

The Efficacy of Transcervical Foley Balloon Plus Vaginal Misoprostol Versus Vaginal Misoprostol Alone For Cervical Ripening In Nulliparous Obese Women: A Randomized, Comparative Effectiveness Trial

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Protocol

**Cervical Ripening for Obese
WomeN(CROWN)**

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1. BACKGROUND

Induction of labor (IOL) is the initiation of labor in a viable pregnancy by artificial means, and occurs before the spontaneous onset of labor. A common obstetric intervention, the rate of IOL increased from 9.5% to 22.8% in the US from 1990 to 2012¹. Obese women (BMI \geq 30 kg/m²) are more likely than their normal-weight counterparts to require IOL because of increased rates of obstetric complications including pregnancy related hypertensive disorders, diabetes, and prolonged gestations^{2,3}. Several studies have shown that obese women experience increased labor duration and oxytocin needs when compared to normal-weight women⁴⁻⁸. This in turn results in increased rates for unplanned cesarean delivery (CD) as a result of failed IOL, arrest disorders and non-reassuring fetal heart rate tracing, that is dose-dependent with increasing class of obesity⁹.

Mechanical and pharmacological agents are routinely used for IOL. The supracervical insertion of a Foley balloon catheter acts by overstretching the lower uterine segment and the cervix. This process strips the fetal membranes from the lower uterine segment and causes rupture of the lysosomes in the decidual cells. The lytic enzymes released include phospholipase A, which acts on phospholipids to form arachidonic acid and is converted to prostaglandins¹⁰. Misoprostol (prostaglandin E1, PGE1) is a prostaglandin analogue used to induce labor that is associated with enzymatic collagen degradation, increased water content in the extracellular matrix and stimulation of the myometrium resulting in intrauterine contractions¹⁰. Both methods are supported and recommended by the American College of Obstetricians and Gynecologists (ACOG) due to their high safety profile and comparative effectiveness¹¹. In addition, they are often preferred over oxytocin alone, PGE2 tablet, gel and insert given their low cost, availability and ease of use.

A number of randomized trials have compared the use of the Foley balloon in combination with misoprostol, against misoprostol alone for labor induction (Table 1). Carbone et.al.¹² randomized 123 women undergoing IOL with singleton pregnancies at \geq 24 weeks' gestation with unfavorable cervix (Bishop score \leq 6) to Foley balloon plus vaginal misoprostol or vaginal misoprostol alone. The mean induction-to-delivery time was shorter with the combined approach when compared to vaginal misoprostol alone (15.3 ± 6.5 compared with 18.3 ± 8.7 hours, difference -3.1 hours, 95% CI -5.9 to -0.30). No differences were noted in labor complications, CD rates (37.3 vs 26.2 %, P = 0.90) or neonatal outcomes, likely due to small sample size. These findings contrast with the results by Kashanian et.al.¹³ and Lanka et.al.¹⁴, who did not find such an association. However, the results from Kashanian et.al. must be interpreted with caution given potential biases due to unclear random sequence generation, high allocation concealment and selective reporting. In a recent meta-analysis of eight studies and 1153 patients by Chen et.al.¹⁵, the use of Foley balloon plus misoprostol was associated with a significant reduction in the mean time to delivery when compared to misoprostol alone (mean difference -2.36 hours, 95% CI -4.07 to -0.66; P = 0.007). Differences in cesarean delivery rates, however, remain elusive likely due to the small sample sizes of the trials included.

