Mifepristone as an Adjunct to Transcervical Balloon for Labor Induction (MiLI): A Randomized Clinical Trial

National Clinical Trial (NCT) Identified Number: 05097326

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Mifepristone as an Adjunct to Transcervical Balloon for Labor Induction: A Randomized Clinical Trial (MiLI)

Objective: Our goal is to generate preliminary data on perinatal outcomes, establish recruitment feasibility, and medication tolerability among patients who receive mifepristone for labor induction for live birth. Our aims are to 1) generate preliminary data on the impact of mifepristone use on obstetric and neonatal outcomes and 2) examine recruitment feasibility and willingness of participants to be randomized to guide recruitment periods for future studies

Organization: Stanford University School of Medicine, Department of Obstetrics and Gynecology

Clinical Center: Stanford/LPCH OB clinic and Labor & Delivery

Design Type: Parallel group, two-arm, non-blinded, randomized control trial

Inclusion Criteria:

1. Pregnant patients between ages 18 to 45 years
2. Singleton, live gestation
3. Nulliparous
4. Gestational age between 37 weeks 0 days – 42 weeks 0 days
5. Fetus in cephalic presentation
6. Patients admitted for labor induction
7. Patients who are not in labor with intact membranes
8 Patients with no contraindication for vaginal delivery (placenta previa, vasa previa, active genital herpes)
9. Patients with no contraindications for mifepristone (chronic adrenal failure, concurrent long-term corticosteroid therapy, history of allergy to mifepristone, or other prostaglandins, hemorrhagic disorders or concurrent anticoagulant therapy, inherited porphyria, or an intrauterine device (IUD) in place)
10. Patients with a Bishop score <6 at time of randomization
11. Transcervical balloon in place <3 hours prior to the time of randomization without prior cervical preparation

*For patients who meet the above inclusion criteria 1-10 and who those who decline randomization will be offered enrollment for chart review only.

Exclusion Criteria:

1. Significant cardiac, renal, or hepatic maternal comorbidities, severe gestational hypertension or preeclampsia with severe features
2. Pregnancies complicated by major fetal anomalies
3. Patients with a uterine scar
4. Pregnancies complicated by fetal growth restriction (Estimated fetal weight <10%)
5. Pregnancies complicated by oligohydramnios
6. Fetuses with an estimated fetal weight >4500 gm by recent ultrasound or Leopold's exam on admission
7. Patients with class 3 obesity (BMI >40)

8. Fetuses with a persistent category 2 or 3 fetal heart tracing at labor induction admission
9. Vaginal bleeding at the time of randomization
10. Any indication for scheduled cesarean delivery
11. Hypersensitivity to oxytocin
12. Uterine contractions ≥ 5 in10 minutes that is sustained for at least 30 minutes
13. Hypersensitivity to prostaglandins

Interventions:

1. Active group: Mifepristone 200 mg po + Transcervical (Cook) Balloon
2. Standard group: Misoprostol 50 mcg po+ Transcervical (Cook) Balloon

Medications:
Mifepristone 200mg po
Misoprostol 50 mcg po

Analysis: Intent to Treat

Outcome Measures:
Primary outcomes:

- Generation of preliminary data comparing obstetric and neonatal outcomes among patients randomized to misoprostol 50 mcg versus mifepristone 200 mg

  Obstetric outcomes:
  - Number of uterine contractions – with and without fetal heart rate decelerations during the time the foley is in place
  - Rate of uterine tachysystole (≥ 5 contractions in 10 minutes that is sustained for at least 30 minutes) or hypertonus (a single contraction lasting more than 2 minutes) during labor
  - Time to delivery
  - Time to complete cervical dilation
  - Total time on the Labor and Delivery unit
  - Rate of cesarean delivery (CD)
  - Rate of failed induction of labor per ACOG guidelines
  - Composite of serious maternal morbidity based on CDC severe maternal morbidity and mortality (including acute myocardial infarction, aneurysm, acute renal failure, adult respiratory distress syndrome, amniotic fluid embolism, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, eclampsia, heart failure/arrest during surgery or procedure, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, blood products transfusion, hysterectomy, temporary tracheostomy, ventilation)

- **Neonatal outcomes:**
    - Comparison of neonatal cord gases (arterial pH) and neonatal APGAR scores at 1 and 5 minutes
    - Composite of serious neonatal morbidity up to 7 days of life (including perinatal death, need for respiratory support within 72 hours after birth, Apgar score of 3 or less at 5 minutes, arterial pH, hypoxic-ischemic encephalopathy, seizure, infection (confirmed sepsis or pneumonia), meconium aspiration syndrome, intracranial or subgaleal hemorrhage, hypotension requiring vasopressor support, admission to the neonatal intensive care unit)

Secondary outcomes

- Examine recruitment feasibility and willingness of participants to be randomized to guide recruitment periods for future studies.
- Plan to assess medication tolerability through participant experience surveys at two time points (after cervical preparation during the labor process and on postpartum day one)

Sample size: 30

1. INTRODUCTION

This manual gives detailed instructions on procedures for the Mifepristone for Labor Induction (MiLI) Trial. It is meant to serve as a reference guide for study staff, including investigators, coordinators, study nurses, and data managers.

1.1 Organizational Structure

This study is governed by Stanford Maternal Fetal Medicine Division, Labor and Delivery, and the Clinical Translational and Research Unit site.

1.1.1 Steering Committee (SC)

A Maternal-Fetal Medicine Clinical Review Unit (CRU) and the study team that brings together the multi-disciplinary will oversee implementation including: finalizing the clinical protocol, training and certification, monitoring recruitment, data coordination and quality control, and IRB-related issues. The SC will also make final decisions about data analysis and interpretation, secondary analyses, presentation at scientific meetings and publications.

1.1.2 Responsibilities

The responsibilities of these individuals are described briefly here:

PI and co-PIs are responsible for ensuring the proper conduct of the study clinic site including recruitment as specified in the protocol and accurate collection of the data.
Other specific duties include:

a. Obtaining and maintaining IRB approval and training for study personnel
b. Obtaining sufficient study areas for study personnel to interview patients and perform study procedures, including storage of study medication and other study supplies.
c. Participate in study- related meetings or conference calls
d. Familiarity and training for REDCap based data entry system by appropriate staff.
e. Screen potential participants for eligibility and consent them. It is important to ensure the patient's primary obstetric provider agrees to follow the study treatment protocol during the intrapartum course.
f. Randomize per protocol to intervention arms – both arms to receive medication
g. Follow participants during the intrapartum period, delivery and 24 hours postpartum: with a patient satisfaction survey to evaluate medication side effects and overall satisfaction associated with treatment
h. Trained research staff will conduct research data abstraction from patient and neonatal medical records, and other direct participant contact as required by the protocol.
i. Investigators will participate in blinded review of outcomes in order to confirm the primary and other key outcomes.
j. The LPCH pharmacy will be responsible for randomizing the medication
k. All newborn outcomes will also be ascertained through birth hospitalization through medical records chart review.

l. Data collection forms for maternal outcomes, newborn outcomes, NICU outcomes, and postpartum patient satisfaction outcomes will be completed by study personnel. These forms will be used to enter the clinical data into the study data base.

