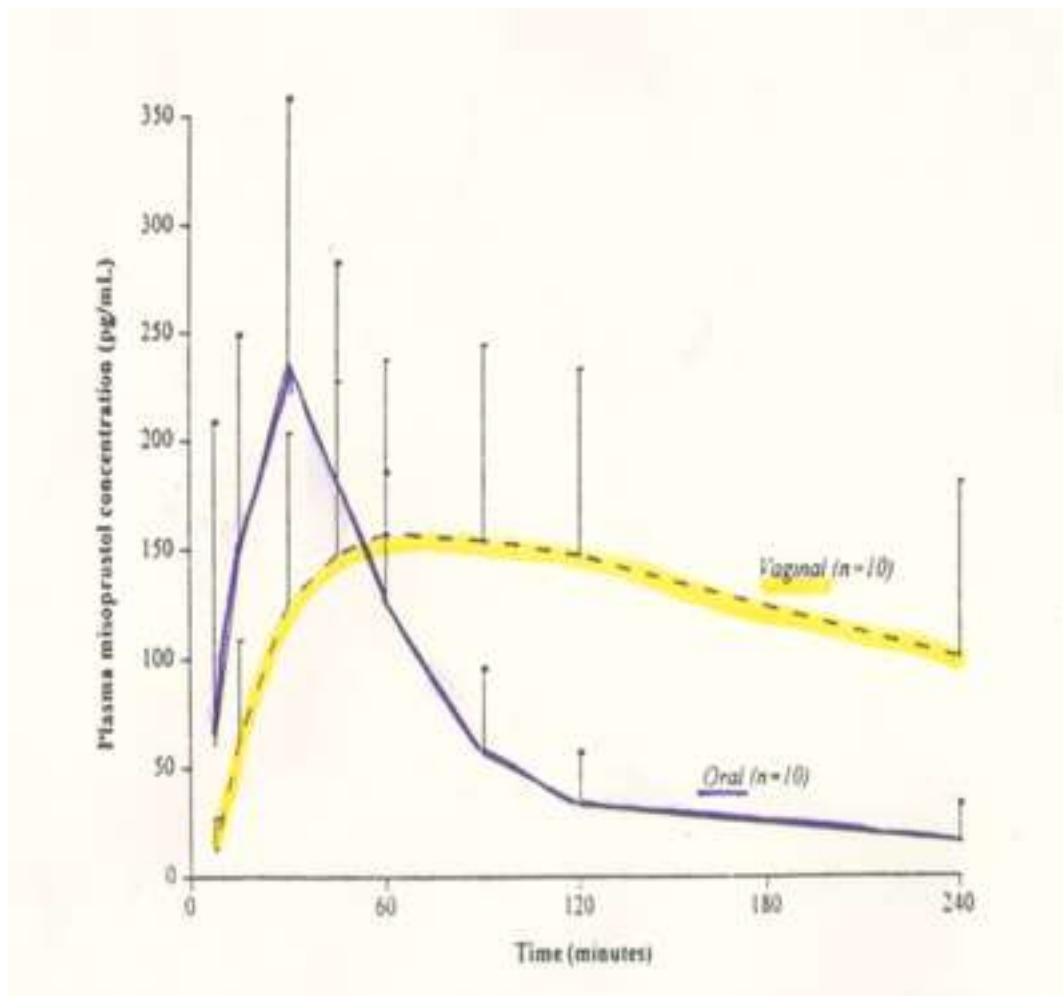


ORAL TITRATED MISOPROSTOL FOR INDUCTION OF LABOR: ANMC

BACKGROUND

The incidence of labor induction has been steadily rising, and the rate of induced labor currently approaches 25 per cent, owing to the large number of referred patients with a medical indication for delivery, principally postdates pregnancy, hypertensive disease of pregnancy, and other maternal and fetal conditions necessitating delivery. Induction of labor can be a long and tedious process and involves considerable resource expenditure. The incidence of cesarean delivery is increased following induced labor, partly due to the risk condition for which the procedure was undertaken, and partly due to a lack of cervical "ripeness" or readiness for labor. The Bishop score is a reasonable clinical guide that references the cervical shortening, softening, and dilation that takes place as pregnancy advances. Bishop scores of 5 or less are considered unfavorable, and are inversely related to the success of the induction and the length of labor.

Both mechanical (Foley balloon, Atad balloon, Cook catheter system, seaweed based dilators) and pharmacologic methods (oxytocin and various prostaglandins, including misoprostol (Cytotec), dinoprostone (Cervidil) have been used to ripen the unfavorable cervix. Review of the current evidence suggests that the prostaglandin misoprostol, administered either orally or intravaginally, are generally considered the more effective agent for cervical ripening and induction of labor. This drug has a good safety profile at the lower dosage range, and is convenient to use, but there are limitations to its use, particularly in women with a uterus previously scarred as a result of cesarean delivery.