To our knowledge no studies have compared the effects of these interventions in

women with obesity (BMI ≥ 30 kg/m²). The exact mechanism of failed cervical ripening and dysfunctional labor patterns in obese women is not completely understood. Elevated cholesterol levels have been shown to decrease uterine contractility, and obese women are more likely to have elevated cholesterol levels than are normal-weight women¹⁶. In addition, obesity has been associated with lower prostaglandin sensitivity when used locally for cervical ripening⁸. This association is directly proportional to obesity class. Although many reviews list obesity as a risk factor for failed IOL, this risk has yet to be quantified by obesity class in relation to the various methods available for cervical ripening. In a large study of 1273 women who underwent IOL with vaginal misoprostol, obese women had a longer induction-to-delivery interval (median 22.7, 24.9 and 27.0 hours for normal weight, BMI between 30-39.9 kg/m² and BMI ≥ 40 kg/m², respectively; P < 0.01) and higher CD rates (21.3%, 29.8% and 36.5% for normal weight, BMI between 30-39.9 kg/m² and BMI ≥ 40 kg/m², respectively; aOR 2.32, 95% CI 1.58-3.42). These results were adjusted for parity, race and treatment group. Noteworthy, obese women were more likely to require a CD during the first stage of labor when compared to normal-weight women (74% and 83% vs 62%, respectively). These results were further confirmed by Wolfe et.al.⁹ in a large cohort of 80,887 women from the Ohio Department of Health's Birth Certificate Database. Indeed, pregnant women with class III obesity had a 2.89 aOR of failed IOL rates when compared to normal-weight women. These authors concur that more research is required to define the best method of cervical ripening that would decrease CD rates in this high risk populations.

The combination of Foley balloon plus vaginal misoprostol has not been prospectively compared to the use of vaginal misoprostol alone among women with BMI ≥ 30 kg/m². We hypothesize that obese pregnant women and unfavorable cervix (Bishop score ≤ 6), IOL ≥ 32 weeks gestation using the Foley balloon plus vaginal misoprostol will result in reduced cesarean delivery rates when compared to vaginal misoprostol alone. To prove this hypothesis, we propose a comparative-effectiveness, open-label, randomized controlled trial of induction of labor with transcervical foley balloon and vaginal misoprostol versus misoprostol alone for cervical ripening in obese pregnant women and a Bishop score ≤ 6 .

Table 1. Studies on Foley balloon and vaginal misoprostol for labor induction

| | Foley catheter and duration | Dose of misoprostol | Mean induction-to delivery interval \pm SD (h) in combination group | Mean induction-to delivery interval \pm SD (h) in misoprostol group | Rate of cesarean delivery in combination group | Rate of cesarean delivery in misoprostol group |
|---|--------------------------------------|--|---|---|--|--|
| Rust et al. 2001¹⁷ (n = 81) | 24-Fr 50 mL for 12 h | 25- μ g 3-hourly for 12 h | 16.38 \pm 7.8 | 17.65 \pm 8.6 | 29.7% | 27.5% |
| Chung et al. 2003¹⁸ (n = 146) | 16-Fr 30 mL for 12 h | 25- μ g 3-hourly, 6 doses | 16.6 \pm 8.2 | 17.5 \pm 9.3 | 41.2% | 36.7% |
| Kashanian et al. 2005¹³ (n = 300) | 16-Fr traction with 500 mL serum bag | 25- μ g 3-hourly, 6 doses | 11.7 \pm 2.5 | 10.5 \pm 3 | 35.0% | 40.0% |
| Carbone et al. 2013¹² (n = 123) | 60-mL balloon | 25- μ g 4-hourly till Bishop score $>$ 6 | 15.3 \pm 6.5 | 18.3 \pm 8.7 | 27.3% | 26.2% |
| Lanka et.al. 2014¹⁴ (n = 126) | 16-Fr 30 mL for 12 h | 25- μ g 4-hourly, 8 doses | 26.52 \pm 15.24 | 27.64 \pm 15.63 | 35.0% | 35.0% |

2. METHODS

2.1. Study Objectives

2.1.1. Objective

To compare the CD rate when transcervical Foley balloon plus misoprostol versus vaginal misoprostol alone is used for cervical ripening among nulliparous obese women ($\text{BMI} \geq 30 \text{ kg/m}^2$) and unfavorable cervix (Bishop score ≤ 6).