The Study Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including recruitment and data collection processes. This responsibility includes the following:

a. Establishing a method of training and monitoring to ensure primary obstetric providers are following the study treatment protocol during the intrapartum period.
b. Establishing a method to ensure that all potential participants receive medications and appropriate randomization
c. Establishing a method that for screening participants who are potentially eligible for the study e.g. review of scheduled term inductions at LPCH
d. Assures that study drug is available at all times by checking the available drug supply at least weekly.
e. Meeting with Stanford Investigational Drug Pharmacist pharmacy if necessary, to understand center specific drug request procedures.
f. Arranging for the ordering and storage of study supplies.
g. Collecting maternal and neonatal information necessary to complete all study forms.
h. Will abstract information related to primary and other key outcomes, and assure that the PI and IRB (if required by institution) is notified of any primary outcome events and adverse events.
i. Training additional staff as needed in data collection, forms completion and data entry.
j. Coordinating data entry, including controlling access to the REDCap and study unit as applicable, and assuring that required back-up security and confidentiality procedures are maintained.
k. Organizing and maintaining records, including the protocol, data forms, reports and correspondence

1.2 Procedures for Participant Confidentiality

The REDCAP database will contain PHI linked to the patient's clinical data. The MFM Research team members are the only people who will be able to access this database. A study/screening number will be used to identify each participant. Site will maintain a log of participant names and medical record numbers.

1.3 Training and Site Initiation

A training session for study coordinators will be held before recruitment starts. The purpose of the training workshop is to review the study design, objectives, procedures, data collection forms and a demonstration of the REDCap data base. The coordinators, in turn, are responsible for training any additional staff assigned to this study. Clinical site initiation to enroll and randomize participants is dependent upon completion of a series of preliminary tasks. These include completion of appropriate regulatory approvals (IRBs).

Site staff training, certification, and receipt of all study supplies including medications will need to be completed as well as the development of a site recruitment plan. Fulfillment of the following are requirements before start of study:

1. Review of the final version of the study protocol, data forms and manual, and study medications.
2. IRB approval and consent forms on file at Stanford. Due to COVID, also consider e-consent process.
3. Completion of training and data entry of forms.

1.4 IRB approval

Approval by an IRB before any participant examination or data collection can begin. Once a study has been approved, any additional information about the study that relates to participant safety (i.e., protocol changes, significant adverse events, changes in the consent form) also needs to be submitted to the IRB.

1.5 Interim IRB Review/Approval

After initial approval, an IRB must be notified any time about:

- Recruitment Brochures and Advertisements
- Form Letters or Study information sent to participants
- Protocol Amendments
- Protocol Deviations
- Serious Adverse Events (SAEs)
- Unanticipated problems
- Consent Form Revisions

1.5.1 Protocol Amendments

All protocol changes must be sent to an IRB as protocol amendments.

1.5.2 Regulatory Binder

The Study Regulatory Binder is the administrative binder that serves as the regulatory record of each clinic's participation in the MiLI study. It should be kept current and available for review by the IRB or in the event of an audit. The binder should include current copies of:

- Protocol and revisions
- All protocol amendments
- IRB submissions and approvals, IRB renewals and any submitted protocol deviations and log, IRB correspondence (adverse events reports)
- Copies of IRB approved informed consent document(s)
- Research participant advertisements, (e.g. patient brochures, pamphlets) patient education materials, newsletters, etc.
- Current correspondences relating to human subjects research (may keep separate correspondence file)

- Enrolled patient log with pertinent identifier information (randomization number if needed)
- List of study drug formulary and package inserts

Other items that may also be included are: recruitment plans, a set of study forms, CVs or biosketches for study staff, staff responsibility logs, essential elements of informed consent checklist, protocol deviation logs or other requirements from Stanford institution

2. STUDY INFORMATION

2.1 Study Rationale

The prevalence of labor induction in the US continues to increase, and is considered safe, and sometimes critical to the wellbeing of a pregnancy.[1] At Lucile Packard Children's Hospital (LPCH), specifically, approximately 37% of all spontaneous vaginal deliveries follow labor induction. Several methods of cervical preparation have been implemented to expedite a successful labor induction and vaginal delivery.[1-5] However, due to a rising incidence of induction of labor (IOL), particularly induction with an unfavorable cervix (Bishop score <6) requiring cervical preparation, the average time a patient occupies a room on Labor and Delivery (L&D) has increased, negatively impacting bed availability and healthcare costs.[6] Mifepristone is an FDA approved medication used in a regimen with misoprostol for first trimester medication abortion, and is used off label as a cervical preparation agent for second and third trimester pregnancy losses and second trimester abortion.[7-10] Previous international studies demonstrated that when compared to placebo, mifepristone is safe and efficacious when used as a cervical preparation agent in term labor induction in both inpatient and outpatient settings.[11-17] No studies in the US have assessed mifepristone as a term labor induction agent.

We propose a pilot study to generate preliminary data, establish recruitment feasibility, and medication tolerability to better inform future studies on mifepristone as an adjunct to the standard of care for term IOL in both inpatient and outpatient settings. This is a randomized control trial (RCT) of nulliparous patients ages 18 to 45 years who are at 37– 42 weeks gestational age induced with a transcervical (Cook) balloon, comparing perinatal outcomes among patients randomized to receive misoprostol versus mifepristone in the inpatient setting.

2.2 Background

Approximately 29% of US births follow induction of labor (IOL), more than doubling since 1990.[18] In 2018, a national multicenter randomized trial, Labor Induction versus Expectant Management in Low-Risk Nulliparous Women (ARRIVE), supported that elective induction after 39 weeks decreases cesarean delivery (CD) and morbidity.[19] Since the ARRIVE trial, the incidence of IOL has increased nationally and institutionally.[6] At LPCH, approximately 37% of vaginal deliveries currently follow IOL, with an average of 20 hours from admission time to delivery, compared to an average of 12-18 hours among those in spontaneous labor.[4,5] As the number of patients electing IOL increases, L&D beds are occupied for a longer duration with a subsequent increase in hospital costs and a decrease in bed availability.[6] IOL frequently begins with cervical preparation when the cervix is not dilated.[1] At LPCH cervical preparation typically begins with prostaglandins (misoprostol and dinoprostone), 12-hours of transcervical (Cook)

balloon placement, or misoprostol and Cook balloon used concurrently. Several studies have compared the cervical preparation methods that achieve the safest, most efficacious, and fastest method that led to spontaneous vaginal delivery.[1-5] With increasing rates of IOL, there is a need for new methods to decrease the hospital induction times and to safely and expeditiously facilitate vaginal delivery.

Misoprostol, a PGE2 prostaglandin, is among one of the most highly utilized cervical preparation agents for term labor induction.[1] Misoprostol is FDA approved for the use of peptic ulcer disease but is widely used off label for term IOL.[1] However, oral misoprostol may cause uterine hyperstimulation due to its effects on uterine contractility or may fail to produce sufficient cervical ripening for labor induction to proceed.[18] Misoprostol is also FDA approved for its use in conjunction with mifepristone, a progesterone antagonist, as a regimen for first trimester medical abortion.[7] Mifepristone, in conjunction with misoprostol, is used off label for second trimester IOL, and induction for second and third trimester pregnancy loss due to its efficacy as a cervical preparation agent.[7,8] Based on the clinical trials in the second trimester, mifepristone reduces the time to delivery 40-50% while decreasing overall maternal morbidity.[9,10] Although preexisting data exists on the safety and efficacy of mifepristone for cervical preparation used in both inpatient and outpatient settings outside the US,[11-19] there are no studies in the US that assess the safety or the efficacy of mifepristone on IOL among term pregnancies.

