Simultaneous mifepristone and misoprostol versus misoprostol alone for induction of labor of nonviable second trimester pregnancy (MIST)*:*
a Pilot Randomized Controlled Trial

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A Introduction

A1 Study Abstract

Up to 3% of pregnancies in the second trimester are nonviable and require delivery due to myriad complications including stillbirth, preterm prelabor rupture of membranes (PPROM) at a previable gestational age, fetal anomalies, or risk to maternal life. Stillbirth complicates in 1 in 160 deliveries, with over half of these occurring in the second trimester.[1-3] Additionally, the rate of preterm previable PPROM is estimated to complicate up to 1% of all pregnancies.[4,5] The rate of neonatal survival after previable PPROM after expectant management is reported to be as low as 20% due to complications from premature delivery, inadequate fetal lung development, and infectious complications. On the other hand, pregnancy continuation in the setting of previable PPROM increases maternal risk of bleeding, infection, sepsis, and even death. Most fetal anomalies including those that are lethal or associated with severe morbidity are diagnosed after 20 weeks' gestation which is the standard time for the ultrasound assessment of fetal anatomy. Lastly, at any time in pregnancy maternal medical complications can arise or worsen that make continuation of pregnancy contraindicated due to threat to maternal life.[6] Patients in these and other complex situations are counseled on options for the pregnancy, and many make the decision to proceed with induction of labor with the understanding that the fetus will not survive to hospital discharge.

The standard of care for labor induction of a nonviable second trimester pregnancy is the use of misoprostol.[3] However, mifepristone's adjunctive use to shorter time to delivery in the second trimester has become a topic of interest. Mifepristone, also known as RU-486, is a well-tolerated competitive progesterone receptor antagonist. Data has demonstrated the safety and efficacy of mifepristone administration followed by misoprostol 1-2 days later in medical management of first-trimester pregnancy loss and in first-trimester medication abortion.[7,8] Newer data suggests that mifepristone administration prior to labor induction with misoprostol in nonviable pregnancies decreases total time in labor, with optimal time interval between mifepristone and misoprostol administration thought to be 24-48 hours.[9-11] However, when considering the time from first medication administration to delivery, the time is longer in those patients receiving mifepristone, owing to the delay from mifepristone administration to induction of labor. A retrospective review of our patients undergoing induction of labor for nonviable second trimester pregnancies from 2018 to 2021 revealed an average length of time from first medication administration to placental delivery of 13.8 hours in patients receiving misoprostol alone, compared to 43.3 hours in those receiving mifepristone at least 24 hours prior to induction of labor ($p<0.01$). In the setting of many second trimester pregnancies requiring delivery, shortening the time from diagnosis of pregnancy complication and initiation of labor induction to delivery is of utmost importance to decrease the risk of maternal morbidity with a continuing pregnancy. Currently, given need to expedite delivery, these patients are generally induced with misoprostol without adjunctive mifepristone as mifepristone's effectiveness given concurrently with labor induction is unknown. However, pharmacokinetic studies of mifepristone demonstrate that peak concentrations are reached within 60-120 minutes and remain elevated for at least 48 hours, thus it is reasonable to suspect that mifepristone administered at the initiation of labor induction could offer some benefit to patients needing urgent delivery.[12,13] Thus, we propose a randomized controlled trial investigating the utility

of simultaneous mifepristone administration at the time of complicated nonviable labor induction with misoprostol in the second trimester.

A2 Primary Hypothesis

We hypothesize that using simultaneous mifepristone and misoprostol for labor induction during the second trimester for nonviable pregnancies will result in higher rates of delivery within 12 hours compared to using misoprostol alone and result in lower rates of maternal complications.

