Update on Induction of Labor Methods

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June 11, 2010

Disclosure

- Principal Investigator for Cytokine Pharmasciences, developer of the misoprostol vaginal insert (MVI)

Labor induction in the United States

Natality Statistics: 2006

- 4.1 million live births
- 21.2% require induction of labor
- Doubled since 1990


Rates of induction of labor by length of gestation in weeks: United States, 1989-2004

Figure 6. Rates of induction of labor by gestational age: United States, 1989-2004
Indications: ACOG Guidelines

- Preeclampsia, eclampsia
- Gestational hypertension
- Premature rupture of membranes
- Chorioamnionitis

Indications: ACOG Guidelines

- Fetal compromise (e.g., severe fetal growth retardation, isoimmunization, oligohydramnios)
- Abruptio placentae
- Postterm pregnancy

Indications: ACOG Guidelines

- Maternal medical problems, inc. diabetes mellitus, renal disease, chronic pulmonary disease, chronic hypertension, antiphospholipid syndrome
- Fetal demise
- Logistic factors (e.g., risk of rapid labor, distance from hospital, psychosocial indications)

Contraindications

- Prior transfundal uterine surgery
- Transverse fetal lie
- Prolapsed umbilical cord
- Placenta or vasa previa
### Cervical Assessment

*Modified Bishop Score*

<table>
<thead>
<tr>
<th>Length (cm)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(&quot;Effacement&quot;)</td>
<td>0-30%</td>
<td>40-50%</td>
<td>60-70%</td>
<td>≥80%</td>
</tr>
<tr>
<td>Dilatation (cm)</td>
<td>&lt;1</td>
<td>1-2</td>
<td>3-4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Station</td>
<td>-3</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Consistency</td>
<td>Posterior</td>
<td>Mid</td>
<td>Soft</td>
<td></td>
</tr>
</tbody>
</table>

### Role of Cervix in Risk of Cesarean Following Induction at Term in Nulliparae

<table>
<thead>
<tr>
<th>Factors (N=7282)</th>
<th>Estimated RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous labor with Bishop score ≥5</td>
<td>Referent</td>
</tr>
<tr>
<td>Bishop score &lt;5</td>
<td>1.76 (1.48-2.09)</td>
</tr>
<tr>
<td>Induction</td>
<td>1.77 (1.46-2.11)</td>
</tr>
<tr>
<td>Induction and Bishop score &lt;5</td>
<td>3.00 (2.38-3.73)</td>
</tr>
</tbody>
</table>

### Methods of cervical ripening

**Mechanical**
- Membrane Sweeping
- Amniotomy
- Hygroscopic dilators
- Foley balloon catheters

**Pharmaceutical**
- Estrogens
- Relaxin
- Oxytocin
- Prostaglandin E1
- Prostaglandin E2

### Cochrane Systematic Review: Mechanical methods for induction of labor

*Issue 4, 2001. Art. No.: CD001233*

- 45 studies
  - Placebo/no treatment
  - Oxytocin
  - Vaginal prostaglandins
  - Cervical prostaglandins
  - Vaginal misoprostol
  - Extra-amniotic saline infusion

• Comparing with vaginal PGE2, only one trial (n=109) reported on vaginal delivery not achieved in 24 hours (73% versus 42%; RR 1.74; 95% CI: 1.21-2.49).

• Compared with intracervical PGE2, only one trial (n=100) reported on vaginal delivery not achieved in 24 hours (68% versus 40%; RR 1.70; 95% CI: 1.15-2.51).


• Compared with misoprostol, effectiveness was similar (34% versus 30%; RR 1.15; 95% CI: 0.80-1.66).

• Mechanical methods reduced risk of hyperstimulation with FHR changes when compared with prostaglandins:
  - Vaginal PGE2: 0% vs 6%; RR 0.14; 95% CI: 0.04-0.53
  - Intracervical PGE2: 0% vs 1%; RR 0.21; 95% CI: 0.04-1.20
  - Misoprostol: 4% vs 9%; RR 0.41; 95% CI: 0.20-0.87


• No difference in risk of cesarean between mechanical methods and prostaglandins.
  - Vaginal PGE2: 25% vs 21%; RR 1.21; 95% CI: 0.94-1.56, 12 studies, n=1139
  - Cervical PGE2: 28% vs 25%; RR 1.13; 95% CI: 0.96-1.32, 12 studies, n=1641
  - Misoprostol: 27% vs 22%; RR 1.22; 95% CI: 0.93-1.61, 4 studies, n=681

• Serious neonatal (three cases) and maternal morbidity (one case) were infrequently reported.


