TITLE: Is more than one dose of misoprostol needed to expedite vaginal delivery in a patient with an unripe cervix?

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## 1. BACKGROUND/SIGNIFICANCE

This study involves a comparison of two different regimens of prostaglandin use for "cervical ripening" prior to induction of labor. Women admitted to the hospital for induction of labor who are found to have "unripe" cervixes at the time of admission, and who agree to participate in the study will be randomly assigned to one of two treatment

groups. In one group, a single dose of 25 µcg of misoprostol will be administered vaginally and four hours later oxytocin induction will be started if clinically indicated. In the second group of women, repeat doses of misoprostol will be given every four hours up to six doses unless labor or cervical ripening occurs sooner. At this point, oxytocin will be started as needed. Success of vaginal delivery by 24 hours, time from initiation of protocol to delivery and cesarean section rates will be compared. Complications such as postpartum hemorrhage, episodes of tachysystole with fetal compromise and chorioamnionitis and endometritis will be monitored.

Induction of labor (IOL) is the use of physical or pharmaceutical measures to initiate labor. Rates of induction have increased dramatically in this country to nearly 40% of pregnancies in some studies." Induction of labor is performed for both maternal and fetal indications. Indications for IOL include both medical and obstetric reasons when the care provider determines that the risk of maintaining the pregnancy is greater than the difficulties of initiating labor. In the U.S. institutions, including ours, common indications for IOL are postdates, hypertensive disease, diabetes and intrauterine growth retardation. As per American College of Obstetrics and Gynecology (ACOG) guidelines, few elective inductions are performed.

It is well known that induction of labor results in an increased rate of cesarean section. [2,] Several factors are associated with "failed inductions" necessitating operative delivery. These include most consistently nulliparity, higher maternal age, and higher body mass index (BMI), and in some studies fetal weight, length of induction and the race of the patient. [,,,] Of note, these characteristics are more common in women undergoing induction than in the general population of pregnant women. These factors are not modifiable when the patient presents for IOL.

Of critical importance, and able to respond to intervention, is the status of the cervix at the time of induction. A patient with an "unripe" cervix has been repeatedly shown to be at higher risk of failed induction, increasing the need for cesarean section by 2-3 fold.[2,] As nearly 50% of inductions occur with women who present with an unfavorable cervix, this is an important factor.[3,4] Some argue that if one controls for the Bishop score, it is not the induction per se that increases the cesarean section rate, but the finding of an unripe cervix in patients presenting for either induction or spontaneous labor.[3,]

Categorizing the cervix as "ripe" or "unripe" is traditionally done using a system of allotted points based on 5 characteristics that make up the Bishop score: cervical position, density, effacement, dilation and station of the presenting part. Although much has been written about modifications in the scale or a more objective system (including sonogram and spectroscopy) the vast majority of studies still uses the Bishop Score.

Traditionally, the scores are dichotomized; patients with scores<6 are considered "unripe" and those with a score ≥ 6 are considered "ripe."

"Failed induction" is a term that is not clearly defined. For the most part it means failure to achieve a vaginal delivery. However, the length of the effort to try to induce labor varies between studies. Patients who are being induced have longer times between initiation of the process and the delivery, in part because of a longer latency period. Prolonged labor, particularly associated with induction, increases the complication rates of uterine atony, postpartum hemorrhage and chorioamnionitis/endometritis. In addition, long labors utilize a significant amount of resources, including staffing and space and thus increase the associated cost and impact on patient satisfaction Not surprisingly, surveys of patients indicate they would prefer shorter periods of time in the labor suite.

