I have no conflict of interest.

This presentation focuses specifically on the off-label use of misoprostol, which is not approved for obstetrical use in Canada.

Objectives
• Pharmacodynamics & kinetics
• Safety & licensing
• Induction of labour
• Post-partum hemorrhage
• Miscarriage management
• Questions & Discussion

Background
• PGE₁ analogue designed to prevent ulcers
• Available as 100 mcg and 200 mcg tablets
• Stable at room temperature
• Cheap: < 5 cents per tablet
  (c.f. Cervidil = $88; Prostin 2 mg = $55)
• Available world-wide
• Not licensed for use in obstetrics
• Obstetric use endorsed by WHO, ACOG, FDA

Background
• Cervical ripening and uterotonic effects
• Variable, dose-dependent response
• Water soluble
• Absorbable orally and trans-mucosally
• Oral administration → first pass liver metabolism
• Trans-mucosal absorption → variable

Tang OS. Int J Gynecol Obstet 2007;99:S160-167
Safety

Why have SOGC and RCOG been reluctant to endorse the use of misoprostol for induction of labour?

Pharmacodynamics

- Uterine sensitivity at term is 20 times greater than in first trimester
- Dose must be adjusted according to G.A.
- 200 mcg tablet → potential for dosing error
  → Systems to prevent dosing errors
  → Caution in grand multiparous women

Pharmacodynamics

- Endogenous prostaglandins form part of inflammatory cascade
  → effect on gastro-intestinal smooth muscle
  → effect on temperature regulation
- Variable individual patient sensitivity
- GI side effects & fever common with doses > 200 mcg

Side Effects

- Nausea, vomiting, diarrhea, abdominal pain, shivering, chills and fever - dose dependent
- Not bronchospasm: OK in asthma
- Excessive uterine activity (dose-dependent):
  - Tachysystole
  - Hypertonus
  - Hyperstimulation (1%)
- ↑ risk hyperstimulation in grand multiparity
- Potential ↑ risk uterine rupture with prior CS

Misoprostol – induced hyperthermia

Figure 4. The incidence (%) of fever with oxytocin and 200, 400 and 600 μg sublingual misoprostol. Elati A. BJOG 2011;118:466-474
Uterine Hyperactivity

- **Tachysystole** = more than 5 contractions per 10 minute period for at least 20 minutes without fetal heart rate changes
- **Hypertonus** = a single contraction lasting greater than 120 seconds without fetal heart rate changes
- **Hyperstimulation** = tachysystole or hypertonus associated with an abnormal FHR tracing

Kinetics: Oral & Sublingual

- Rapidly absorbed; Tmax = 20-30 min.
- Bioavailability: oral 50% of sublingual
- Most drug gone after 4 hours
- Sublingual:
  - thin mucosa; rich blood supply
  - lower dose required = precision more difficult.
- Oral:
  - First pass liver metabolism = less effect
  - tablet must be swallowed, not held in the mouth
  - higher dose required = easier dosing

Kinetics: Buccal, Rectal, Vaginal

- Slower absorption; Tmax = 70-80 min.
- Longer duration of action = 6 hours +
- No first-pass metabolism
- **Vaginal**: absorption depends on bleeding & lubricant: tablets often found intact much later
- **Rectal**: poor absorption and bioavailability
- **Buccal**: slow onset - thicker squamous mucosa? - portion swallowed?

“Sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration, and the greatest bioavailability.”

Tang OS. Int J Gynecol Obstet 2007;99:S160-167
Term Misoprostol IOL

- Eligibility
- Indications & Contraindications
- Patient Evaluation
- Preparations
- Protocol & Standing Orders

• Eligibility:
  • Clear indication for induction of labour
  • Inpatient induction only

• Indications:
  • Term PROM & PPROM (oral or s.l. misoprostol causes cervical ripening & avoids vaginal exams)
  • Prolonged pregnancy
  • Gestational hypertension/ pre-eclampsia
  • Gestational diabetes
  • Any indication where prostaglandin suitable

Contraindications

• < 34 weeks gestation
• Previous C/S or major uterine surgery
• Para ≥ 4 (dose adjustment possible)
• Abnormal fetal heart rate / NST
• Fetal growth restriction
• Abnormal uterine artery doppler
• Regular or painful uterine contractions

Patient Evaluation

• Routine assessment including VS & NST
• IV in-situ?
• CBC, blood group and screen
• Continuous EFM for 30 min after each dose
• Continuous EFM for 1 hour after any increase in uterine activity within 4 h of misoprostol dose
• Patient may ambulate after 30 min with stable uterine activity & FHR
• Patient to remain in hospital between doses

Protocol

• If not in active labour and contractions are absent or mild four hours after the last misoprostol dose, the woman may return home for sleep as needed
• Patient to return to LDR for EFM anytime there is an increase in uterine contractions
• Standard instructions to return for vaginal bleeding, vaginal fluid, or increasing contraction strength

Excess Uterine Activity

• Immediate notification of the attending physician
• Intra-uterine resuscitation (maternal position changes, oxygen, and IV bolus 500cc NS)
• V/E to assess Cx & rule out prolapsed cord
• Application of a scalp electrode if possible
• NTG s.l. ready for administration. At the direction of the attending physician, the obstetrical RN can give a single dose of 0.3mg s.l.
• Immediate preparation for C/S if these measures do not resolve abnormal FHR
Misoprostol Dosing

Sublingual is twice as potent as oral

25 mcg s.l. = 50 mcg p.o.

