*Original Research*

# Mechanical and Pharmacologic Methods of Labor Induction

## *A Randomized Controlled Trial*

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**OBJECTIVE:** To evaluate the effectiveness of four commonly used induction methods.

**METHODS:** This randomized trial compared four induction methods: misoprostol alone, Foley alone, misoprostol–cervical Foley concurrently, and Foley–oxytocin concurrently. Women undergoing labor induction with full-term (37 weeks of gestation or greater), singleton, vertex-presenting gestations, with no contraindication to vaginal delivery, intact membranes, Bishop score 6 or less, and cervical dilation 2 cm or less were included. Women were enrolled only once during the study period. Our primary outcome was time to delivery. Neither patients nor health care providers were blinded to assigned treatment group because examinations are required for placement of all methods; however, research personnel were blinded during data abstraction. A sample size of 123 per group (n=492) was planned to compare the four groups pairwise ($P \leq .008$) with a 4-hour reduction in delivery time considered clinically meaningful.

**RESULTS:** From May 2013 through June 2015, 997 women were screened and 491 were randomized and analyzed. Demographic and clinical characteristics were similar among the four treatment groups. When comparing all induction method groups, combination methods achieved a faster median time to delivery than single-agent methods (misoprostol–Foley: 13.1 hours, Foley–oxytocin: 14.5 hours, misoprostol: 17.6 hours, Foley: 17.7 hours, $P<.001$). When censored for cesarean delivery and adjusting for parity, women who received misoprostol–Foley were almost twice as likely to deliver before women who received misoprostol alone (hazard ratio 1.92, 95% confidence interval [CI] 1.42–2.59) or Foley alone (hazard ratio 1.87, 95% CI 1.87 1.39–2.52), whereas Foley–oxytocin was not statistically different from single-agent methods.

**CONCLUSION:** After censoring for cesarean delivery and adjusting for parity, misoprostol–cervical Foley resulted in twice the chance of delivering before either single-agent method.

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Four million women give birth each year in the United States with more than 20% of them undergoing induction of labor.[1] As such, induction is one of the most common procedures performed during a woman's pregnancy. Despite this, the fastest and most effective method of inducing labor is unknown.[2,3–5]

Both mechanical and pharmacologic agents are used for induction of labor.[3–5] These agents, when used individually, reduce the incidence of cesarean delivery in women undergoing induction.[3,4] Plausibly, combining both mechanical and pharmacologic methods may have a synergistic effect in achieving labor. Some studies have shown promise in reducing labor

time and risk of cesarean delivery with combination methods,[6,7] but others have not.[8–11]

Therefore, the objective of our study was to compare the time to delivery among four different, routinely used cervical-ripening methods for induction of labor, including two different combination methods. Our hypothesis was that women who undergo an induction with combined methods will have a shorter time to delivery than those who undergo induction with a single method.

## MATERIALS AND METHODS

We conducted this randomized clinical trial (the "FOR MOMI" trial: Foley or Misoprostol for the Management of Induction) at the Hospital of the University of Pennsylvania to compare time to delivery among four different methods of induction: misoprostol alone, Foley alone, misoprostol–cervical Foley concurrently, and cervical Foley–oxytocin concurrently. Before initiation of the study, approval was obtained from a convened institutional review board at the University of Pennsylvania and registered with ClinicalTrials.gov (NCT01916681).

Participants were at least 18 years of age with a full-term (37 weeks of gestation or greater), singleton gestation in cephalic presentation. Both nulliparous and multiparous women were included. Women were required to have intact membranes, a Bishop score of 6 or less, and cervical dilation 2 cm or less to be eligible. Women were excluded if there was a contraindication to a vaginal delivery or to misoprostol, fetal demise, or major fetal anomaly. Non–English-speaking women, women with human immunodeficiency virus, and women with medical conditions requiring an assisted second stage were also excluded. Additional exclusion criteria were as follows: category 3 fetal heart rate tracing; hemolysis elevated liver enzymes, and low platelet count syndrome or eclampsia; growth restriction less than the 10th percentile (based on Hadlock growth curves) with reversal of flow in umbilical artery Doppler studies; and growth restriction less than the fifth percentile with elevated, absent, or reversal of flow in umbilical artery Doppler studies. No woman had a prior attempt at induction in this pregnancy. Women were included in the study only once. Gestational age was determined using routine obstetric guidelines.[12]

Patients were approached in the obstetric unit by health care providers trained in the study consenting process before the start of their induction. Once written consent was obtained, the participants were randomized to one of the four treatment groups. An Internet-based clinical trial management system, Research Electronic Data Capture, REDCap,[13] was accessed to enter enrollment information, ensure eligibility, and request randomized treatment allocation. An independent consultant created a computer-generated randomization scheme that used balanced treatment allocation in blocks of 20. Randomization was stratified by parity.