• When compared with oxytocin, mechanical methods reduced the risk of cesarean section (4 trials: 198 women; 17% versus 32%; RR 0.55; 95% CI: 0.33-0.91).

• No reported cases of serious maternal morbidity and severe neonatal morbidity.
Cochrane Systematic Review: Mechanical methods for induction of labor

• When comparing extraamniotic infusion with any prostaglandins, women were more likely to not achieve vaginal delivery within 24 hours (57% vs 42%; RR 1.33; 95% CI: 1.02-1.75).
• Risk of cesarean increased (31% vs 22%; RR 1.48; 95% CI: 1.14-1.90), without a reduction of the risk of hyperstimulation.

Cochrane Systematic Review: Mechanical methods for induction of labor

• Insufficient evidence to evaluate the effectiveness, in terms of likelihood of vaginal delivery in 24 hours, of mechanical methods compared with placebo/no treatment or with prostaglandins.
• Risk of hyperstimulation was reduced when compared with all prostaglandins.

Cochrane Systematic Review: Mechanical methods for induction of labor

• Compared to oxytocin in women with unfavorable cervix, mechanical methods reduce the risk of cesarean deliveries.
• No evidence to support the use of extra-amniotic infusion.

Single vs. double balloon catheters

• Three arms: double balloon catheter (107 women); 16F Foley catheter (110 women) and PGE(2) gel (2 mg) (113 women).
• No difference in cesarean rates (double balloon 43%, single balloon 36%, PGE(2) 37%, P = 0.567).
• Induction to delivery interval was longer in double balloon group (median 24.5; 95% CI 23.7, 30.6 hours) than single balloon (23.2; 20.8, 25.8 hours) or PGE(2) (23.8; 21.7, 26.8 hours) (P = 0.043).
• Uterine hyperstimulation 14% PGE(2) group with none occurring with mechanical cervical ripening.

**Single vs. double balloon catheters**

- Cord blood gases (median arterial pH) double balloon 7.26 (range 7.03-7.40); single balloon 7.26 (7.05-7.44); PGE(2) 7.25 (6.91-7.41) (P = 0.050).
- Cervical ripening single balloon was associated with significantly less pain (pain score > 4: double balloon 55%, single balloon 36%, PGE(2) 63%, P < 0.001).


**CONCLUSIONS:**

- Labor induction in nullipara with unfavorable cervices results in high cesarean rates.
- Similar efficacy
- Single balloon catheter offers best combination of safety and patient comfort.


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**Cochrane Systematic Review:**

**Vaginal prostaglandins for cervical ripening and induction of labor**

(Issue 4, 2009, Art. No.: CD003101)

- 63 trials, involving 10,441 women
- Primary comparisons:
  - Placebo/no treatment
  - Oxytocin
  - Vaginal prostaglandins
  - Cervical prostaglandins
  - Vaginal misoprostol

**Cochrane Systematic Review:**

**Vaginal prostaglandin for cervical ripening and induction of labor**

- Compared to placebo or no treatment reduced:
  - Failure to achieve vaginal delivery (18.1% vs. 98.9%, [RR 0.19, 95% CI 0.14, 0.25], 2 trials, n=284)
  - Failure to achieve cervical ripening within 12 to 24 hours was reduced (21.6% vs. 40.3%, [RR 0.46, 95% CI 0.35, 0.62], 5 trials, n=467)
  - Oxytocin augmentation (35.1% vs. 43.8%, [RR 0.83, 95% CI 0.63, 0.94], 12 trials, n=1231)
Cochrane Systematic Review: Vaginal prostaglandins for cervical ripening and induction of labor

- Rate of cesarean similar when prostaglandin E2 was compared with placebo (13.4% vs 14.9%, RR 0.89, 95% CI 0.79 to 1.00, 34 trials, 6399 women).
  - This finding was mirrored when considering parity, membrane status and cervical favorability.
- Uterine hyperstimulation with FHR changes increased (4.4% vs 0.49%, RR 4.14, 95% CI 1.93 to 8.90, 14 trials, 1259 women)

Cochrane Systematic Review: Vaginal prostaglandins for cervical ripening and induction of labor

- PGE2 tablet, gel and pessary appear to be as efficacious as each other.
- PGE2 vaginal insertion associated with reduction in instrumental vaginal delivery rates (9.9 % vs 19.5%, RR 0.51, 95% CI 0.35 to 0.76, NNT 10 (6.7 to 24.0), five trials, 661 women) when compared to vaginal PGE2 gel or tablet.