In order to address the problem of failed induction, several cervical ripening techniques have been used. These include both mechanical (such as intracervical placement of a foley catheter) and pharmacologic means. The most commonly used drugs for this purpose are the prostaglandins. (This despite the fact that it is an "off label" use; ACOG has made it clear that misoprostol is appropriately used for this purpose.[4]) Over the course of a normal pregnancy and labor, the cervix goes from being strong enough to contain the pregnancy despite the weight of the fetus and gravity to malleable enough to soften, thin and dilate. Ripening of the cervix is associated with an increase in water, restructuring of its collagen, an increase in interleukin and an inflammatory-like process. The mechanisms for these changes are poorly understood. Some researchers feel that they may occur simultaneously but be triggered by different mediators. In vitro, stimulation with prostaglandin increases interleukin 8 production. It is known that an increase in prostaglandins occurs with labor, but its exact role is unclear. Prostaglandin is thought to act on four prostaglandin receptors in the cervix but also on myocytes. The latter may be more related to its use for inducing labor as differentiated from cervical ripening.

The prostaglandins misoprostol and dinoprostone are both commonly used for cervical ripening. Once the cervix is "ripe," regular uterine contractions are present or a preset time limit (usually 24 hours) has been reached, the induction itself is started with oxytocin. In reviewing the literature on prostaglandins there seems to be an overlap in their use for cervical ripening and labor induction. In this study, we are concerned with their role for preparing the cervix before oxytocin is started.

Misoprostol is a synthetic analogue of prostaglandin E1. It can be administered vaginally, sublingually, buccally, or orally. When given vaginally it has a plasma half-life of less than one hour. An extensive body of research supports the safety and efficacy of misoprostol.[4] There are multiple studies evaluating different doses and different routes of delivery." Overall, 25 or 50 µcg of misoprostol vaginally are recommended. The

smaller dose is less effective in some studies but the higher dose is associated with more episodes of tachysystole. Tachysystole, defined as 5 contractions within a 10 minute period, is one of the well-recognized complications of prostaglandin use.[4] In the majority of studies it is not accompanied by a change in fetal heart rate which is the primary concern when contractions occur too often, and has been infrequently associated with a need for cesarean section that can be attributable to the use of this medication. The recommended dosing of 25-50 µcg misoprostol is placed in the posterior fornix of the vagina and repeated every 3-8 hours. Repeat doses are given if the cervix still has a Bishop score < 6, but held if regular frequent contractions (defined as ≥ 3 contractions in a 10-minute period for at least 30 minutes) begin or there is a contraindication to continuing induction, such as a change in fetal or maternal status that requires immediate intervention. In practice, this results in most women receiving more than one dose of misoprostol before oxytocin is started as the standard of care.

There is little data addressing the repeat dosing of misoprostol. While 3 hours might be the most appropriate interval based on the half-life, it is not known how well serum level correlates with clinical effect. We don't know if repeat doses results in a cumulative effect or if there is a latency period between the application of the drug and the changes in the cervix. One study suggests a single dose is very effective if it is given 12 hours before oxytocin is started. This regimen would make it possible to administer prostaglandin, monitor the patient and fetus for a few hours and then letting the patient return the following day for the actual induction. The repeat dosing requires a long period in labor and delivery. We do not know if there is a threshold at which the cervical changes occur or whether the change occurs over a long period of time.

We believe there is equipoise between the two arms of the study as receiving oxytocin sooner will likely result in an earlier delivery than patients who received multiple doses. This is the crux of the study. Shortening induction time is clearly a benefit. If this results in an increased rate of cesarean section remains to be seen but the benefit of earlier delivery seems a reasonable advantage in balance. Prior to the introduction of misoprostol, the standard of care for induction was oxytocin alone and this clearly resulted in primarily normal vaginal births.

## 2. RESEARCH OBJECTIVES.

Primary:

1. To compare the rate of vaginal delivery within 24 hours in patients who receive a single dose of misoprostol versus those receiving multiple doses of this medication. While we will also record and evaluate total length of time from initiation of induction to delivery, the majority of studies use 24 hours as "success" of induction. In general, it is difficult to say an induction has failed before that time unless there has been another problem requiring immediate delivery. After 24 hours, the incidence of infection and uterine atony increase. We did not include mode of delivery as a primary outcome since we anticipate that patients in both groups will achieve similar proportions of vaginal deliveries as both groups will receive adequate oxytocin to achieve normal deliveries. The advantage of the misoprostol (singly or in multiple doses) is to move an individual from the "unripe cervix" group to the "ripe cervix" group. The oxytocin is actually the inducing agent. (This may be somewhat confusing as misoprostol has been studied as an induction agent alone but, in this study and the standard of care at Weiler, it is being used as a ripening agent.) All patients will be managed until their delivery regardless of the length of time that takes and the study will compare overall rates of cesarean section vs. vaginal delivery.

