Oral Titrated Misoprostol for Induction of Labor at Alaska Native Medical Center (ANMC)

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BACKGROUND

The incidence of labor induction has been steadily rising over the past decades. The rate of induced labor reached 34.5% in the United States during 2024, which is an increase of 32-67% from 2016. Specifically in Alaska, the percent change in induction of labor rate from 2016 (26.1%) to 2024 (36.8%) was 41%. There are numerous fetal or maternal medical indications for delivery. Induction of labor (IOL) without a medical indication may occur on/after 39 0/7 weeks gestation if the patient has been thoroughly counseled about the risks and benefits of labor induction versus expectant management.

The increased rate of labor induction is likely multifactorial in nature, but a large study, the ARRIVE Trial (A Randomized Trial of Induction Versus Expectant Management), also likely contributed to this increase. The ARRIVE Trial was a large, randomized controlled trial over 41 institutions with 94% adherence that evaluated the risks and benefits of IOL in low-risk nulliparous women at 39 weeks of gestation. The findings demonstrated decreased rates of cesarean delivery, decreased rates of hypertensive disorders, no difference in composite adverse neonatal outcomes, and better outcomes for both mothers and babies. The American College of Obstetricians and Gynecologists (ACOG) supports using these findings to guide shared decision making and accommodate elective inductions of labor.

METHODS FOR INDUCTION OF LABOR

Induction of labor can be a long process with considerable resource expenditure. The Bishop score (Table 1) is a clinical tool to determine if a cervix is favorable or “ripe” for induction. If the score is five or less, the cervix is unfavorable and cervical ripening agents should be used. If the score is eight or higher, the cervix is favorable and there is a high chance of a vaginal delivery.

Cervical ripening increases the likelihood of a vaginal birth within 24 hours when compared with use of oxytocin alone. There are mechanical and pharmacologic agents that are effective at cervical ripening. There are many different mechanical options such as a Foley balloon, Atad balloon, Cook cervical ripening balloon, seaweed-based dilators (Laminaria), and osmotic agents (Dilapan). Pharmacologic methods primarily include prostaglandins such as misoprostol (Cytotec) and dinoprostone (Cervidil), although occasionally oxytocin (Pitocin) is used in select candidates. Review of the current evidence suggests that the prostaglandin misoprostol, administered either orally or intravaginally, is generally considered the most effective agent for cervical ripening. Misoprostol has a good safety profile at the lower dosage range, and is convenient to use, but there are limitations to its use. Although safe and used commonly for labor induction, misoprostol use for cervical ripening is currently off label.

MISOPROSTOL DOSING

The optimal dose of misoprostol for labor induction is 25 mcg or less, administered orally or vaginally. As misoprostol is supplied in 100 or 200 mcg tablets, dosing in less than 50 mcg fragments may be inaccurate and inconsistent. Likewise, misoprostol may not be evenly distributed within the inert material of the tablet, making failure of response, or an exaggerated response, unpredictable.

In response to this challenge, dissolving a 200 mcg tablet in 200 mL of water is proposed as an accurate, safe, and efficacious method of using the drug in lower doses. The dosing interval of every two hours for

oral misoprostol is based on the known pharmacokinetics of the drug. When misoprostol is administered orally, it requires 30 to 60 minutes to achieve peak plasma levels, but is then promptly metabolized, and is essentially undetectable after 120 minutes. (Figure 1)

MISOPROSTOL CONTRAINDICATIONS AND CAUTIONS

Misoprostol use is contraindicated in those that have a hypersensitivity reaction to its components, history of uterine rupture, or history of prior full thickness myometrial surgery such as cesarean delivery or myomectomy. Misoprostol can be associated with uterine tachysystole, which may result in fetal heart rate abnormalities, an effect which is both dose and route of administration dependent.

CERVICAL RIPENING/INDUCTION WITH LOW DOSE TITRATED ORAL MISOPROSTOL AT ANMC

CANDIDATES

1. Women with a cephalic singleton pregnancy, no contraindications to misoprostol, and with an unfavorable cervix (Bishop score ≤ 5) who are:
    a. Preterm (≤ 36 6/7 weeks) with a medical indication for delivery or
    b. Full term (≥ 37 0/7 – 39 0/7 weeks) with a medical indication for delivery or
    c. Full term (≥ 39 0/7 weeks) with or without a medical indication for delivery (elective).
2. Women with a breech singleton pregnancy, no contraindications to misoprostol, an unfavorable cervix (Bishop score ≤ 5), an OB provider skilled in vaginal breech delivery, and appropriate counseling with shared decision making.
3. Women with a multifetal gestation (dichorionic/diamniotic twin pregnancy or monochorionic/diamniotic twin pregnancy), cephalic presenting fetus, no contraindications to misoprostol, have a provider skilled in multifetal deliveries who previously counseled the patient and is available for the induction and delivery process, and with an unfavorable cervix (Bishop score ≤ 5).

