Pitocin or **O**ral **M**isoprostol for **PROM** IOL in Nulliparous Women with Unfavorable Cervical Exams

NCT04028765

Protocol Version 3

Uploaded March 5, 2024

Last updated January 27, 2020

Study Summary

Title	**P**itocin or **O**ral **M**isoprostol for **PROM** IOL in Nulliparous Women with Unfavorable Cervical Exams
Short Title	POM PROM
Methodology	Randomized trial
Study duration	24 Months
Study Center (s)	Single-center
Objective	To determine if Pitocin (oxytocin) or oral misoprostol results in a shorter interval to delivery after the start of induction in nulliparous women with unfavorable cervical exams with premature rupture of membranes (PROM).
Number of Subjects	155
Diagnosis and Main Inclusion Criteria	PROM $\geq$ 36 weeks gestation; Singleton gestation in vertex presentation; Cervix $\leq$ 2 cm dilated and Bishop < 8; No contraindication to vaginal delivery; No evidence of infection
Study Product (s), Dose, Route, Regimen	Oral Misoprostol – 50 mcg q4H IV Pitocin (Oxytocin) – 2 mU/min, increased by 2 mU/min to achieve 4-5 contractions in 10 minutes with cervical change. Max dose 40 mU/min
Duration of administration	Oral Misoprostol – Max 6 doses or until cervical ripening and/or delivery has been achieved Pitocin – Until delivery
Primary Outcome	Time from IOL to delivery (hours)
Statistical methodology	Intention to treat analysis, chi-square test for categorical variables, two-sample t-test for continuous variables

1 BACKGROUND AND RATIONALE

1.1 Condition Background

Premature rupture of membranes (PROM) occurs in approximately 8% of pregnancies at term.[1] Although onset of spontaneous labor is often prompt after membrane rupture, a delay from PROM to labor is associated with an increased risk of intrauterine infection and its associated maternal and fetal complications. For this reason, ACOG endorses induction of labor for PROM "if spontaneous labor does not occur near the time of presentation."[1]

1.2 Rationale

The optimal method for PROM induction is less clear. Prior literature has examined the use of Pitocin (Oxytocin), vaginal and oral misoprostol, and dinoprost with mixed results. The TermPROM study found an increased risk of chorioamnionitis and NICU admission among women treated with vaginal misoprostol for induction.[2]

The postulated link between vaginal misoprostol and chorioamnionitis is the need for vaginal examination for placement of the misoprostol; more vaginal examinations could potentially increase the risk for infection. Utilizing oral misoprostol would eliminate the need for a vaginal exam for administration, thereby potentially mitigating this risk of infection. Currently, vaginal and oral misoprostol as well as Pitocin (Oxytocin) are used routinely in clinical care based on provider discretion.

Among 7 randomized controlled trials examining the use of oral misoprostol as compared to Pitocin (Oxytocin), two found oral misoprostol to result in faster induction to delivery, two found Pitocin to result in faster deliveries, and the remaining two found no difference between the two.[3-8] These studies are limited by small sample size, inadequate reporting of patient demographics, varied misoprostol and Pitocin (Oxytocin) protocols, and inconsistent primary outcomes. Therefore, the utility of oral misoprostol in this population has not been established. Furthermore, its efficacy in specific patient populations is unreported in the literature.

2 STUDY AIMS

2.1 AIM 1:

To determine if Pitocin (Oxytocin) or oral misoprostol results in a shorter interval to delivery after the start of induction among nulliparous women with unfavorable cervical exams with PROM.

2.2 Endpoints

2.2.1 Primary Endpoint

- Time (hours) from start of IOL to delivery

2.2.2 Secondary Endpoints

- Suspected intraamniotic infection (Defined as maternal fever plus 1 or more of maternal leukocytosis, purulent cervical drainage, or fetal tachycardia
- Time (hours) from PROM to delivery
- Time (hours) from IOL to vaginal delivery
- Time (hours) from PROM to vaginal delivery
- Cesarean delivery
- Composite maternal outcome

    - Postpartum hemorrhage, blood transfusion, endometritis, wound infection, VTE, hysterectomy, ICU admission, readmission within 4 weeks, death
- Composite neonatal outcome
    - ICN adm > 48 hours, neonatal blood transfusion, HIE, IVH grade 3 or 4, headcooling, severe RDS, NEC, Sepsis, Death
- Patient satisfaction – as measured by Birth Satisfaction Scale- Revised (BSS-R)