2.1.2. Rationale

Obese pregnant women are less sensitive to local use of prostaglandins for cervical ripening. Although the best agent and method for IOL remains uncertain among obese women, it is biologically plausible that a combination of a mechanical device (Foley balloon) and a local pharmacological agent (misoprostol) may have an additive or synergistic effect, resulting in a greater degree of cervical ripening, shorter induction-to-delivery time and reduced need for CD due to dystocic labor patterns. The addition of misoprostol to the Foley balloon may also overcome the frequent observation of cervical dilation with the Foley balloon without significant effacement.

2.1.3. Primary Outcome Measures

- Cesarean delivery rate

2.1.4. Secondary Outcome Measures: Maternal

- Indication for CD
- Induction-to-delivery interval (hours)
- Need for oxytocin augmentation
- Occurrence of tachysystole (≥ 5 contractions in a 10 minute period averaged over a 30-minute window) requiring terbutaline or Pitocin cessation.
- Clinical chorioamnionitis: maternal fever $\geq 100.4\text{F}$, uterine fundal tenderness, maternal or fetal tachycardia ($>100/\text{min}$ and $>160/\text{min}$, respectively) and purulent or foul amniotic fluid¹⁹
- Need for operative vaginal delivery
- Composite of maternal morbidity:
 - Maternal ICU admission
 - Postpartum endometritis
 - Surgical-site infections prior to discharge
 - Venous thromboembolism
 - Need for transfusion
 - Maternal death

2.1.5. Secondary Outcome Measures: Neonatal

- Neonatal intensive care unit (NICU) admission
- Transient tachypnea of the newborn (TTS)
- Respiratory distress syndrome (RDS)
- Meconium aspiration syndrome
- Culture proven sepsis
- Seizures
- Composite of adverse neonatal outcomes:
 - Apgar score ≤ 7 at 5 mins
 - Umbilical cord pH < 7.1
 - Neonatal injury: brachial plexus injury, fracture
 - Perinatal death

2.2. Design Summary

This is a comparative-effectiveness, open-label, randomized controlled trial of induction of labor with transcervical Foley balloon and vaginal misoprostol versus misoprostol alone in nulliparous obese pregnant women and Bishop score ≤ 6 .

2.3. Inclusion Criteria

- Nulliparous women aged 18 or above
- BMI ≥ 30 at the time of labor induction
- Singleton gestation
- Cephalic presentation (includes successful external cephalic version)
- Intact fetal membranes
- Unfavorable cervix (Bishop score of ≤ 6)
- Gestational age ≥ 32 weeks

2.4. Exclusion Criteria

- Patient not candidate for IOL with misoprostol as deemed by the treating physician
- Multiple gestation
- Major fetal anomalies
- Fetal demise

2.5. Recruitment and Feasibility

Recruitment will occur at the Labor and Delivery units at Memorial-Hermann Hospital – Texas Medical Center, Lyndon B. Johnson General Hospital and Kern Medical, Bakersfield, CA.

2.6. Randomization

Randomization will be achieved by computer-generated random sequences. Permuted block randomization will be performed, stratified by center. Women will be randomized to either Foley balloon plus misoprostol or misoprostol alone as the method of choice for IOL. Enrollment number and assignments will be placed in opaque sealed envelopes. Envelopes will be kept secured in a locked office and will be accessible only by the research personnel.

