**WHAT IS THE MOST EFFICIENT METHOD OF LABOR INDUCTION?**

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Antepartum and Intrapartum Management Conference
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**Disclaimers**

- Principal Investigator for Cytokine Pharmasciences, developer of the misoprostol vaginal insert (MVI)
- Consultant for Ferring Pharmaceuticals
- Off-label use of misoprostol will be discussed
- Author, UpToDate

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**Objectives**

- To discuss various pharmacologic and mechanical methods of labor induction and the evidence-base for their use
- To evaluate if an optimal method for labor induction exists

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**Labor induction in the United States**

*Natality Statistics: 2014*

- 3.99 million live births
- 23.2% require induction of labor
- Doubled since 1990

Cervical Assessment

Modified Bishop Score

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (cm)</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(*Effacement)</td>
<td>0-30%</td>
<td>40-50%</td>
<td>60-70%</td>
<td>&gt;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>Firm</td>
<td>Moderate</td>
<td>Soft</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Posterior</td>
<td>Mid</td>
<td>Anterior</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
- Nitric oxide donors

Cochrane Systematic Review:
Mechanical methods for induction of labor
Issue 2, 2012. Art. No.: CD001233

- 71 studies, n=9722
- Comparison with no treatment:
  - Women who did not achieve vaginal delivery within 24 hr (RR 0.90; 95% CI 0.64 to 1.26).
  - Risk of cesarean was similar between groups (6 studies; 416 women, RR 1.00; 95% CI 0.76 to 1.30).
  - There were no cases of severe neonatal and maternal morbidity.
Comparison with vaginal PGE2 (17 studies; 1894 women):
- Women who did not achieve vaginal delivery within 24 hrs was not significantly different (3 studies; 586 women RR 1.72; 95% CI 0.90 to 3.27)
- No increase in cesareans (RR 1.19, 95% CI 0.62-2.29).

Comparison with intracervical PGE2 (14 studies; 1784 women), no significant difference in women not achieving vaginal delivery within 24 hrs
- Reduced the risk of hyperstimulation with FHR changes when compared with vaginal prostaglandins: vaginal PGE2 (8 studies; 1203 women, RR 0.16; 95% CI 0.06 to 0.39) and misoprostol (3% versus 9%) (9 studies; 1615 women, RR 0.37; 95% CI 0.25 to 0.54).

Comparison with oxytocin, reduced risk of cesarean (5 studies; 398 women, RR 0.62; 95% CI 0.42 to 0.90).
- Likelihood of vaginal delivery within 24 hr was not reported.
- Hyperstimulation with FHR changes was reported in one study (200 participants), and did not differ.
- No reported cases of severe maternal or neonatal morbidity.

Risk of cesarean between mechanical methods and prostaglandins was comparable.
- Frequency of undelivered within 24 hrs similar although slightly higher rate in multiparas.
- Lesser hyperstimulation.

- 70 trials, involving 11,487 women
- PGE2 probably increase successful vaginal delivery rates in 24 hours and increase uterine hyperstimulation with FHR change rates, but do not effect or reduce cesarean rates.
- PGE2 increases cervical favorability but do not increase operative delivery rates.

PGE2 tablets, gels and pessaries appear to be as effective as each other, any differences between formulations are marginal but may be important.

Cost considerations should be made.

Cochrane Systematic Review: Vaginal misoprostol for cervical ripening and induction of labor (Issue 10., 2010. No.: CD000941)

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

Vaginal misoprostol in doses above 25 mcg four-hourly was more effective than conventional methods of labor induction, but with more uterine hyperstimulation.

Lower doses were similar to conventional methods in effectiveness and risks.
Cochrane Systematic Review:
Vaginal misoprostol for cervical ripening and induction of labor: CONCLUSIONS

- Vaginal route should not be researched further as another Cochrane review has shown that the oral route of administration is preferable to the vaginal route.
- Professional and governmental bodies should agree guidelines for use of misoprostol, based on best available evidence and local circumstances.

