

Outpatient Foley for Starting Induction of Labor at Term (OFFSITE); Randomized-Controlled Study Protocol

Study Protocol and Statistical Analysis Plan

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Spencer G. Kuper, M.D., Principal Investigator

University of Alabama at Birmingham

Birmingham, AL 35294

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1. Study Abstract

Induction of labor is necessary in one-fourth of women and a large proportion require cervical ripening. Cervical ripening is necessary to shorten the time to delivery and increases the chances of a vaginal delivery. The superior method for cervical ripening has long been debated. The two techniques utilized are mechanical and pharmacological methods. Pharmacological techniques center on formulations of prostaglandin but are associated with higher risks of tachysystole compared to mechanical methods. The primary mechanical method used is a transcervical Foley catheter with the balloon filled with 30-80 mL of sterile fluid. Downward tension on the internal os by the filled balloon leads to production of endogenous prostaglandins leading to remodeling of the cervix. A Cochrane review has shown similar efficacy between pharmacological and mechanical methods, but both were found to be superior to oxytocin for cervical ripening.

There has only been one randomized controlled study evaluating the transcervical Foley catheter for cervical ripening in the outpatient setting. The primary outcome of this study was a change in the Bishop score between the groups, and it found the Bishop scores were similar between the two groups. While not powered to detect a difference, it did show women in the outpatient group spent less time in the hospital without any adverse events. Outpatient cervical ripening is an attractive alternative to women and physicians because of the decreased amount of time spent in the hospital and opportunity for patients to be in the comforts of their home; however, few have adopted this method since there is only one study evaluating outpatient cervical ripening with a transcervical Foley catheter. The safety of the transcervical Foley catheter has been well-established, though, and it is not associated with increased risks of adverse events such as chorioamnionitis, endometritis, placental abruption, or stillbirth.

We will conduct a randomized controlled trial comparing outpatient to inpatient cervical ripening using a transcervical Foley catheter. The primary outcome is the time from admission to delivery. We hypothesize that women in the outpatient group will have shorter durations from admission to delivery than the standard inpatient cervical ripening group. We also predict the outpatient patients will have a higher satisfaction than the inpatient group because of the opportunity to be in their own home during the ripening period. Women will be randomized to undergo inpatient or outpatient transcervical Foley catheter cervical ripening beyond their 39th week of gestation. Women and their infants will be followed until the time of their discharge.

1.1 Primary Hypothesis

Patients in the outpatient transcervical Foley catheter group will have a shorter time interval from admission to delivery than the inpatient group.

1.2 Secondary Hypotheses

- a. Patients in the outpatient group will have higher satisfaction scores than those undergoing cervical ripening in the inpatient setting.
- b. The following hypotheses pertain to the incidence of the following events:
 - a. Outpatient cervical ripening will not increase the incidence of adverse outcomes compared to inpatient cervical ripening. Based on prior studies evaluating the safety of the transcervical Foley catheter, we do not anticipate there to be heavy vaginal bleeding, immediate need for delivery for a non-reassuring fetal heart tracing, or stillbirths in either group.
 - b. A small number of patients in the outpatient transcervical Foley catheter group will require admission prior to their scheduled arrival time because of intractable pain from the transcervical Foley catheter. Additionally, a small number of patients will require an epidural for pain control while the Foley catheter remains in situ.
 - c. Immediate delivery for non-reassuring fetal heart rate tracings after placement of the transcervical Foley catheter will not be required in either group.
 - d. A small number of patients in the outpatient transcervical Foley catheter group will present to the Maternity Evaluation Unit (MEU) for evaluation prior to their scheduled admission time.
 - e. Spontaneous rupture of membranes (SROM) will occur at similar rates in the two groups.
 - f. Outpatient cervical ripening with the Foley catheter will not increase infectious morbidity as compared to inpatient cervical ripening.
- c. Epidural usage, and thus immobilization, will be higher in the inpatient group compared to the outpatient group.
- d. The outpatient and inpatient groups will have similar rates of vaginal and cesarean deliveries.
- e. The following hypotheses pertain to oxytocin usage between the two groups:
 - a. The inpatient group will require longer duration of oxytocin infusion, higher cumulative doses, and higher maximum rates than the outpatient transcervical Foley catheter group.
- f. The outpatient group will have lower labor and delivery charges than the inpatient group.
- g. Outpatient cervical ripening will not increase the risk of adverse neonatal outcomes compared to inpatient cervical ripening, as assessed by a composite neonatal outcome. This composite neonatal outcome measure will include Apgar score < 7 at 5 minutes, arterial cord blood gas pH < 7.1, arterial cord blood gas base deficit or excess < -12, and/or admission to the neonatal intensive care unit.