2.7. Intervention and Procedures

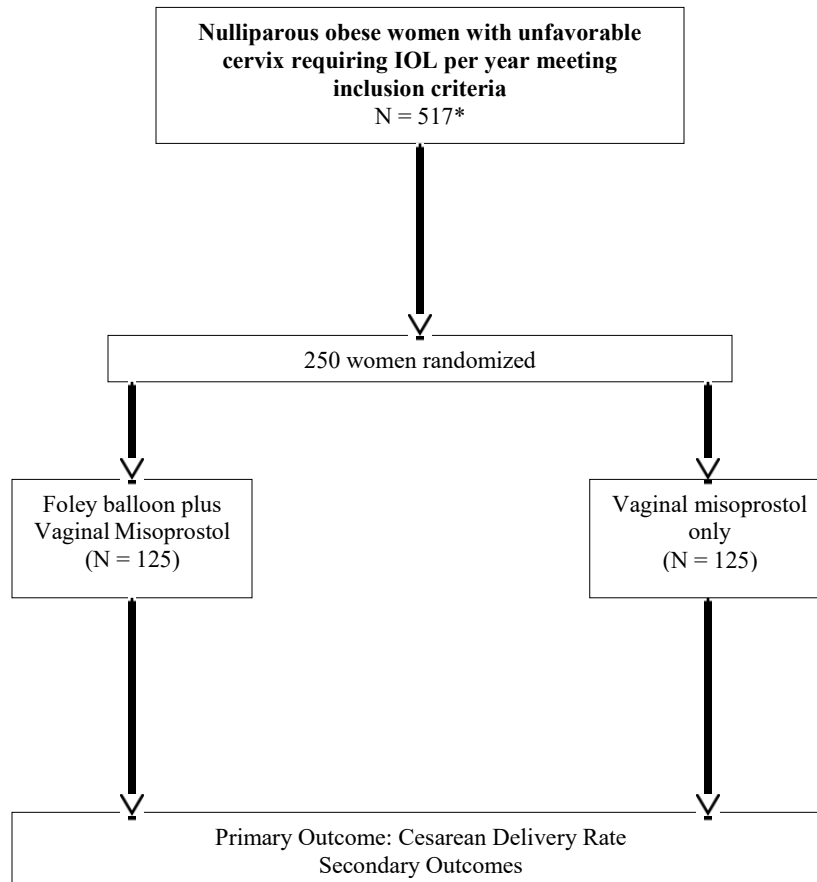
Nulliparous pregnant women at ≥ 32 weeks' gestation admitted to labor and delivery for IOL and who meet the inclusion and exclusion criteria will be approached by the research staff (Figure 1). Group 1 will be composed of women allocated to the Foley balloon plus misoprostol. These women will receive vaginal misoprostol per standard protocol at 25 micrograms every 4 hours. In addition, a 26 Fr-Foley balloon catheter will be inserted by routine clinical standards. The Foley will be inserted through the internal cervical os, filled with 60 mL of normal saline, and then pulled snugly against the internal os. The catheter of the Foley will be taped to the patient's inner thigh under gentle traction. If the Foley is unable to be placed, the patient will be reexamined in 1 hour and placement will be reattempted if Bishop's score is still 6 or less by the healthcare provider. When the Foley balloon had fallen out or had to be removed because 12 hours have passed since insertion as per protocol, further management of labor will be left at the discretion of the labor team.

Group 2 will be composed of women allocated to vaginal misoprostol-only. These women will receive 25 micrograms of misoprostol per vagina every 4 hours. This time interval has been shown to be more effective than different time intervals in a Cochrane review²⁰. Once the cervix becomes favorable (Bishop score > 6), misoprostol administration will be discontinued. Similarly, further management will be left at the discretion of the labor team.

In both groups, if IV oxytocin is indicated, it will be withheld until 4 hours after the last dose of misoprostol to prevent uterine hyperstimulation. Other aspects of labor management will be similar for both groups, including continuous electronic fetal monitoring with external Doppler device or fetal scalp electrode. Uterine contraction assessment will be performed with either an external tocodynamometer or an intrauterine pressure catheter.

Participant data including demographic characteristics, medical and obstetric history, labor course and outcomes will be collected by a dedicated research nurse.