Specifically, several studies have focused on assessment of maternal and neonatal outcomes. Previous studies have demonstrated that when compared to expectant management, those treated with mifepristone are more likely to be in labor or have a favorable cervix (Bishop score >6) at 24 and 48 hours, are less likely to need augmentation with oxytocin, and less likely to undergo CD.[11-17] In a large Cochrane Review, neonates were more likely to have abnormal fetal heart tracing, however, abnormal tracings did not correlate with difference in objective neonatal outcomes including NICU admission, cord blood gas, and APGAR scores.[12] Specifically in a randomized control trial comparing placebo to different doses of mifepristone, neonatal outcomes did not differ on the Apgar score at 1 and 5 minutes, the proportion of children requiring resuscitation, the transfer rate to neonatal intensive care units, cord artery blood pH, cord artery blood gas values, and neonatal hypoglycemia. Likewise, there was no significant difference in neonatal systolic or diastolic blood pressure on days 1 and 2.[13] Studies have shown that mifepristone crosses the placenta and the fetus is exposed to maternal mifepristone intake and is maternal dose dependent with fetal levels at about one third of maternal levels. Maximum fetal plasma concentrations of mifepristone occur 4 hours after treatment with a subsequent decrease at 24 and 48 hours.[11,13] Despite low neonatal plasmas concentration, there were no signs of peripheral cortisol deprivation in the neonates or differences in the above neonatal outcomes.[13]

Based on previous studies and pharmacokinetics, we hypothesize that mifepristone prepares the cervix for IOL without causing increased uterine contractions or fetal heart rate abnormalities, compared to misoprostol.[11-19] This pilot study would provide preliminary data for future studies of mifepristone as an outpatient induction agent to reduce time on L&D and improve perinatal outcomes as the incidence of IOL increases.

2.3 Risk/Benefit Assessment

<u>Mifepristone 200mg, oral use</u>

2.3.1 Known Potential Benefits

Mifepristone is a progesterone receptor antagonist that has been used off-label for second-trimester induction of labor. It has been shown to reduce the time to delivery 40-50% while decreasing overall morbidity in second-trimester induction.[9,10] Induction of labor is used as a therapeutic option when the benefits of delivery outweigh the risks of continuing the pregnancy.[1] Prolonged pregnancy is associated with significantly increased risks of perinatal and maternal complications.[1] To successfully, safely and expeditiously induce labor and vaginal delivery without increasing the CD rate, ACOG endorses cervical preparation methods to facilitate cervical softening, thinning, and dilation. Several methods of cervical preparation have been implemented to expedite a successful labor induction and vaginal delivery, and ultimately decrease hospital stays and healthcare costs.[1]

2.3.2 Assessment of potential risks

Mifepristone is an FDA-approved drug for medical termination of intrauterine pregnancy through 70 days gestation. It is used off-label labor for cervical preparation for second trimester induction of labor.

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness.

It is contraindicated to use this medication among patients who have a confirmed/suspected ectopic pregnancy (not applicable to term pregnancies), chronic adrenal failure, concurrent long-term corticosteroid therapy, history of allergy to mifepristone, misoprostol, or other prostaglandins, hemorrhagic disorders or concurrent anticoagulant therapy, inherited porphyria, or an intrauterine device (IUD) in place.

When taken with misoprostol, risk of fetal malformations in ongoing pregnancy (if not terminated) is unknown. However, mifepristone will be administered to term pregnant participants and will be far outside of the window of organogenesis (fetal development), thus risk for teratogenicity is nullified by the fact that the study will take place in term pregnancies long after fetal development is completed.

As with other pregnancies, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been established.

Mifepristone is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk.

Animal studies:

Mifepristone has been shown to induce labor in rats,[20] through opposition to progesterone-induced suppression of oxytocin receptors, and enhanced synthesis of prostaglandins.

Mifepristone has also been shown to induce preterm birth in mice, associated with a rise in prostaglandins and cytokines.[21] A randomized-controlled trial in beef heifers found a mean time to delivery of 43 hours after mifepristone administration, compared to 182 hours in placebo treated controls.[22] In a primate model (the macaque), mifepristone administration induced prostaglandin F2 alpha production by decidua, but not prostaglandin E2 production by amnion.[23]

The FDA Mifeprex (mifepristone) information describes teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), stating that because of the antiprogesterone activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action. As stated above, mifepristone will be administered to term pregnant participants and will be far outside of the window of organogenesis (fetal development), thus risk for teratogenicity is nullified by the fact that the study will take place in term pregnancies long after fetal development is completed.

Safety measures for this study include the following:

- Obtain VITALS (blood pressure, mean arterial blood pressure, heart rate, respiratory rate) throughout labor induction, every 15 minutes for the first hour of the induction process and then hourly during the first 4 hours of the induction process. (see table below for reference range in pregnancy). In addition, oral temperature will be taken per standard protocol
- Pregnant patients in this study may receive up to a maximum dose of 200 mg mifepristone only; this is the max dose per course as outlined by the package label instructions. Each dose will be given as 200 mg orally, once at the induction initiation
- Monitor patients for adverse symptoms of mifepristone
- All patients will undergo continuous electronic fetal heart rate monitoring and tocometry until the time of delivery

Cardiac, Respiratory and Hematologic Physiologic Changes in Pregnancy

	Direction of Change	Percentage of Change or Normal Range in Pregnancy
Blood volume	↑	30%-40% increase
Heart rate	↑	Increases by 10-20 bpm
Cardiac output	↑	30%-60% increase
Systemic vascular resistance	↓	25%-30% decrease
Blood pressure	↓	10-15 mm Hg decrease in first two trimesters
Colloid oncotic pressure	↓	10%-15% decrease
Total lung capacity	↓	4%-5% decrease
Functional residual capacity	↓	20% decrease
Diffusion capacity	↔	No change
Tidal volume	↑	Increased
Respiratory rate	↔	No change
Minute ventilation	↑	50% increase
PaO_2	↑	Average 100-105
$PcaCo_2$	↓	Average 28-32
pH	↑	Mild respiratory alkalosis
A-a gradient	↑	Increase in late gestation to approximately 20
Protein S	↓	
Activated protein C resistance, fibrinogen, factor V, VIII, IX, X	↑	
Plasminogen activator inhibitor type 1 and 2	↑	
Activity of tissue plasminogen	↓	

Modified from Miller MA, Bourjeily G. Management of the critically ill pregnant patient. Pulmonary and Critical Care Update (PCCU). April 2009, 23 (Lesson 8); with permission.

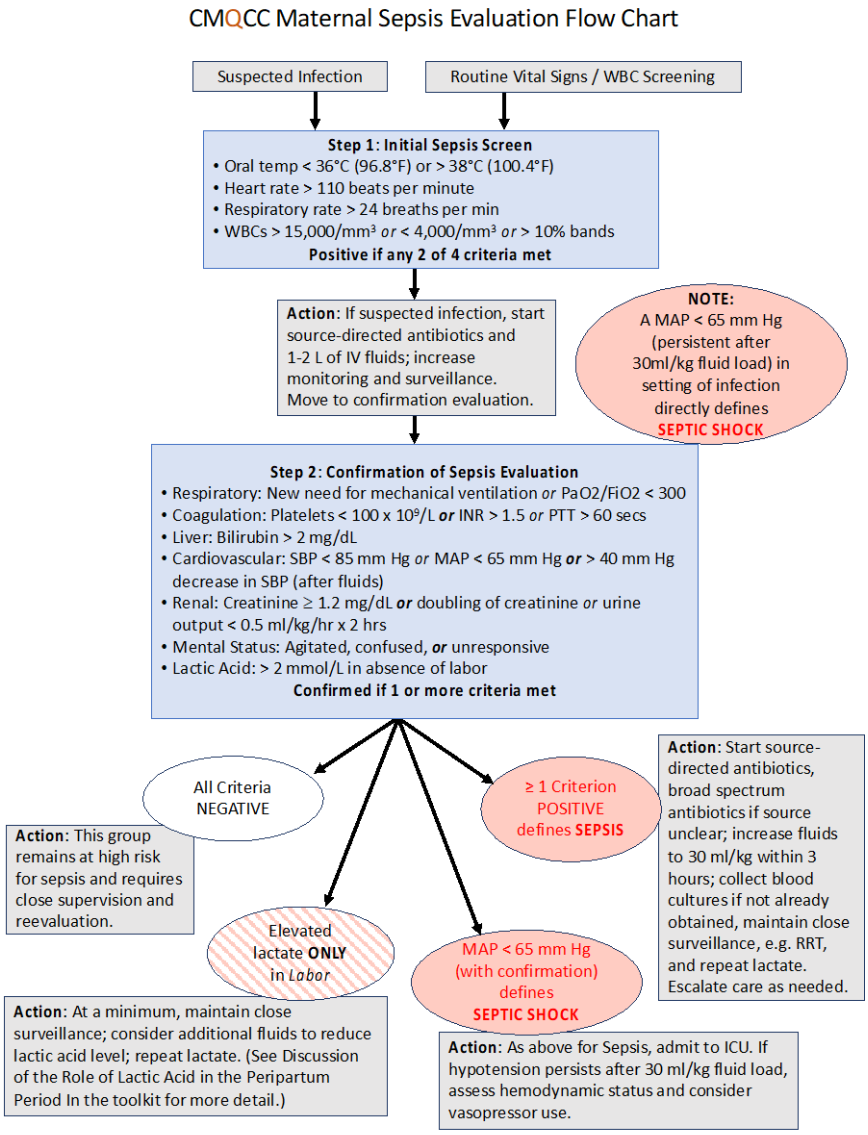
Source: Williams Obstetrics and Gynecology, 25th Edition