1.3 Purpose of the Study Protocol

The purpose of this study is to determine whether outpatient cervical ripening with a transcervical Foley catheter in multiparous women shortens the total time in labor and delivery from the time of admission to the time of delivery compared to women who undergo cervical ripening in the standard inpatient fashion. This protocol describes the rationale, design, and organization of this randomized control study.

2. Background

2.1 Introduction

In developed countries, approximately 20-25% of pregnant women undergo an induction of labor [WHO 2011, Kelly 2013]. Fifteen percent of these women will require cervical ripening [Wing 1999]; in the setting of an unfavorable cervix, oxytocin alone can lead to longer times to delivery, tachysystole, and increased rates of cesarean delivery [Alfirevic 2009]. Methods for cervical ripening can be pharmacologic or mechanical. A Cochrane review demonstrated that mechanical methods of cervical ripening were equivalent to prostaglandin and superior to oxytocin administration [Jozwiak 2012]; furthermore, mechanical methods were safer, with decreased rates of adverse outcomes such as hyperstimulation [Jozwiak 2012].

Given rising medical costs and the length of the latent phase of labor, the concept of outpatient cervical ripening is attractive to both practitioners and patients [Farmer 1996]. Studies have shown outpatient induction is feasible and safe. The majority of the studies have evaluated outpatient induction of labor using prostaglandin E2 [Dowswell 2010, O'Brien 1995, McKenna 1999]. One of the greatest fears of outpatient induction of labor is nonreassuring fetal heart tracings. The lower risk of hyperstimulation associated with mechanical methods makes Foley catheter induction of labors particularly more attractive for use in the outpatient setting. Sciscione et al [Sciscione 2001] published the first randomized controlled trial comparing outpatient transcervical Foley catheter induction of labor to standard inpatient management. They demonstrated a decreased length of stay of 9.6 hours in the outpatient group without any adverse maternal or neonatal outcomes in the outpatient group [Sciscione 2001]. This study led the American College of Obstetricians and Gynecologists (ACOG) to make the profound statement regarding outpatient Foley catheters for induction of labor, "mechanical methods may be particularly appropriate in the outpatient setting. [ACOG 2009]" However, few obstetricians have incorporated this endorsement from ACOG.

In our institution, cervical ripening is exclusively performed using a transcervical 16 French Foley catheter with 30mL of sterile saline. This method has been proven to shorten the time to delivery compared to the PGE2 vaginal insert without increasing the cesarean delivery rate [Edwards 2014]. Additionally, Pettker et al [Pettker 2008] demonstrated there was not benefit to adding oxytocin to the transcervical Foley catheter induction method. Patients requiring cervical ripening spend a considerable amount of time in the latent phase. This prolonged period of time represents a significant portion of patients' intrapartum hospital costs. Additionally, while patients are not confined to bed, many patients choose to immobilize themselves during this period. As such, our objective is to evaluate the feasibility, safety, patient satisfaction, and cost associated with outpatient as compared to inpatient induction of labor with Foley catheterization for cervical ripening in low-risk women in a single academic institution in the southern United States. Contrary to Sciscione et al's [Sciscione 2001] study where the primary outcome was change in Bishop score, our study will be powered to detect a 12 hour reduction in time from admission to delivery.

2.2 Current recommendations for cervical ripening

Cervical ripening is necessary when the cervix is not softened and thinned, which are normal architectural remodeling processes the body goes through in preparation for labor. The most commonly used mechanical dilating method in the United States is the transcervical Foley catheter balloon. In this technique, a sterile urological 14-26 French catheter is inserted through the cervix, and then the tip is inflated with 30-80 mL of fluid. This downward pressure of the tip of the catheter cause endogenous prostaglandins to be released which potentiates the remodeling process required for cervical ripening.