Misoprostol is associated with uterine tachysystole, which may result in fetal heart rate abnormalities, an effect which is both dose and route of administration dependent. This adverse effect may result in the induction being terminated urgently by a cesarean delivery, which otherwise would not have been indicated. The optimum dose of misoprostol at present is considered to be 25 mcg or less, administered by the oral or vaginal route, Dosing of the drug is problematic in our setting as misoprostol is only supplied as 100 or 200 mcg tablets, making accurate fractionation of the drug into less than 50 mcg fragments virtually impossible. Likewise, the drug 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 the 200 mcg tablet in 200 mL of water is proposed as an accurate, safe, and efficacious method of using the drug in safe low dose 20 mL/20 mcg aliquots, and is referred to as use of low dose titrated oral misoprostol. The dosing interval of every 2 hours for oral misoprostol is based on the known pharmacokinetics of the drug, which, in contradistinction to vaginal dosing, when the drug is administered by the oral route, requires 30 to 60 minutes to achieve peak plasma levels, but is then promptly metabolized, and is essentially undetectable after 120 minutes.

(see diagram - after Zeiman et al).

Candidates for ripening/induction with low dose titrated oral misoprostol

- a. Women at term with an unfavorable cervix (defined as a Bishop score 5 or less) with a medical indication for delivery are reasonable candidates for use of this protocol.
- b. Medical indications for delivery where women would be considered candidates for induction of labor, examples include but not limited:
 - Postdates pregnancy (41 weeks or more of gestation)
 - Hypertensive disease of pregnancy
 - Other indications, (fetal growth restriction, diabetes mellitus, other maternal or fetal conditions)
- c. Women who would NOT be candidates for this protocol include those with:
 - Prior cesarean delivery (or other prior uterine incision)
 - Non-reassuring antenatal fetal surveillance (significant persistent decelerations of the fetal heart rate noted on cardiotocography requiring urgent delivery)
 - Active labor already in process (more than 3 palpable contractions lasting greater than 30 seconds in 10 minutes, or cervical dilation greater than 4 cm)
 - Any known obstetric contraindication to labor (e.g., placenta previa, malpresentation, active herpes simplex infection, etc.)

PROCEDURE

- a. Prior to beginning the drug, the patient will have a 20-minute pre-ripening cardiotocogram.
- b. If any of these are met, the patient would not be considered a ripening candidate:
 - baseline fetal heart pattern abnormalities
 - Bishop score of 6 or greater
 - regular painful uterine contractions every 3 minutes lasting 30 seconds
 - in active labor.
- c. Women will be dosed as follows:
 1. Misoprostol 200 mcg will be dissolved in 200 mL of tap water, constituting a solution of 20 mcg in 20 mL. This solution may be used for up to 24 hours.
 2. An initial dose of 20 mcg (20 mL measured in a syringe) will be given by mouth, and the time of the first dose recorded.
 - the same dose will be repeated **every hour** for 3 hours (total of 4 doses).

3. Patients may ambulate and take oral fluids and light foods ad lib during the ripening/induction procedure.
4. The patient will be monitored with the fetal heart tracing and cardiotocogram (CTG) 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 patient is then placed back on the fetal heart tracing and cardiotocogram (CTG) 20 minutes prior to the next dose.
5. Uterine tachysystole, (defined as more than 5 contractions in 10 minutes, averaged over a 30 minute window) **without** worrisome fetal heart rate changes, will not be an indication to stop the ripening-induction procedure. If the fetal heart tracing is reassuring, then the medication can be advanced per guideline.
6. Tachysystole **with** fetal heart rate abnormalities (Category II or III tracings should result in misoprostol not being given in the subsequent hour, or until the abnormal pattern has resolved. Lateralization, oxygen, and a fluid bolus will be given as per routine.
7. 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:
 - the dose may be increased to 40 mcg (40 mL) **every 2 hours** until active labor is established.
8. The patient will be monitored with the fetal heart tracing and cardiotocogram (CTG) 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 patient is then placed back on the fetal heart tracing and cardiotocogram (CTG) 20 minutes prior to the next dose.
9. A cervical exam will be performed 12 hours after the first dose of misoprostol has been given. If active labor (defined as above) has still not begun in 12 hours, misoprostol 60 mcg will be continued at 2 hourly intervals as long as the fetal heart rate pattern is reassuring.
10. The patient will be monitored with the fetal heart tracing and cardiotocogram (CTG) 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.
11. A cervical exam will be performed 24 hours after the first dose of misoprostol has been given. If active labor has still not begun in 24 hours, the provider will decide on the patient's management
12. If active labor is established, but then 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), then the labor may be **augmented** with titrated oral misoprostol
 - 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.
 - The patient will be monitored with the fetal heart tracing and cardiotocogram (CTG) 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.