3 PATIENT ELIGIBILTY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is consented and randomized.

3.1 Inclusion Criteria

English-speaking

≥ 18 years of age

PROM ≤24 hours with no evidence of labor

PROM – Standard clinical diagnosis

Labor – >3 painful contractions in a 10 minute period, averaged over 30 minutes

≥ 36 weeks gestation

Agreeable to induction of labor

Singleton pregnancy

Vertex presentation

Cervical dilation ≤ 2 cm and Bishop score < 8

Exam done by senior resident, fellow, midwife or attending to confirm eligibility

3.2 Exclusion Criteria

Contraindication to misoprostol (Prior Cesarean section, prior uterine surgery)

Other contraindication to vaginal delivery

Intrauterine fetal demise

Major congenital anomaly

Chorioamnionitis at time of admission

36w-36w6d with unknown Group B Strep (GBS) status

3.3 Vulnerable patient populations

Pregnant women are considered a vulnerable population. As the condition of interest is a

pregnancy-related and specific condition, it is unavoidable to exclude pregnant women from this research study. Oral misoprostol and Pitocin (Oxytocin) however, are currently used in clinical practice so the risks to this population are minimally increased from that experienced in routine clinical care.

Furthermore, neonates are considered a vulnerable population. We will be collecting data on neonates for our composite neonatal outcome. All risks to this vulnerable population will be less than minimal risk as it will involve chart review only after delivery. Subjects will be made aware that we will be collecting information on their neonates within the consent form.

3.4 Ensuring Necessary Medical Interventions

Enrollment in this study will alter the induction agent utilized after diagnosis of PROM. Continuous EFM and tocometry will occur on all patients in labor, consistent with standard of care. Mechanical cervical ripening will not be performed. The remainder of clinical care in labor will be at the covering OB providers' discretion. The frequency and timing of cervical examinations will occur per provider discretion. Standard treatment for GBS positive and GBS unknown patients will occur. The use of internal fetal monitoring and intrauterine pressure catheter will be at the discretion of the OB provider. Standard obstetric indications for cesarean delivery will be also be at the discretion of the OB provider.

3.5 Potential Benefit to Participants

Participation in this study is for research purposes and there is no direct health benefit to the subjects.

4 TREATMENT ARMS

4.1 Treatment Dosage and Administration

- Oral Misoprostol 50 mcg q4H for up to 6 doses
    - Transition to Pitocin (Oxytocin) as determined by primary OB provider after cervical ripening is no longer indicated
- Pitocin (Oxytocin) – The standard hospital protocol will be utilized. This regimen starts at a dose of 2 mU/min IV.
    - The dose is increased by 2 mU every 15 minutes until contractions q2-3 minutes apart resulting in cervical change.
    - The max dose is 40 mU/min.

4.2 Toxicities

- There are no known toxicities with the doses of misoprostol and Pitocin(Oxytocin) that we are using. One known possible side effect of oral misoprostol is GI distress (nausea, vomiting, diarrhea). If this occurs, attempts will be made to treat these symptoms with antiemetics or antidiarrheals as needed. If unresponsive to treatment, the medication will be discontinued. All women receiving misoprostol will also be monitored for frequency of contractions. The medication will not be administered if contractions >3 per 10 minute period, averaged over a 30 minute period.
- All women receiving Pitocin (Oxytocin) will also be monitored for frequency of contractions. The dose will be titrated to prevent tachysystole and fetal distress as per current Hospital of UPenn protocol. If tachysystole or fetal distress develop, the medication will be discontinued and the condition managed per OB provider discretion. Medication can be restarted upon resolution of tachysystole or confirmation of fetal well-being.

4.3 Concomitant Medications/Treatments

- No additional induction agents will be utilized in conjunction with misoprostol or Pitocin (Oxytocin).

4.4 Duration of Therapy

- Oral misoprostol can be continued until max dose has been reached or the primary OB provider has deemed cervical ripening is no longer indicated
- Pitocin (Oxytocin) can be continued throughout the course of labor as per current HUP guidelines.