2. To compare change in Bishop score prior to oxytocin initiation in those women receiving a single dose misoprostol versus those receiving a multiple doses of misoprostol.

3. To determine if there is a difference in the rate of chorioamnionitis (defined by the criteria of fever, uterine tenderness, fetal tachycardia) between the two groups.

Secondary:

1. To determine the interval from initiation of misoprostol to delivery in each group.

2. To determine if there are significant adverse intrapartum or postpartum events such as fever, tachysystole and postpartum hemorrhage between the two intervention groups

3. STUDY DESIGN

This is a randomized-controlled non-blinded study involving women with singleton gestation at 37 weeks or greater admitted for induction of labor. As per routine treatment, an initial sterile vaginal exam will be performed to determine the patient's Bishop score (dilation, effacement, station, consistency and position) and fetal

monitoring will be initiated. If the patient is found to have an unfavorable cervix, as defined by a Bishop score of < 6 and there are no contraindications to the use of misoprostol, the patient will be asked to participate in the study. Patients who agree will be randomized to one of two groups: 1) one dose of misoprostol or 2) multiple doses of misoprostol. Allocation concealment procedures will occur with the use of sequentially numbered, opaque, sealed envelopes with carbon paper. A block randomization sequence will be used as determined by Randomization.com. After randomization occurs, the labor care staff (e.g. residents, attending and nurses) will be notified of the treatment arm. The appropriate treatment group will be placed on the chart as well as on the whiteboard located by the nursing station and in the patient's room.

For all patients enrolled, misoprostol 25 µcg will be administered vaginally. For the group receiving only one dose, oxytocin will be started 4 hour later to initiate labor if needed. In the other study group, doses of misoprostol 25 µcg will be repeated vaginally every 4 hours for a maximum of 4 doses. Oxytocin will then be initiated for labor if needed. Prior to insertion of each repeat dose, the patient will be evaluated. If the Bishop score is ≥6, the patient is contracting regularly, or fetal monitoring is not category 1, no further misoprostol will be given and oxytocin will be initiated if the patient is not in labor and as per the Labor and Delivery protocol. The main outcome is to evaluate the rate of vaginal delivery in 24 hours from the initial intervention.

## 4. SAFETY MONITORING

A data safety monitoring board (DSMB) consisting of two obstetricians and one statistician will be established to review the data every 3 months for safety and efficacy of the therapeutic regimens.

## 5. STUDY POPULATION

Women aged 18 to 50 with singleton pregnancies and "unripe" cervixes (Bishop score < 6) admitted for either elective or indicated induction of labor will be asked to participate in this study. Patients who agree to participate will be randomized to the two treatment arms (one vs. multiple doses of misoprostol). The sample size was calculated with the assumption that 50% of women deliver vaginally within 24 hours in the multiple dose of misoprostol group and that the use of oxytocin after a single dose misoprostol

would increase the vaginal delivery rate by 15 percent. Assuming a 3% withdrawal rate, we determine that a sample size of 350 patients (175 patients per group) will be necessary to achieve a power of 80% and an alpha of 0.05. The number of minors who present for induction of labor is minimum in our institution and thus are not included in this study.