2.3 Prior studies on outpatient induction of labor

There has only been one randomized controlled trial investigating the outpatient use of a transcervical Foley catheter for cervical ripening. Sciscione et al (2001) included 111 women in their trial (n = 61 inpatient and n = 50 outpatient), and their primary outcome was a change in the Bishop score. The Bishop score was recorded at placement of the transcervical catheter and then again when the catheter extruded or when the outpatient group presented for induction of labor. There was not a difference in Bishop scores between the two groups. There were not any adverse events in the outpatient group, and the outpatient group spent nearly 10 hours less in the hospital than the inpatient group. Other studies investigating outpatient cervical ripening have focused on prostaglandins, which increased the rates of tachysystole, but did not increase maternal or neonatal morbidity or mortality.

2.4 Safety of outpatient induction of labor

There is limited data on outpatient cervical ripening, and thus, this prompted authors of a Cochrane review (Kelly et al 2013) to conclude there was not sufficient evidence to establish the safety of cervical ripening in the outpatient setting. Sciscione et al (2014) created a theoretical cohort of outpatient transcervical Foley catheter for cervical ripening and reviewed labor and delivery as well as neonatal outcomes in over 1900 women. This "low-risk" cohort excluded patients with gestational hypertension, preeclampsia, multiple gestations, pregestational diabetes, and stillbirth, and found no adverse events in the group. There were not any cases of placental abruption or stillbirths. Only 2/1905 had an emergent cesarean section after placement of the transcervical Foley catheter for non-reassuring fetal heart rate tracings during the immediate postplacement monitoring. Only 3/1905 required a cesarean section for non-reassuring fetal heart rate tracings during the theoretical "outpatient" time period.

We have reviewed 43 consecutive privately insured cervical ripening admissions at the University of Alabama at Birmingham. In this cohort, transcervical Foley catheters were placed without initiation of oxytocin. There were not any placental abruptions, non-reassuring fetal heart rate tracings necessitating delivery, or stillbirths between placement of the transcervical Foley catheter and the next morning, which represented a theoretical "outpatient" time period.

2.5 Rationale for a clinical trial

While the American College of Obstetricians and Gynecologists (ACOG) stated in the Practice Bulletin Induction of Labor, “mechanical methods may be particularly appropriate in the outpatient setting,” few obstetricians practice outpatient cervical ripening because of only one randomized controlled trial investigating this method.

2.6 Innovation

There is a critical need for further studies to establish the safety, efficacy, and patient satisfaction of transcervical Foley catheter for cervical ripening in the outpatient setting. The only study investigating outpatient transcervical Foley catheter conducted to date was powered to detect a change in the Bishop score between the two groups and not total inpatient time. Our study will be the first randomized controlled trial powered to detect a difference in admission to delivery time between the two groups.

3. Study Design

This is a randomized controlled trial comparing time from admission to delivery in outpatient versus inpatient groups undergoing transcervical Foley catheter placement for cervical ripening.

3.1 Primary Research Question

Does outpatient cervical ripening with a transcervical Foley catheter shorten the admission to delivery time compared to the standard inpatient transcervical Foley catheter cervical ripening method?

3.2 Secondary Research Aims

- a. To assess patient satisfaction in both groups of patients to determine if patients in the outpatient Foley catheter group have higher satisfaction rates compared to the standard inpatient induction method.
- b. To assess the incidence of adverse outcomes in both groups. This will be evaluated by vaginal bleeding greater than bloody show, intractable pain requiring early admission in the outpatient (intervention) group, intractable pain requiring epidural placement while the Foley bulb remains in situ, nonreassuring fetal heart rate tracings upon admission in the outpatient group, and nonreassuring fetal heart rate tracing prompting immediate delivery.
- c. To assess the incidence of the following:
 - a. Outpatient group presenting to the Maternity Evaluation Unit (MEU) prior to their scheduled admission time.
 - b. Outpatient group having spontaneous rupture of membranes (SROM) prior to their scheduled admission time.
 - c. Chorioamnionitis or endometritis in each group.
- d. To assess the total time of epidural use in each group.
- e. To compare the mode of delivery between the two groups.
- f. To assess the following oxytocin parameters between the two groups.
 - a. Total time of infusion.
 - b. Total cumulative dose of oxytocin infused.
 - c. Maximum rate (milliunits/min) of oxytocin infused.
- g. To compare labor and delivery charges between the two groups.
- h. To assess a composite neonatal outcome between the two groups based on the following parameters:
 - a. Apgar score < 7 at 5 minutes
 - b. Arterial cord blood gas pH < 7.1
 - c. Arterial cord blood gas base deficit > -12
 - d. Admission to the neonatal intensive care unit.

