Implementation of Evidence-Based Cervical Ripening Protocol: Outcomes and Next Steps

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Abstract

Objective   A prominent randomized controlled trial demonstrated that low-dose misoprostol with the concurrent cervical Foley shortened the median time to delivery when compared with either method alone. Our study aims to address implementation of this protocol and evaluate its impact on time to delivery.

Study Design   This was a retrospective before-and-after study of nulliparous women who delivered nonanomalous, term, singletons at the University of California San Francisco (UCSF) in two separate 2-year periods before and after changes in UCSF's cervical ripening protocol. The primary outcome was time from first misoprostol dose to delivery.

Results   A total of 1,496 women met inclusion criteria, with 698 in the preimplementation group and 798 in the postimplementation group. There were no statistically significant differences in time to delivery (29 vs. 30 hours, $p = 0.69$), rate of cesarean delivery (30 vs. 26%, $p = 0.09$), or cesarean delivery for fetal indications (11 vs. 8%, $p = 0.15$) between the groups.

Conclusion   Implementing evidence-based low-dose misoprostol with the concurrent cervical Foley did not change the time to delivery, time to vaginal-delivery, or likelihood of vaginal delivery in our population. This may be due to differences in labor management practices and incomplete fidelity to the protocol. Real-world effectiveness of these interventions will vary and should be considered when choosing an induction method.

Keywords
► induction of labor
► cervical ripening
► misoprostol
► Foley
► quality improvement

Induction of labor is performed in more than 20% of all pregnancies in the United States.[1] In the setting of an unfavorable cervix, labor induction is more successful when the cervix is ripened with pharmacological methods (e.g., administration of misoprostol, a synthetic prostaglandin) and/or through mechanical methods (e.g., placement of the cervical Foley).[2] Misoprostol alters collagen breakdown, rearranges collagen fibers, and increases intracellular calcium to promote cervical softening and myometrial contractions.[3,4] Mechanical methods appear to have two mechanisms of action: exerting pressure on the internal cervical os promotes both mechanical dilation and release of endogenous prostaglandins from the adjacent decidua (Ferguson's reflex).[3–7]

Prior studies have shown that as single agents, the cervical Foley and misoprostol are both effective methods of cervical ripening; however, it is not clear whether one is superior to the other.[1,8,9] Sequential use of oral misoprostol and the cervical Foley does not conclusively appear to improve time to delivery or vaginal delivery rates in comparison to simply using oral misoprostol alone.[7,10,11] However, the simultaneous use of oral misoprostol and the cervical Foley has consistently been demonstrated to shorten time to delivery

and decrease the risk of failed induction of labor (IOL) in comparison to misoprostol alone. The best example of this is the FOR MOMI trial, a large randomized controlled trial, that investigated these methods as single agents and also in dual use in a four-arm study design.[8] They compared cervical ripening prior to induction with the cervical Foley alone, misoprostol alone, cervical Foley and vaginal misoprostol, or cervical Foley and oxytocin. The FOR MOMI trial demonstrated that simultaneous use of the cervical Foley and low-dose vaginal misoprostol resulted in a shorter median time to delivery (~4 hours) when compared with either method alone, with no change in mode of delivery or harms to mother or neonate.[8] These encouraging results prompted many providers to adopt dual agent ripening for IOL. However, most of the data on dual-agent cervical ripening are randomized controlled trials that reflect study efficacy rather than effectiveness. This study aims to address effectiveness in the real world, namely, how implementation of an evidence-based protocol impacted the time to delivery in two historical cohorts pre- and postimplementation of low-dose misoprostol with the concurrent cervical Foley.