Figure 1. Flow Diagram – CROWN Trial

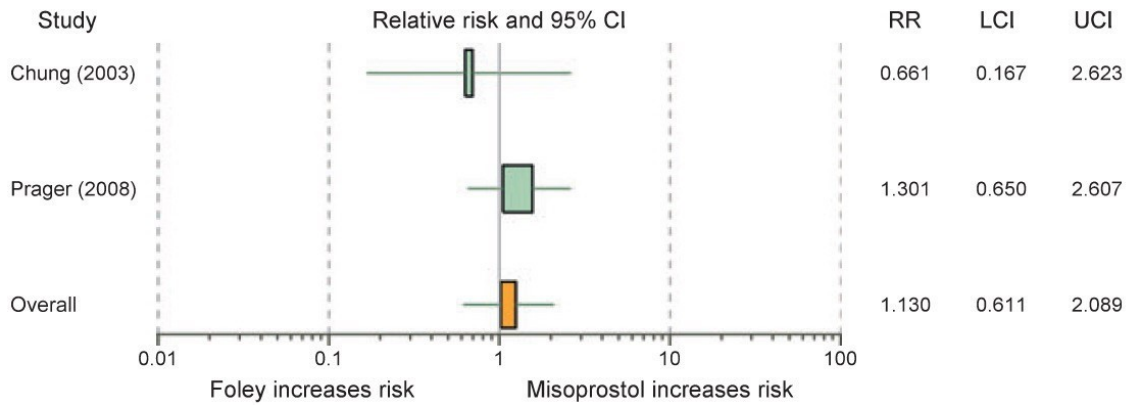


2.8. Safety Assessment

2.8.1 Risks Associated with Vaginal Misoprostol of Foley Balloon for Labor Induction

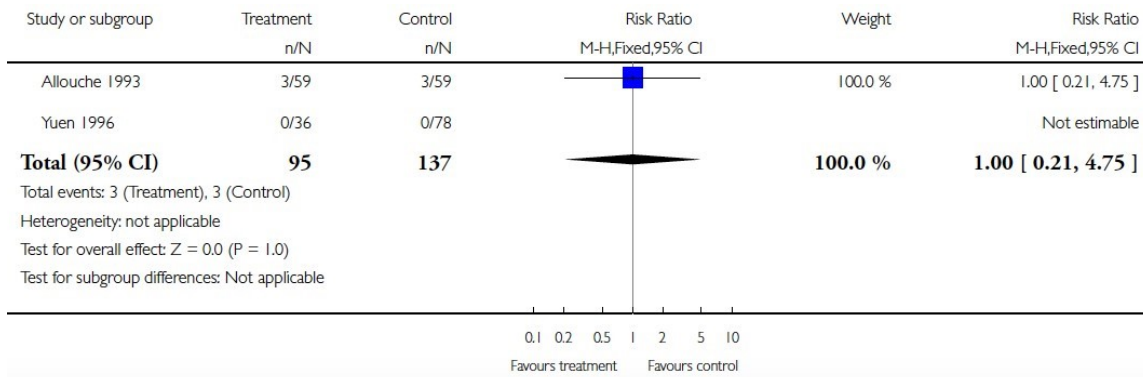
There is biologic plausibility that a Foley balloon catheter for cervical ripening may be associated with an increased rate of chorioamnionitis because it represents a foreign body in the lower uterine segment and could potentially facilitate an ascending infection. However, a systematic review by Fox et.al.²¹ (Figure 2) and a Cochrane review from Jozwiak et.al.^{22,23} (Figure 3) concluded that the rates of chorioamnionitis were comparable for the Foley balloon and misoprostol when used independently. Carbone et. al.¹² also reported no differences in the rates of chorioamnionitis when the Foley balloon was used concomitantly with misoprostol versus misoprostol alone.

Figure 2. Impact of Misoprostol vs Foley Balloon on Risk of Chorioamnionitis



Adapted from Fox NS, Saltzman DH, Roman AS, Klausner CK, Moshier E, Rebarber A. Intravaginal misoprostol versus Foley catheter for labour induction: a meta-analysis. *BJOG Int J Obstet Gynaecol* 2011;118:647–54.
 Abbreviations: CI, confidence interval; LCI, lower confidence interval; UCI, upper confidence interval

Figure 3. Impact of Prostaglandins vs Balloon catheter on Risk of Chorioamnionitis



Adapted from Jozwiak M, Bloemenkamp KWM, Kelly AJ, Mol BWJ, Irion O, Bouvain M. Mechanical methods for induction of labour. *Cochrane Database Syst Rev* 2012;3:CD001233.
 Abbreviations: CI, confidence interval