3.3 Design Summary

This is a randomized control trial. Multiparous “low-risk” patients who meet inclusion criteria will be offered participation in the study. The intervention group will have a transcervical Foley catheter placed in the outpatient setting for cervical ripening after cephalic presentation is confirmed and the fetus has had a reassuring fetal heart rate tracing. The patients in the intervention group will then be sent home until a scheduled time to arrive the next morning to begin their induction of labor. The inpatient (control) group will undergo cervical ripening in the standard fashion with a transcervical Foley catheter while inpatient. Concurrent oxytocin administration with the transcervical catheter in situ will be at the discretion of the attending physician. Intervention (outpatient) group patients will be managed exactly the same as the control (inpatient) group once they are admitted. Thus, if the transcervical Foley catheter remains in situ when admitted, it can remain in place for up to 24 hours post-placement. Oxytocin may be started concurrently with the transcervical catheter in place, and amniotomy timing is at the discretion of the attending physician. The primary outcome is the time from admission to delivery between the two groups. Analysis will be on intent to treat basis.

3.4 Study Population and Eligibility Criteria

a. Inclusion criteria:

- i. Age ≥ 18
- ii. Multiparous
- iii. Singleton gestation
- iv. Gestational age between 39+0 and 42+0 weeks.
- v. Vertex presentation
- vi. Cervix ≤ 3 cm. If cervix is between 2 and 3 cm dilated, it must be $<80\%$ effaced
- vii. No prior cesarean section or uterine surgery
- viii. Resides within Jefferson County
- ix. Access to a telephone
- x. Reliable transportation

b. Exclusion criteria:

- i. Unsuitable for outpatient Foley placement management (IUGR, oligohydramnios, prior cesarean delivery, gestational hypertension, preeclampsia, uncontrolled chronic hypertension, complex maternal disease, provider discretion). Women with pregestational diabetes and those with gestational diabetes requiring medication will be excluded.
- ii. Latex allergy
- iii. Contraindication to induction of labor
- iv. Evidence of labor
- v. Fetal anomaly or demise
- vi. Inability to give consent (non-English, inability to read or write)

3.5 Gestational Age Determination

The gestational age will be already be determined prior to enrollment since all patients will be receiving care at the University of Alabama affiliated clinics. Per our Ultrasound Utilization in Obstetrics guideline, the ultrasound estimated due date (EDD) is based on the earliest ultrasound and not the stated last menstrual period (LMP) because of the inaccuracies and variability in menstrual cycles.

3.6 Study groups

There will be two intervention groups:

a. All patients:

- a. Patients will present to the 2nd floor of the CRWH for a scheduled OFFSITE study visit. This will occur every weekday except Friday.
- b. The order of events in the CRWH for all patients will be as follows:
 - i. Blood pressure evaluation
 - ii. Transabdominal ultrasound
 - iii. Vaginal examination
 - iv. Continuous fetal heart rate and tocometry monitoring for 20 minutes.
- c. If the patient's blood pressure is normal (<140 mmHg systolic and < 90 mmHg diastolic), ultrasound identifies a vertex fetus with normal amniotic fluid, cervix meets inclusion criteria (< 3 cm. If between 2-3 cm, then < 80% effaced), and the fetal heart rate tracing is category 1* without evidence of three contractions in a ten minute period, then the patient will be consented and randomized to either group 1 (standard treatment) or group 2 (intervention) and management will follow as detailed below.
 - i. Patients who do not meet cervical dilation criteria because of not needing cervical ripening (cervix >3 cm, or if 2-3 cm dilated and > 80%) will have their induction of labor canceled unless they are patients of the PrimeCare division.

b. Group 1 (Standard treatment)

- a. The patient will return the next day for her scheduled induction of labor at a pre-assigned time.
- b. Patient will be admitted to the labor and delivery floor and will be registered in the standard fashion by the nurse. The physician will be notified when the patient has had a reassuring fetal heart rate tracing and is ready for placement of the Foley catheter.
- c. The physician will perform an ultrasound to confirm vertex position and check the cervix. The patient will remain in the study even if she no longer meets cervical exam requirements (≤ 3 cm, if 2 cm, < 80% effaced) since the study design is intent to treat.

