labor timing and methods will not change for this study.

Confidentiality and protection of patient health information will be protected to the best of our ability. Data will be abstracted from medical records by research personnel and all data will be de-identified and located on a secure server in a locked research office. The database will be only accessible to the study personnel. This study does not deviate from accepted standard of care for labor induction.

Subject Data and Safety Monitoring:

At 50% of enrollment, a planned analysis by the Data Safety and Monitoring (DSM) committee for this study will be performed. If analysis shows a statistically significant harmful impact of using foley bulb in combination with oral misoprostol in women with an unfavorable cervix undergoing induction of labor, the study will be halted. Likewise, if a strong, statistically significant increase in vaginal delivery can be correlated with foley bulb use in combination with oral misoprostol for induction of labor, consideration will be made in early study termination, as not to deny the combination method to women who would benefit from it in achieving vaginal delivery. Thirdly, if the trial is deemed to be futile, meaning that further sampling will yield little additional useful information (or a negligible chance of demonstrating efficacy if fully enrolled, given the results to date), consideration will be made to halt the study.

Procedures to Maintain Confidentiality:

To maintain patient confidentiality, all records will remain within the hospital system. After the study dataset has been created by the departmental biostatistician (Don McIntire, co-investigator) using datasets maintained for operations with a secure file server that is password protected and encrypted, all identifiers will be removed and replaced with a non-identifiable code. The key to the coding system will be located in an electronic file that is also password protected and encrypted and able to be accessed only by the departmental biostatistician (Don McIntire, co-investigator). Following publication, the key to the coding system will be destroyed by purging the file so there is no direct or indirect link to subject identifiers or other information.

Results will only be furnished to the investigators, and to the UT Southwestern IRB, as needed. The information obtained from this study may be published, but the subjects will not be identified individually.

Potential Benefits:

As women who have primary cesarean delivery are more likely to have subsequent repeat cesarean than vaginal delivery, the potential benefit of a successful vaginal delivery can result in savings to the patient in hospitalization days, maternal and fetal complications from multiple cesarean deliveries, and in complications from surgery itself including wound infections, organ injuries and delayed recovery.

With the increasing frequency of cesarean delivery and the increasing morbidity of multiple cesarean deliveries, a successful vaginal delivery in a woman whose only alternative is cesarean delivery has the potential to improve quality of life, save cost in hospitalization days, wound complications, and improve the chance for subsequent

vaginal delivery, compounding the savings during a woman's lifetime. If the study shows no improvement in vaginal delivery rates or increased adverse outcomes in the study group, the study may prevent healthcare providers from utilizing an induction method which has little potential benefit other than convenience to the provider.

Biostatistics:

The current vaginal delivery rate at Parkland Hospital among women undergoing induction of labor is 76%, which has been consistent for at least the past 4 years (internal data). This study will be conducted as a superiority trial with analysis performed as intent to treat. To detect a 5% increase in vaginal delivery from 76% to 81% with a power of 80% and a type I error of 5%, a sample size of 2118 is required, with 1059 women in each group with comparisons using the Pearson chi-squared test. A planned interim analysis by the Data Safety Monitoring Board take place at 50% recruitment. In order to preserve the overall type I error rate of 0.05 we will apply the Lan-DeMets spending function with the O'Brien-Fleming type boundaries. This reduces the ultimate significance level of the trial through the completion of the trial from 0.05 to 0.049 and alters the sample size to 1065 women in each arm or 2130 total. A ten percent dropout rate still requires approximately 2500 participants to be screened (2130/0.90 = 2367).

In 2015 at Parkland Hospital, approximately 885 women at term (greater or equal to 37 weeks gestation) with cervical dilation equal to or less than 2cm received at least one dose of oral misoprostol for induction of labor. Based on these frequencies, recruitment will take approximately 2.5 years to achieve the study goal of 2130 women who meet inclusion criteria. Statistical analysis will be performed using SAS 9.3 and include Student's t-test, Wilcoxon rank-sum test, Pearson chi-squared test, and logistic

regression. We will plan a prespecified secondary analysis of the primary outcome stratified by parity.

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