Methods

This was a retrospective before-and-after study of all nulliparous women with term ($\geq$37 weeks) singleton pregnancies who underwent a scheduled IOL at the University of California San Francisco (UCSF) from May 2015 to April 2017 and from June 2017 to May 2019. Those with preterm delivery of <37 weeks, multifetal gestation, nonvertex fetal presentation, multiparity, prior cesarean delivery, rupture of membranes prior to initiation of IOL, and major fetal anomalies were excluded. In May 2017, the term IOL cervical ripening protocol was changed from misoprostol 50 to 100 µg PO every 4 hours with subsequent placement of the cervical Foley once cervical dilation was 1 to 2 cm (the preimplementation protocol, based on a 2005 prospective IOL trial[12]) to misoprostol 25 µg PO every 2 hours with simultaneous placement of the cervical Foley filled to 60 mL (the postimplementation protocol, inspired in large part by the results of the FOR MOMI trial).[2] The decision to use 25-µg oral misoprostol administered every 2 hours (rather than 25-µg vaginal misoprostol administered every 3 hours, as per the original FOR MOMI protocol) was based on several lines of evidence. Pharmacokinetic data indicate that oral absorption of misoprostol is highly reliable, with minimal variability between patients, compared with vaginal absorption.[13,14] However, the half-life is much shorter, thus requiring more frequent administration to maintain serum levels.[13,14] The American College of Obstetricians and Gynecologists (ACOG) provides minimal guidance surrounding the best dosing schedule for misoprostol administration.[1] However, the World Health Organization (WHO),[15] International Federation of Gynecology and Obstetrics (FIGO),[16] and the Royal College of Obstetricians and Gynaecologists (RCOG),[17] all recommend low dose but frequently administrated misoprostol, based on systematic reviews showing this strategy to be both effective and superior in terms of safety.

For all deliveries at UCSF, details regarding maternal demographics, labor characteristics, and pregnancy outcomes are collected at the time of delivery by the managing clinicians and stored within the UCSF Perinatal Database. Chart review is performed by trained abstractors to ensure complete and accurate information, while monthly review of the database is performed by physicians for quality assurance. We utilized the UCSF Perinatal Database to obtain information regarding maternal demographics (age, race, body mass index [with obesity defined as body mass index $\geq$ 30 kg/m^2], and parity), details of antepartum and intrapartum course (pregnancy-related hypertension, chronic hypertension, gestational diabetes, preexisting diabetes, maternal cardiac disease, fetal growth restriction, placental abruption, gestational age at delivery, and mode of delivery) and neonatal characteristics (birthweight, Apgar's scores, and neonatal intensive care unit [NICU] admission).

The primary outcome was time from first misoprostol dose to delivery. Secondary outcomes included overall cesarean delivery rate, cesarean delivery for fetal indications, cumulative misoprostol dose, number of misoprostol administrations, need for oxytocin augmentation, time from oxytocin initiation to delivery, postpartum hemorrhage, chorioamnionitis, low Apgar's score (defined as 5-minute Apgar's score < 7), and NICU admission.

The Kruskal–Wallis test was used to compare median values for nonparametric continuous variables, and Fisher's exact and Chi-squared tests were used to compare proportions for categorical variables. Statistical analyses were performed using STATA v13.0 (StataCorp., College Station, TX). This study was approved by the UCSF Committee on Human Research (study number 19–28095).

Results

During the study period, a total of 1,496 women met criteria for inclusion, with 698 women in the preimplementation group and 798 in the postimplementation group. There were no statistically significant differences in maternal demographics between the two groups (►Table 1). There was a higher incidence of pregnancy-related hypertension in the preimplementation group compared with the postimplementation group (36 vs. 28%, $p < 0.001$); there were no differences in other pregnancy complications or in gestational age at delivery between the two groups.

There was no difference in the primary outcome of time to delivery between the two groups (median of 29 hours for the preimplementation group vs. 30 hours in the postimplementation group, $p = 0.68$; ►Table 2). The preimplementation group had a significantly higher cumulative misoprostol dose than the postimplementation group (150 vs. 100 µg, $p < 0.001$), while the postimplementation group had significantly more misoprostol administrations (4 vs. 2 doses, $p < 0.001$). A smaller proportion of the preimplementation group required oxytocin augmentation when compared with the postimplementation group (81 vs. 88%, $p = 0.001$; ►Table 2).