Each of the four treatment groups had a standardized protocol for induction and active-phase labor management. A brief description of the protocols is described subsequently. The complete algorithm for the induction groups and active labor management can be found in the supplemental information (Appendices 1–5, available online at http://links.lww.com/AOG/A897). Neither the patients nor the health care providers were blinded to the assigned treatment group because this would not be practical. However, trained research personnel were blinded to study group during data abstraction.

Women in the misoprostol-only group received 25 micrograms of misoprostol per vagina every 3 hours, repeated up to five additional times for a maximum of 24 hours. Oxytocin was initiated if there was a contraindication to another misoprostol dose or if additional cervical ripening was not indicated (Appendix 1, http://links.lww.com/AOG/A897).

Women in the cervical Foley-only group had a 18-F Foley catheter with a 30-cc balloon inserted digitally or by direct visualization with a speculum. The Foley bulb was placed just above the level of the internal os and inflated with 60 cc of sterile water.[6,7,11,14] The catheter was taped to the inner thigh with gentle traction and deflated and removed after 12 hours if still in place. The oxytocin protocol was initiated once the Foley bulb was no longer in place (Appendix 2, http://links.lww.com/AOG/A897).

Women in the misoprostol–cervical Foley group had both misoprostol and a cervical Foley placed concurrently using the same procedures as noted for the individual groups (Appendix 3, http://links.lww.com/AOG/A897).

Women in the cervical Foley–oxytocin group had a cervical Foley placed using the same protocol as described in the cervical Foley-only group. Oxytocin was initiated concurrently at the start of induction (Appendix 4, http://links.lww.com/AOG/A897).

For all participants, our hospital-based oxytocin protocol was used. The protocol begins with 2 milliunits/min of oxytocin, increasing by 2 milliunits every 15 minutes until regular uterine contractions occur. The maximum dose of oxytocin is considered to be 40 milliunits, with no limit as to the length of time a participant can remain at 40 milliunits.