B Background

B1 Prior Literature and Studies

Multiple studies published recently have demonstrated that mifepristone administration prior to induction of labor in the second trimester decreases time in labor, especially when given at least 24 hours prior to labor induction.[9,14] However, the total time from first medication administration (mifepristone or misoprostol if mifepristone not given) to delivery is longer in the mifepristone group, owing to the delay between mifepristone administration and initiation of labor. The shortest time interval between mifepristone and misoprostol administration that has been studied is 6 hours.[15] In this case, mifepristone still appeared to have a positive effect on time to delivery. However, this study was performed in first trimester abortions so it's applicability to nonviable second trimester pregnancies is uncertain.

A recent retrospective study reported on the time to delivery with same-day mifepristone and misoprostol compared to misoprostol alone and found that mifepristone use was associated with shorter labor times.[16] However, the same-day mifepristone group included women who received mifepristone up to 11 hours prior to misoprostol. Another retrospective study evaluated time to delivery in second trimester labor induction termination with mifepristone administered <12h prior to labor induction compared to those receiving mifepristone 12-24h before induction and those receiving mifepristone 24-48h before induction.[17] This cohort demonstrated shorter total abortion time and similar induction time in all groups. There was a statistically higher rate for need for intervention for retained placenta in the 12-24h group, compared to the <12h and 24-48h group and a trend towards increased risk of chorioamnionitis in the 24-48h group. These studies clearly suggest a potential benefit for mifepristone at shorter intervals than 24h but cannot comment on simultaneous administration, and given the retrospective nature of these studies each group may represent different clinical scenarios. Thus, this data to is limited in its ability to guide patient care.

On the other hand, a randomized controlled trial demonstrated no impact on cervical dilation 4-6 hours after simultaneous mifepristone and misoprostol compared to misoprostol alone in women undergoing cervical preparation prior to second trimester dilation and evacuation. However, as these patients underwent dilation and evacuation, this study was unable to comment on whether mifepristone would affect time to delivery in those undergoing labor induction in the second trimester.[18]

This will be the first RCT to our knowledge to compare simultaneous mifepristone and misoprostol to misoprostol alone in nonviable second trimester pregnancies.

B2 Rationale for this Study

When time allows, administration of mifepristone prior to second trimester induction of labor decreases total labor time. However, in the setting of many pregnancy complications, decreasing time from diagnosis of nonviable pregnancy to delivery is of utmost importance to decrease risk of maternal complications. Previous data has shown that total abortion time is longer in the group receiving mifepristone owing to the delay between mifepristone administration and initiation of misoprostol induction of labor. Thus, we aim to investigate whether simultaneous mifepristone and misoprostol has benefits over misoprostol alone when labor induction of a nonviable second trimester cannot be delayed.

C Study Objectives

C1 Primary Aim:

Compare the rate of delivery within 12 hours between those receiving simultaneous mifepristone and misoprostol versus misoprostol alone for labor induction during the second trimester for nonviable pregnancies.

C2 Secondary Aim:

Compare the rate of delivery complications between those receiving simultaneous mifepristone and misoprostol versus misoprostol alone for labor induction during the second trimester for nonviable pregnancies. Delivery complications of interest will include failed induction of labor (failure of fetal delivery vaginally), retained placenta, clinical chorioamnionitis, and postpartum hemorrhage.

C3 Rationale for the Selection of Outcome Measures

Rate of delivery within 12 hours was selected as the primary outcome because the main intention of mifepristone is to shorten time from pregnancy complication diagnosis to delivery and the current average time to delivery is 13.8 hours in our population. Shortening this interval will hopefully decrease the risk of complications associated with pregnancy continuation in the setting of nonviable second trimester pregnancy.

In Aim 2, we will assess the risk of maternal morbidity associated with the intervention as the hope to decrease time to delivery is to decrease maternal morbidity.

D Study Design

D1 Overview or Design Summary

This is a randomized controlled trial comparing simultaneous mifepristone and misoprostol administration to misoprostol alone for induction of labor for a nonviable second trimester pregnancy.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Pregnant patients aged 18 years or old admitted to labor and delivery between 14 and 28 weeks' gestation undergoing induction of labor of a singleton nonviable fetus, i.e. fetal demise or abortion of nonviable fetus. Patients must be eligible for mifepristone administration.

