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High Dose Vaginal Misoprostol Versus Concentrated Oxytocin + Low Dose Vaginal Misoprostol for Mid-Trimester Labor Induction: A Randomized Trial

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Abstract

Objective—To compare the efficacy and side effects of a high-dose vaginal misoprostol regimen to concentrated intravenous oxytocin plus low-dose vaginal misoprostol for mid-trimester labor induction.

Study Design—Women at 14-24 weeks, with obstetric or fetal indications for delivery and no prior cesarean, were randomly assigned to receive either vaginal misoprostol 600 μg ×1, then 400 μg q 4 hr × 5 (Group 1) or escalating-dose concentrated oxytocin infusions (277-1667 mU/min) plus vaginal misoprostol 400 μg × 1, then 200 μg q 6 hr × 2, then 100 μg × 1 (Group 2). Analysis was by intent to treat. Primary outcomes were live birth rate and induction-to-delivery interval.

Results—The intended sample size was 70 women per group; however, the trial was terminated at the initial interim analysis due to a highly significant difference in one of the primary study outcomes. Twenty women were assigned to Group 1 and 18 were assigned to the Group 2. Median induction-to-delivery interval was significantly shorter in Group 1 (12 hr, range 4 - 44 hr) versus Group 2 (18 hr, range 7 - 36 hr; p=0.01). Induction success rate at 12 hours was significantly higher in the Group 1 (60%), compared to Group 2 (22%, p=.02). No significant difference was noted in the live birth rate between Group 1 and 2 (13%, 0%, p = 0.16). The incidence of retained placenta requiring curettage, chorioamnionitis, intrapartum fever, nausea, emesis, and diarrhea were similar between both groups.

Conclusion—Compared to concentrated oxytocin plus low-dose vaginal misoprostol, high-dose vaginal misoprostol significantly shortens mid-trimester labor inductions.

Keywords

Misoprostol; Concentrated Oxytocin; Pregnancy Termination; Labor Induction; Prostaglandins

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Introduction

A variety of management strategies have been reported for second trimester pregnancy interruption.[1-7] Such techniques include dilation and evacuation, intraamniotic prostaglandin $F_{2\alpha}$ instillation, prostaglandin E_2 (PGE_2) vaginal suppositories, and high dose oxytocin.[1-18] Misoprostol (Cytotec®,), a potent uterotonic agent, has also been shown to be effective for second trimester pregnancy interruption.[1, 3, 6, 8-18] Several recent comparative investigations have demonstrated that the use of high dose oral or vaginal misoprostol is more efficacious than alternative methods (e.g. concentrated oxytocin, PGE_2, etc) for second trimester pregnancy interruption, with an acceptable side-effect profile.[1, 3, 8-18]

Indeed, we recently demonstrated that a high dose vaginal misoprostol regimen was superior to concentrated oxytocin plus low-dose vaginal PGE_2 with respect to significantly shortened induction-to-delivery interval, fewer side effects, less medication for the treatment of side effects, and lower incidence of retained placenta requiring dilation and curettage, reduction in side effects, and fewer cases of retained placenta requiring dilation and curettage.[18] However, we noted a relatively high live birth rate and therefore devised the current study

The ultimate goal of a successful therapeutic strategy for second trimester pregnancy interruption should be to combine efficacy (i.e. shortened interval from induction to delivery), with minimal side-effect profile *and* low live birth rate. While the use of a high dose vaginal misoprostol regimen achieves the former of these factors (shortened induction-to-delivery interval and reduced side effect profile), the regimen is associated with a relatively high live birth rate (20-40%), a common finding among solely prostaglandin-based regimens.[1, 2] This is in contrast to a concentrated oxytocin ± low dose PGE_2 regimen, where the live birth rates are lower, ranging from 3-17%.[1-4]