REFERENCES:

1. Aalami-Harandi R, Karamali M, Moeini A. Induction of labor with titrated oral misoprostol solution versus oxytocin in term pregnancy: randomized controlled trial. Rev Bras Ginecol Obstet. 2013 Feb;35(2):60-5.
2. Abramovici D, Goldwaser S, Mabie BC, Mercer BM, Goldwasser R, Sibai BM. A randomized control trial of oral misoprostol versus Foley catheter and oxytocin for induction of labor at term. Am J Obstet Gynecol 1999; 181:1108-12.
3. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Medley N, Dias S, Jones LV, Caldwell DM. Methods to induce labour: a systematic review, network meta-analysis and cost-effectiveness analysis. BJOG. 2016 Aug;123(9):1462-70
4. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, Navaratnam K, Caldwell DM. Labour induction with prostaglandins: a systematic review and network meta-analysis. BMJ. 2015 Feb 5;350:h217.

5. Berard V, Fiala C, Cameron S, Bombas T, Parachini M, Gemzell-Danielsson K. Instability of misoprostol tablets stored outside the blister: a potential serious concern for clinical outcome in medical abortion. *PLoS One*. 2014 Dec 15;9(12):e112401.
6. Bricker L, Peden H, Tomlinson AJ, Al-Hussaini TK, Idama T, Candelier C, Luckas M, Furniss H, Davies A, Kumar B. Titrated low-dose vaginal and/or oral misoprostol to induce labour for prelabour membrane rupture: a randomised trial. *BJOG*. 2008;115:1503-1511.
7. Cheng SY, Hsue CS, Hwang GH, Chen W, Li TC. Comparison of labor induction with titrated oral misoprostol solution between nulliparous and multiparous women. *J Obstet Gynaecol Res*. 2010 Feb;36(1):72-8
8. Cheng SY, Ming H, Lee JC. Titrated oral compared with vaginal misoprostol for labor induction: a randomized controlled trial. *Obstet Gynecol*. 2008;111:119-125.
9. Cheng SY, Chen TC. Pilot study of labor induction with titrated oral misoprostol. *Taiwan J Obstet Gynecol*. 2006;45:225-229
10. Dallenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. *Am J Obstet Gynecol* 2003;188:162-7.
11. Dodd JM, Crowther CA, Robinson JS. Oral misoprostol for induction of labour at term: randomised controlled trial. *BMJ* 2006;332:509-513;
12. Elati A, Week AD. The use of misoprostol in obstetrics and gynecology. *BJOG* 2009; 116(S1):61-9.
13. French L. Oral prostaglandin E2 for induction of labour. *Cochrane Database Syst Rev* 2001; CD00309.
14. Ho M, Cheng SY, Li TC. Titrated oral misoprostol solution compared with intravenous oxytocin for labor augmentation: a randomized controlled trial. *Obstet Gynecol*. 2010 Sep;116(3):612-8.
15. Hofmeyr GJ, Alfirevic Z, Matonhodze B, et al. Titrated oral misoprostol solution for induction of labor: a multicenter randomized trial. *BJOG* 2001; 108:952-9.
16. Hofmeyr GJ, Matonhodze BB, Alfirevic Z, Campbell E, de Jager M, Nikodem C. Titrated oral misoprostol solution--a new method of labour induction. *S Afr Med J*. 2001 Sep;91(9):775-6.
17. How HY, Leaseburg L, Khoury JC, Siddi I TA, Spinnato JA, Sibai BM. A comparison of various routes and dosages of misoprostol for cervical ripening and induction of labor. *Am J Obstet Gynecol* 2001; 185:911-5.
18. Kundodyiwa TW, Alfirevic Z, Weeka AD. Low dose oral misoprostol for induction of labor: a systematic review. *Obstet Gynecol* 2009; 113:374-83.
19. Majoko F, Zwizwai M, Nystrom L, Lindmark G (2002) Vaginal misoprostol for induction of labour: a more effective agent than prostaglandin f2 alpha gel and prostaglandin e2 pessary. *Central African Journal of Medicine*. pp. 123-128.
20. Matonhodze BB, Hofmeyr GJ, Levin J. Labour induction at term: a randomized control trial comparing Foley catheter and titrated oral misoprostol solution, titrated oral misoprostol solution alone, and dinoprostone. *South African Med J* 2003; 93:375-9.
21. Moodley J, Venkatachalam S, Songca P. Misoprostol for cervical ripening at and near term--a comparative study. 2003 *South African Medical Journal*. pp. 371-374.
22. Rehan-Uddin K, El-Refaey H, Sharma S, et al. Oral, rectal, and vaginal pharmacokinetics of misoprostol. *Obstet Gynecol* 2004; 103:866-70.
23. Rouzi AA, Alsibiani S, Mansouri N, Alsanani N, Darhouse K. Randomized clinical trial between hourly titrated oral misoprostol and vaginal dinoprostol for induction of labor. *Am J Obstet Gynecol* 2014; 210:56.e1-6.
24. Rouzi AA, Alsahly N, Alamoudi R, Almansouri N, Alsinani N, Alkafy S, Rozzah R, Abduljabbar H. Randomized clinical trial between hourly titrated and 2 hourly static oral misoprostol solution for induction of labor. *Am J Obstet Gynecol*. 2016 Dec 14
25. Souza AS, Feitosa FE, Costa AA, Pereira AP, Carvalho AS, Paixão RM, Katz L, Amorim MM. Titrated oral misoprostol solution versus vaginal misoprostol for labor induction. *Int J Gynaecol Obstet*. 2013 Dec;123(3):207-12.
26. Souza AS, Scavuzzi A, Rodrigues DC, Oliveira RD, Feitosa FE, Amorim MM. Titrated oral solution of misoprostol for labour induction: a pilot study. *Rev Bras Ginecol Obstet*. 2010 May;32(5):208-13. [Article in Portuguese]