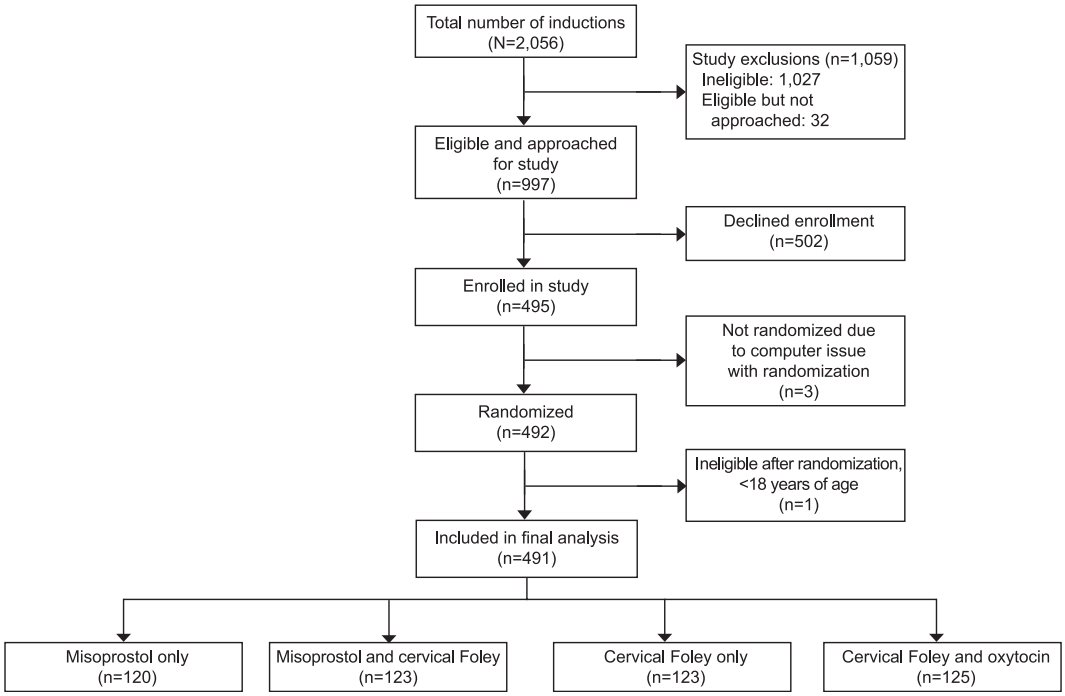


**Fig. 1.** Flowchart of patients enrolled.

*Levine. Randomized Trial of Four Induction Methods. Obstet Gynecol 2016.*

Health care providers were able to perform an amniotomy at any point during the labor course. If the patient had not yet had membranes ruptured and the cervix was 4 cm or greater dilated, it was recommended that an amniotomy be performed at this time, if clinically feasible. Once cervical dilation was 5 cm or greater, health care providers were instructed to proceed with the active labor management protocol (Appendix 5, http://links.lww.com/AOG/A897), although active labor itself was defined as cervical dilation 6 cm or greater. Labor interventions including amnioinfusion, fetal scalp electrode, tocolysis, and management of the second stage (including operative delivery) were at the discretion of the managing health care provider. All patients had continuous fetal monitoring throughout induction, labor, and delivery. Cesarean delivery was at the discretion of the health care provider. Recommendations specific for this study included cesarean delivery if not in active labor after 36 hours of cervical ripening or if the patient was undelivered 12 hours after achieving active labor.

The primary outcome measure was time to delivery (hours) defined as time from initiation of induction method to delivery time, regardless of mode of delivery. Secondary outcome measures were cesarean delivery rate, time to vaginal delivery (hours), time to delivery censored for cesarean delivery, time to active labor (defined as dilatation 5 cm or greater), delivery within 12 hours, delivery within 24 hours, and maternal length of stay (defined as length of time from admission for induction to discharge postpartum, days) and indication for cesarean delivery. A composite maternal morbidity outcome was prespecified to include one or more of the following during labor, delivery, or in the 4 weeks postpartum: third- or fourth-degree perineal laceration, blood transfusion, endometritis, wound separation–infection (defined by the need for additional wound closure or the need for antibiotics), venous thromboembolism, hysterectomy, intensive care unit admission, or death. Other maternal secondary outcomes analyzed were chorioamnionitis (defined by the presence of maternal fever 100.4°F or greater in the presence of maternal or fetal tachycardia or fundal tenderness), use of terbutaline, intrauterine pressure catheter, amnioinfusion, or analgesia use.

A composite neonatal morbidity outcome was prespecified to include one or more of the following before neonatal discharge: severe respiratory distress syndrome (defined as intubation and mechanical ventilation for a minimum of 12 hours), culture-proven presumed neonatal sepsis, neonatal blood transfusion, hypoxic–ischemic encephalopathy, intraventricular hemorrhage grade 3 or 4, necrotizing