CONTRAINDICATIONS

1. Women who are NOT candidates for this protocol include those with:
    a. Prior full-thickness myometrium uterine surgery (cesarean delivery or myomectomy).
    b. Non-reassuring antenatal fetal surveillance (i.e. significant recurrent decelerations of the fetal heart rate noted during fetal monitoring).
    c. Active labor: more than three palpable contractions lasting greater than 30 seconds in 10 minutes, or cervical dilation greater than 4 cm.
    d. Any known obstetric contraindication to labor (i.e. placenta previa, vasa previa, breech fetal position without an OB provider skilled in vaginal breech delivery, active genital herpes simplex infection, etc).
    e. Hypersensitivity reaction to misoprostol or its components.

ORAL MISOPROSTOL INDUCTION OF LABOR PROCEDURE

1. In the pharmacy, misoprostol 200 mcg is dissolved in 200 mL of tap water, constituting a solution of 20 mcg in 20 mL. This solution may be used for up to 48 hours. (USP 795)
2. Induction of labor medication regimen:
    a. 20mcg given orally every one-hour x 4 doses.
    b. 40mcg given orally every two hours x 4 doses.
    c. 60mcg given orally every two hours x 4 doses.
3. Once the patient is admitted to Labor & Delivery and orders have been placed, obtain vital signs, perform a sterile vaginal exam, confirm fetal presentation, and perform a 20-minute fetal non-stress test (NST).
    a. If any of the following occurs, the patient is NOT considered a ripening candidate with oral misoprostol:
        i. Nonreactive NST with or without decelerations
        ii. Bishop score ≥ 6
        iii. Regular painful uterine contractions every 3 minutes lasting 30 seconds
        iv. Active labor
        v. Contraindications to a vaginal delivery (see above)
4. An initial dose of **misoprostol 20 mcg** (20 mL measured in a syringe) will be given by mouth, and the time recorded by the nurse.
    a. The same dose will be repeated every hour for three hours (total of four doses).
    b. Patients may ambulate, take a bath, eat, and drink during the ripening procedure.
    c. The patient will be monitored with an NST and tocography 20 minutes after receiving the medication. If fetal status remains reassuring and there are no other indications for monitoring, then the patient can be off the monitor for 20 minutes. The patient is then placed back on the monitor 20 minutes prior to the next dose.
5. If the FHR remains reassuring, and regular uterine contractions (3 contractions every 10 minutes lasting at least 30 seconds) have *not* ensued after 4 hours:
    a. The misoprostol dose may be increased to **40 mcg** (40 mL) every two hours until active labor occurs.
    b. Again, the patient will be monitored with an NST and tocography for 20 minutes after receiving the medication If fetal status remains reassuring and there are no other indications for monitoring, then the patient can be off the monitor until 20 minutes prior to the next dose.
    c. If not previously performed, a sterile vaginal exam should be performed 12 hours after the first dose of misoprostol has been given.
6. If active labor has still not begun in 12 hours, the misoprostol dose may be increased to **60 mcg** (60 mL) every two hours as long as the fetal heart rate pattern remains reassuring and other contraindications have not occurred.
    a. Similarly, the patient will be monitored with an NST and tocography for 20 minutes after receiving the medication If fetal status remains reassuring and there are no other indications for monitoring, then the patient can be off the monitor until 20 minutes prior to the next dose.
    b. If not previously performed, a sterile vaginal exam should be performed 24 hours after the first dose of misoprostol. If active labor has not yet begun, the provider will decide on the patient's management.

ORAL MISOPROSTOL LABOR AUGMENTATION PROCEDURE

1. If active labor is established, but contractions become inadequate (less than 3 contractions in 10 minutes lasting 30 seconds over a 2-hour period), or labor is arrested (no further dilation over 2 hours), and the patient declines other augmentation methods, then the labor may be ***augmented*** with titrated oral misoprostol
    a. Beginning at 5 mcg every hour, progressing to 10 mcg every hour, or 20 mcg every hour (maximum dose permitted) every hour until adequate labor progress is established.
    b. The patient will be monitored with cardiotocography for 20 minutes after receiving the medication. If fetal tolerance has been assured, then the patient can be off the monitor for 20 minutes. The pt is then placed back on the fetal heart tracing and cardiotocogram (CTG) 20 minutes prior to the next dose.

