

Combined Use of the Controlled Release Dinoprostone Insert and Foley Catheter Compared to the Foley Catheter Alone for Cervical Ripening and Labor Induction in Term Women: A Randomized Controlled Trial

Investigator Initiated Trial in Women's Health
Tracking Number IIt-2016-100752

Rodney K. Edwards, MD, MS
Professor and Section Chief, Maternal-Fetal Medicine
Chair of Perinatal Research
Director, MFM Fellowship Program
Department of Obstetrics and Gynecology
University of Oklahoma College of Medicine
Oklahoma City, OK, USA

Study Coordinator
Christy Zornes
Christy-Zornes@ouhsc.edu

Request Date July 26, 2016



1
IRB NUMBER: 7491
IRB APPROVAL DATE: 07/21/2017

Background/Rationale

About 25% of pregnant women in the United States undergo labor induction (1). The rate has more than doubled in recent years, having been less than 10% in 1990 (2). Cervical ripening agents are used to start labor inductions in the setting of an unfavorable cervix. The reason for this fact is that administration of oxytocin is less successful in achieving vaginal delivery in the setting of an unfavorable cervix (3).

Options for cervical ripening include mechanical agents, such as Foley catheter, and pharmacologic methods, primarily synthetic prostaglandins. In a recent systematic review and meta-analysis, it was concluded that the controlled release dinoprostone insert was superior to repeated prostaglandin administration (either dinoprostone or misoprostol) due to a lower cesarean delivery rate and less oxytocin use (4).

The author of this application led a multicenter randomized controlled trial of Foley compared to the dinoprostone insert that demonstrated that, compared to the dinoprostone insert, starting labor inductions for women with unfavorable cervixes with the Foley catheter leads to shorter times to delivery (median 21.6 vs. 26.6 hours; $p=0.003$) (5). Our findings differ from those of other authors (6,7), but those studies were underpowered and were conducted in populations that were thin, overwhelmingly Caucasian, and where a minority received epidural analgesia. Our findings are more generalizable to obstetric populations in the United States.

There is a precedent for using multiple agents for cervical ripening. Misoprostol and Foley combined have been shown to result in shorter times to delivery than Foley alone (8). However, not all authors have found a decreased time to delivery with this combination and have seen more uterine tachysystole with the addition of misoprostol (9). This unwanted effect with misoprostol is what causes many to favor agents besides misoprostol, despite that drug's low cost. The combination of the dinoprostone insert and Foley catheter for cervical ripening and labor induction has not been studied (Pubmed and clinicaltrials.gov searches using the terms "dinoprostone" AND "Foley" on July 23, 2016).

Here, we propose a pilot randomized trial to estimate the parameters necessary to accomplish the power calculation for a multicenter randomized controlled trial to compare the combined use of the dinoprostone vaginal insert and Foley catheter with Foley catheter alone for cervical ripening and labor induction in term pregnant women. In both this pilot study and the larger multicenter trial to follow, both efficacy and safety outcomes will be evaluated.

Hypothesis

In term women presenting for labor induction, combined use of the controlled release dinoprostone vaginal insert and Foley catheter for cervical ripening will decrease the median time from induction to vaginal delivery by at least four hours compared to the Foley catheter alone.

Objectives/Specific Aims

1. To estimate the median times from placement of ripening agents to vaginal delivery in both of the following groups:

- a. Dinoprostone vaginal insert and Foley catheter
 - b. Foley catheter alone
2. To evaluate the safety of the above combination by estimating in the above groups, stratified by parity (nulliparous or parous):
- a. Cesarean delivery rates
 - b. Uterine tachysystole rates
 - c. Puerperal infection rates
 - d. Oxytocin use rates
 - e. Neonatal ICU admission rates

Study Design Methodology

This is an open-label trial. The study will be approved by the local IRB. Women meeting enrollment criteria will be approached for enrollment. Those who provide informed consent will be allocated by an online randomization system either to placement of a transcervical Foley catheter and an intravaginal dinoprostone controlled release insert or a Foley catheter alone. Randomization will be stratified by parity (nulliparous or parous).

In both study groups, the balloon on the end of the Foley catheter will be inflated with 30 mL of sterile water, pulled back against the internal os of the cervix, and taped to the maternal thigh under minimal tension. Also in both groups, the Foley catheter will be removed if any of the following occurs: 1) expulsion, 2) fetal heart rate tracing mandating evaluation for membrane rupture and placement of internal monitors, 3) spontaneous membrane rupture, or 4) if 12 hours has elapsed since placement. The dinoprostone insert will be removed if: 1) the fetal heart rate tracing mandates evaluation for membrane rupture and placement of internal monitors, 2) tachysystole develops (more than 5 contractions per 10 minutes averaged over 30 minutes, 3) spontaneous membrane rupture, or 4) 12 hours has elapsed since placement. Though these are the criteria for insert removal, in keeping with the pragmatic design of this trial, the decision regarding removal will be left to the discretion of the attending physician.