4.5 Duration of Follow Up

Women/neonate dyads will be followed for the development of any maternal or neonatal complications through the duration of the postpartum hospital stay as well as for readmissions within four weeks of delivery.

4.6 Blinding

Due to the nature of the treatment arms, neither providers nor participants will be blinded to their treatment arm.

5 STUDY PROCEDURES

5.1 Screening for Recruitment and Recruitment Process

Women meeting the criteria listed in section 3.1 will be invited to participate in the study and written informed consent will be obtained from those who choose to participate.

5.2 Randomization

Eligible, consented women will be randomized via a random generated randomization scheme within RedCap. The randomization scheme will be generated by a statistical associate not involved in the study.

5.3 Procedures During Treatment

After randomization, the appropriate medication will be ordered in Epic by the covering clinician and obtained through inpatient pharmacy as is the current clinical practice. The resulting trial arm will be disclosed to the patient and the patient RN.

- For participants randomized to oral misoprostol, the RN will administer and record the time of first dose. Re-dosing of medication will occur per the schedule described in sections 4.1
- For participants randomized to Pitocin (Oxytocin), the RN will begin Pitocin (Oxytocin) infusion and record the time of infusion start. Dose adjustments will be made according to the clinical protocol described in section 4.1.

The remainder of clinical care in labor and delivery will occur as per primary OB provider's discretion as described in section 3.4.

5.4 Follow-up Procedures

During the postpartum hospital stay, women will be approached to complete a validated patient satisfaction survey, the BSS-R.

5.5 Protections Against Physical Risk

There is minimal risk to the use of oral misoprostol or Pitocin(oxytocin) during labor. Both of these medications are currently employed in clinical use at the Hospital of the University of

Pennsylvania. A DSMB comprised of individuals who are not investigators on the trial will be utilized to monitor for adverse outcomes. A list of mandatory events that should be reported to the DSMB within 24 hours of occurrence will be supplied to all clinicians and research coordinators managing trial patients. Also all serious adverse events will be recorded and reported to the institutional review board.

5.6 Protection against Loss of Privacy/Breech of Confidentiality

In order to protect a potential subject's privacy, study staff will only approach potential subjects in a private setting. Once consented, we will take multiple steps to protect the study subject from breach of confidentiality. The list linking the subject's name and medical record number will be kept behind the hospital firewall in a password-protected file. This file is only accessible through the hospital server to those individuals given password approval to access the file. Furthermore, the electronic database (REDCap) will be coded with a unique study identifier rather than with any individually identifiable private information. No PHI will be shared with anyone outside the institution.

6 ADVERSE EVENTS

6.1 Adverse Event Monitoring

Adverse event data collection and reporting will be done to ensure the safety of subjects who will enroll be enrolled in thus study. Adverse events will be reported in a routine manner at scheduled times during the trial. Additionally, certain adverse events will be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

6.2 Definitions

6.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

6.2.2 Severity of Adverse Events

The severity of an AE is graded as follows:

<u>Mild (grade 1):</u> the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

6.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

Is life-threatening (i.e. the patient was at risk of death at the time of the event).

Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

Results in persistent or significant disability or incapacity.

Is an important medical event. Essentially, any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event.

For the purposes of this study, the adverse events that would meet any of these criteria are: maternal death, ICU admission, anaphylaxis, hysterectomy will be documented and reported as a SAE. In addition, any unexpected event which the PI believes to have been cause or contributed to by the intervention, regardless of whether it resulted in hospitalization, will also be considered an AE or SAE.

6.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.

- Unrelated – The AE *is clearly NOT related* to the study treatment.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

6.4 Reporting Requirements for Adverse Events

6.4.1 Expedited Reporting

- The Principal Investigator will be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The University of Pennsylvania IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

6.4.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

6.5 Stopping Rules

This study does not have a primary safety endpoint or place study subjects at high risk.

7 STUDY DESIGN/STUDY ENDPOINTS

This will be a prospective, randomized, single center study on the efficacy of Pitocin(oxytocin) versus oral misoprostol for PROM induction in nulliparous women with unfavorable cervical examinations. Please refer to section 2.3 for endpoints.

7.1 Sample Size and Accrual

The sample size is based on the mean time to delivery with Pitocin(oxytocin) after PROM IOL of 10.4 hours, with a standard deviation of 4.3 hours. For a power of 80% and an alpha of 0.05, 148 women would be needed to find a 2-hour difference in time to delivery. To account for drop out, we plan to enroll 155 women.