UTERINE TACHYSYSTOLE DURING MISOPRROSTOL ADMINISTRATION

1. Definition: more than 5 contractions in 10 minutes, averaged over a 30-minute window.
2. Uterine tachysystole ***without*** worrisome fetal heart rate changes, is not an indication to stop the misoprostol procedure.
3. Uterine tachysystole ***with*** fetal heart rate abnormalities (Category II or III tracings) should result in holding the next misoprostol dose and discussing the plan of care with the provider. Routine resuscitative measures such as maternal repositioning or fluid boluses can be given per unit guidelines.

TRANSITIONING FROM MISOPROSTOL TO OXYTOCIN

1. Timeline:
    a. Wait at least one hour after administering 20mcg misoprostol orally.
    b. Wait at least two hours after administering either 40mcg or 60mcg orally.

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VERSION HISTORY

Revised 5/17/26 pca
Revised 4/15/23 njm
Revised 4/16/21 njm
Revised 5/31/17 njm
Written 3/28/17njm

TABLES

TABLE 1: BISHOP SCORE

Cervical Exam	**Points**			
	0	1	2	3
Dilation (cm)	Closed	1-2cm	3-4cm	5-6cm
Effacement (%)	0-30%	40-50%	60-70%	80%
Station	-3	-2	-1, 0	+1, +2
Consistency	Firm	Medium	Soft	
Position	Posterior	Mid	Anterior	

TABLE 2: CERVICAL RIPENING – ORAL TITRATED MISOPROSTOL PROTOCOL

Dose	**Frequency**	**Number of Doses**	**Fetal Monitoring**
20 mcg in 20 mL	Every one hour	Four	20 minutes pre-dose 20 minutes post-dose
40 mcg in 40 mL	Every two hours	Four	20 minutes pre-dose 20 minutes post-dose
60 mcg in 60 mL	Every two hours	Four	20 minutes pre-dose 20 minutes post-dose

TABLE 3: AUGMENTATION – ORAL TITRATED MISOPROSTOL PROTOCOL

Dose	**Frequency**	**Number of Doses**	**Fetal Monitoring**
5 mcg in 5 mL	Every one hour	One	20 minutes pre-dose 20 minutes post-dose
10 mcg in 10 mL	Every one hour	One	20 minutes pre-dose 20 minutes post-dose
20 mcg in 20 mL	Every one hour	Until active labor	20 minutes pre-dose 20 minutes post-dose

FIGURES
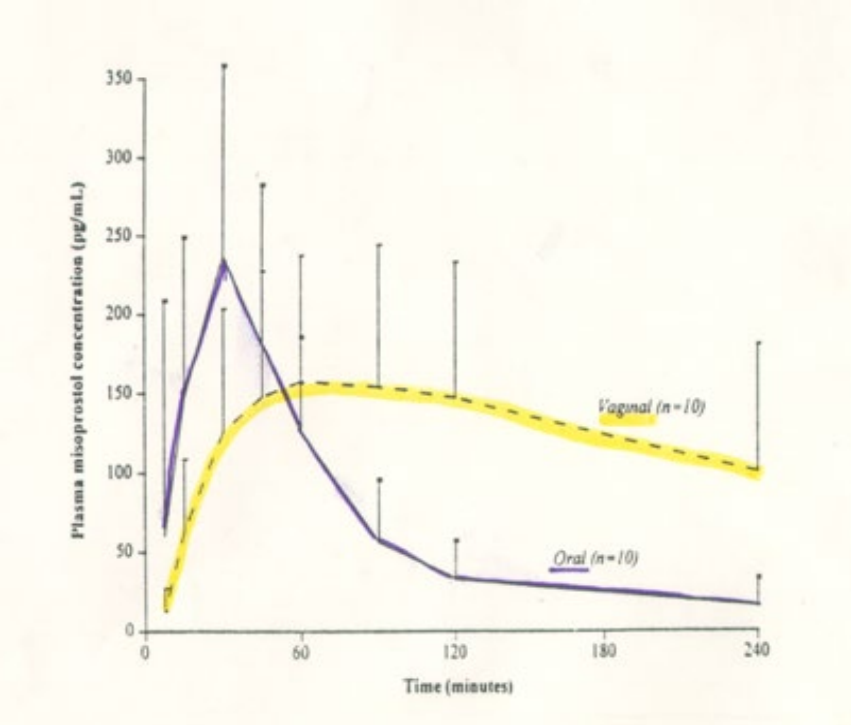
FIGURE 1: LEVEL OF PLASMA MISOPROSTOL CONCENTRATION OVER TIME (ZEIMAN, ET AL).