Cochrane Systematic Review: Vaginal misoprostol for cervical ripening and induction of labor

- 77 trials
- Primary comparisons:
  - Placebo/no treatment
  - Oxytocin
  - Vaginal prostaglandins
  - Cervical prostaglandins
  - Low dosage versus higher dosage

Cochrane Systematic Review: Vaginal misoprostol for cervical ripening and induction of labor

- Compared to placebo or no treatment, failure to vaginal delivery was reduced (RR 0.36, 95% CI, 0.19 to 0.68, 5 trials, n=339).
- Uterine hyperstimulation, without FHR changes, was increased (RR 11.66 95% CI 2.78 to 494 trials).
Cochrane Systematic Review: Vaginal misoprostol for cervical ripening and induction of labor

- Compared with vaginal prostaglandin E2, intracervical prostaglandin E2 and oxytocin, vaginal misoprostol was associated with:
  - Less epidural analgesia use
  - Fewer failures to achieve vaginal delivery within 24 hours
  - Vaginal: RR 0.80, 95% CI 0.73 to 0.87, 13 trials
  - Intracervical: RR 0.68, 95% CI 0.59 to 0.78, 5 trials
  - Oxytocin: RR 0.66, 95% CI 0.44 to 1.00, 1 trial
- More uterine hyperstimulation

Cochrane Systematic Review: Vaginal misoprostol for cervical ripening and induction of labor

- Compared with vaginal or intracervical prostaglandin E2, oxytocin augmentation was less common with misoprostol (RR 0.65, 95% CI 0.57 to 0.73, 25 trials vaginal; 13 trials, RR 0.56, 95% CI 0.51 to 0.61, 13 trials intracervical) and meconium-stained liquor more common.

Cochrane Systematic Review: Vaginal misoprostol for cervical ripening and induction of labor

- Lower doses of misoprostol compared to higher doses were associated with more need for oxytocin augmentation and less uterine hyperstimulation, with and without fetal heart rate changes (13 trials, n= 2138).
  - Dosage range: 12.5 vs 25 mcg 6-hourly (1 trial); 25 vs 50 mcg 3 to 6-hourly (7 trials); 35 vs 50 mcg 4.5-hourly (1 trial); and 50 vs 100 mcg 4 to 6-hourly (4 trials)

ACOG Recommendations (Level A)

- Prostaglandin E analogues are effective in promoting cervical ripening and inducing labor
- Before 28 weeks of gestation, vaginal misoprostol appears to be the most efficient method of labor induction regardless of Bishop score.

ACOG Practice Bulletin No. 107. 2009
ACOG Recommendations (Level A)

- Approximately 25 mcg of misoprostol should be considered as the initial dose for cervical ripening and labor induction. The administration frequency should not be more than every 3-6 hours.

ACOG Practice Bulletin No. 107, 2009

ACOG Recommendations (Level A)

- Foley catheter is a reasonable and effective alternative for cervical ripening and inducing labor.

ACOG Practice Bulletin No. 107, 2009

ACOG Recommendations (Level B)

- Misoprostol (50 mcg every 6 hours) to induce labor may be appropriate in some situations, although higher doses are associated with an increased risk of complications, including uterine tachysystole with FHR decelerations.

ACOG Practice Bulletin No. 107, 2009

Misoprostol Vaginal Insert

- Hydrogel polymer base measuring approximately 30 x 10 x 0.8 mm
- Absorbable reservoir dose of misoprostol (the MVI); the MVI is not biodegradable
- Retrieval system
Miso-Obs-001
Pharmacokinetics

- 12 healthy volunteers
- MVI 100, 200, 400µg
- Results:
  - Confirmed that misoprostol is vaginally bioavailable via the MVI
  - Controlled release continues over entire 24h
  - Dose-dependent increase in systemic levels of misoprostol with increasing dose

Miso-Obs-002 in Parous Women

- MVI 25, 50, 100 and 200 µg in 124 parous women
- For the MVI 100 µg and MVI 200 µg:
  - Median time to delivery: 13.1 h (MVI 100) and 10.6 h (MVI 200)
  - 47% (MVI 100), 53% (MVI 200) had delivered by 12 hours;
  - 81% (MVI 100), 70% (MVI 200) by 24 hours