There was no statistical difference in cesarean deliveries overall or cesarean deliveries for fetal indication

Table 1 Maternal demographics and characteristics among nulliparous patients undergoing induction of labor before (preimplementation) and after (postimplementation) the implementation of an evidence-based protocol for cervical ripening

Demographics	Preimplementation (*n* = 698)	Postimplementation (*n* = 798)	*p*-Value
Maternal age (y)	33 (30–37)	34 (31–37)	0.210
Race			
Caucasian	354 (51%)	431 (54%)	0.757
African American	33 (5%)	31 (4%)	
Hispanic	63 (9%)	67 (8%)	
Asian	161 (23%)	182 (23%)	
Other	78 (11%)	80 (10%)	
Unknown	9 (1%)	7 (1%)	
Obese	97 (14%)	95 (12%)	0.250
Chronic hypertension	49 (7%)	49 (6%)	0.493
Pregnancy-induced hypertension	256 (37%)	225 (28%)	<0.001
Preexisting diabetes	11 (2%)	14 (2%)	0.788
Gestational diabetes	185 (27%)	205 (26%)	0.720
Fetal growth restriction	28 (3%)	27 (3%)	0.567
Placental abruption	11 (2%)	16 (2%)	0.534
Gestational age at delivery	39.9 (38.7–41.1)	39.9 (39.0–41.0)	0.882

Note: Continuous variables with nonparametric distribution reported as median (interquartile range).

(preimplementation of 30% and postimplementation of 26% [*p* = 0.086] for any indication; 8 vs. 11% [*p* = 0.145] for fetal indication). Multivariate logistic regression to control for potential confounders (maternal age, preexisting diabetes mellitus, gestational diabetes mellitus, chronic hypertension, and pregnancy-related hypertensive disease) failed to find a statistically significant difference in cesarean delivery (adjusted odds ratio [aOR] = 0.80, 95% confidence interval [CI]: 0.63–1.00) or cesar-

ean delivery for fetal indication (aOR = 0.74, 95% CI: 0.52–1.05) between the two groups.

The postimplementation group had a significantly higher postpartum hemorrhage rate than the preimplementation group (15 vs. 11%, *p* = 0.013); however, there was no statistically significant difference in the rate of postpartum blood transfusion between the two groups (6 vs. 6%, *p* = 0.83). There was no difference in the rate of low Apgar's

Table 2 Pregnancy outcomes among nulliparous patients undergoing induction of labor before (preimplementation) and after (postimplementation) the implementation of an evidence-based protocol for cervical ripening

Demographics	Preimplementation (*n* = 698)	Postimplementation (*n* = 798)	*p*-Value
Time from misoprostol start to delivery (h)	29.1 (20.5–41.7)	29.9 (20.1–40.5)	0.689
Cumulative misoprostol dose (µg)	150 (50–250)	100 (50–150)	0.0001
Total number of misoprostol administrations	2 (1–3)	4 (2–6)	0.0001
Required oxytocin for augmentation	568 (81%)	700 (88%)	0.001
Time from Pitocin start to delivery (h)[a]	16 (9.27–22.3)	15 (9.70–21.78)	0.817
Cesarean delivery for any indication	208 (30%)	206 (26%)	0.086
Cesarean delivery for fetal indication	74 (11%)	67 (8%)	0.145
Postpartum hemorrhage	74 (11%)	119 (15%)	0.013
Blood transfusion	41 (6%)	49 (6%)	0.829
Chorioamnionitis	70 (10%)	94 (12%)	0.280
Low Apgar's score	29 (4%)	50 (6%)	0.067
NICU admission	117 (17%)	76 (10%)	<0.001

Abbreviation: NICU, neonatal intensive care unit.
Note: Continuous variables with nonparametric distribution reported as median (interquartile range).
[a]*n* = 568 for preimplementation group and *n* = 700 for postimplementation group.

scores between the two groups, but there was as a significantly higher rate of NICU admission in the preimplementation group compared with the postimplementation group (17 vs. 10%, $p < 0.001$; ►**Table 2**).

Discussion

We found that implementation of an evidence-based concurrent dual agent cervical ripening protocol did not change the median time to delivery or likelihood of vaginal delivery.