27. Sciscione AC, Nguyen L, Manley J, Pollock M, Maas B, Colmorgen G. A randomized control trial of transcervical Foley catheter to intravaginal misoprostol for preinduction cervical ripening. *Obstet Gynecol* 2001; 97:603-7.
28. Tang OS, Schweer H, Sebberth HW, et al. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002; 17:332-6.
29. Thaisomboon A, Russameecharoen K, Wanitpongpan P, Phattanachindakun B, Changnoi A. Comparison of the efficacy and safety of titrated oral misoprostol and a conventional oral regimen for cervical ripening and labor induction. *Int J Gynaecol Obstet*. 2012 Jan;116(1):13-6. doi: 10.1016/j.ijgo.2011.07.027. Epub 2011 Sep 28.
30. Wang X, Yang A, Ma Q, Li X, Qin L, He T. Comparative study of titrated oral misoprostol solution and vaginal dinoprostone for labor induction at term pregnancy. *Arch Gynecol Obstet*. 2016 Jan 8.
31. Weeks A, Alfirevic Z, Foundes A, Hofmeyr GJ, Safar P, Wing D. Misoprostol for induction of labour with a live fetus. *Int J Gynecol Obstet* 2007; 99:S194-7.
32. Zvandasara P, Saungweme G, Mlambo J, Chidembo W, Madzivanzira N, et al. Induction of labour with titrated oral misoprostol suspension. A comparative study with vaginal misoprostol. *Central African Journal of Medicine*. (2008) pp. 43-49.
33. Zeiman M, Fong SK, Benowitz NL, et al. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; 90:88-92.

Reviews

Cheng SY. Individualized misoprostol dosing for labor induction or augmentation: A review. *World J Obstet Gynecol* 2013; 2(4): 80-86 <http://www.wjgnet.com/2218-6220/full/v2/i4/80.htm#B23>

Vogel JP, West HM, Dowswell T. Titrated oral misoprostol for augmenting labour to improve maternal and neonatal outcomes. *Cochrane Database Syst Rev*. 2013 Sep 23;(9):CD010648. doi: 10.1002/14651858.CD010648.pub2.

Cheng SY. How to Manage Labor Induction or Augmentation to Decrease the Cesarean Deliveries Rate, Cesarean Delivery, Dr. Raed Salim (Ed.), 2012.

ISBN: 978-953-51-0638-8, (Accessed 7/6/16) InTech,

Available from: www.intechopen.com

<http://www.intechopen.com/books/cesarean-delivery/how-to-manage-labor-induction-or-augmentation-with-titrated-oral-misoprostol-to-decrease-the-ces>

Written 3/28/17njm

Table 1: Cervical Ripening – Oral Titrated Misoprostol

20 mcg in 20 mL	Q one hr	4 doses	Monitor 20 min pre-dose
			Monitor 20 min post-dose
40 mcg in 40 mL	Q two hrs	4 doses	Monitor 20 min pre-dose
			Monitor 20 min post-dose
60 mcg in 60 mL	Q two hrs	6 doses	Monitor 20 min pre-dose
			Monitor 20 min post-dose

Table 2: Augmentation – Oral Titrated Misoprostol

5 mcg in 5 mL	Q one hr	One dose	Monitor 20 min pre-dose
			Monitor 20 min post-dose
10 mcg in 10 mL	Q one hr	One dose	Monitor 20 min pre-dose
			Monitor 20 min post-dose
20 mcg in 20 mL	Q one hr	Until active labor	Monitor 20 min pre-dose
			Monitor 20 min post-dose