Women will remain recumbent for 30 minutes after agent placement and, except for trips to the restroom, will undergo continuous monitoring of uterine contractions and fetal heart rate. Oxytocin, according to standard intravenous protocol, will be allowed only after removal of cervical ripening agent(s). After specified cervical ripening, labor management will be at the discretion of the attending obstetrician, in keeping with the pragmatic nature of the study design.

Antibiotics will be administered if indicated for prophylaxis against early-onset neonatal infection with group B streptococci or for treatment of chorioamnionitis. Cesarean delivery will be performed, per the discretion of the attending obstetrician, for standard maternal or fetal indications.

Medical records will be reviewed no less than 30 days after delivery. Demographic, intrapartum, and outcome data will be entered into a computerized database.

Primary Endpoint

Median time from placement of transcervical Foley catheter to vaginal delivery

Secondary Endpoints

1. Proportion of patients delivered by 12 hours
2. Proportion of patients delivered by 24 hours
3. Proportion of patients delivered vaginally by 12 hours
4. Proportion of patients delivered vaginally by 24 hours
5. Chorioamnionitis (defined as a temperature of 38C or higher and one or more of the following: maternal heart rate over 100, baseline fetal heart rate over 160, uterine tenderness, and/or purulent or foul-smelling cervical discharge)
6. Endometritis (defined as a postpartum temperature of 38C or higher on 2 or more occasions and no other source of fever apparent)
7. Wound infection (defined as a cesarean wound disruption and treatment with antibiotics for that indication); specifically excludes antibiotic treatment for “wound cellulitis” not associated with spontaneous or iatrogenic wound disruption
8. Puerperal infection (5, 6, or 7 above)
9. Cesarean delivery rate
10. Uterine tachysystole (defined as more than 5 contractions per 10 minutes, averaged over 30 minutes)
11. Neonatal information at delivery and discharge status (birth weight, Apgar scores, cord pH, NICU admission, other complications, neonatal death)

Sample Size

N=100

Inclusion Criteria

1. Cervix ≤ 2 cm dilated; if 2 cm, <80% effaced
2. Gestational age 37 weeks or more
3. Singleton gestation
4. Cephalic presentation
5. Live fetus

Exclusion Criteria

1. Contractions more frequent than every 5 minutes
2. Premature rupture of membranes
3. Prior uterine incision
4. Temperature 38C or higher
5. Fetal anomalies
6. Placenta previa
7. Suspected abruption or undiagnosed bleeding more than spotting
8. Fetal heart rate tracing prior to enrollment with no more than minimal variability, late decelerations, or more than two variable decelerations

9. HIV infection
10. Allergy to Prostaglandins
11. Clinical suspicion or definite evidence of fetal distress
12. Unexplained vaginal bleeding during this pregnancy
13. Evidence or strong suspicion of marker cephalopelvic disproportion
14. Oxytocic drugs are contraindicated
15. Already receiving intravenous oxytocic drugs
16. Multipara with 6 or more previous term pregnancies

Statistical Plan

This proposal is for a pilot study to estimate the parameters that will be used to inform the power calculation for a next-step multicenter randomized controlled trial. We will randomize, in a 1:1 ratio, stratifying 1:1 nulliparous and parous patients, 100 total patients to receive either:

1. Both the dinoprostone controlled release insert and a transcervical Foley catheter, or
2. Foley catheter alone

Patient characteristics and outcomes will be compared between the two study groups using two-sample t-tests for continuous measures and chi-square tests of association for categorical measures. Since time to delivery is known to not be a normally distributed outcome, we will estimate that parameter with medians and its variance with interquartile ranges.

Since this is a pilot study, we will estimate the outcomes to be evaluated in the planned next-step multicenter trial. Not surprisingly, the proposed sample size for this pilot study has less than 50% power to detect a 4-hour difference between groups. The rationale for stratifying a 1:1 ratio of nulliparous:parous patients is that doing so will maximize the precision with which the endpoints are estimated when stratified by parity.

Planned Publications

Results will be submitted for presentation at a national meeting, probably SMFM. Also, will submit results for publication as a full-length original article--probably *Obstetrics&Gynecology*.

Gender/Minority/Pediatric Inclusion for Research

Since only women become pregnant and undergo labor induction, all subjects in this study will be pregnant woman and fetus/infant dyads. The inclusion of minorities is anticipated in keeping with the racial/ethnic distribution of our obstetric population. Therefore, we anticipate including about 15% African-Americans, 45% Caucasians, 29% Hispanics, and 11% of other ethnicities.

Human Participants

We will enroll women age 18-50 who meet the above enrollment criteria. No specimens will be collected. Clinical data will be recorded at the time of enrollment. Clinical data also will be abstracted later from the medical record. A data collection form is attached.