Our study expands on the FOR MOMI trial by examining the real-world effects of clinically implementing a protocol of low-dose misoprostol with the concurrent cervical Foley placement.[8] Unlike the FOR MOMI trial, we did not find a decrease in the median time to delivery with the use of this protocol. Importantly, the median time to delivery in the FOR MOMI trial for the misoprostol with the concurrent cervical Foley group was 13 hours, whereas the median time to delivery in the post implementation group in our study was 30 hours. This discrepancy may be due numerous factors. First, the FOR MOMI trial included both multiparous and nulliparous patients, whereas our study included only nulliparous patients, who have longer induction to delivery times.[3,11] Second, the cesarean rate for nulliparous woman in the FOR MOMI trial receiving dual-agent was 44%, compared with 26% in our population. Our lower cesarean rate likely reflects differences in the institutional management of labor and may be due to fewer cesareans for failed induction. Lastly, the variation in route of misoprostol administration (vaginal in FOR MOMI, oral in the present study) may have also contributed to the differences in time to delivery. A recent meta-analysis demonstrated that among all prostaglandins, low-dose ($<50\,\mu g$) oral misoprostol had the lowest probability of cesarean delivery over time, whereas vaginal misoprostol had the highest probability of achieving a vaginal delivery within 24 hours.[18,19] This finding aligns with our report of low cesarean delivery rates in the postimplementation (low-dose oral misoprostol) group but longer time to delivery than the FOR MOMI trial, which used the vaginal route.

This study also demonstrated that the postimplementation group had a significantly higher rate of postpartum hemorrhage, which is likely due to the implementation of quantitative blood loss (QBL) measurement during the postimplementation period, rather than a true increase in blood loss at delivery. QBL measurements are more accurate than estimated blood loss (EBL) measurements, which tend to underestimate hemorrhage.[20] This is supported by the stable rate of transfusions across the time periods.

We also found that the postimplementation group had significantly fewer NICU admissions, a result that is congruent with multiple studies that used similar doses of misoprostol in combination with the cervical Foley.[21,22] A recent meta-analysis of eleven randomized controlled trials found that the combination of misoprostol and the cervical Foley was associated with a reduced risk of NICU admission (relative risk [RR] $= 0.75$, 95% CI: 0.58–0.97, $p = 0.03$) compared with either method alone.[21] To our knowledge, there were no other significant changes in NICU admission criteria to explain this finding.

Strengths and Limitations

The major strength of this study is the evaluation of the implementation of an evidence-based cervical ripening method into real-world practice, with a sample size six times larger than the original FOR MOMI trial, which included 123 women in the misoprostol plus the cervical Foley group. Furthermore, our institutional cesarean delivery rate is much lower, likely reflecting different practice patterns and strategies of labor management. Institutions may need to compare their cesarean delivery rates to those reported in randomized controlled trials of induction methods to determine whether those data will be generalizable to their own populations.

The major limitation of this study is its retrospective nature, which relies on historical cohorts and is limited to what has previously been documented in the electronic medical record. Of note, the indication for NICU admission was not included in the data analysis. Furthermore, the comparison included changes made in dosing of oral misoprostol and in timing of the cervical Foley placement, which limits our ability to determine which changes contributed to the differences we found. Additionally, while the low-dose misoprostol with the concurrent cervical Foley protocol aimed to have the simultaneous cervical Foley and misoprostol, many women still received sequential methods if providers felt that the cervical Foley placement would be difficult; we do not have clear data on the frequency of this occurrence.

Conclusion

Based on this study and the existing literature, no method of cervical ripening is clearly superior to the others outside of the context of a randomized controlled trial; even then, the differences between the methods are the modest at the best ($\sim$2–4 hours). As such, we recommend that undergoing cervical ripening for IOL be counseled in a shared decision-making model. This counseling should include the beneficial evidence of dual agent cervical ripening over individual methods, as well as the differences in timing and frequency of misoprostol administration, timing of the cervical Foley placement, and the impacts on time to delivery and cesarean delivery. Shared decision making in maternity care can decrease decisional conflict, increase satisfaction with the delivery experience, generate more positive feelings toward the newborn, and decrease depressive symptoms.[23,24]

In conclusion, implementing an evidence-based protocol of low-dose misoprostol with the concurrent cervical Foley was not associated with a change in median time to delivery or vaginal delivery rates. While randomized controlled trial data are useful for calculating efficacy of induction methods, real-world effectiveness of these interventions will vary based on local and institutional practice and should be considered when choosing an induction method.

Conflict of Interest
None declared.

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