**Table 1. Maternal Characteristics by Randomized Treatment Group**

| Characteristic | Misoprostol Only (n=120) | Misoprostol–Foley (n=123) | Foley Only (n=123) | Foley–Oxytocin (n=125) |
|---|---|---|---|---|
| Age (y) | 26.7 [21.8–31.0] | 28 [22.4–33.1] | 27.3 [22.3–32.9] | 26.5 [22.4–31.7] |
| BMI (kg/m$^2$) | 27.5 [24.3–35.9] | 28.3 [23.9–32.6] | 29.1 [24.4–35.7] | 30.1 [24.6–35.8] |
| Race, black | 94 (78.3) | 93 (75.6) | 99 (80.5) | 95 (76.0) |
| Insurance, public | 80 (66.7) | 78 (63.4) | 81 (65.9) | 87 (69.6) |
| Prenatal care provider, clinic | 78 (65.0) | 72 (58.5) | 70 (56.9) | 77 (61.6) |
| No. of prenatal visits | 9.5 [7–11] | 10 [8–12] | 10 [8–12] | 10 [7–12] |
| Nulliparous | 70 (58.3) | 73 (59.4) | 73 (59.4) | 74 (59.2) |
| Gestational age at induction (wk) | 39.1 [37.9–40.1] | 39.6 [38.3–40.7] | 39.3 [38.3–40.4] | 39.1 [38.3–40.6] |
| Bishop score at randomization | 3 [2–4] | 3 [2–4] | 3 [2–4] | 3 [2–4] |
| Dilation at randomization | 1 [0.5–1.5] | 1 [1–1.5] | 1 [0.5–1.5] | 1 [0.5–1.5] |
| Bishop score at induction | 3 [2–4] | 3 [3–4] | 3 [2–4] | 3 [2–4] |
| Dilation at induction | 1 [1–1.5] | 1.5 [1–2] | 1 [1–1.5] | 1 [1–1.5] |
| Dilation at amniotomy | 4 [3–4] | 4 [4–5] | 4 [4–4.5] | 4 [4–5] |
| Diabetes | | | | |
| Gestational | 6 (5.0) | 8 (6.5) | 5 (4.1) | 14 (11.2) |
| Pregestational | 3 (2.5) | 2 (1.6) | 4 (3.3) | 2 (1.6) |
| Chronic hypertension | 7 (5.8) | 10 (8.1) | 10 (8.1) | 12 (9.6) |
| Pregnancy-related hypertension | | | | |
| GHTN or mild preeclampsia | 22 (18.3) | 27 (22.0) | 33 (26.8) | 32 (25.6) |
| Severe or superimposed preeclampsia | 13 (10.8) | 14 (11.4) | 12 (9.8) | 11 (8.8) |
| History of other medical morbidity | 10 (8.3) | 19 (15.5) | 8 (6.5) | 17 (13.6) |
| Tobacco use in pregnancy | 9 (7.5) | 9 (7.3) | 10 (8.1) | 15 (12.0) |
| Induction scheduled | 55 (45.8) | 55 (44.7) | 47 (38.2) | 62 (49.6) |
| Indication for induction | | | | |
| Late term or postterm* | 12 (10.0) | 20 (16.3) | 18 (14.6) | 17 (13.6) |
| Maternal† | 28 (23.3) | 37 (30.1) | 38 (30.9) | 44 (35.2) |
| Fetal‡ | 64 (53.3) | 57 (46.3) | 54 (43.9) | 50 (40.0) |
| Elective or other§ | 16 (13.3) | 9 (7.3) | 13 (10.6) | 14 (11.2) |
| Female sex | 61 (50.8) | 65 (52.9) | 54 (43.9) | 60 (48.0) |

BMI, body mass index; GHTN, gestational hypertension.
Data are median [interquartile range] or n (%) unless otherwise specified.
Categorical comparisons with $\chi^2$ or Fisher exact tests and continuous comparisons with Kruskal-Wallis test unless otherwise specified.
* Defined as 41 weeks of gestation or greater.
† Examples include chronic hypertension, gestational hypertension, preeclampsia, diabetes, renal disease, history of venous thromboembolism, cardiac disease, or other chronic medical condition in which induction was recommended.
‡ Examples include oligohydramnios, intrauterine growth restriction, abnormality on fetal testing.
§ Examples of "other" include history of an intrauterine fetal demise, vaginal bleeding at term, cholestasis.

enterocolitis, or receipt of head cooling. Other neonatal outcomes analyzed were neonatal intensive care unit admission, neonatal intensive care unit admission greater than 48 hours, and neonatal length of stay (days).

Trained research staff, uninvolved with the clinical care, collected all induction, labor and delivery information, maternal demographics, and maternal and neonatal outcomes.

A data safety monitoring board was established to independently evaluate the safety of the study. An interim safety analysis was performed for predefined adverse outcomes with recommendations to continue the study without changes.

A 4-hour reduction in time to delivery was considered clinically meaningful. In the literature, the mean time to delivery for patients undergoing induction of labor was $18 \pm 8.5$ hours.[6–8] Because there is not one method of induction that is thought to be standard of care, we chose to compare all four groups with six separate comparisons. Therefore, a type I $\alpha$ error rate of 0.008 was selected. Assuming 80% power, equal group sizes, and a two-sided $P$ value, we would need 112 patients in each group for a total sample size of 448. A crossover–dropout rate of 10% was assumed leading to a final desired sample size of 492.