One area of great interest, which has not been well studied, is the potential synergy of concentrated oxytocin and misoprostol in a combined induction regimen. To date, the majority of studies evaluating the efficacy of misoprostol for second trimester pregnancy interruption have evaluated misoprostol alone, or in combination with mifepristone. The potential synergistic cervical ripening and uterotonic effects of a combined prostaglandin/oxytocin regimen has been noted in our previous work evaluating concentrated oxytocin with and without low-dosePGE_2.[4, 7] This synergistic effect noted with the combined use of PGE_2 and concentrated oxytocin is likely one which may be relevant to misoprostol as well. The benefits of such a combined regimen may allow for exploitation of the advantages of both individual techniques (i.e. low live birth rate, shortened time to delivery interval, minimization of maternal side effects, and a low incidence of retained placenta). We are currently unaware of any published studies which have evaluated a regimen which has utilized a combination of misoprostol and concentrated oxytocin for second trimester pregnancy interruption. As such, we conducted a randomized clinical trial designed to compare our current standard induction regimen (high-dose vaginal misoprostol)[18] to a combined concentrated oxytocin plus low-dose vaginal misoprostol regimen for second trimester pregnancy interruption

Materials and Methods

We conducted a randomized clinical trial designed to compare a high-dose vaginal misoprostol regimen to concentrated oxytocin plus low dose vaginal misoprostol for second trimester pregnancy termination. All women presenting to our labor and delivery unit for an indicated labor induction with an unfavorable cervix (< 2 cm dilatation) between 14 and 24 weeks' gestation (according to the best obstetric dating criteria) were evaluated for participation. Women were excluded from participation if any of the following criteria were

encountered: 1) clinical chorioamnionitis, 2) spontaneous labor (regular uterine contractions with cervical change), 3) contraindication to prostaglandin therapy (e.g. unstable cardiopulmonary status, hypersensitivity to prostaglandins, etc.), or 4) previous cesarean delivery or other significant uterine surgery. The investigation was approved by the Institutional Review Board at the University of Alabama at Birmingham

Consenting, eligible women were randomly assigned to receive treatment with either high-dose vaginal misoprostol or concentrated oxytocin plus low-dose vaginal misoprostol. Randomization was accomplished using a secure web-based clinical trial randomization system to maintain concealed treatment allocation.[19] An independently created, stratified block randomization schedule with four main randomization strata based on induction indication was used for the investigation: 1) Fetal anomaly/aneuploidy, 2) Preterm premature rupture of membranes, 3) Intrauterine fetal demise (IUFD), and 4) Primary maternal indication (eg. severe preeclampsia).

Women randomized to the high-dose vaginal misoprostol group received an initial 600 μg (3 - 200 μg tablets) dose of misoprostol (Cytotec®, G.D. Searle and Co., Skokie, IL) placed intravaginally followed by an additional 400 μg (2 - 200 μg tablets) of misoprostol administered intravaginally every 4 hours (maximum of 5 applications of the 400 μg dose; total 2,600 μg). Women assigned to the concentrated oxytocin plus low dose vaginal misoprostol group received escalating doses of concentrated oxytocin (277-1667 mU/min) according to an established protocol [4] (50 × units of oxytocin in 500 cc bag of normal saline administered intravenously over 3 hours followed by a 1 hour washout prior to next dose increment, where X ranged progressively from 1 to a maximum of 6), plus vaginal misoprostol 400 μg initially, followed by 200 μg every 6 hours for 2 doses, then 100 μg for one dose (total 900 μg). In each treatment arm, the assigned medications were continued until either the maximum dose was administered or fetal delivery occurred – whichever came first. In addition to the assigned treatment, all women enrolled in this investigation (except for those women with ruptured membranes) received concurrent extra-amniotic saline infusion at 30 cc per hour through a transcervical 26-French (or smaller) Foley catheter to promote cervical ripening.[5] The catheter was placed under sterile conditions and direct visualization through the internal cervical os and the infusion continued until the catheter was either spontaneously expelled or was removed. A subsequent cervical examination was performed 6 hours later and if the catheter had been dislodged, the balloon was deflated and the catheter removed. Otherwise, the catheter remained in place for an additional 6 hours and was electively removed after a total of 12 hours.

All study participants were initially premedicated with acetaminophen 650 mg, promethazine 25 mg, and diphenoxylate hydrochloride plus atropine as prophylaxis against fever, nausea, and diarrhea, respectively. Subsequent dosing of these medications, however, was based on the occurrence of the above noted side effects. Pain was controlled with intravenously administered narcotics and/or epidural analgesia as indicated by patient preference. Side effects were recorded by the obstetric nurses and house staff in the medical record and were abstracted after delivery. All intrapartum and postpartum management was conducted by the labor and delivery house staff. Neither the patients nor the managing physicians were blinded to treatment allocation.