Vital signs which suggest hemodynamic instability or suspicion for sepsis

- Oral Temperature <36 °C (96.8 °F) or >38°C (100.4°F)
- Heart rate > 110 beats per minute or <50 beats per minute
- MAP <65 mm Hg
- Respiratory rate > 24 breaths per minute or less than < 10 breaths per minute

If the patient experiences 2 vital signs that are outside of normal parameters, the standard of care work up will be initiated.

If the patient experiences a fever in labor, per standard of care, antibiotics are started, and an infectious workup is initiated. If the patient has a fever with abnormal vital signs per CMQCC guidelines (see below), assessment for infection is initiated per standard of care.



2.3.3 Risk Benefit/Ratio

As the incidence of labor induction increases, the average time a patient is occupying a room on Labor & Delivery increases, impacting bed availability and cost. There is an urgent need for new methods and models to decrease the labor induction times. Studies have determined maternal and neonatal safety when using mifepristone as a cervical preparation agent. Assessment of outcomes in this study will determine how treatment can improve maternal and neonatal outcomes.

Any serious adverse event or unanticipated problem will be reported to the Stanford IRB. The study team encompasses the responsibility to monitor all aspects of the study and monitor data and oversee participant safety.

We satisfy all requirements for this to be IND exempt.

Misoprostol 50 micrograms po

2.3.4 Assessment of potential benefits

Misoprostol can induce or augment uterine contractions and is used as part of the standard of care for labor induction. Vaginal and oral administration of misoprostol, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. Misoprostol is well studied for obstetric use and is used as a standard of care for labor induction internationally.[1-5]

According to ACOG, misoprostol, a synthetic PGE_1 analogue, can be administered intravaginally, orally, or sublingually and is used for both cervical ripening and induction of labor. It currently is available in a 100-mcg (unscored) or a 200- mcg tablet, and can be broken to provide 25-mcg or 50- mcg doses. There is extensive clinical experience with this agent and a large body of published reports supporting its safety and efficacy when used appropriately.[1]

2.3.5 Assessment of potential risks

No studies indicate that intrapartum exposure to misoprostol (or other prostaglandin cervical ripening agents) has any long-term adverse health consequences to the fetus in the absence of fetal distress, nor is there a plausible biologic basis for such a concern. Although misoprostol currently is approved by the U.S. Food and Drug Administration (FDA) for the prevention of peptic ulcers, the FDA in 2002 approved a new label on the use of misoprostol during pregnancy for cervical ripening and for the induction of labor. This labeling does not contain claims regarding the efficacy or safety of misoprostol, nor does it stipulate doses or dose intervals.[1]

According to the FDA, the major adverse effect of the obstetrical use of misoprostol is hyperstimulation of the uterus which may progress to uterine tetany. There is an increase in uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy) among patients with a known history of a previous uterine surgery.

There may be an increased risk of uterine tachysystole, meconium passage, meconium staining of amniotic fluid, and Cesarean delivery due to uterine hyperstimulation with the use of higher doses of misoprostol. In this study, the standard dose of 50 mcg and 100 mcg as the second dose if indicated will be used. It is established that oral misoprostol reduces risk for cesarean section rate and has a low incidence of uterine hyperstimulation.[5] The risk of uterine rupture increases with advancing gestational ages and with prior uterine surgery, including cesarean birth and these patients are excluded from this study.

The following have been reported as adverse events in subjects receiving misoprostol: Gastrointestinal: In subjects receiving misoprostol 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14-40% and in all studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo. However, patients will not receive doses greater than 100 micrograms, minimizing the risk for gastrointestinal side effects.

Due to potential risks of misoprostol, the same safety guidelines as stated in 2.3.2 will remain in this study group.

2.3.6 Risk Benefit/Ratio

As stated above, the incidence of labor induction increases, the average time a patient is occupying a room on Labor & Delivery increases, impacting bed availability and cost. There is an urgent need for new methods and models to decrease the labor induction times. Studies have determined maternal and neonatal safety when using misoprostol as a cervical preparation agent. Misoprostol is among one of the most common medications used for labor induction at LPCH and internationally. The benefits of improving labor induction success and decreasing rates of cesarean birth outweigh the potential of uterine tachysystole with continuous external fetal monitoring. Our study population excludes patients with uterine scars, including cesarean birth, and this mitigates the risk of uterine rupture.

Any serious adverse event or unanticipated problem will be reported to the Stanford IRB. The study team encompasses the responsibility to monitor all aspects of the study and monitor data and oversee participant safety.

3. OBJECTIVES

3.1 Primary Outcome

Generation of preliminary data comparing obstetric and neonatal outcomes among patients randomized to misoprostol 50 mcg versus mifepristone 200 mg

Obstetric outcomes:

- Number of uterine contractions – with and without fetal heart rate decelerations during the time the foley is in place
- Rate of uterine tachysystole (≥ 5 contractions in 10 minutes that is sustained for at least 30 minutes) or hypertonus (a single contraction lasting more than 2 minutes) during labor
- Time to delivery

- Time to complete cervical dilation
- Total time on the Labor and Delivery unit
- Rate of cesarean delivery (CD)
- Rate of failed induction of labor per ACOG guidelines
- Composite of serious maternal morbidity based on CDC severe maternal morbidity and mortality (including acute myocardial infarction, aneurysm, acute renal failure, adult respiratory distress syndrome, amniotic fluid embolism, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, eclampsia, heart failure/arrest during surgery or procedure, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, blood products transfusion, hysterectomy, temporary tracheostomy, ventilation)

- **Neonatal outcomes:**
  - Comparison of neonatal cord gases (arterial pH) and neonatal APGAR scores at 1 and 5 minutes
  - Composite of serious neonatal morbidity up to 7 days of life (including perinatal death, need for respiratory support within 72 hours after birth, Apgar score of 3 or less at 5 minutes, arterial pH, hypoxic-ischemic encephalopathy, seizure, infection (confirmed sepsis or pneumonia), meconium aspiration syndrome, intracranial or subgaleal hemorrhage, hypotension requiring vasopressor support, admission to the neonatal intensive care unit)

Secondary outcomes

- Examine recruitment feasibility and willingness of participants to be randomized to guide recruitment periods for future studies.
  Plan to assess medication tolerability through participant experience surveys at two time points (after cervical preparation during the labor process and on postpartum day one)

4. STUDY DESIGN

4.1 Overall Design

We will perform a parallel group, two-arm, non-blinded, randomized control trial comparing mifepristone to misoprostol in pregnant patients at term delivering their first neonate.