Miso-Obs-003 in Nulliparae

- MVI 25, 50, 100, 200, and 300 µg in 44 nulliparae
  - Dose-ranging, MTD
  - For the MVI 100 µg and MVI 200 µg:
    - Median time to delivery: 14.4 hours (MVI 100); 22.0 hours (MVI 200)
    - 9% (MVI 100), 27% (MVI 200) had delivered by 12 hours;
    - 82% (MVI 100), 49% (MVI 200) had delivered by 24 hours

Phase II Summary of Safety

- No surprises; similar to published reports with misoprostol tablets
- Dose-response increase in uterine hyperactivity
- Hyperstimulation uncommon below 200 µg
- No dose-dependent increase in nonreassuring fetal heart rate patterns
Phase II Conclusions

- Easy to use; single dose in 24h
- Self-titrating
- Well-defined pharmacokinetics and drug release
- Successful cervical ripening
- Reduced need for oxytocin
- Promoted rapid delivery
  - Over 80% of both nulliparous and parous women deliver by 24h
- Acceptable safety profile

Phase III Study Miso-Obs-004

- Study Design: A randomized, double-blind, phase III study of the efficacy and safety of MVI 50 and MVI 100 compared to dinoprostone 10 mg vaginal insert (Propess®)
- Co-primary Objectives:
  - Determination of time to vaginal delivery;
  - Determination of rate of cesarean delivery.
- Secondary Objectives:
  - Efficacy: Time to onset of labor; success on mBS at 12 hours;
  - Safety: assessment of maternal, fetal and neonatal adverse events.

Phase III Study Miso-Obs-004

- 46 Sites in the US; 3 Sites in Canada
- 1308 women recruited (1307 analyzed)
- MVI 100, MVI 50 and Cervidil
- 428 (MVI 100), 443 (MVI 50), 436 (Cervidil)
- 62% nulliparous; 38% parous
- Same entry criteria as phase II with exception that entry mBS was ≤4
- Same duration of treatment (up to 24 hours) and study drug removal criteria as phase II

Primary Reason for Study Drug Removal

<table>
<thead>
<tr>
<th>Reason</th>
<th>MVI 50 (N=443)</th>
<th>MVI 100 (N=428)</th>
<th>Dinoprostone (N=436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Active Labor</td>
<td>140 (31.6%)</td>
<td>182 (42.5%)</td>
<td>169 (38.8%)</td>
</tr>
<tr>
<td>Study drug in situ for 24 h</td>
<td>148 (33.4%)</td>
<td>66 (15.4%)</td>
<td>83 (19.0%)</td>
</tr>
<tr>
<td>Study drug fell out</td>
<td>100 (22.6%)</td>
<td>93 (21.7%)</td>
<td>100 (22.9%)</td>
</tr>
<tr>
<td>Maternal-Fetal Complications</td>
<td>28 (6.3%)</td>
<td>59 (13.8%)</td>
<td>57 (13.1%)</td>
</tr>
<tr>
<td>Maternal Request</td>
<td>8 (1.8%)</td>
<td>6 (1.4%)</td>
<td>9 (2.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (4.3%)</td>
<td>22 (5.1%)</td>
<td>17 (3.9%)</td>
</tr>
</tbody>
</table>
### Kaplan-Meier Plot of Time to Vaginal Delivery

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. Subjects</th>
<th>No. Subjects (Censored)*</th>
<th>Kaplan-Meier Median Time to Vaginal Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction to Delivery Interval (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVI 50</td>
<td>443</td>
<td>137 (30.9%)</td>
<td>2127* (35.5 h)</td>
</tr>
<tr>
<td>MVI 100</td>
<td>428</td>
<td>126 (29.4%)</td>
<td>1596* (26.6 h)</td>
</tr>
<tr>
<td>Dinoprostone</td>
<td>436</td>
<td>127 (29.1%)</td>
<td>1650 (27.5 h)</td>
</tr>
</tbody>
</table>

*Subjects who underwent Cesarean or went home without delivery were censored.
*P<0.01 compared to dinoprostone
*P=0.97 compared to dinoprostone

### Miso-Obs-004 Efficacy Results: Vaginal Delivery within 12 & 24 hours

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group</th>
<th>MVI 50 (N=443)</th>
<th>MVI 100 (N=428)</th>
<th>Dinoprostone (N=436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects having Vaginal Delivery</td>
<td></td>
<td>306</td>
<td>302</td>
<td>321</td>
</tr>
<tr>
<td>≤ 12 hours</td>
<td>23* (7.5%)</td>
<td>36* (11.9%)</td>
<td>72 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>≤ 24 hours</td>
<td>128** (41.8%)</td>
<td>185** (61.3%)</td>
<td>262 (60.2%)</td>
<td></td>
</tr>
</tbody>
</table>