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-303: PHASE III MVI

- Multi-center trial, n=1300
- Comparison of MVI 200 mcg versus dinoprostone vaginal insert
- Efficacy
  - Time to vaginal delivery
- Safety markers: Cesarean rates, uterine contractile abnormalities, neonatal outcomes
- Clinical Trials: NCT01127581

Primary Efficacy
Median Time to Vaginal Delivery

Proportion of Subjects with Vaginal Delivery, %

Kaplan-Meier estimates of time to vaginal delivery. P < .001 (2-sided log-rank test).
Women with cesarean deliveries were censored using a time of 109.1 hours.
Women who did not deliver during the first hospitalization were censored using a time of 76.2 hours.
MVI = misoprostol vaginal insert; DVI = dinoprostone vaginal insert.
**Secondary Efficacy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MVI 200 (n = 678)</th>
<th>DVI (n = 680)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to any delivery, hr (95% CI)</td>
<td>18.3 (17.2 — 19.5)</td>
<td>27.3 (26.2 — 28.9)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median time to active labor, hr (95% CI)</td>
<td>12.1 (12.0 — 12.9)</td>
<td>18.6 (18.1 — 22.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Predelivery oxytocin administration, n (%)</td>
<td>324/674 (48.1)</td>
<td>497/671 (74.1)</td>
<td>&lt; .001b</td>
</tr>
</tbody>
</table>

a P values from 2-sided log-rank tests.

b P values obtained from a Fisher’s exact test for women who delivered during the first hospitalization.

MVI = misoprostol vaginal insert; DVI = dinoprostone vaginal insert; CI = confidence interval.

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**Primary Safety**

**Cesarean Rates**

<table>
<thead>
<tr>
<th>Cesarean Delivery, %</th>
<th>MVI 200 (n = 678)</th>
<th>DVI (n = 680)</th>
<th>P = .65</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26.0%</td>
<td>27.1%</td>
<td></td>
</tr>
</tbody>
</table>

Analysis based on the ITT population: MVI 200, n = 678; DVI, n = 680. MVI = misoprostol vaginal insert; DVI = dinoprostone vaginal insert.

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**Summary of Safety**

**Drug-Related Adverse Events**

<table>
<thead>
<tr>
<th>Incidence of Related AEs</th>
<th>Subject/Neonate, n (%)</th>
<th>MVI 200 (n = 678)</th>
<th>DVI (n = 680)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrapartum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate disorder</td>
<td>89 (13.1)</td>
<td>29 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Abnormal labor affecting fetus</td>
<td>34 (5.0)</td>
<td>9 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Abnormal uterine contractions</td>
<td>41 (6.0)</td>
<td>8 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Meconium in amniotic fluid</td>
<td>13 (1.9)</td>
<td>4 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal burning sensation</td>
<td>8 (1.2)</td>
<td>4 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Premature separation of placenta</td>
<td>2 (0.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postpartum c</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Neonatal c</td>
<td>5 (0.7)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

a As determined by the investigator.

b A subject who reported 2 or more adverse events with different preferred terms in the same system organ class was counted only once for that term using the incident with the strongest relationship to the study treatment.

Safety

- **Tachysystole:** 13.1% v. 4.3%, p=0.001
Conclusions

• Use of MVI 200 reduced the time to vaginal delivery by more than 11 hours compared with DVI
• MVI 200 reduced the times to any delivery and active labor with reduced need for oxytocin

Conclusions

• Both treatments had similar cesarean delivery rates
• Abnormal labor affecting the fetus and FHR disorder considered related to study drug were more common with MVI 200
• No clear evidence of a difference in maternal or neonatal safety outcomes for MVI 200 compared with DVI

Cochrane Systematic Review: *Oral misoprostol for cervical ripening and induction of labor*  
(Issue 3, 2013, Art. No.: CD001338.)

• 76 trials, 14,412 women:
  • Comparing oral misoprostol with placebo (9 trials, 1109 women):
    • More likely to give birth vaginally within 24 hr (RR 0.16, 95% CI 0.05 to 0.49; 1 trial; 96 women), need less oxytocin (RR 0.42, 95% CI 0.37 to 0.49; 7 trials; 933 women) and have a lower cesarean rate (RR 0.72, 95% CI 0.54 to 0.95; 8 trials; 1029 women).

• Comparing oral misoprostol with vaginal dinoprostone (12 trials, 3859 women):
  • Women were less likely to be delivered by cesarean (RR 0.88, 95% CI 0.78 to 0.99).
  • Had slower inductions, but there were no other statistically significant
Cochrane Systematic Review: Oral misoprostol for cervical ripening and induction of labor
(Issue 3, 2013, Art. No.: CD001338.)

- Comparing oral misoprostol with vaginal misoprostol (37 trials, 6417 women):
  - No statistically significant difference in serious neonatal morbidity/death or serious maternal morbidity or death.
  - Vaginal birth not achieved in 24 hrs, uterine hyperstimulation with FHR changes, and cesarean were highly heterogeneous - related to dosage.

Cochrane Systematic Review: Oral misoprostol for cervical ripening and induction of labor
(Issue 3, 2013, Art. No.: CD001338.)