Inclusion criteria

- Any pregnant woman undergoing induction of labor
- Live singleton pregnancy ≥ 37 week gestation
- Bishop score < 6
- Category I fetal heart rate

Exclusion criteria

- Contraindications to vaginal delivery (e.g. vasa previa, placenta previa, non-vertex presentation, umbilical cord prolapse, and active genital herpes infection.)
- Pregnancies complicated by major fetal anomalies
- Any contraindication to the use of misoprostol, including
    - History of previous c-section or major uterine surgery
    - Prior allergic reaction
- Category II or III fetal heart rate
- Regular uterine contractions ≥ 3 in a 10-minute period persistent for at least 30 minutes
- Estimated fetal weight < 10 percentile
- Premature rupture of membranes
- Age < 18 years old
- Women who do not have the capacity to consent

6. PARTICIPANT RECRUITMENT

Patients will be approached by the OB provider team (labor and delivery attendings, residents and nurses) to ask if they would consider enrolling in a study. Once patients agree to participate, the study investigators will be notified. By definition these patients are not in labor and therefore should not be in pain. Patients who do not have the capacity to give consent will not be asked to participate.

## 7. INFORMED CONSENT

The study investigators will approach the patient in Labor and Delivery once she agrees to participate on the study and obtain informed consent. The investigators will explain the study, including the risks and benefits. The participants will not receive any remuneration and there will be no additional cost to them. All tests done and data obtained are standard practice for the induction of labor, delivery and postpartum management. No additional tests or procedures will be performed.

The risks associated with the use of misoprostol in the doses recommended in this study have not been shown to increase the need for cesarean section or emergency delivery. Misoprostol has been associated with tachysystole (frequent contractions) but generally without fetal heart rate changes. The possibility of hyperstimulation is minimized by the low dose planned for in this study. Further, the management in both arms of the study are currently standard of care and consistent with the department's protocol.

All data will be de-identified once the patient is discharged from the hospital, at which time data collection should be complete for that individual. Data will be locked in the researcher's office.

Patients assigned to the single dose misoprostol may benefit from an increased likelihood of a vaginal delivery. Participants can be credited for participation in a study that may affect future patients requiring induction of labor.

By the nature of this research, blinding cannot take place. But, we have defined the major endpoints to be objective, i.e. length of time from first misoprostol to delivery and mode of delivery. Measurements of Bishop score are more subjective but will be done by experienced individuals.

Other concerns are the other factors involved in successful inductions, specifically parity, maternal age, BMI. Given the patient population here, with random allocation, we anticipate approximately equivalent populations.

## 8. DATA COLLECTION

The following data will be collected for each patient during the patients' hospitalization:

- Maternal characteristics:
- Age, Gravity, Parity, BMI, Race
- Reason for induction of labor
- Maternal co-morbidities
- FHR category
- Timing of every misoprostol dose
- Timing of start of oxytocin
- Presence of tachysystole
- Bishop score prior to each intervention
- Mode and timing of delivery
- Reason for cesarean delivery, if indicated
- Maternal complications including postpartum hemorrhage, blood transfusion, use of extra uterotonics (in addition to standard oxytocin) or chorioamnionitis defined as fever (temperature $\geq$ 100.4°F) in the presence of uterine tenderness or foul smelling lochia
- Baby weight and APGAR scores
- NICU admission

Once the data collection is completed, i.e. at the time of patient discharge from the hospital, all records will be de-identified and stored in a locked cabinet within the researcher's office.

## 9. DATA ANALYSIS

Data will be analyzed on an intent-to-treat basis. Differences with a $p < 0.05$ will be considered significant. Continuous variables will be compared by Student t test. Categorical variables will be evaluated by $\chi^2$ analysis and Fisher's exact test where appropriate.

We do not anticipate any loss to follow. We anticipate that study withdrawal will be minimum and no more than 3%. Analysis will be done according to the initial randomization group (i.e. intent to treat).

## 10. DATA QUALITY CONTROL AND DATABASE MANAGEMENT

Data corresponding to each patient will be entered into a data collection sheet during the patient's hospitalization and then transferred into a database for statistical analysis. Quality control will be performed every 3 months to assure that data were entered correctly. The database will be de-identified and password protected. The datasheet will be stored in a locked-file cabinet in the PIs office.