Women with scheduled labor inductions will be screened by study personnel for eligibility. If



potentially eligible and the plan from the medical team is to begin the labor induction with cervical ripening using a Foley catheter, women will be approached about participation when the present for their scheduled induction. Since these women will not be in labor and it will be emphasized that participation is not required, coercion should not be an issue. Those women agreeing to participate will be consented by trained study personnel in their preferred language. We will have both English and Spanish consent forms. Those women who agree to participate will have a transcervical Foley catheter placed according to standard clinical practice. Once the Foley is placed, they will be randomized to either also have a Cervidil placed in the posterior vaginal fornix (according to package insert instructions) or not.

Because we will have consent forms in both English and Spanish, and since our patient population is 29% Hispanic, we anticipate enrolling non-English speaking participants. In addition to the Spanish consent form, hospital translation services will be utilized.

Since both Foley catheter and Cervidil are within the standard of care for starting labor inductions in the setting of an unfavorable cervix, risks associated with the study are anticipated to be no greater than the risks associated with pregnancy, labor induction and delivery. These include discomfort; abnormal labor progress, fetal heart rate tracing abnormalities, or other considerations leading to cesarean delivery; and postpartum complications such as hemorrhage or infection. Likelihood and seriousness should be no greater than similar patients not in the study who are undergoing labor induction.

To protect the privacy and confidentiality of research subjects, we will assign each participant a study ID number. This ID number will be linked to the patient's name and medical record number only via a key that will be maintained in a locked file drawer in the research coordinator's locked office. Once data collection is complete, the key will be destroyed, and the de-identified will not be able to be linked to participants.

The only potential benefit to subjects would be an increased likelihood of vaginal delivery or a shorter duration of labor induction if one of the treatment groups is superior. However, since this is a pilot study aimed at estimating the parameters needed for a next-step clinical trial, we do not anticipate a statistically significant difference in those outcomes in this study. The study, and participants' inclusion is important, since obtaining the data needed to conduct the next-step study will get us closer to optimizing labor inductions for future patients. Despite lack of a high likelihood of direct benefit, subject inclusion is reasonable since the risks are essentially the same as a labor induction if not included in the study.

Data and Safety Monitoring Plan

All adverse events will be reviewed by the PI and co-investigators and reported to the IRB according to institutional guidelines. All research data will be stored on a password-protected computer in the administrative offices of the Section of Maternal-Fetal Medicine. Any paper records and CRFs will be stored in a locked file drawer in the locked office of the research coordinator that is also located in the administrative offices of the Section of Maternal-Fetal Medicine. Since this study is a pilot including only 100 participants, we are not assembling a data and safety monitoring board.

References

1. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Wilson EC, Mathews TJ. Births: final data for 2010. *Natl Vital Stat Rep* 2012; 61:1-72.
2. Ventura SJ, Martin JA, Curtin SC, Menacker F, Hamilton BE. Births: final data for 1999. *Natl Vital Stat Rep* 2001; 49:1-100.
3. Alfirevic Z, Kelly AJ, Dowswell T. Intravenous oxytocin alone for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art No:CD003246.
4. Facchinetti F, Fontanesi F, Del Giovane C. Pre-induction of labour: comparing dinoprostone vaginal insert to repeated prostaglandin administration: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2012; 25:1965-9.
5. Edwards RK, Szychowski JM, Berger JL, Petersen M, Ingersoll M, Bodea-Braescu AV, Lin MG. Foley catheter compared with the controlled release dinoprostone insert: a randomized controlled trial. *Obstet Gynecol* 2014; 123:1280-7.
6. Jozwiak M, Rengerink KO, Ten Eikelder MLG, van Pampus MG, Dijksterhuis MGK, de Graaf IM, et al. Foley catheter or prostaglandin E2 inserts for induction of labour at term: an open-label randomized controlled trial (PROBAAT-P trial) and systematic review of literature. *Eur J Obstet Gynecol Reprod Biol* 2013; 170:137-45.
7. Cromi A, Ghezzi F, Agosti M, Serati M, Uccella S, Arlant V, et al. Is transcervical Foley catheter actually slower than prostaglandins in ripening the cervix? A randomized study. *Am J Obstet Gynecol* 2011; 204:338.e1.7.
8. Aduloju OP, Akintayo AA, Adanikin AI, Ade-Ojo IP. Combined Foley's catheter with vaginal misoprostol for pre-induction cervical ripening: a randomised controlled trial. *Aust N Z J Obstet Gynaecol*. [Epub ahead of print]
9. Lanka S, Surapaneni T, Nirmalan PK. Concurrent use of Foley catheter and misoprostol for induction of labor: a randomized clinical trial of efficacy and safety. *J Obstet Gynaecol Res* 2014; 40:1527-33.