Primary study outcomes for the investigation were the rate of live birth and the induction-to-delivery interval. Secondary outcomes assessed included induction success, maternal side effects, medication utilization, and complications. Induction success was defined as an induction-to-delivery interval ≤ 24 hours. Women in either group who were undelivered by 24 hours subsequently crossed over to the alternative study treatment regimen until delivery. Following delivery, all women received standardized active management of the third stage

of labor which included up to 3 hours of a 50 unit concentrated oxytocin infusion to facilitate separation of the placenta. If the placenta remained undelivered after 3 hours, an attempt was made at manual extraction. If manual extraction failed or if significant vaginal bleeding was noted during the third stage, uterine curettage was performed. Retained placenta was defined as the need for uterine curettage for placental removal. Post-partum hemorrhage was defined as estimated blood loss > 500 cc. Live birth was defined by a one minute Apgar score ≥ 1.

Planned sample size for this investigation was conservatively based on a clinically significant difference in the live birth rate rather than a difference in the induction-to-delivery interval. Assuming a baseline live birth rate of 25% for the high dose misoprostol regimen, a sample size of 70 women/group with a live fetus at the start of the induction would be required to detect a 15% absolute reduction in the live birth rate (i.e. 25% → 10%) with an α=0.05, β=0.80 using a one tailed t-test. We chose a 1-sided test because of the consistency of prior observations of comparative live birth rates using prostaglandin E_1 versus concentrated oxytocin. This sample size also was adequate to detect a clinically significant 4-hour difference in the induction-to-delivery interval with α=0.05, β=0.80 using a two tailed t-test. Additional patients with an intrauterine fetal demise were enrolled to increase the power for detection of the secondary outcomes. Analysis was by intent-to-treat. Because of the novel nature of the combined concentrated oxytocin plus low dose misoprostol regimen, a planned interim analysis was scheduled after the first quarter of the planned sample size was enrolled. The technique of stochastic curtailment was used to compute the conditional power of the study at the interim analysis for detecting significant intergroup differences in the live birth rate.

Statistical analyses were performed with the SAS version 8.0 (SAS Institute, Inc, Cary, NC). Proportional data were compared with the χ^2 or the Fisher exact test, as determined by the expected cell size. Continuous data were compared with either the Student *t*-test or the Wilcoxon rank-sum test, as determined by the Shapiro-Wilk statistic.

Results

Between June 17th,2003 and March 5th, 2004, a total of 38 women were randomized. Planned interim analysis was performed at this time to evaluate efficacy and safety measures of the study regimens. Although a non-significant difference was noted with respect to the outcome of live birth rate, a highly significant difference was noted in the induction-to-delivery interval; thus, the trial was terminated. No protocol violations were reported. All women who had treatment initiated were delivered during the index hospital admission.

Twenty women were assigned to the high dose vaginal misoprostol group and 18 were assigned to the concentrated oxytocin plus low dose vaginal misoprostol regimen. Both groups were similar with respect to maternal age, gestational age at time of induction initation, height, weight at admission, parity, race, and indication for induction (Table 1/ Table 2). Median induction-to-delivery interval was significantly shorter (approximately 6 hours) in the high dose vaginal misoprostol group versus the concentrated oxytocin plus low dose misoprostol group (p=0.014)(Table 3). Induction success rate at 12 hours was also significantly higher in the high dose misoprostol group compared to the concentrated oxytocin plus low dose misoprostol group (p=0.019)(Table 3). The rates of induction success at 24 hours, however, were similar between the treatment groups (Table 3).

The incidence of uterine curettage, chorioamnionitis, intrapartum fever, nausea, emesis, diarrhea, postpartum hemorrhage, symptomatic hypotension, and chorioamnionitis were comparable between the high-dose misoprostol and concentrated oxytocin plus low dose

misoprostol groups (Table 4). Change in hematocrit from pre to post induction (8-12 hours post delivery) was also similar between the study groups (Table 4). Although the incidence of live birth was higher in women who received high-dose misoprostol, the difference did not reach statistical significance in this prematurely terminated study (p=0.157). Use of medications for pain and side effect control were similar between the study groups (Table 5).