Tachysystole is a common complication of misoprostol administration for cervical ripening, and tachysystole with FHRT changes is more frequent among women receiving misoprostol than among those treated with mechanical devices, alternate prostaglandin compounds or oxytocin^{20,24,25}. However, the frequency of uterine tachysystole with FHRT changes was lower when a Foley balloon catheter was added to misoprostol than when misoprostol alone was used^{22,26}, purportedly due to the reduced need for additional doses of vaginal misoprostol. The combination could provide extra benefits to patients who are at higher risk of fetal hypoxemia, such as those with sickle cell disease, oligohydramnios, fetal growth restriction or other chronic diseases for which the use of misoprostol is not considered contraindicated^{27,28}.

2.8.2. Specification of Safety Parameters

Both of the interventions proposed are done in routine clinical care and have been tested in prior trials. Choriamnionitis is in fact a risk but is comparable to standard of care. The medications/interventions are not new in pregnancy and misoprostol is known to not be teratogenic in the third trimester. Therefore, the establishment of a safety data monitoring board is not necessary. The principal investigator (PI) and mentor will monitor the progress of study and determine the safety parameters.

2.8.3. Management of Adverse Events

Any adverse events will be reported to the Committee for the Protection of Human Subjects (CPHS). Due to the use of medications that have been used in pregnancy in the past, there is no increased anticipation of severe adverse events.

2.8.4. Procedures in the Event of Abnormal Clinical Findings

In the event of an abnormal clinical finding, the health care provider caring for the participant will be notified to allow treatment in the usual clinical manner.

2.9. Statistical Considerations

2.9.1. Sample Size

Assuming a cesarean delivery rate of 53% at Memorial Herman Hospital among nulliparous obese women who underwent IOL in 2012 at ≥ 32 weeks and met our inclusion criteria, 250 women (125 women per group) would be required for 80% power to detect a 33% cesarean delivery rate reduction between the 2 groups using a two-tailed t test and α of 0.05 (Table 2). Interim analysis after 50% enrollment will be performed in order to determine if the risk of adverse events discussed in the secondary outcomes is increased in one arm relative to the other arm.

Table 2. Proposed Sample Size

| % decrease in CD rate | Power (%) | | |
|-----------------------|-----------|-----|-----|
| | 80 | 85 | 90 |
| 33 | 250 | 270 | 316 |
| 40 | 172 | 196 | 228 |

| | | | |
|----|-----|-----|-----|
| 50 | 100 | 114 | 134 |
|----|-----|-----|-----|

2.9.2. Statistical Tests

An intent-to-treat analysis will be conducted. Selected baseline characteristics and outcome measures will be compared using the independent t test for continuous variables and the X^2 or Fisher's exact test for categorical variables as appropriate. Mann-Whitney U test will be used for non-parametric comparisons. Tests with a p-value < 0.05 will be considered significant.

2.10. Ethical Considerations

2.10.1. Informed Consent

A copy of the informed consent document in both English and Spanish to be used will be submitted by the PI to the Institutional Review Board (IRB) for review and approval prior to the start of the study. A properly executed written informed consent shall be obtained from each patient prior to entering the study. All prospective study candidates will be given a full explanation of the consent form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the Investigator is assured that the individual understands the requirements of the study, the subject will be asked to sign the consent. The Investigator shall provide a copy of the signed and dated informed consent to the patient and the original shall be maintained in the patient's study files. Patients who do not sign the consent form will not be permitted to participate in the study.

2.10.2. Institutional Review Board

Before initiation of the study, the PI will obtain approval of the research protocol and from the IRB. The study will be registered in www.clinicaltrials.gov as required by the US law for public access.

2.10.3. Subject Confidentiality

Each study's subject anonymity will be maintained throughout the study. Prior to collection of the data a unique study number will be assigned to each case thus de-identifying the individual subject. Each study site will maintain a log of the study subject to the assigned study number.

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