We estimate 15-20 eligible women deliver at HUP per month. We anticipate approaching 80% of these women or approximately 14 per month. With an estimated 50% consent rate, we would enroll approximately 7 women per month. Therefore, we would need 24 months to reach our target enrollment of 155 women.

7.2 Data Analyses Plans

Measures of relative risk will include 95% confidence intervals. Descriptive statistics will be presented as mean with standard deviation, median with interquartile range, or proportion with 95% confidence interval based on data type and distribution. Comparisons between groups will be performed using a Chi-square or Fisher's exact test for categorical variables and parametric or non-parametric tests for continuous variables, as appropriate. Intention-to-treat analyses will be conducted such that all patients with available follow-up measures will be included in the analysis. Statistical analyses were conducted in STATA, version 12.0 (College Station, Texas). Two-tailed P values of <0.05 will be considered statistically significant.

8 STUDY MANAGEMENT

8.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the PI and the IRB. All investigators will follow the University's conflict of interest policy.

8.2 Collection of data

We will record data on each patient regarding their demographics, obstetrical and medical history, labor and delivery admission through postpartum discharge. We will also collect neonatal outcomes on their infants through hospital discharge.

8.2.1 Private information

Only the study staff listed on the protocol approved by the Institutional Review Board will have access to individually identifiable private information about human subjects. The only individually identifiable private information about human subjects that will be collected for research purposes is the subject's name and medical record number for the purpose of linking the subject to their unique study identifier.

8.2.2 Data Protection

The individually identifiable private information that will be collected is name and medical record number for the purposes on linking the subject to their unique study number for chart review. The file linking the study number to the name, medical record number and phone number will be kept in a password-protected file on a secure server. Data will be

collected primarily by the research team. The electronic database (REDCap) will be stored behind the institution's firewall in a password-protected file.

8.3 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.4 Data Management and Monitoring/Auditing

8.4.1 Data Safety and Monitoring Plan

Safety monitoring will be performed periodically by the principal investigator. This will include assessment of accuracy of data recording, assuring de-identification of data, and that there is appropriate locked storage of data material. There will be no planned interim analyses. An advisory board will be created for continual oversight of the project. It will be comprised of faculty members within the department with extensive experience in prospective clinical trials. They will perform periodic reviews of safety data from this study. The DSMB that will be created is attached.

8.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

8.5.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, the ensuing guidelines will be followed:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9 References

[1]Prelabor rupture of membranes. ACOG Practice Bulletin No 188. 2018.

[2]Hannah ME, Ohlsson A, Farine D eta al. Induction of labor compared with expectant management for prelabor rupture of membranes at term. TERMPROM Study Group. New England Journal of Medicine. 1996; 334(16): 1005-1010.

[3]Al-Hussaini TK, Abdel-Aal SA, Youssef MAM. Oral Misoprostol v. intravenous oxytocin for labor induction in women with prelabor rupture of membranes at term. International Journal of Gynecology and Obstetrics. 2003; 82(1): 73-75.

[4]Mozurkewich E, Horrocks J, Daley S et al. The MisoPROM study: A multicenter randomized comparison of oral misoprostol and oxytocin form premature rupture of membranes at term. American Journal of Obstetrics and Gynecology. 2003; 4(189): 1026-1030

[5]Crane J, Delaney T, Hutchens D. Oral misoprostol from premature rupture of membranes at term. American Journal of Obstetrics and Gynecology. 2003; 3(189): 720-724.

[6]Ngai S, Chan Y, Lam S, Lao T. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with prelabour rupture of membranes. BJOG. 2000; 2(107): 222-227.

[7]Butt K, Bennett K, Crane J, Hutchens D, Young D. Randomized comparison of oral misoprostol and oxytocin for labor induction in term prelabor membrane rupture. Obstetrics and Gynecology. 1999; 94(6): 994-999.

[8]Mbaluka CM, Kamau K, Karanja JG, Mugo N. Effectiveness and safety of 2-hourly 20 mcg oral misoprostol solution compared to standard IV oxytocin in labour induction due to prelabor rupture of membranes at term: a randomized clinical trial at Kenyatta National Hospital. East African Medical Journal. 2014;91(9): 303-310.