- d. Using the standard technique (dorsal lithotomy, betadine prep, sterile ring forceps, balloon inflated to 30 ml sterile saline), the transcervical Foley catheter will be placed transcervically. It is at the provider's discretion to tape this to the inner thigh or to leave it un-taped.
 - i. If the transcervical catheter is unable to be placed with a speculum and ring forceps, the provider may place with digital guidance.
- e. If the Foley catheter is unable to be placed secondary to the patient not being dilated enough to pass the catheter through the cervix, the patient will be asked to return in 24-72 hours later to again attempt placement of the Foley catheter. If the cervix is closed, there is a higher chance of a failed induction and cesarean section with proceeding with the induction of labor.
- f. As is standard in our practice, oxytocin will be initiated concurrently, and the fetal heart rate will be continuously monitored per protocol. The patient will remain NPO.
- g. A nurse or physician will assess the Foley bulb every 2-4 hours with gentle traction. It may be re-taped at this point.

c. Group 2 (Intervention)

- a. The transcervical Foley catheter will be placed in the exact manner as described in the above group 1 (standard treatment) description.
 - i. As the cervix effaces and dilates (aka ripens), it is normal to have a small amount of bleeding. Since this is a Foley catheter designed for use of draining urine from the bladder, the end of the catheter can drain a small amount of blood.
 - ii. If the Foley catheter is unable to be placed secondary to the patient not being dilated enough to pass the catheter through the cervix, the patient will be asked to return in 24-72 hours to again attempt placement of the Foley catheter. If the cervix is closed, there is a higher chance of a failed induction and cesarean section with proceeding with the induction of labor.
- b. The patient will undergo 30 more minutes of fetal monitoring and be discharged home if it is Category I. ‡
- c. The patient will then be given a sheet containing important information regarding reasons to present to the hospital prior to the scheduled induction the next morning. Importantly, the direct physician 24-hour triage line (MEU) will be clearly listed on the paper.
 - i. Reasons to return to the hospital or call the physician include:
 1. Standard labor precautions (decreased fetal movement, concern for rupture of membranes or contractions every 5 minutes for one hour)
 2. Uncontrolled pain, and/or vaginal bleeding soaking a pad or their underwear.

- ii. Patients will be instructed that a small amount of vaginal bleeding is to be expected as well as it is normal for the Foley catheter to be expelled as the cervix ripens.
 1. Thus, patients will be instructed to record the time of expulsion and report for their induction as scheduled unless any of the aforementioned conditions exist.
- iii. If a patient is admitted to the hospital prior to her scheduled induction time, she will remain in the study, and the time of admission will be recorded as the “admit” time.
- d. All women will have a time to arrive to the Women and Infants Center (WIC) for their scheduled induction.
- e. Upon admission to labor and delivery the next morning, the patients will undergo routine maternal and fetal assessment by the physician and nursing staff.
- f. The patient will be managed exactly the same as the inpatient (control) arm once admitted. Thus, if the Foley catheter is still firmly in place, it can remain for up to 24-hours post placement time. Similarly, oxytocin will be started upon admission. As in the control arm, timing of amniotomy is at the discretion of the attending physician.

* Should the initial fetal heart rate tracing not be a category 1 before the placement of the Foley catheter, the patient will be directly admitted to the labor room for induction of labor since she will be greater than 39 weeks. Since this is an intention-to-treat randomized controlled trial, the induction of labor will proceed as described in the “Inpatient Foley” arm of the study. The patient will be included in the outpatient group for the analysis.

‡ Should the fetal heart rate tracing not be a category 1 after placement of the Foley bulb or significant vaginal bleeding or rupture of membranes occurs, the patient will be directly admitted to the labor room for immediate evaluation. If stable to continue with induction of labor, the patient will be managed as described in the “Inpatient Foley” arm of the study. Outcomes will be analyzed in the outpatient group since this is an intention-to-treat analysis.