- Fewer babies born with low Apgar scores in the oral group (RR 0.60, 95% CI 0.44 to 0.82; 19 trials; 4009 babies)
- Decrease in postpartum hemorrhage (RR 0.57, 95% CI 0.34 to 0.95; 10 trials; 1478 women).
- Increase in meconium-stained liquor (RR 1.22, 95% CI 1.03 to 1.44; 24 trials; 3634 women).

Cochrane Systematic Review: Oral misoprostol for cervical ripening and induction of labor
(Issue 3, 2013, Art. No.: CD001338.)

- Oral misoprostol is more effective than placebo, as effective as vaginal misoprostol and results in fewer cesareans than vaginal dinoprostone or oxytocin.

Cochrane Systematic Review: RECOMMENDATIONS

- If using OM, clinicians should use a dose of 20 to 25 mcg in solution.
- Oral regimens are recommended over vaginal regimens.
  - This is especially important in situations where the risk of ascending infection is high and the lack of staff means that women cannot be intensely monitored.
Cochrane Systematic Review: RECOMMENDATIONS

1. **Safety**: Oral route is associated with considerably less uterine hyperstimulation with FHR changes.
2. **Convenience and comfort**.
3. Because of short half-life, oral dose can be titrated against uterine response.
   - Start with a low dose, e.g. 25 mcg q2hr, and increase prn in nulliparous women to maximum dose of 50 mcg q2hr.

Cochrane Systematic Review: RECOMMENDATIONS

4. **Accuracy of dosage**. In many countries, misoprostol is available only as 200 mcg or 100 mcg tablets.
   - Breaking these tablets into small fragments carries risk of inappropriate dosage.
   - Accurate oral dosage by dissolving misoprostol in water and administering as a solution.
   - Left over solution should be discarded 24 hr after preparation.

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

<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>
Network meta-analysis: Comparison of all prostaglandins

- 280 randomized clinical trials, n=48,068
- Maternal/neonatal mortality & morbidity were rare.
- Unresolved inconsistency was observed for hyperstimulation.
- Relative to placebo, odds of failing to achieve a vaginal delivery were lowest for vaginal misoprostol (≥50 µg) (OR 0.06 (95% credible interval 0.02 to 0.12)), with a 39% absolute probability of event (95% credible interval 1% to 94%).

CONCLUSIONS: Low dose(<50 µg) titrated oral misoprostol solution had lowest probability of cesarean, whereas vaginal misoprostol (≥50 µg) had highest probability of achieving vaginal delivery within 24 hrs.

Findings have important implications for current national and international guidelines for induction of labor and future research in this area.

A twist: Foley and Misoprostol

Four-arm randomized trial, U Penn

- Misoprostol/Foley, Foley/Pitocin, Misoprostol alone, Foley alone
- Combinations shortened time to delivery (by ~2X) compared to single agents
  - MF: 13.1 [9.1-18.3]; FP: 14.5 [9.3-20.0]; M: 17.6 [12-26.7]; P: 17.7 [12.6-24.9], p=0.0001
- No differences in cesarean rates
  - Range 24.0% (M) to 30.4% (FP), p=0.07

Levinne L. Am J Obstet Gynecol 2016; 47:S4
Cochrane Systematic Review:

**Induction of labor: PREVIOUS CESAREAN**

Issue 6, 2011, Art. No.: CD009792

- 2 studies evaluated, n=80
- PGE2 vs. oxytocin (Taylor): One uterine rupture in PGE2 group (after the use of PGE2 & oxytocin) (42 women; RR 3.00, 95% CI 0.13 to 69.70).
- PGE1 vs. oxytocin (Wing): Two uterine ruptures in 2/17 PGE1-treated women (38 women; RR 6.11, 95% CI 0.31 to 119.33)
- Insufficient information regarding the optimal method of labor induction.

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 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 Recommendations (Level A)

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

FUTURE INVESTIGATION

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

Is there an optimal method of labor induction?

NO

Cochrane Systematic Review:

Outpatient v. inpatient induction

Issue 3, 2013. Art. No.: CD007273

- Consumerism
- Patient-centeredness
- Cost-consciousness
Cochrane Systematic Review:  
**Outpatient v. inpatient induction**  
Issue 3, 2013. Art. No.: CD007273

- 4 trials, 1439 women; all different methods
- A. Vaginal PGE2 (2 studies, 1028 women).
  - No differences for most review outcomes.
  - No evidence of a difference between likelihood of women requiring instrumental delivery in either setting (RR 1.29; 95% CI 0.79 to 2.13).
  - Overall length of hospital stay was similar.