4.2 Justification for Dose

The FDA has approved mifepristone in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Historically mifepristone 600 mg followed by a prostaglandin were used, however, preferred dosing of mifepristone 200 mg is the current FDA approved dose due to its equal efficacy and safety as compared to 600 mg (Poppema, 1999 and Raymond, 2013).

Mifepristone 200 mg in adjunct to misoprostol is used off-label for management of pregnancy loss before 20 weeks and second trimester abortion, including induction of labor and dilation and

evacuation. Mifepristone used with misoprostol reduces time to delivery and leads to fewer adverse effects when compared to misoprostol alone. [7,8]

Mifepristone 200 mg dosing received FDA approval in 2016 and is used as the standard dose in conjunction with misoprostol. Mifepristone 200 mg dose was used as the standard dose among studies of inducing labor at term.[11,12] However, one study compared mifepristone 50 mg, 100 mg, 200 mg, 400 mg, and 600 mg and found no difference in maternal or neonatal outcomes among dosing.[13]

The recommended FDA approved adult oral dose of misoprostol for reducing the risk for NSAID-induced gastritis is 200 mcg four times daily, however, the dose varies for labor induction.

According to ACOG, one quarter of an unscored 100-mcg tablet (ie, approximately 25 mcg) of misoprostol should be considered as the initial dose for cervical ripening and labor induction. However, this is based on a vaginal route. The standard of care at LPCH is 50 mcg orally, based on previous literature that suggests stepwise oral misoprostol (50 mg followed by 100 mg) appears to be as effective as vaginal misoprostol (25 mg) for cervical ripening with a low incidence of hyperstimulation, no increase in side effects, a high rate of patient satisfaction, and is associated with a lower cesarean section rate.[5]

The frequency of administration should not be more than every 3–6 hours. In hour study, we have chosen repeat dosing at 4 hour intervals based on routine management at LPCH. In addition, oxytocin should not be administered less than 4 hours after the last misoprostol dose. Misoprostol in higher doses (50 mcg every 6 hours) may be appropriate in some situations, although higher doses are associated with an increased risk of complications, including uterine tachysystole with FHR decelerations.

4.3 End of Study Definition

The study will be complete once enrollment has been completed. The goal is 30 patients with 15 in each arm.

4.4 Sample Size

We plan to recruit 15 patients per group (30 total) based on the “rule of 12” that is recommended for pilot studies that aim to estimate average values and variability to plan larger studies,[24] and to accommodate an estimated 25% intrapartum cesarean rate. Based on 80% power, a two-sided alpha of 0.05, and prior data, we estimate that this sample size would enable us to detect a difference of at least 25 uterine contractions between the two study groups (140-150 on average during labor for patients induced with misoprostol and Cook balloon). The analysis plan and sample size calculation were developed in consultation with Maternal-Fetal Medicine Senior Biostatistician, Stephanie Leonard, PhD (Co-I).

4.5 Timeline

Year 1	July-22	Aug-22	Sept-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	April-23	May-23	June-23
Recruitment	x	x	x	x	x	x	x	x	x			
Data collection	x	x	x	x	x	x	x	x	x			
Data analysis									x	x		
Manuscript											x	x

5. STUDY POPULATION

(see Study Design Figure below)

5.1. Screening and Inclusion/Exclusion Criteria

General Screening guidelines

I. We will recruit patients receiving prenatal care at San Mateo County Health Clinics, LPCH, and private practices who deliver at LPCH at LPCH OB clinic and Labor and Delivery
   a. Patients will be eligible for the study if they are scheduled for or admitted for induction of labor at LPCH
   b. All other eligibility criteria must me bet to be included in the study
   c. Among those screened and meeting eligibility at LPCH OB clinic, will require rescreening once admitted for labor induction to confirm the participant meets all study eligibility criteria
   d. Gestational age must be validated prior to enrollment using the latest ACOG criteria that compares LMP derived gestational age with ultrasound parameters. The ACOG criteria for gestational age determination based on ultrasound is as follows:

Table 1. Guidelines for Redating Based on Ultrasonography ⇦

Gestational Age Range*	Method of Measurement	Discrepancy Between Ultrasound Dating and LMP Dating That Supports Redating
≤13 6/7 wk	CRL	
• ≤ 8 6/7 wk		More than 5 d
• 9 0/7 wk to 13 6/7 wk		More than 7 d
14 0/7 wk to 15 6/7 wk	BPD, HC, AC, FL	More than 7 d
16 0/7 wk to 21 6/7 wk	BPD, HC, AC, FL	More than 10 d
22 0/7 wk to 27 6/7 wk	BPD, HC, AC, FL	More than 14 d
28 0/7 wk and beyond†	BPD, HC, AC, FL	More than 21 d

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CRL, crown–rump length; FL, femur length; HC, head circumference; LMP, last menstrual period.

*Based on LMP.

†Because of the risk of redating a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone are especially problematic and need to be guided by careful consideration of the entire clinical picture and close surveillance.

Source: ACOG Committee Opinion No 700: Methods for Estimating the Due Date

II. Patients admitted for scheduled labor induction or admitted from Labor and Delivery triage will be screened by chart review
   a. Patients will need to be scheduled or admitted for a term labor induction at LPCH
   b. Review of electronic medical record will include pregnancy dating information using the initial ultrasound, and medical history information taken at the prenatal visits or time of admission. Baseline information, including contact information, vitals, demographics, pregnancy history information, and maternal and neonatal medical information will be reviewed to assess eligibility for study participation.
   c. Patients will undergo a fetal non-stress test at time of admission as part of standard of care. The OB provider or PI's will review the non-stress test. Category 1 or not a persistently Category 2 or 3 fetal heart tracing, according to ACOG criteria is required for eligibility.
   d. Patients will undergo a cervical exam by the OB provider at time of admission as part of standard of care, to assess for eligibility.

III. Patients screened at LPCH OB clinic will be screened by chart review
   a. Patients will need to be scheduled for a term labor induction at LPCH
   b. Review of electronic medical record will include pregnancy dating information using the initial ultrasound, and medical history information taken at the prenatal visits or time of admission. Baseline information, including contact information, vitals, demographics, pregnancy history information, and maternal and neonatal medical information will be reviewed to assess eligibility for study participation.

Throughout screening period we will record number of patients screened, eligible, and approached in the REDCap database.

5.2 Inclusion Criteria

Nulliparous patients aged 18 to 45 years, with singleton live pregnancies of gestational age 37 weeks 0 days – 42 weeks 0 days, with a planned labor induction, not in labor, with intact membranes with no contraindication for vaginal delivery, misoprostol or mifepristone, and a Bishop score <6 with **transcervical balloon in place <3 hours prior to the time of randomization, without prior cervical preparation.**

For patients who meet the above inclusion criteria 1-10 and who those who decline randomization will be offered enrollment for chart review only.

5.3 Exclusion Criteria

If the basic screening criteria are met, the next step is to review the exclusion criteria. Those without exclusions should be approached for study participation.

Assess the following exclusions:
1. Significant cardiac, renal, or hepatic maternal comorbidities, severe gestational hypertension or preeclampsia with severe features
2. Pregnancies complicated by major fetal anomalies
3. Patients with a uterine scar

4. Pregnancies complicated by fetal growth restriction (estimated fetal weight <10%)
5. Pregnancies complicated by oligohydramnios
6. Fetuses with an estimated fetal weight >4500 gm by recent ultrasound or Leopold's exam on admission
7. Patients with class 3 obesity (BMI >40)
8. Fetuses with a persistent category 2 or 3 fetal heart tracing at labor induction admission
9. Vaginal bleeding at the time of randomization
10. Any indication for scheduled CD
11. Hypersensitivity to oxytocin
12. Uterine contractions ≥ 3 in10 minutes
13. Hypersensitivity to prostaglandins

Patients who meet inclusion criteria and do not have exclusion criteria may be approached for the informed consent process.