### Miso-Obs-004 Safety Results: Cesarean Delivery

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>MVI 50</th>
<th>MVI 100</th>
<th>Dinoprostone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=443)</td>
<td>(N=428)</td>
<td>(N=436)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>124 (28.0%)</td>
<td>119 (27.8%)</td>
<td>115 (26.4%)</td>
</tr>
<tr>
<td>Parous</td>
<td>103 (37.6%)</td>
<td>99 (37.1%)</td>
<td>99 (36.8%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>21 (12.4%)</td>
<td>20 (12.4%)</td>
<td>16 (9.6%)</td>
</tr>
</tbody>
</table>

- P<0.05 compared to dinoprostone
Miso-Obs-004 Outcomes and AEs of Special Interest

<table>
<thead>
<tr>
<th></th>
<th>MVI 50 (N=443)</th>
<th>MVI 100 (N=420)</th>
<th>Dinoprostone (N=438)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-reassuring Fetal Heart Rate Pattern</td>
<td>12.2%</td>
<td>14.7%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Uterine Hypertonus</td>
<td>2.0%</td>
<td>2.8%</td>
<td>25.7%</td>
</tr>
<tr>
<td>Uterine Tachysystole</td>
<td>8.1%</td>
<td>15.0%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Uterine Hyperstimulation Syndrome</td>
<td>1.4%</td>
<td>4.0%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Antepartum hemorrhage</td>
<td>0</td>
<td>0.2%</td>
<td>0</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>0</td>
<td>0.7%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Meconium in Amniotic Fluid</td>
<td>2.7%</td>
<td>4.4%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Meconium Aspiration</td>
<td>0</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Low 5' Apgar Score</td>
<td>0.7%</td>
<td>0.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Neonatal Respiratory Distress Syndrome</td>
<td>0.5%</td>
<td>0</td>
<td>0.9%</td>
</tr>
<tr>
<td>Neonatal Respiratory Difficulty</td>
<td>0.2%</td>
<td>1.4%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Need for Tocolysis</td>
<td>4.1%</td>
<td>6.8%</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

Miso-Obs-004: Conclusions

- MVI 100 achieved cervical ripening success at 12 hours with a rate of 59.3%.
- MVI 100 and MVI 50 have comparable safety profiles.

Miso-Obs-004 Conclusions

- Did not meet efficacy endpoint of superiority for time to vaginal delivery over Cervidil.
- Median time to vaginal delivery for MVI 100 was 26.6 hrs, and for MVI 50 was 35.5 hrs.
- MVI 100 and MVI 50 had similar rates for co-primary safety endpoint of rate of Cesarean delivery.
  - Cesareans occurred in 28.0% and 27.8% of subjects in MVI 50 and MVI 100 groups, respectively.

Labor induction trials: Sample size considerations

- Primary outcome: Cesarean births
  - Assume that a difference of more than 30% (RR 0.7) would be clinically unacceptable
  - Standard sample size calculation (80% power, alpha 0.05): N=1300 women to show a difference of 6% (20% to 14%) to become statistically significant
**Labor induction trials: Sample size considerations**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline rate</th>
<th>Important change</th>
<th>RR</th>
<th>Total sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to achieve vaginal delivery</td>
<td>30%</td>
<td>21%</td>
<td>0.7</td>
<td>778</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>20%</td>
<td>14%</td>
<td>0.7</td>
<td>1294</td>
</tr>
<tr>
<td>Hyperstimulation</td>
<td>1%</td>
<td>0.7%</td>
<td>0.7</td>
<td>30,716</td>
</tr>
<tr>
<td>Perinatal morbidity and mortality</td>
<td>0.5%</td>
<td>0.35%</td>
<td>0.7</td>
<td>61,686</td>
</tr>
<tr>
<td>Maternal death or serious morbidity</td>
<td>0.2%</td>
<td>0.14%</td>
<td>0.7</td>
<td>154,598</td>
</tr>
</tbody>
</table>

**Future Investigation**

- Alternative methods of misoprostol administration
  - Time-release vaginal pessary
  - Oral
  - Buccal
  - Sublingual
- Mechanical cervical ripening
  - Double balloon device
- Outpatient cervical ripening
- Biomarker and/or bioassay use for prediction of success
- Mechanistic studies