3.7 Informed Consent

Institutional Review Board (IRB) approved informed consent forms will be presented to the patient, and informed consent must be obtained prior to enrolling the patient in this randomized controlled trial. The full list of potential risks to the patient and her neonate will be listed in the informed consent. The nature and purpose of the study will also be detailed in the informed consent. The patient will be provided a copy of the signed informed consent. The informed consent will only be in English, and thus, only English-speaking individuals may participate in the study.

4. Study Procedures

4.1 Screening for Eligibility and Consent

All patients will be identified utilizing the IRB-approved UAB Obstetric Automated Recording (OBAR) system (IRB X030604010). This system will be used to identify patients entering the 37th-42nd week of pregnancy. Those initially meeting eligibility criteria by chart review will be called via the “phone script” (see phone script attached). If the patient continues to meet eligibility criteria after completing the “phone script,” she will be scheduled in the UAB Obstetrics Complications Clinic (OBCC) for her next appointment (between 37th-42nd weeks of gestation) where a co-investigator will present the study which will include the risks, benefits, procedures, and alternatives. The informed consent will be signed after all questions have been answered. The induction of labor will not be conducted prior to 39+0 weeks’ gestation.

4.2 Randomization

Randomization will occur after eligibility/exclusion criteria are confirmed and informed consent is obtained. Randomization will occur by a predetermined computer-generated block randomization scheme prepared by a study statistician. A variable block design will be utilized.

Women randomized to the standard inpatient (control) group will be scheduled for cervical ripening in the UAB Women and Infants Center. The patients randomized to the outpatient (intervention) group will undergo placement of the transcervical Foley catheter per the protocol, and a scheduled time to report to the UAB Women and Infants Center the following morning for their induction of labor will be given to the patient.

4.3 Management of patients in whom the transcervical Foley catheter cannot be placed

A patient who has a cervix completely closed where a transcervical Foley catheter cannot be traversed is at a high likelihood of having a failed induction of labor. Thus, if the transcervical Foley catheter is unable to be placed, regardless of the assigned group, the patient will be scheduled to return in 24-72 hours for another attempt. This will allow additional time for the cervix to ripen naturally and therefore increase the patient’s likelihood of having a successful induction of labor.

4.4 Management of patients who cannot tolerate placement of the transcervical Foley catheter

Some patients may not tolerate placement of the transcervical Foley catheter. If patients are between 39-40^{6/7} weeks, they will be offered the option of withdrawing from the study and returning in spontaneous labor as long as fetal heart rate tracing is Category I. We will request permission from patients withdrawing from the study to assess labor and delivery outcomes. If patients are inpatient, they will be offered epidural placement or intravenous pain medications

If the patient cannot tolerate the placement of the transcervical Foley catheter, she will be induced by another method. Since the analysis is intent to treat, the patient will remain in the assigned group.

4.5 Adherence

Patients in either group may request to have the transcervical Foley catheter removed at any time secondary to discomfort if conservative measures, such as acetaminophen, do not relieve the discomfort. If a patient in the outpatient (intervention) group presents to the MEU with complaints of pain, she will be admitted and cervical ripening/induction of labor will continue. If the transcervical Foley catheter extrudes from the vagina while the patient is at home, she will be instructed to place it in a provided bag and write down the time it extruded from her vagina.

4.6 Participant follow-up

Patients will be followed-up once during their postpartum inpatient hospitalization. This follow-up will be done post-delivery and before their discharge and will include a short series of surveys evaluating patient satisfaction regarding inpatient and outpatient cervical ripening. Investigators and principal investigators experienced in abstracting obstetrical and perinatal outcomes will review the patients' and neonates' charts after delivery to abstract the necessary variables to satisfy the primary and secondary outcomes. No further patient follow-up will occur after discharge from the UAB Women and Infants Center.

4.7 Adverse Event Reporting

A Data Safety Monitoring Board (DSMB) will be formed and consist of three individuals within the Division of Maternal-Fetal Medicine and Department of Pediatrics who have no ties to the study design, evaluation of results or potential authorship of the manuscript. The primary purpose of the DSMB will be to monitor patient safety. The members of this board are Drs. Joseph Biggio (obstetrician), Alan Tita (epidemiologist), and DeeAnne Jackson (pediatrician).