Misoprostol Preparation

- Pre-cut, one-half portions of 100 mcg tablets, individually packaged by pharmacy
- Ensure that the tablet is a 100 mcg tablet and not a 200 mcg tablet
- Larger 200 mcg tablets are used for postpartum hemorrhage and treatment of first and second trimester miscarriage
- 200 mcg tablets are contraindicated in a pregnant patient at term (risk of hyperstimulation & uterine rupture)

Misoprostol Dosing

- Give 50 mcg of misoprostol orally with a drink of water and ensure that it is swallowed (to avoid mucosal absorption)
- Repeat 50 mcg orally q4h as long as contractions are absent or mild (not painful)
- Oxytocin should not be given within four hours of the last misoprostol dose

Misoprostol Dosing

- Grand multips: use misoprostol solution
  → 200 mcg tablet crushed finely with back of a spoon
  → dissolved well in 200 cc clean tap water
  → solution = 1 mcg/cc
  → 20 cc (20 mcg) p.o. q2-3h prn
  → titrate up slowly if no response

1. Patient admitted under Dr. ______________ for inpatient induction of labour.
2. When not in labour, vital signs q2h. When in active labour, vital signs and fetal monitoring per active labour protocol.
3. Place #18 or larger IV – saline lock.
4. CBC; blood group and antibody screen on admission.
5. Give 50 mcg of misoprostol (1/2 of a 100mcg tablet) orally with water. The tablet must be swallowed and not kept in the mouth or under the tongue.
6. As long as patient does not have painful contractions, repeat 50 mcg misoprostol orally every four hours to a total maximum of 5 doses in 24 hours.
7. Continuous electronic fetal monitoring for 30 minutes after each misoprostol dose. Continue monitoring for 1 hour if patient is feeling contractions.
8. Patient may ambulate after initial monitoring.
9. When contractions begin or whenever they increase, patient should be reassessed and monitored using EFM for at least 1 hour.
10. Notify physician immediately for tachysystole (more than 5 contractions in 10 minutes), or hypertonus (contraction last longer than 120 seconds), or if there is less than one minute resting tone between contractions.
11. If hyperstimulation occurs (tachysystole or hypertonus with abnormal FHR), call physician STAT, institute intra-uterine resuscitation, and prepare nitroglycerine spray for administration upon physician’s arrival.
12. Oxytocin induction/augmentation should not be administered within 4 hours of a dose of misoprostol.
Oral Misoprostol Augmentation!

PG & VBAC: Lydon-Rochelle, NEJM 2001

<table>
<thead>
<tr>
<th>Type of Delivery</th>
<th>No. of Women</th>
<th>Incidence (per 10000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated cesarean delivery without labor</td>
<td>6,980</td>
<td>1.6</td>
</tr>
<tr>
<td>Spontaneous onset of labor</td>
<td>10,789</td>
<td>5.2</td>
</tr>
<tr>
<td>Induction of labor without prostaglandins</td>
<td>1,960</td>
<td>7.7</td>
</tr>
<tr>
<td>Induction of labor with prostaglandins</td>
<td>366</td>
<td>24.5</td>
</tr>
</tbody>
</table>

Retrospective aggregate data; ICD 9 codes exaggerate rupture by 100%; PG dose, route, and frequency unknown.

Misoprostol & VBAC: Landon, NEJM 2004

Prospective data collection
Review of operative reports
PG dosing not known

52/227 had misoprostol alone

PG & VBAC: Grobman, O&G 2007

Prospective data collection = monitored practice
Review of operative reports


"The protocols of prostaglandin administration in (prior) studies… were either not specified or consisted of high and/or closely repeated prostaglandin doses, regimens that might account for the (reported) increased rates of complications.

The aim of this … study … was … to compare uterine rupture and maternal and perinatal morbidity rates after low-dose prostaglandin -induced cervical ripening or spontaneous onset of labor.

Schmitz, PLoS One 2013
Medical Miscarriage Mgmt.
- Outpatient management of 1st TM S.A.
- Missed abortion without bleeding: 80% effective
- Incomplete abortion with bleeding: 90% effective
- Embryonic demise with bleeding: 90% effective
- Dose 400 mcg s.l. q4-6h repeated up to 6 doses
- Clinical resolution: heavy bleeding that stops
- No routine F/U ultrasound or hCG
- U/S if prolonged bleeding

Intrauterine Fetal Demise
- 13 – 17 weeks: 200 mcg s.l. q4h prn
- 18 – 26 weeks: 100 mcg s.l. q4h prn
- 27 – 32 weeks: 50 mcg s.l. q4h prn
- > 33 weeks: 50 mcg p.o. q4h prn
- Lower dose > 26 weeks with prior C/S
- Increase subsequent dose if no effect after first two doses

Postpartum Hemorrhage
- Prophylactic use immediately post-partum in women at increased risk of PPH
- Alternative to oxytocin for routine third stage management in environments without refrigeration or easy access to needles
- 400 mcg s.l. → only dose/route to remember
- For treatment of PPH, remember, effect takes 15 minutes – oxytocin, bimanual compression, ergometrine, hemabate are all quicker
## Dose Summary

- IOL at term: 50 mcg p.o. q4h
- 1st TM Miscarriage: 400 mcg s.l. q4-6h
- 2nd TM stillbirth: 100-200 mcg s.l. q4h
- 3rd TM stillbirth: 50-100 mcg s.l./p.o. q4h
- PPH: 400 mcg s.l.; repeat q2-3h prn

## Availability & Cost

- Misoprostol 100mcg tabs: 2.7 cents/tab
- Misoprostol 200mcg tabs: 4.5 cents/tab.
- McKesson, AA Pharma Generic
- Cervidil vaginal PGE1: $88
- Prostin vaginal PGE2: $55