2.b Exclusion Criteria

Patients less than 18 years of age, medical contraindication to mifepristone, patients undergoing second trimester abortion without an indication to waive Missouri 72 hour waiting period, patients undergoing surgical termination of nonviable pregnancy via dilation and curettage or dilation and evacuation, patients undergoing induction of labor with a viable fetus or with plans to consider neonatal resuscitation after delivery, patients undergoing induction of labor with plans to initiate labor induction with any medication, device or instrument except misoprostol (i.e. transcervical catheter, oxytocin, dinoprostone), patients who decline mifepristone administration, patients with contraindication to vaginal delivery of second trimester nonviable fetus (i.e. placenta previa, placenta accreta spectrum disorder), patients who elect to wait at least 24 hours between mifepristone and misoprostol administration.

2.c Subject Recruitment Plans and Consent Process

All women admitted to Barnes-Jewish Hospital who require second trimester delivery of a nonviable fetus will be screened for eligibility criteria and approached by trained research staff for informed consent. Prior to being approached by research team, the patient must have an assessment by an obstetrician who has completed an approved Ob/Gyn residency who is not a study team member. This clinician must confirm that the pregnancy is not viable and that delivery is indicated. The obstetrics team will discuss options for delivery which may include dilation and evacuation or labor induction. Only those patients desiring induction of labor for a nonviable second trimester pregnancy will be approached. If the induction of labor meets criteria for an abortion based on Missouri law, the patient will not consented for the study until the appropriate abortion consents are completed by the patient and qualified healthcare provider. The Missouri law defines an abortion as: (a) The act of using or prescribing any instrument, device, medicine, drug, or any other means or substance with the intent to destroy the life of an embryo or fetus in his or her mother's womb; or (b) The intentional termination of the pregnancy of a mother by using or prescribing any instrument, device, medicine, drug, or other means or substance with an

intention other than to increase the probability of a live birth or to remove a dead or dying unborn child.

Notably, administration of mifepristone for pregnancy termination for any indication does require the patient to sign a Patient Agreement Form (https://www.plannedparenthood.org/uploads/filer_public/95/87/9587109f-4848-4ceb-97f2-369bff70f5b7/mifeptagree-e.pdf). All patients willing to participate in the study will need to review this form with their healthcare provider and be willing to sign it if randomized to the mifepristone group in order to be eligible for the study.

The study staff will review the informed consent with the patient in a private setting free of coercion and undue influence. The study staff are not directly involved in the patient's care. When the study staff believes the patient understands fully about the study, the staff will ask the patient if he or she accepts to be enrolled in the study. The patient will be notified and made aware that her decision to enroll or decline will not impact her clinical care. If the patient agrees to be in the study: the study staff will obtain the patient's signature and current date on the consent form. The study staff will sign his or her own name on the consent form, and write the current date on the consent form. A copy of the signed consent form will be given to the patient. If the patient does not agree to be in the study: The study staff will end the discussion, and thank the patient for her time, the patient will not be enrolled in the study, the study staff will emphasize that the patient's access to medical care and/or other services provided will not be affected by her decision whether or not to screen for or take part in the study. Furthermore, she will be notified that she has the right to withdraw from the study at any point.

2.e Randomization Method and Masking

After informed consent is obtained, the research team will proceed with randomization. Using a computer-generated sequence in variable block sizes, a list of randomized assignments will be created and uploaded to REDCap. Patients will be randomized to simultaneous administration of mifepristone and misoprostol or misoprostol alone.

Multiple factors make masking this study impossible, most notably the separate patient consent required to use mifepristone in pregnancy. Thus, the patient and staff will not be blinded to the study group. However, to minimize bias, perinatal data assessors will be masked to the allocation of the patients and allocation will be concealed within our database. Our research staff is experienced in screening, consenting, and enrolling patients with multiple prior large randomized trials at our institution and are well-trained to minimize bias in their approaches.