The conditional power analyses considered two different scenarios. First, we assumed that the true population rates of live birth in women treated with each of the 2 investigational regimens were 12.5% and 0%, our observed values. Considering that 31 of the planned 140 participants were enrolled and evaluated, there was an 81% chance that had the study continued, we would have observed a statistically significant difference in the live birth rates. Since the observed rates were different than what had been previously reported (a live birth rate of 0% seemed implausible), we also evaluated the original estimates for these values, 25% and 10%. Under these assumptions the conditional power was only 50%. Thus, using our original assumptions, even the planned sample size would have been underpowered to observe a significant intergroup difference, if a difference of that magnitude actually exists.

Discussion

Misoprostol is a potent uterotonic agent which is highly efficacious for labor induction.[1, 3, 6, 8-18] Use of misoprostol for second trimester pregnancy interruption was initially described by Jain et al. in 1994; however, this regimen utilized a relatively low-dose misoprostol regimen (200 ug vaginally every 12 hours).[6] Several recent investigations have suggested that higher dose misoprostol regimens may be more efficacious.[1, 2, 8-18].

In our investigation, we sought to evaluate the potential synergy between misoprostol with concentrated oxytocin to allow for exploitation of the advantages of both individual techniques (i.e. low live birth rate, shortened time to delivery interval, minimization of maternal side effects, and a low incidence of retained placenta). Both live birth rate and induction-to-delivery interval were the main study outcomes for our trial as these factors represented the major factors of clinical importance for second trimester labor induction.

Our trial was prematurely terminated at the interim analysis following evaluation by the departmental research advisory committee. The committee noted a highly significant and clinically important reduction in the induction-to-delivery interval in women who received treatment with the high-dose vaginal misoprostol regimen. The live birth rate in our study, however, was higher in the high-dose misoprostol group, but this difference was not significantly different from that observed in the concentrated oxytocin plus low-dose misoprostol group at the time of the interim analysis. Post-hoc sample size calculation suggested that if the trial continued to the intended sample size for the trial, a significant difference in the live birth rate may have emerged, however the live birth rate observed was lower than our baseline estimate, so it is uncertain that even in that scenario we would have been able to note a difference. The final decision to terminate the study was based on this knowledge in combination with the belief that most practitioners would be unlikely to choose a regimen that was associated with a significantly longer induction time and was more complicated to administer, even if it was associated with a low live birth rate. Therefore, the departmental research advisory committee did not believe that it could justify committing limited resources to a study, that was not likely to influence practice patterns, even if the null hypothesis (for live births) was rejected. As live birth is a potential complication of any midtrimester medical induction with a living fetus, a clear management plan for such an occurrence is essential.[1, 2]

Use of misoprostol for second trimester labor induction is advantageous given its low cost and ease of use. While previously contraindicated for use in pregnancy as a labor induction agent, the US Food and Drug Administration recently revised the labeling for misoprostol such that it is only contraindicated in pregnancy for the treatment/prevention of non-steroidal anti-inflammatory drug-induced ulcers; thus, the use of misoprostol in pregnancy for other indications is no longer contraindicated.[20] Concerns remain regarding the potential for uterine rupture, especially when misoprostol is used in women with a previous cesarean delivery.[20-23] Because of this issue, we excluded women with a previous cesarean delivery from participation in our investigation as our investigation would have been substantially underpowered to address this uncommon morbid outcome had women with a prior cesarean been included.

Our investigation confirms the superior efficacy of a high-dose vaginal misoprostol regimen, as measured by significant shortening of the induction-to-delivery interval and increased rate of induction success at 12 hours, for second trimester pregnancy termination. Concurrent use of low-dose vaginal misoprostol with concentrated oxytocin, failed to demonstrate the anticipated synergistic benefits (i.e. both reduction in induction-to-delivery interval and live birth rates) in our trial. Further refinement of strategies to facilitate second trimester labor induction, therefore, are still needed to further optimize induction success rates while minimizing side effects and associated live births.