5.4 Screening/Re-screening

Patients may be included in the study up to 42 weeks gestation. If the above inclusion criteria are met and exclusion criteria are absent, patients should be approached for study participation. The screening number will be generated electronically with REDCap is accessed and participant information is entered.

The patients screened at LPCH OB clinic will require re-screening at the time of labor induction admission.

5.5 Gestational Age Determination

Gestational age will be determined by the most recent ACOG criteria (see table in Section 5.1) with ultrasound required prior to randomization. If no ultrasound examination has been performed previously, one will be performed before the patient is randomized. **Only pregnant patients with gestational age ≥ 37 0/7 weeks will be included.**

5.6 Informed Consent Process

An informed consent must be obtained before entry into the randomized trial. Full disclosure of the nature and potential risks of participating in the trial including the risks of being in the standard care group will be made. All potential participants will undergo the informed consent process as approved by the Institutional Review Board at each participating center. Any person who is potentially eligible will be told about the study and asked if they are willing to participate. The point in the screening process at which a signed informed consent is required will be prior to randomization. The study personnel conducting the informed consent process should emphasize the following study criteria during the informed consent process:

- Randomization to a treatment arm with mifepristone for a cervical preparation agent, with 50% chance to be assigned to either arm:
    - One group will receive mifepristone

    - One group will receive misoprostol
- Participants to sign medical release
- American College of Obstetrics and Gynecology recommends cervical preparation for labor induction, including the use of a transcervical (Cook) balloon
- Follow up to occur through a numerical rating scale patient satisfaction survey on postpartum day one to evaluate medication side effects and overall satisfaction associated with treatment

Patients who did not give informed consent for randomization but meet eligibility criteria 1-10, or who are unable to receive a Cook balloon based on their initial exam will be offered enrollment for chart review only. Patients undergoing induction with a Cook balloon alone will be offered enrollment for chart review. These patients will consent to chart review without participating in the study's randomization, they will receive standard of care at LPCH.

Due to a large proportion of Spanish speaking patients at LPCH, we will also have consents and short form consents available in Spanish, and translators will be available for the consent process. A short form consent may also be used depending on the participant's preferred language.

All patients who are considered for participation in the study (consent for randomization, consent for chart review, decline or ineligible) should have a data entry form and entered into the electronic data system even if not randomized. Patients who do not meet criteria at the LPCH OB clinic screening, may be re-screened at the labor induction.

5.7 Requesting Medical Release Forms

In order to obtain medical records from participants, each participant should sign a "Release of Medical Information" form. A signed Release of Medical Information form should be obtained at the time of, and preferably before, randomization. Clinical Site staff will be able to answer any questions about the procedure at the very beginning of their participation in the study. Also, reluctance to supply medical records may serve as a potential "red flag" that a potential participant may be an adherence or retention risk.
If a participant refuses to sign a Medical Release Form, probe for reasons for the refusal. Explain the importance of the records for the study and why they are needed. Some participants may be willing to sign a release that is specific to information needed for a particular outcome. If the participant continues to refuse, note the refusal in the participant's chart and continue to follow them according to the protocol if they consent to the study at labor induction admission.

6. RANDOMIZATION

Randomization will occur at the time of labor induction admission.
Randomization may occur upon confirmation that all exclusion/inclusion criteria are satisfied, after verification of participant consent and HIPAA authorization, and a transcervical balloon is placed by the OB provider. Of particular importance, careful consideration will be given to the patient's history and fetal status to determine final eligibility. Study staff will also verify participant contact information and obtain a Release of Information.

The MFM Research team will review the following before randomization:

- Complete review of all exclusion and inclusion criteria
- Informed consent obtained
- Fetal status and cervical exam to confirm eligibility
- Verification by OB provider that transcervical balloon is in place

Pharmacy randomization:

- The LPCH pharmacy will randomize the study medication and dispense to the Labor and Delivery medication dispense system, Pyxis.
- The L&D nurse caring for the participant will provide the medication and instructions

The LPCH pharmacy will attain records of randomization.

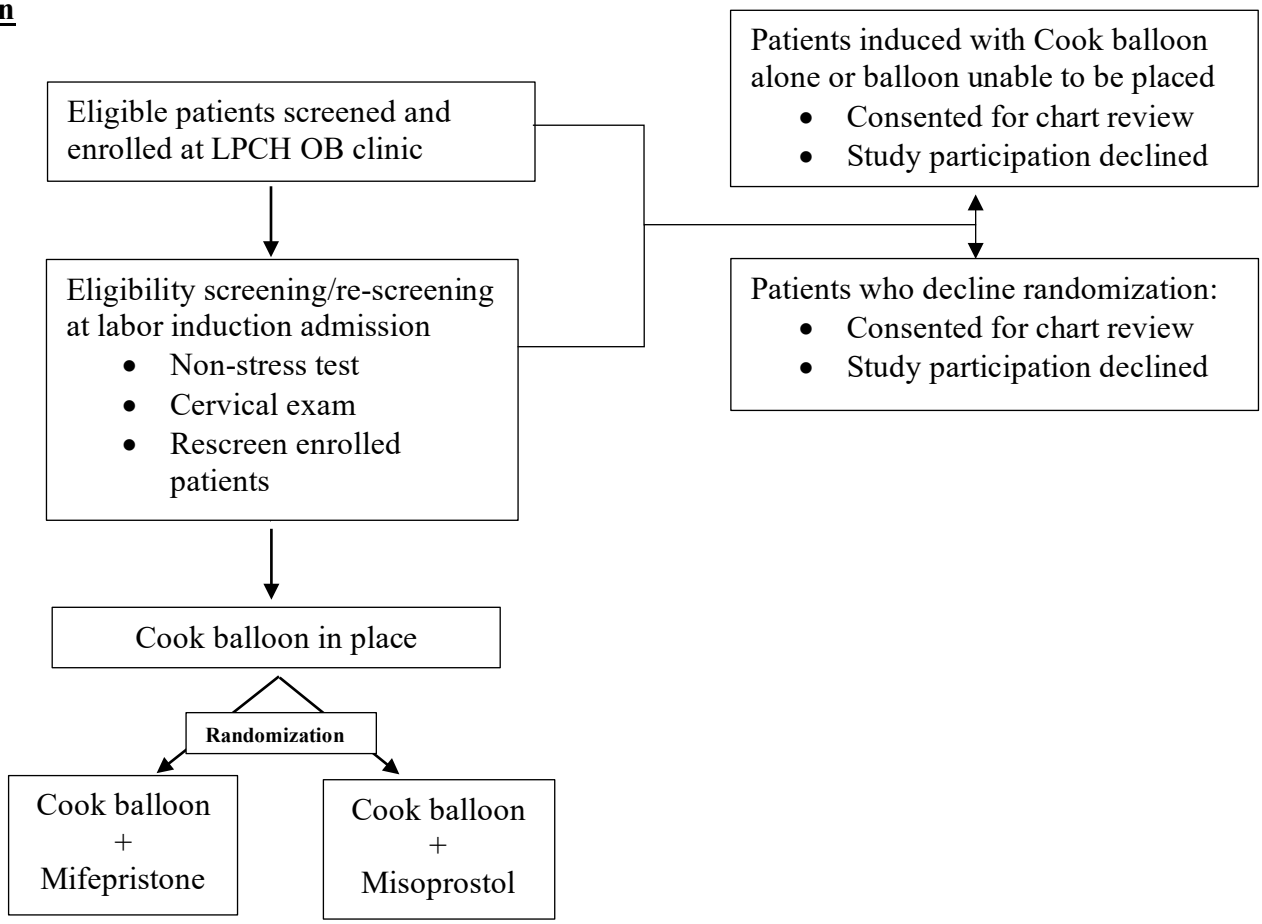
Both groups, will undergo continuous external fetal monitoring and tocometry throughout the entirety of labor induction per standard of care.