2.f Risks and Benefits

The proposed study involves potentially rare risks to the subjects, including loss of confidential health information and provision of poor feedback to families regarding outcome. Mifepristone administration is generally well-tolerated. The most common side effects of mifepristone are all also commonly seen with misoprostol which every patient in the study will receive. These include vaginal bleeding, nausea, vomiting, diarrhea, dizziness, and fatigue. Severe allergic reaction to mifepristone is exceedingly rare. We anticipate minimal additional risks or side effects with the administration of mifepristone.

In the rare event that a patient undergoing termination of pregnancy with a living fetus decides to stop her induction of labor with the goal to continue the pregnancy to a point at

which the fetus would be viable, there is a risk of fetal anomalies and demise. Both misoprostol and mifepristone have been implicated in fetal anomalies when given to a continuing pregnancy in the first trimester. The risk is lower in this population as fetal organogenesis is complete by the second trimester. More likely is the risk of delivery or fetal demise after administration of either medication as these medications are intended to end the pregnancy. To decrease the risk of this occurrence, patients will be thoroughly counseled by an OB provider and will have decided and consented for termination of pregnancy prior to being approached for participation in the study.

The study is not designed to provide direct benefits to research participants. Nonetheless, if our hypothesis that simultaneous mifepristone administration at time of misoprostol induction of labor reduces the time to delivery is correct, then subjects randomized to mifepristone will have the benefits of decreased time in labor and decreased risks associated with pregnancy prolongation. More importantly, results from this study have the potential to improve outcomes for women undergoing induction of labor of a nonviable second trimester pregnancy. Because the anticipated risk to participants is minimal, the risks-benefit ratio is very favorable.

2.g Protection Against Risk

Pre-screening for eligibility criteria via medical record review will be conducted, and potential participants will be approached on Labor and Delivery. The study design, expectations, and risks/benefits will be explained, and potential subjects will be given a written informed consent form by a study team member. Consent will be documented by using a signed consent form. Trained study team members will have sufficient time to explain the study and the informed consent carefully in a private room, and eligible patients may decide to enroll at any time as long as they still meet eligibility criteria.

Informed consent will always be obtained before a subject participates in any component of the protocol. For all participants, the consent form will be explained to participants as well as having them read the consent themselves. This consent will contain a detailed description of all study procedures, as well as any possible risks and/or benefits. Patients will be asked to sign the consent form. It will be clearly communicated to the patients during the consent process that their decision to participate will not affect their obstetric care. A copy of the consent forms will be kept in a locked cabinet in the research office and participants will be given a copy of the consent forms for their own records.

Clinical data will be entered into REDCap, a secure, web-based application. Access to the data username/password keys is restricted in accordance with our University's HIPAA policy. Data will be anonymized with study identifier only.

Given the particular vulnerability of pregnant patients, especially those potentially pursuing a termination of pregnancy, patients will not be approached for this study until the following has been confirmed by a residency-trained obstetrician:

1. Fetus is not viable (intrauterine fetal demise, gestational age less than 22 weeks' gestation, lethal fetal anomalies, etc.)
2. Delivery is indicated at current gestational age. Indications for delivery will be determined by clinician
3. Patient-desired mode of delivery (dilation and evacuation, labor induction, cesarean delivery)

4. Appropriate consents of delivery are completed. This includes completion of Missouri Termination of Pregnancy consents, if applicable.

Adverse events will be monitored by a data and safety monitoring board (see separate section).

2.h Withdrawal of Subjects

Patients or their primary obstetric providers may choose to withdraw their patients at any point in the study. The study staff will be notified and all study interventions not yet administered will be withdrawn appropriately (or randomization will be held if this decision is made prior to randomization). Patients will be notified of this process at the time of consent. Notably, while there have been case reports of patients deciding to continue a pregnancy after mifepristone or misoprostol administration, these reports are all after administration in the first trimester. Data does suggest that both medications are associated with increased risk for fetal anomalies; however, as organogenesis is complete in all patients we plan to enroll, we feel this risk is less likely. More likely is the risk of delivery or fetal demise after administration of either medication as these medications are intended to end the pregnancy. To decrease the risk of this occurrence, patients will be thoroughly counseled by an OB provider and will have decided and consented for termination of pregnancy prior to being approached for participation in the study.