The purpose of the study is to determine whether outpatient cervical ripening shortens the admission to delivery timing compared to the standard inpatient method. The safety of a transcervical Foley catheter has already been established, and it does not increase the risk of adverse events such as chorioamnionitis, placental abruption, non-reassuring fetal heart rate tracings, cesarean section, or stillbirth.

We define an adverse event as an undesirable experience or outcome occurring in a research participant, regardless of whether participation in the research study caused the event to occur. For example, placental abruption and/or stillbirth are known risks of pregnancy, and while not known to be related to transcervical Foley catheter usage, would be considered an adverse event if it occurred during the study. All serious adverse events will be reported to the DSMB and IRB. A serious adverse event will include the following events.

- a. Death
 - a. Maternal
 - b. Fetal (stillbirth)

- b. Life-threatening
- c. Prolonged hospitalization
- d. Disability or permanent damage
- e. Intervention required in an attempt to prevent permanent impairment or damage (i.e. non-reassuring fetal heart rate tracing while the transcervical Foley catheter is in place necessitating an emergent delivery.
- f. Other serious or important medical events:
 - a. Placental abruption
 - b. Chorioamnionitis diagnosed while the transcervical Foley catheter remains in place
 - c. Any other serious event necessitating a higher level of care, such as a transfer to an intensive-care unit.
- g. Any other event not listed that the investigators believe may have been caused by the intervention.

4.8 Study Outcome Measurements and Ascertainment

4.8.1. Primary outcome

The primary outcome is the time from admission to delivery.

4.8.2. Secondary outcomes

- a. Patient satisfaction
- b. Placental abruption
- c. Early admission for intractable pain (outpatient group)
- d. Intractable pain requiring epidural anesthesia while the transcervical catheter remains in situ
- e. Non-reassuring fetal heart rate tracing upon admission in the outpatient group
- f. Non-reassuring fetal heart rate tracing while the transcervical catheter remains in place requiring immediate delivery
- g. MEU visits prior to scheduled admission time (outpatient group)
- h. SROM occurring in the outpatient group prior to scheduled admission time
- i. Chorioamnionitis or endometritis
- j. Total time of epidural use
- k. Mode of delivery
- l. Total time of oxytocin infusion
- m. Total cumulative dose of oxytocin infused
- n. Maximum rate (milliunits/min) of oxytocin infused
- o. Labor and delivery charges
- p. Composite neonatal outcomes
 - a. Apgar score < 7 at 5 minutes
 - b. Arterial cord blood gas pH < 7.1
 - c. Arterial cord blood gas base deficit > 12

- d. Admission to the neonatal intensive care unit.

4.8.3. Follow-up and Outcome Ascertainment Periods

The primary outcome will be ascertained by recording the time of admission and delivery listed in the electronic medical record. The total length of time will be computed in minutes. Follow-up will occur during the postpartum period prior to maternal discharge. Neonatal information will be collected from the neonate's electronic medical record.

5. Statistical Considerations

5.1 Sample Size for Primary Outcome

Assuming an alpha of 0.05 with an 80% power and a standard deviation of 24 hours, 64 patients will be needed in each group to detect a 12 hour difference in means between the groups.

5.2. Power for Other Outcomes

We will have limited power to detect small differences in groups for the secondary outcomes with the exception of patient satisfaction. The surveys being used require limited sample sizes to detect a difference, and 64 patients in each group will adequately satisfy these requirements.

5.3. Analysis Plan

Standard baseline characteristics between the two groups will be collected at baseline. It is assumed that randomization will evenly distribute baseline characteristic differences between the two groups, and thus, we do not anticipate adjusting for these in the primary analysis. Secondary analyses will, though, be analyzed using regression adjustments to account for any possible confounding covariates between the two groups. The primary analysis will be done in an intent-to-treat basis.

The primary analysis will compare the total admission to delivery time in minutes between the two groups. This will be analyzed using a two-sided student's t-test.

5.4. Secondary Aims:

The secondary analyses will be to compare the incidence of certain events between the two groups. A Chi-square p-value, relative risk, and 95% confidence interval will be calculated.