The categories of patients randomized:

Patients consenting to the study will be randomized in 1:1 blocks to two treatment groups

Group 1: Patients randomized to the mifepristone group will receive mifepristone 200 mg po treatment.
Group 2: Patients randomized to the misoprostol group will receive misoprostol 50 mcg po treatment.

Study Design



6.1 Informed Consent

No study activities will be conducted until an IRB approval is obtained. Potential participants who may be eligible will be approached by the research staff. The research staff will only introduce the study with the patients after a member of the clinical care team acquires permission from the potential participant that they can be approached for a study. If interested, the research staff will discuss the study and obtain an informed consent from the participant.

Sufficient time will be given to participants to read the consent form, and to ask questions to ensure understanding.

An IRB-approved study brochure may be given to potential participants to provide more information about the study and the procedures involved.

6.2 Induction of Labor: Study Groups

At LPCH cervical preparation typically begins with prostaglandins (misoprostol and dinoprostone), 12-hours of transcervical (Cook) balloon placement, or misoprostol and Cook balloon used concurrently. For the purposes of our study, all patients will receive the standard of care for labor induction at LPCH, starting with mechanical induction of labor with the transcervical (Cook) balloon. The Cook balloon will remain in place for a maximum of 12 hours. After 12 hours of Cook balloon placement, the OB provider will deflate the Cook balloon and perform a cervical exam. If the balloon spontaneously expels prior to 12 hours, the time will be noted and a cervical exam performed. The balloon will be removed at any point in the setting of spontaneous rupture of membranes (SROM) per standard of care, to minimize risk of intraamniotic infection. After a balloon expulsion, balloon removal in the setting of SROM or after 12 hours of balloon placement and removal, the provider will manage the labor induction based on standard of care practice, including using up-titration of oxytocin, amniotomy when deemed safe and appropriate, and transitioning to cesarean or operative birth if deemed necessary by the provider. Patients who receive misoprostol will be eligible to receive additional doses of misoprostol 50 – 100 mcg, because of its known safety. Patients who receive mifepristone will not be eligible for additional doses of misoprostol because based on the pharmacokinetics of mifepristone, the ripened cervix could potentiate uterine tachysystole.

Once the patient achieves complete cervical dilation, time spent in the second stage of labor will be at the discretion of the OB provider given variability among patients and providers.

As the standard of care, oxytocin is indicated when a modified Bishop score of 8 or greater is observed or if spontaneous rupture of membranes occurs during the ripening process. Intravenous oxytocin will begin at 1 milliunits per minute about 12 hours after mifepristone dispense and will be titrated per LPCH protocol. Amniotomy will performed at the discretion of the provider.

Maternal pulse and blood pressure will be recorded during the ripening process to assess for the incidence of maternal blood pressure or maternal heart rate changes; mean arterial pressures and

pulse measurements will be recorded every 15 minutes for the first hour of the induction process and then hourly during the first 4 hours of the induction process. If 2 vital sign abnormalities are noted during this period, the OB provider will be notified, and the standard of care work up will be initiated. (See section 2.3.2) Abnormal vital signs include Heart rate > 110 beats per minute or <50 beats per minute, systolic blood pressure (mm Hg) > 160 or < 45 or diastolic blood pressure > 110 or < 85 *or* MAP <65 mm Hg. Patients will assessed for the presence of known potential side effects from mifepristone or misoprostol by patient interview on postpartum day one. All patients will undergo continuous electronic fetal heart rate monitoring and tocometry until the time of delivery.

Cervical exams will be performed per standard of care by OB providers and recorded. The primary outcome is time to complete cervical dilation. Once the patient achieves complete cervical dilation, time spent in the second stage of labor will be at the discretion of the provider.

Placentas will be sent out to Pathology after delivery if deemed indicated for both groups by the provider. Both groups will have their placentas analyzed if there are clinical indications for the test.

Time and mode of delivery will be recorded into the REDCap database.

6.3. Standard Dose of Medications

The FDA has approved mifepristone in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Historically mifepristone 600 mg followed by a prostaglandin were used, however, preferred dosing of mifepristone 200 mg is the current FDA approved dose due to its equal efficacy and safety as compared to 600 mg.[26,27]

Mifepristone 200 mg in adjunct to misoprostol is used off-label for management of pregnancy loss before 20 weeks and second trimester abortion, including induction of labor and dilation and evacuation. Mifepristone used with misoprostol reduces time to delivery and leads to fewer adverse effects when compared to misoprostol alone.[7,8]

Mifepristone 200 mg dosing received FDA approval in 2016 and is used as the standard dose in conjunction with misoprostol. Mifepristone 200 mg dose was used as the standard dose among studies of inducing labor at term.[11,12] However, one study compared mifepristone 50 mg, 100 mg, 200 mg, 400 mg, and 600 mg and found no difference in maternal or neonatal outcomes among dosing.[13]

According to ACOG, one quarter of an unscored misoprostol 100-mcg tablet (ie, approximately 25 mcg) of misoprostol should be considered as the initial dose for cervical ripening and labor induction. However, this is based on a vaginal route. The standard of care at LPCH is 50 mcg orally, based on previous literature that suggests stepwise oral misoprostol (50 mg followed by 100 mg) appears to be as effective as vaginal misoprostol (25 mg) for cervical ripening with a low incidence of hyperstimulation, no increase in side effects, a high rate of patient satisfaction, and is associated with a lower cesarean section rate.[5]

Frequency of dosing varies between every 3-6 hours. At LPCH standard of care is every 4 hours. Repeat doses of misoprostol 50-100 mcg orally will be given if indicated starting 4 hours after first dose.

7. POST RANDOMIZATION

7.1 Post Randomization Patient Satisfaction Survey

All patients will complete a numerical rating scale patient satisfaction survey after balloon removal and on postpartum day one to evaluate medication side effects and overall satisfaction associated with treatment.

7.2 Management of patient's intolerance to study intervention

Most common adverse reactions (>15%) to mifepristone include nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness.

If the patient experiences side effects, the standard of care medications will be used for the patients: .

> For nausea and vomiting the patient will be offered Zofran 4 milligrams IV or po every 6 hours as needed, Compazine 10 milligrams IV or po every 6 hours as needed, Reglan 10 milligrams IV or po every 6 hours as needed.
> For headache the patient will be offered Tylenol 1 gram po every 8 hours as needed.
> For diarrhea the patient will be offered Lomotil 5 milligrams every 6 hours as needed.
> For dizziness and weakness, a comprehensive workup will be established to ensure the etiology is neither infectious or neurological.

As stated in 2.3.2, if the patient experiences 2 vital signs that are outside of normal parameters, the standard of care work up will be initiated.

If the patient experiences a fever in labor, per standard of care, antibiotics are started, and an infectious workup is initiated. If the patient has a fever with abnormal vital signs per CMQCC guidelines (see 2.3.2), assessment for infection is initiated per standard of care.

7.8 Study Drug, Dispensing

Stanford's investigational pharmacy will dispense either mifepristone or to LPCH pharmacy. LPCH pharmacy will dispense/administer study drug to research participant's nurse via the Pyxis. The nurse will dispense the medication to the participant.