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Table 1

Patient Demographics

	High Dose Vaginal Misoprostol (n= 20)	Concentrated Oxytocin + Low-dose Vaginal PGE_1 (n=18)	p value
Age (yr) *	25.3 ± 7.0	24.3 ± 6.1	0.652
Gestational age (wk) *	20.3 ± 2.2	20.5 ± 1.8	0.793
Height (inches) *	64.7 ± 2.3	63.8 ± 4.1	0.426
Weight (lb) *	160.4 ± 28.2	153.2 ± 28.8	0.452
Initial Cervical Dilation (cm) *	0.1 ± 0.3	0.0 ± 0.0	0.163
Parity:			
Primiparous	50.0% (10/20)	50.0% (9/18)	
Multiparous	50.0% (10/20)	50.0% (9/18)	1.000
Race:			
Caucasian	50.0% (10/20)	38.9% (7/18)	
African-American	50.0% (10/20)	61.1% (11/18)	0.492

* Mean± Standard Deviation

Table 2

Indication for Induction

	High-Dose Vaginal Misoprostol (n=20)	Concentrated Oxytocin + Low-dose Vaginal PGE_1 (n=18)	p value
Fetal Anomaly/Aneuploidy	65.0% (13/20)	66.7% (12/18)	
Preterm Premature Rupture of Membranes	20.0% (2/20)	5.5% (1/18)	
Fetal Demise	10.0% (4/20)	16.7% (3/18)	
Maternal Indication	5.0% (1/20)	11.1% (2/18)	0.831

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Table 3

Labor Induction Outcomes

	High-Dose Vaginal Misoprostol (n=20)	Concentrated Oxytocin + Low-dose Vaginal PGE_1 (n=18)	p value
Induction to Delivery Interval (hours) *	11.6 (3.5-43.5)	18.0 (7.3-36.3)	0.014
Successful Induction at 12 hours	60.0% (12/20)	22.2% (4/18)	0.019
Successful Induction at 24 hours	95.0% (19/20)	83.3% (15/18)	0.328
Successful Induction at 48 hours	100.0% (20/20)	100.0% (18/18)	1.000

* Median (range)

Table 4

Adverse Obstetric Outcomes

	High-Dose Vaginal Misoprostol (n=20)	Concentrated Oxytocin + Low-dose Vaginal PGE_1 (n=18)	p value
Live Birth *	12.5% (2/16)	0.0% (0/15)	0.157
Retained Placenta Requiring Dilation and Curettage	5.0% (1/20)	11.1% (2/18)	0.595
Postpartum Hemorrhage > 500 cc	5.0% (1/20)	0.0% (0/18)	1.000
Hypotensive Reaction Requiring Treatment	0.0% (0/20)	0.0% (0/18)	1.000
Transfusion Required	0.0% (0/20)	0.0% (0/18)	1.000
Uterine Rupture	0.0% (0/20)	0.0% (0/18)	1.000
Chorioamnionitis	5.0% (1/20)	5.6% (1/18)	1.000
Side Effects:			
Isolated Fever >100.0 °F	65.0% (13/20)	55.6% (10/18)	0.552
Nausea	25.0% (5/20)	11.1% (2/18)	0.410
Emesis	15.0% (3/20)	5.6% (1/18)	0.606
Diarrhea	0.0% (0/20)	5.6% (1/18)	0.474
Δ Hematocrit % (pre/post) †	- 3.5 (-7.0 – 2.0)	-2.0 (-7.0 – 1.0)	0.295

*Excludes women with an intrauterine fetal demise at onset of induction

†median (range)

Table 5

Intrapartum Pharmacologic Therapy

	High-Dose Vaginal Misoprostol (n=20)	Concentrated Oxytocin + Low-dose Vaginal PGE_1 (n=18)	p value
Epidural Use	50.0% (10/20)	38.9% (7/18)	0.492
Meperidine (mg) *	200 (0-900)	250 (50-700)	0.454
Acetaminophen (mg) *	1300 (0-2600)	1300 (650-2600)	0.493
Lomotil (number of tablets) *	2 (0-4)	2 (0-8)	0.199
Metoclopramide (mg) *	10 (10-30)	20 (10-40)	0.247
Promethazine (mg) *	25 (0-125)	25 (0-75)	0.989

* Median (range)

† Diphenoxylate/atropine