5.5. Interim Monitoring

We propose an interim analysis when 32 patients in each group have completed the study (50% completion) to determine whether continuation of the study is necessary. We do not propose a formal stopping rule for safety, but the DSMB will continually monitor the study for safety.

6. Future studies

If our results show outpatient transcervical Foley catheter placement is safe, well-tolerated, and reduces hospital admission time to delivery, we will submit a Patient Centered Outcomes Research Institute (PCORI) grant to conduct a multi-center trial in an attempt to alter current induction methods and ultimately improve patient satisfaction and outcomes.

7. References

- 1) World Health Organization: WHO recommendations for induction of labour, Department of reproductive health and research. Geneva, Switzerland: World Health Organization; 2011:32.
- 2) Kelly AJ, Alfirevic Z, Ghosh A. Outpatient versus inpatient induction of labour for improving birth outcomes. *Cochrane Database Syst Rev.* 2013 Nov 12; 11:CD007372.
- 3) Wing DA. Labor induction with misoprostol. *Am J Obstet Gynecol* 1999 Aug;181(2):339-45.
- 4) Alfirevic Z, Kelly AJ, Dowswell T. Intravenous oxytocin alone for cervical ripening and induction of labour. *Cochrane Database Syst Rev.* 2009 Oct 7;4():CD003246.
- 5) Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Bouvain M. Mechanical methods for induction of labor. *Cochrane Database Syst Rev.* 2012 Mar 14;3:CD001233.
- 6) Farmer KC, Schwartz WJ, Rayburn WF, Turnbull G. A cost-minimization analysis of intracervical prostaglandin E2 for cervical ripening in an outpatient versus inpatient setting. *Clin Ther.* 1996 Jul-Aug;18(4):747-56
- 7) Dowswell T, Kelly A, Livio S, Normal J, Alfirevic Z. Different methods for the induction of labour in outpatient settings. *Cochrane Database Systematic Rev* 2010 Aug 4;(8):CD007001
- 8) O'Brien JM, Mercer BM, Cleary NT, Sibai BM. Efficacy of outpatient induction with low-dose intravaginal prostaglandin E2: a randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol.* 1995 Dec; 173(6):1855-9.
- 9) McKenna DS, Costa SW, Samuels P. Prostaglandin E2 cervical ripening without subsequent induction of labor. *Obstet Gynecol.* 1999 Jul; 94(1):11-4.
- 10) Sciscione AC, Muench M, Pollock M, Jenkins TM, Tildon-Burton J, Colmorgen GH. Transcervical Foley catheter for preinduction cervical ripening in an outpatient versus inpatient setting. *Obstet Gynecol.* 2001 Nov; 98(5 Pt 1):751-6.
- 11) American College of Obstetricians and Gynecologists. Induction of labor. *Practice Bulletin No 107.* *Obstet Gynecol* 2009. Aug; 114(2 Pt 1):386-97.
- 12) Edwards RK, Szychowski JM, Berger JL, Petersen M, Ingersoll M, Bodea-Braescu AV, Lin MG. Foley catheter compared with the controlled-release dinoprostone insert: a randomized controlled trial. *Obstet Gynecol* 2014 June; 123(6):1280-7.
- 13) Pettker CM, Pocock SB, Smok DP, Lee SM, Devine PC. Transcervical Foley Catheter with and without oxytocin for cervical ripening: a randomized controlled trial. *Obstet Gynecol.* 2008 June; 111(6):1320-6.
- 14) Sciscione AC, Bedder CL, Hoffman MD, Ruhstaller K, Shlossman PA. The timing of adverse events with Foley catheter preinduction cervical ripening: implications for outpatient use. *Am J Perinatol* 2014 Oct;31(9):781-6.
- 15) Henry A, Madan A, Reid R, Tracy SK, Austin K, Welsh A, Challis D. Outpatient Foley catheter versus inpatient prostaglandin E2 gel for induction of labour: a randomised trial. *BMC Pregnancy Childbirth* 2013 Jan 29;13:25.
- 16) McMaster K, Sanchez-Ramos, Kaunitz AM. Evaluation of a transcervical foley catheter as a source of infection: a systematic review and meta-analysis. *Obstet Gynecol.* 2015 Sep; 126(3):539-51.