7.9 Biospecimens

Placentas will be sent out to Pathology after delivery if deemed indicated for both groups by the provider. Both groups will have their placentas analyzed if there are clinical indications for the

test. Assessment will be performed with the standard of care for all LPCH delivering participants.

8. POST-DELIVERY

Outcome Data Collection and Chart Review Delivery Outcomes will be ascertained on an ongoing basis until discharge.
Study personnel will abstract the hospital charts and complete information for REDCap entry:

- Labor and Delivery Data
- Neonatal Outcome Data
- Placental Pathology (if obtained)
- NICU admission form (if indicated)
- Adverse Event
- Study Intervention Discontinuation and Participation discontinuation/withdrawal

9. PROCEDURES FOR INACTIVE/ LOST/ REFUSED PARTICIPANTS AND MISSED VISITS

9.1 Overview

Staff will use a systematic approach in attempting to recover reluctant participants, i.e., those who have either expressed interest in dropping out of the study or appear to be likely to drop-out with any aspect of the study.

The goals to avoid drop-out and accomplish drop-out recovery include the following:
1. to ensure that participants are not pushed to the point that they refuse to participate further
2. to continue to engage participants through some form of contact (e.g., phone, e-mail) and allow an opportunity to determine participants' concerns and problem-solve for solutions to concerns and barriers to participation,
3. to foster some form of continued participation

The general approach to drop-out recovery will involve contact by the study coordinator in an attempt to:
1. identify barriers to participation
2. problem-solve for solutions to overcome identified barriers
3. apply motivational enhancement methods

In situations where a participant's behavior suggests that they **do not** wish to participate, the participant can be removed from the study.

9.2 Definition of Participant Status.

For purposes of the study, we define the following terms related to trial participation status:

• Active status – active if medication therapy is managed according to the study algorithm. The participant continues labor induction per study protocol, which is the standard of care at LPCH.

• Inactive status – participant consents to chart review for study purposes, but does not consent to randomization.

• Lost status –lost-to-follow-up if the participant does not arrive for planned labor induction and cannot be contacted by any ordinary means (e.g., home phone, cell phone, mail, email, fax, etc.), clinic staff does not know the participant's whereabouts, and alternative contacts either do not know where the participant is or cannot be contacted themselves.

• Withdrawn/Refused status –participant is considered to be withdrawn if they have withdrawn consent to participate in the study and refuses further contact for any reason or if the participant consented and no longer meets study eligibility criteria at any point in the study.

10. ADVERSE EVENT REPORTING

Serious adverse events that meet any of the following criteria:

• fatal or life-threatening
• result in significant or persistent disability,
• require or prolong hospitalization,
• neonatal death,
• are important medical events that investigators judge to represent significant hazards or harm to research participants.

Specifically, any AE that meets any of these criteria (maternal death, ICU admission stroke, myocardial infarction, cardiomyopathy, fetal death or neonatal death) will be documented and reported as a SAE.

In addition, any unexpected event/ unanticipated problems which the investigator identifies will be reported.

10.1 Data Safety Monitoring Plan

A DSMP will be in place to ensure the safety of participants by analyzing data and to oversee the validity and integrity of the data.

Any serious adverse event or unanticipated problem will be reported to the Stanford IRB. A Data Safety Monitoring Plan (DSMP) will be established to guide all aspects of the study and oversee participant safety. DSMP participants include the research team. The DSMP will be implemented to monitor safety, to advise on study progress and performance, protocol modification, or whether there should be early termination.

The outcome of reviews will be relayed to the IRB and protocol director.

10.2 Reporting of Adverse Events

In addition, the following maternal or neonatal events are examples of adverse events to be reported:

- Maternal or perinatal allergic reaction
- Angioedema, anaphylaxis or generalized skin rash
- Transfer to Chronic Care facility (neonatal)
- Maternal arrhythmia (especially QT prolongation) or congestive cardiac failure (EF<45%)
- Neonatal arrhythmia (especially QT prolongation)
- Any adverse event leading to discontinuation of study medication or suspected to be due to the medication
- Maternal pulmonary thromboembolism
- Maternal admission to ICU
- Neonatal IVH Grade III or IV
- Prolonged maternal or term neonatal hospitalized

11. QUALITY CONTROL

Quality control and assurance are the responsibility of every member of the MiLI trial.

All clinic personnel are responsible for understanding the protocol procedures.

Research Staff responsibilities:

- Maintaining the integrity of the protocol and regulatory document binder.
- Developing a data entry system that incorporates real-time data quality assurance features, such as range and logic checks
- Monitoring site initiation requirements.
- Monitoring the screening and randomization processes to ensure randomization of eligible participants and appropriate randomization allocation of participants.
- Generating timely web-based reports describing clinic and study performance, including but not limited to: a) recruitment b) visit adherence and visit completeness c) study intervention) data entry e) data completeness f) outcomes documentation
- Monitoring documentation of 100% of potential outcomes

12. STATISTICAL ANALYSIS

12.1 Statistical Considerations

Efficacy Endpoint(s): The primary outcomes include generation of preliminary data comparing obstetric and neonatal outcomes among patients randomized to misoprostol 50 mcg versus mifepristone 200 mg **a) obstetric outcomes**: number of uterine contractions– with and without

fetal heart rate decelerations in labor, uterine tachysystole (more than 5 contractions in 10 minutes with and without fetal heart rate decelerations) or hypertonus (a single contraction lasting more than 2 minutes) during the time the foley is in place. We will also be assessing time to complete dilation and delivery, total time on L&D, rate of cesarean delivery, number of patients able to achieve active labor, and severe maternal morbidity- composite of 21 indicators, such as hysterectomy, eclampsia, sepsis, and blood products transfusion **and b) neonatal outcomes:** neonatal cord gases (arterial pH), neonatal Apgar scores at 1 and 5 minutes, and a composite of serious neonatal morbidity up to 7 days of life defined as need for respiratory support within 72 hours after birth, hypoxic-ischemic encephalopathy, seizure, infection, meconium aspiration syndrome, intracranial or subgaleal hemorrhage, hypotension requiring vasopressor support, admission to neonatal intensive care unit.

Secondary Efficacy Endpoint(s): The secondary outcomes are to examine recruitment feasibility, willingness of participants to be randomized to guide recruitment periods for future studies, and to assess medication tolerability through participant experience surveys.

12.2 Sample size determination

We plan to recruit 15 patients per group (30 total) based on the "rule of 12" that is recommended for pilot studies that aim to estimate average values and variability to plan larger studies,[24] and to accommodate an estimated 25% intrapartum cesarean rate. Based on 80% power, a two-sided alpha of 0.05, and prior data, we estimate that this sample size would enable us to detect a difference of at least 25 uterine contractions between the two study groups (140-150 on average during labor for patients induced with misoprostol and Cook balloon).

There were approximately 800 inductions among nulliparous patients at LPCH in 2020. We anticipate excluding ~200 patients based on eligibility criteria. Based on previous institutional studies and institutional practices, we expect 50% of patients to be approached for enrollment based on our experience and approximately 50% of patients who are approached to agree to participate in research study. This will result in approximately 150 patients who would agree to participate during one year.

The analysis plan and sample size calculation were developed in consultation with Maternal-Fetal Medicine Senior Biostatistician, Stephanie Leonard, PhD (Co-I).

12.3 Analyses

We will compare the number of uterine contractions and other continuous variables using Mann-Whitney U test and will use Fisher's exact test for categorical variables. Differences will be considered statistically significant using two-sided tests ($P<0.05$).

13. POTENTIAL CONTINGENCY PLANS

There may be slower than expected enrollment in the study, thus we plan to seek approval to advertise in all practices delivering at LPCH. We plan to recruit additional research staff support to assist in recruitment in the case of slower than expected enrollment.