Descriptive statistics for the primary and secondary labor outcomes are reported both overall and by parity.

Statistical analyses were performed using an intention-to-treat principle. Bivariate analyses were carried out using analysis of variance and Kruskal-Wallis for normally and nonnormally distributed continuous variables, respectively, and Pearson $\chi^2$ or Fisher exact for categorical variables, as appropriate. Time to event regression analysis for labor length (regardless of delivery mode) was modeled with a Cox proportional hazard model. Labor length with censoring at the time of cesarean delivery was also modeled using a Cox proportional hazards model. Risk of cesarean delivery was estimated using a generalized linear model with robust error variance.[15] Final models were adjusted for parity. Hazard ratios (HRs) and risk ratios with 95% confidence interval are reported. Statistical significance for the primary outcome was set at $P<.008$.

A sensitivity analysis was also performed using the induction methods that the patient actually received to determine whether crossovers may have influenced the results.

## RESULTS

There were 2,056 inductions of labor during the study period of May 2013 to June 2015. Of the 997 women who met eligibility criteria and were approached for enrollment, 502 declined enrollment, and 492 were randomized into one of the four treatment groups (Fig. 1). One woman was excluded postrandomization after it was discovered that she was younger than 18 years old, yielding a final sample size of 491 women.

Demographic and clinical characteristics were similar among the four treatment groups including Bishop score, cervical dilation at induction, or indication for induction among the groups (Table 1).

Overall, combination methods achieved a faster median time to delivery than the single agents ($P<.001$; misoprostol–Foley: 13.1 hours, Foley–oxytocin: 14.5 hours, misoprostol alone: 17.6 hours, Foley alone: 17.7 hours; Table 2; Fig. 2). The faster time to delivery for combined methods was observed in both nulliparous and multiparous women and remained true when analysis was restricted to women who had a vaginal delivery (Table 2). The proportion of women delivered by 24 hours and by 12 hours was significantly greater for the combined induction methods.

Assumptions for proportional hazard were met for all analyses. When censoring for cesarean delivery and adjusting for parity, the Foley–oxytocin group is no longer significantly faster than single-agent methods and the misoprostol–Foley group is superior (Table 3). When using misoprostol alone or cervical Foley alone as the reference group, women with combined misoprostol–Foley are twice as likely to deliver earlier (HR 1.92, HR 1.87, respectively; Table 3). In other words, among women who have not yet delivered, women with misoprostol only or

**Table 2. Time-to-Delivery Outcomes Among Treatment Groups**

| Outcome | Misoprostol Only (n=120) | Misoprostol–Foley (n=123) | Foley Only (n=123) | Foley–Oxytocin (n=125) | P* |
|---|---|---|---|---|---|
| Time to delivery (h) | 17.6 [11.9–26.7] | 13.1 [9.1–18.3] | 17.7 [12.6–24.9] | 14.5 [9.3–20.0] | <.001 |
| Nulliparous | 21.4 [15.6–33.3] | 16.2 [11.5–21.6] | 21.0 [15.8–26.4] | 17.7 [11.9–22.0] | <.001 |
| Multiparous | 12.9 [9.9–18.7] | 9.3 [6.7–13.0] | 15.5 [10.1–18.2] | 10.4 [6.8–14.8] | <.001 |
| Time to vaginal delivery (h) | 16.6 [11.2–23.8] | 11.0 [8.0–15.5] | 16.3 [11.2–21.0] | 11.0 [8.4–16.5] | <.001 |
| Nulliparous | 19.1 [15.1–28.7] | 15.3 [10.2–17.9] | 18.2 [13.4–24.4] | 15.2 [9.7–20.0] | <.001 |
| Multiparous | 12.9 [9.9–18.2] | 9.1 [6.6–12.6] | 14.8 [10.1–17.7] | 10.1 [6.6–13.5] | <.001 |
| Time to active labor (h) | 13.3 [9.1–22.4] | 7.4 [4.4–10.7] | 11.0 [7.9–14.9] | 8.1 [5.3–11.2] | <.001 |
| Nulliparous | 17.7 [10.1–25.7] | 8.8 [5.5–11.5] | 12.2 [8.3–18.1] | 9.0 [7.2–13.7] | <.001 |
| Multiparous | 10.9 [7.8–16.0] | 5.7 [3.9–8.5] | 9.4 [7.6–11.8] | 6.4 [4.2–9.9] | <.001 |
| Delivery within 24 h | 84 (70.0) | 108 (87.8) | 90 (73.2) | 105 (84.0) | .001 |
| Nulliparous | 38 (54.3) | 59 (80.8) | 42 (57.5) | 58 (78.4) | <.001 |
| Multiparous | 46 (92.0) | 49 (98.0) | 48 (96.0) | 47 (92.2) | .52 |
| Delivery within 12 h | 31 (25.8) | 55 (44.7) | 27 (22.0) | 51 (40.8) | <.001 |
| Nulliparous | 9 (12.9) | 20 (27.4) | 8 (11.0) | 19 (25.7) | .02 |
| Multiparous | 22 (44.0) | 35 (70.0) | 19 (38.0) | 32 (62.8) | .003 |
| Cesarean delivery | 29 (24.2) | 34 (27.6) | 35 (28.5) | 38 (30.4) | .74 |
| Nulliparous | 23 (32.9) | 32 (43.8) | 30 (41.1) | 30 (40.5) | .58 |
| Multiparous | 6 (12.0) | 2 (4.0) | 5 (10.0) | 8 (15.7) | .27 |