Cochrane Systematic Review:  
**Outpatient v. inpatient induction**  
Issue 3, 2013. Art. No.: CD007273

- B. Controlled release PGE2 10 mg (1 study 300 women).
  - No evidence of differences for most review outcomes, including success of induction.
  - During induction period itself, women in outpatient group were more likely to report high levels of satisfaction with care (satisfaction rated >7, RR 1.42; 95% CI 1.11 to 1.81), but satisfaction scores measured postnatally were similar in two groups.

Cochrane Systematic Review:  
**Outpatient v. inpatient induction**  
Issue 3, 2013. Art. No.: CD007273

- C. Foley catheter (1 study, 111 women).
  - No evidence of differences between groups for cesarean rates, total induction time and the numbers of babies admitted to neonatal intensive care.

**CONCLUSIONS:** Data available to evaluate the efficacy or potential hazards of outpatient induction are limited.

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### Outcomes for diabetic women after labor induction with PG inserts

<table>
<thead>
<tr>
<th></th>
<th>DVI (n=144)</th>
<th>MVI (200 mcg) (n=98)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Modified Bishop score</td>
<td>2.0 (2.3)</td>
<td>3 (1.25, 3)</td>
<td>0.67</td>
</tr>
<tr>
<td>Time to active labor (≥ 4 cm, min)*</td>
<td>1444 (1217, 1675)</td>
<td>788 (720, 952)</td>
<td>8.78 x 10^-6</td>
</tr>
<tr>
<td>Time to delivery (min)*</td>
<td>1774 (1639, 2037)</td>
<td>1207 (1129, 1339)</td>
<td>1.37 x 10^-5</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>32.6%</td>
<td>27.5%</td>
<td>0.40**</td>
</tr>
</tbody>
</table>

Data presented as median (IQR) or median (%95 CI) from two MVI Phase III trials.

*Estimates of median survival time based on Kaplan-Meier estimator of the survival curve, **Fisher’s exact test.
### Adjusted estimates of relative treatment effect of MVI vs. DVI for time to event endpoints: Diabetics

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LCI (HR)</th>
<th>UCI (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to active labor</td>
<td>2.49</td>
<td>1.86</td>
<td>3.30</td>
<td>8.14 x 10^-10</td>
</tr>
<tr>
<td>Time to delivery</td>
<td>2.41</td>
<td>1.83</td>
<td>3.17</td>
<td>3.99 x 10^-10</td>
</tr>
</tbody>
</table>

**Competing Risk Analysis**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LCI (HR)</th>
<th>UCI (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to vaginal delivery</td>
<td>3.12</td>
<td>2.19</td>
<td>4.45</td>
<td>3.07 x 10^-10</td>
</tr>
<tr>
<td>Time to cesarean</td>
<td>1.77</td>
<td>1.06</td>
<td>2.96</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adjusted for gestational age, maternal age, parity, BMI at induction, race, and baseline modified Bishop score

*HRs are cause specific hazard ratios

### Outcomes for hypertensive women after labor induction with PG inserts

<table>
<thead>
<tr>
<th>Time to active labor (min)*</th>
<th>1438 (1125, 1557)</th>
<th>930 (792, 1076)</th>
<th>0.0004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to delivery (hours) *</td>
<td>1791 (1662, 1969)</td>
<td>1292 (1182, 1447)</td>
<td>1.75x10^-5</td>
</tr>
</tbody>
</table>

Data presented as median (IQR) or median (%95 CI) from two MVI Phase III trials

*Estimates of median survival time based on Kaplan-Meier estimator of the survival curve

### Adjusted estimates of the relative treatment effect of MVI vs. DVI for time to event endpoints: Hypertensives

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LCI (HR)</th>
<th>UCI (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to active labor</td>
<td>1.67</td>
<td>2.08</td>
<td>0.3228</td>
<td>3.31x10^-6</td>
</tr>
<tr>
<td>Time to delivery</td>
<td>1.76</td>
<td>1.43</td>
<td>2.17</td>
<td>7.26x10^-8</td>
</tr>
</tbody>
</table>

**Competing Risk Analysis**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LCI (HR)</th>
<th>UCI (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to vaginal delivery</td>
<td>1.86</td>
<td>1.46</td>
<td>2.38</td>
<td>7.10x1--7</td>
</tr>
<tr>
<td>Time to cesarean</td>
<td>1.49</td>
<td>1.02</td>
<td>2.19</td>
<td>0.0407</td>
</tr>
</tbody>
</table>

Adjusted for gestational age, maternal age, parity, BMI at induction, race, and baseline modified Bishop score

*HRs are cause specific hazard ratios