For patients that withdraw after randomization, clinical outcomes will be followed and recorded securely. For patients that withdraw before randomization, no clinical data will be followed or recorded.

D3 Study Drug

3.a Description

The current standard of care is misoprostol use for nonviable second trimester induction of labor; however, recent data suggests that mifepristone administration prior to induction decreases time to delivery, but if simultaneous mifepristone administration at time of induction of labor offers benefits in patients with a contraindication to delaying induction of labor is unclear. Therefore, the intervention being tested is mifepristone given at the same time as the first dose of misoprostol for labor induction. There will not be a placebo in this trial as it is a pilot study.

3.b Treatment Regimen

The dose of mifepristone will be 200mg orally. This medication will be given to the patient under the direct supervision of the physician that counseled the patient on the use of mifepristone and reviewed the Mifepristone Patient Agreement Form with the patient. Legally, if this induction of labor is an abortion by Missouri state laws, the mifepristone must be administered by the provider who consented the patient for the abortion procedure. Immediately after the administration of mifepristone, the patient's induction of labor will be started with misoprostol. The dosing and route of administration of the initial misoprostol and the continued labor induction management will be left to the discretion of the obstetrician.

Patients randomized to the misoprostol alone group will have their labor induction started with misoprostol. The dosing and route of administration of the initial misoprostol and the continued labor induction management will be left to the discretion of the obstetrician.

3.c Medication Dispensing and Return

Patients randomized to the mifepristone study group will have an order for mifepristone 200mg orally placed in Epic and dispensed by the BJH pharmacy. In the event that the medication needs to be returned to the pharmacy, the medication will be returned using standard protocols for any medication administered in the hospital.

E Study Procedures

E1 Screening for Eligibility

Study staff will screen potential subjects who are admitted to Labor and Delivery with a nonviable second trimester pregnancy against our inclusion/exclusion criteria. Eligible patients will be approached to see if they are interested in learning more about the research study. If a patient declines to learn more, she will be thanked for her time.

E2 Safety and Adverse Events

2.a Safety and Compliance Monitoring

If subjects have any issues or concerns, or feel as though they were harmed in any way they will be instructed to contact the PI or a member of the research team. Contact information will be provided in the informed consent document.

Data and research monitoring will be undertaken annually by the study's PIs and the WUSM IRB.

All maternal adverse events will be reviewed by a data and safety monitoring board (DSMB) composed of three individuals with expertise in obstetrics and clinical trials (Whitney Ross, MD, Ashley Veade, MD, and Lindsay Kuroki, MD). The DSMB receive a report of any severe and/or non-severe adverse neonatal or maternal outcomes within 72 hours of occurrence.

For confidentiality, only members of the research team will have access to the study information. Subjects will be assigned a unique study ID that will be used. This data base is in REDCap, which is a HIPAA-compliant, encrypted, WU-approved, password protected database. Any hard copies will be maintained in a locked cabinet in a locked office by a member of the study team. Work will only be done on secure WUSTL computers. Specimens will be marked with the subject ID and transported securely to the lab by research staff. Specimens will be processed and stored per research protocols.

The PI and study staff will meet monthly to review compliance and protocol adherence. Nursing staff are encouraged to communicate openly with the study team with concerns regarding the protocol.

2.b Definitions of Adverse Events

Detailed information concerning reportable adverse events will be collected and evaluated throughout the conduct of the protocol (**Table 1 a and b**).