Data are median [interquartile range] or n (%) unless otherwise specified.
Categorical variables were compared with $\chi^2$ or Fisher exact tests, and continuous variables were compared with Kruskal-Wallis tests.
* *P* values are significance level for four-group comparisons.

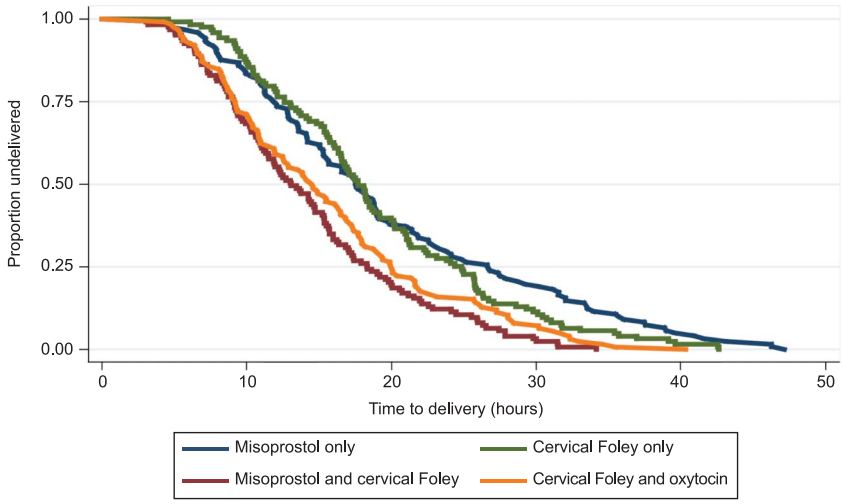


**Fig. 2.** Estimated time to delivery by study group. This figure displays the Kaplan-Meier survival curves for time to delivery for the four induction method groups, $P<.001$.

*Levine. Randomized Trial of Four Induction Methods. Obstet Gynecol 2016.*

Foley only were almost 50% less likely to deliver before women with misoprostol–Foley concurrently (HR 0.52, HR 0.53, respectively). There was no significant difference between Foley–oxytocin and any of the three other groups.

There was no statistical difference in the cesarean delivery rate among the groups, both overall and when stratified by parity (Table 2). There were no statistically significant differences in the indication for cesarean delivery or the composite maternal morbidity among the four groups. There were no cases of thromboembolism, hysterectomy, intensive care unit admission, or death (Table 4).

There were no statistically significant differences in neonatal outcomes among the four groups. There were no cases of neonatal blood transfusion, hypoxic–ischemic encephalopathy, intraventricular hemorrhage grade 3 or 4, necrotizing enterocolitis, or need for head cooling; therefore, the initial a priori composite neonatal outcome was not evaluated.

There were 31 (6.3%) women who received a different induction method than assigned by randomization. The main reasons for starting with a different agent were inability to place the cervical Foley or the patient was unable to tolerate Foley placement (n=9) and rapid advancement in cervical dilation from randomization to induction of labor, precluding the need for cervical ripening (n=10). There were 11 (2.2%) women who received the correct initial induction agent but had their method changed before active labor. When analyses were repeated using the "as-treated" method, results were unchanged (data available on request).

## DISCUSSION

This randomized clinical trial compares four different labor induction methods in a head-to-head trial. After censoring for cesarean delivery and adjusting for parity, we demonstrated misoprostol–cervical Foley to be the superior method with women twice as likely to deliver before those who received either misoprostol alone (HR 1.92) or cervical Foley alone (HR 1.87). Additionally, there was a higher proportion of women delivered by 12 hours and by 24 hours with combination methods.

Our findings of a faster delivery with combined methods are consistent with other studies.[6,7] However,

**Table 3. Hazard Ratios for Pairwise Comparisons of Time to Delivery***

| Group | Misoprostol Only | Foley Only | Misoprostol–Foley | Foley–Oxytocin |
|---|---|---|---|---|
| Misoprostol | — | 1.03 [0.76–1.38] ($P$=.87) | **1.92 [1.42-2.59] ($P$<.001)** | 1.39 [1.03–1.87] ($P$=.03) |
| Foley | 0.9 [0.72–1.31] ($P$=.87) | — | **1.87 [1.39-2.52] ($P$<.001)** | 1.35 [1.00–1.82] ($P$=.047) |
| Misoprostol–Foley | **0.52 [0.39-0.74] ($P$<.001)** | **0.53 [0.40-0.72] ($P$<.001)** | — | 0.72 [0.54–0.97] ($P$=.03) |
| Foley–oxytocin | 0.72 [0.54–0.97] ($P$=.03) | 0.74 [0.55–1.00] ($P$=.047) | 1.38 [1.03–1.87] ($P$=.03) | — |

The reference groups are listed on the left side of the table.
Bold indicates statistically significance ($P\leq.008$).
* Censored for cesarean delivery and adjusted for parity.

**Table 4. Secondary Outcomes Among Treatment Groups**

| | Misoprostol Only (n=120) | Misoprostol–Foley (n=123) | Foley Only (n=123) | Foley–Oxytocin (n=125) | P* |
|---|---|---|---|---|---|
| Maternal Outcome | | | | | |
| Indication for cesarean delivery† | | | | | |
| Failed induction | 10 (34.5) | 12 (35.3) | 16 (45.7) | 14 (36.8) | .76 |
| Arrest of dilation | 4 (13.8) | 9 (26.5) | 8 (22.9) | 12 (31.6) | .40 |
| Arrest of descent | 5 (17.2) | 5 (14.7) | 0 (0) | 4 (10.5) | .05 |
| NRFHT | 15 (51.7) | 19 (55.9) | 20 (57.1) | 16 (42.1) | .56 |
| Elective or other | 5 (17.2) | 2 (5.9) | 5 (14.3) | 4 (10.5) | .52 |
| Intrauterine pressure catheter | 53 (44.2) | 53 (43.1) | 70 (56.9) | 69 (55.2) | .05 |
| Amnioinfusion | 27 (22.5) | 23 (18.7) | 36 (29.3) | 29 (23.2) | .27 |
| Regional analgesia | 111 (92.5) | 114 (92.7) | 114 (92.7) | 121 (96.8) | .43 |
| IV narcotics | 9 (7.5) | 11 (8.9) | 19 (15.5) | 18 (14.4) | .14 |
| Terbutaline used | 32 (26.7) | 19 (15.5) | 23 (18.7) | 25 (20.0) | .17 |
| Oxytocin use in active labor | 72 (68.6) | 82 (70.7) | 98 (89.9) | 115 (98.3) | <.001 |
| Chorioamnionitis | 9 (7.5) | 15 (12.2) | 17 (13.8) | 20 (16.0) | .22 |
| Maternal morbidity | 8 (6.7) | 5 (4.1) | 13 (10.6) | 10 (8.0) | .26 |
| Endometritis | 1 (0.8) | 0 (0) | 0 (0) | 0 (0) | .24 |
| Third- or fourth-degree laceration | 2 (2.2) | 1 (1.1) | 6 (6.8) | 3 (3.5) | .20 |
| Blood transfusion | 2 (1.7) | 1 (0.8) | 5 (4.1) | 4 (3.2) | .36 |
| Wound separation or infection | 1 (0.8) | 1 (0.8) | 1 (0.8) | 3 (2.4) | .73 |
| Readmission | 2 (1.7) | 2 (1.6) | 3 (2.4) | 7 (5.6) | .24 |
| Total maternal length of stay (d) | 3 [3–4] | 3 [3–4] | 3 [3–4] | 3 [3–4] | .20 |
| Postpartum length of stay (d) | 2 [2-2] | 2 [2-2] | 2 [2-2] | 2 [2–3] | .59 |
| Neonatal outcomes | | | | | |
| Birth weight (g) | 3,178 [2,635–3,625] | 3,240 [2,875–3,600] | 3,230 [2,855–3,575] | 3,240 [2,920–3,595] | .16‡ |
| Apgar score at 1 min | 8 [7.5–9] | 8 [8–9] | 8 [8–9] | 8 [8–9] | .06 |
| Apgar score at 5 min | 9 [9-9] | 9 [9-9] | 9 [9-9] | 9 [9-9] | .26 |
| Neonatal length of stay (d) | 2 [2–3] | 2 [2–3] | 2 [2–3] | 2 [2–3] | .82 |
| NICU admission | 15 (12.5) | 10 (8.1) | 17 (13.8) | 11 (8.8) | .40 |
| NICU admission greater than 48 h | 6 (5.0) | 4 (3.3) | 5 (4.1) | 2 (1.6) | .46 |
| Severe RDS | 1 (0.8) | 0 (0) | 2 (1.6) | 0 (0) | .29 |
| Neonatal sepsis | 2 (1.7) | 1 (0.8) | 1 (0.8) | 1 (0.8) | .82 |