Table 1a: Adverse events (Less likely/less common)

Adverse Event	Definition
Severe postpartum hemorrhage	Estimated blood loss >1000ml for vaginal delivery and >2000ml for cesarean
Failed induction of labor	Need for cesarean delivery, dilation and curettage, or dilation and evacuation for fetus and placenta

Table 1b: Serious adverse events (Rare)

Serious adverse event	Definition
Maternal	
Maternal death	Any maternal death
Life-threatening maternal event	Life threatening events in the mother are defined as those that in the view of the research staff and PI put the individual patient at imminent substantial risk of dying, or if continued participation in the study might have resulted in death
Maternal admission to the intensive care unit	Maternal admission to the intensive care unit for any indication
Unplanned hysterectomy	Unplanned hysterectomy performed during cesarean or following a vaginal delivery

The DSMB will review all Adverse Event Reports and other interim safety data and will report back to the study PI. The Study PI will then report findings to the IRB. If a participant develops a serious adverse event, the safety of continuing the intervention will be ascertained by the participant's obstetric care provider.

2.c Adverse Event Reporting Period

Adverse events will be reported to the DSMB and PI within 72 hours.

E3 Study Outcome Measurements

Aim 1: Primary Outcome: Completion of delivery (including placenta) within 12 hours. **Secondary Outcome:** Completion of delivery (including placenta) within 18 and 24 hours, time to delivery of placenta, time to delivery of fetus

Aim 2: Primary Outcome: Composite obstetric morbidity score of failed induction of labor (failure of fetal vaginal delivery), postpartum hemorrhage, chorioamnionitis, and retained placenta.
Secondary Outcomes: Estimated/quantitative blood loss, total dose of misoprostol, hospital length of stay, need for surgical procedure, use of other

medications/instruments/devices for labor induction/augmentation, readmission of pregnancy complication within 30 days of delivery

These outcomes will assessed by review of electronic medical records by trained study staff.

F Statistical Plan

F1 Sample Size Determination and Power

As this is a pilot trial to assess feasibility of a larger scale trial, we plan to enroll **30 patients (15 mifepristone/misoprostol and 15 misoprostol alone)**. Assuming a 34.0% delivery rate within 12 hours with misoprostol alone,[16] we will be powered to detect an increase to 82.0% delivery rate within 12 hours with a power of 80% and alpha of 0.05. This high rate of delivery by 12 hours has been seen in prior studies utilizing mifepristone.[9] More importantly, the data will be used to inform sample size for a larger trial. The data collected from this study will be used to determine the number of patients needed to enroll in a larger trial. We do not anticipate loss to follow up as all patients will deliver on our Labor and Delivery unit during the same hospitalization as randomization. We deliver approximately 60-75 patients with second trimester nonviable pregnancies per year at Barnes-Jewish Hospital. We have experience with consent rates of approximately 50-75% in prior trials in patients on Labor and Delivery. Therefore, we anticipate meeting this sample size within 1 year.

F2 Analysis Plan and Statistical Methods

Baseline characteristics will be compared between groups using appropriate descriptive statistics. The primary analysis will be by intention-to-treat. Primary and secondary outcomes will be compared between groups using the Chi-squared, Fisher's exact, Mann-Whitney U or student's t-tests, as appropriate. A p-value of <0.05 will be considered significant. We will calculate relative risks and 95% confidence intervals for the primary outcome.

If there is an imbalance in baseline characteristics, we will perform adjusted analyses to account for relevant covariates using multivariable logistic or linear regression. We will perform the following prespecified subgroup analyses for the primary outcome: parity (nulliparous vs multiparous) membrane status (ruptured vs intact), and cervical dilation at time of induction of labor (less than 2 cm vs 2 cm or more).

G Study Timeline

	0-2 months	3-6 months	7-9 months	10-12 months	12-18 months
Protocol development	x				
Trial registration	x				
Staff training	x				
Study forms and database	x				
Data collection & management		x	x	x	
Protocol & IRB finalized	x				
Recruitment start		x			
50% recruitment			x		
100% recruitment				x	
Data analysis complete					x

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