NRFHT, nonreassuring fetal heart tracing; IV, intravenous; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome.
Data are n (%) or median [interquartile range] unless otherwise indicated.
Categorical variables are compared with $\chi^2$ and Fisher exact tests and continuous variables are compared with Kruskal-Wallis tests unless otherwise indicated.
* *P* values are significance level for four-group comparison.
† If reported as the primary or secondary indication, it was counted in this summary. Therefore, percentages do not sum to 100%.
‡ Comparison performed with analysis of variance.

these studies only included two treatment groups (one combination method, one single-agent method). The optimal way to determine whether there is a superior method is to evaluate all four methods under the same conditions, in a head-to-head trial, as we have in our study. Additionally, in contrast to our study, previous studies that did not find a difference in time to delivery were limited by small sample size, different dosing of misoprostol, and heterogeneous labor management.[8–11]

Our study has significant clinical implications for obstetric care. Induction of labor is one of the most common procedures among pregnant women. Most recently, the induction rate in the United States was estimated to be 23.3%,[1] which equates to 932,000 women undergoing an induction annually.

If combination methods were used for all of these women, there would be more than 3 million fewer hours, or more than 125,000 fewer days that women spend in labor in the United States alone, which has large implications for health care utilization and delivery. The ability to shorten the length of time women spend in labor without increasing morbidity has large clinical and financial implications given the cost and known maternal–neonatal risks associated with both prolonged labor and cesarean delivery. Additionally, this may have an important effect on patient satisfaction; a recent survey of women's experiences after induction showed that 40% of women who underwent an induction stated that the speed of induction was the most important aspect of the procedure they would like to have changed.[16]

Strengths of this study include that it was a large, appropriately powered, randomized trial that compared, head to head, four common methods of induction. The management of induction and active labor was standardized so differences among the four methods can be attributed to the methods themselves and not the labor management. Our study took place at one institution that limits practice variation and more easily ensures compliance with the labor protocol. Additionally, we excluded very few indications for induction, increasing the generalizability of our findings.

Limitations are as follows: neither patients nor health care providers were blinded to the assigned treatment because examinations are required for placement of all methods. However, the use of labor protocols for all enrolled patients should have reduced variations in practice by the unblinded health care providers. Another important limitation of this study is that although we were powered to detect differences in time to delivery, for most outcomes, including cesarean delivery and maternal and neonatal adverse outcomes, we lacked statistical power to discern potentially important differences across groups.

Future studies should focus on validating our findings in studies in which protocols or patient populations may be different than those in the current study and should be large enough to evaluate maternal and neonatal outcomes, which could not be adequately evaluated in this study.

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