RESEARCH ARTICLE

Efficacy of Mifepristone in Preinduction Cervical Ripening in Term Pregnancy

Sujithra S[1], Syamala Onimi[2], Usha Rani Godla[3]

Abstract

Objective: To study the efficacy of mifepristone in preinduction cervical ripening in term pregnancy.

Study design: This is a prospective observational study, done in a tertiary care hospital. Fifty pregnant women in the study group were given oral mifepristone 200 mg for preinduction cervical ripening (second dose after 24 hours if applicable) and another 50 pregnant women who underwent expectant management were included in the expectant group. The primary objective was to assess the effect of mifepristone on the change in Bishop score. The secondary objective was to assess the induction–delivery interval and the mode of delivery.

Results: In this study, the mean modified Bishop score 24 hours after oral mifepristone (single dose) was (7.34 ± 1.533) which was statistically significant compared to the expectant group's Bishop score (4.28 ± 1.179) p <0.001. Similarly, the mean modified Bishop score 48 hours after oral mifepristone (two doses) was 7.50 ± 0.57 which was statistically significant when compared to the expectant group (4.28 ± 1.155) p <0.001. The requirement for further inducing agents has also been significantly less in the study group compared to the expectant group (p <0.001). Twenty-four percent went into spontaneous labor within 24 hours of the first dose of oral mifepristone without the requirement of a prostaglandin E2 (PGE2) gel. Augmentation with oxytocin was required in 60% of the study group and 86% of the expectant group in active labor. The mean duration between the initiation of PGE2 gel induction and delivery was 13.45 ± 4.536 hours in the study group and 20.41 ± 3.896 hours (p <0.001). Spontaneous vaginal delivery was 82% in the study group and 80% in the expectant management group.

Conclusion: Oral mifepristone given for preinduction cervical ripening was found to be effective and safe with a reduction in the need for additional prostaglandins and oxytocin and also shorter induction-to-delivery interval with no serious maternal or fetal adverse effects.

Keywords: Mifepristone, Preinduction cervical ripening, Term gestation.

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Introduction

Induction of labor is on the rise universally, and failed inductions add to the cesarean section rates.

Cesarean section for the failure of induction of labor is a major reason for primary cesarean section. Different methods of labor-inducing agents are widely practiced. Optimizing the response to a labor-inducing agent in order to achieve maximum vaginal delivery rates is one of the ultimate goals of obstetrics.

The aim of induction of labor is a successful vaginal delivery, which depends on the favorability of the cervix.

Mifepristone/RU-(486), an antiprogestin, is a potential molecule that can promote the onset of labor in term pregnancy through its actions by competitive antagonism of progesterone. This can increase uterine contractility and the sensitivity of the uterus to the actions of prostaglandins.

The aim of our study is to evaluate the efficacy of mifepristone in preinduction ripening of the cervix in term pregnancies.

Materials and Methods

This was a prospective observational study conducted in the Department of Obstetrics and Gynecology, Sri Ramachandra Institute of Higher Education and Research Institute from November 2017 to September 2019.

Inclusion Criteria

Singleton, term, live pregnancies, with a cephalic presentation, and a cervical Bishop score of less than 6 were included in the study.

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Exclusion Criteria

Exclusion criteria were: (a) parity greater than four, (b) malpresentation, (c) premature rupture of membranes, (d) previous history of cesarean section or any uterine surgery , and (e) multiple pregnancies.

Fifty women who were receiving oral mifepristone 200 mg for preinduction cervical ripening were included in the study group and another 50 women who underwent expectant management were included in the expectant group. Informed consent to participate in the study was taken. A detailed history and general examination of the women were done. A complete obstetric examination was done. A modified Bishop score was calculated, following a vaginal examination.

Study Group

The study group participants, with a modified Bishop score of less than 6, were given the first dose of tablet mifepristone 200 mg orally. Modified Bishop score was reassessed after 24 hours of the first dose of tablet mifepristone 200 mg. At the end of 24 hours if a modified Bishop score is more than 6, intracervical prostaglandin E2 (PGE2) gel was kept every six hourly (maximum three doses).

At the end of 24 hours if a modified Bishop score is <6, the second dose of tablet mifepristone 200 mg was given orally and a modified Bishop score reassessed after 24 hours of the second dose of tablet mifepristone.

Induction was done with PGE2 gel at the end of two doses of mifepristone irrespective of the modified Bishop score or after one dose of mifepristone if there was a good change in the modified Bishop score. Artificial rupture of membranes and oxytocin augmentation were done if necessary.

Expectant Group

The expectant group participants with a modified Bishop score of less than 6 were observed for a period of 48 hours without any intervention for any spontaneous change in the modified Bishop score. Following 48 hours of masterly inactivity, they were induced with PGE2 gel six hourly (maximum three doses).

Artificial rupture of membranes and oxytocin augmentation were done if necessary. Maternal and fetal well-being were ensured throughout the study.

Statistical Analysis

Proportions were analyzed using Chi-square test.

The unpaired student's *t*-test was used to compare groups of continuous normally distributed variables. Mann–Whitney *U*-test was used to compare groups of non-normally distributed variables.

Tests were two-sided, with a *p*-value of <0.05 being statistically significant.

Results

Age and parity distribution of women included in this study were as follows:

There were 38 primi and 12 multigravida in the study group.

There were 36 primi and 14 multigravida in the expectant group.

The mean age of both groups was 26 years (Fig. 1).

Bishop's Score at Admission

Eight percent of the study group and 14% of the expectant group had a modified Bishop score of 3 at admission.

The majority of them had a modified Bishop score of 4 at admission (58% in the study group and 64% in the expectant group had a score of 4).

The remaining 24% in the study group and 22% in the expectant group had a modified Bishop score of 5 at admission.

Bishop Score Following Mifepristone in Study Group vs Expectant Group

Of the 50 women in the study group, 40 women (80%) had a favorable modified Bishop score of >6 at the end of 24 hours with one dose of oral mifepristone 200 mg. The remaining 10 women (20%) had a modified Bishop score of <6 at the end of 24 hours. And, hence, they were given the second dose of oral mifepristone 200 mg (Fig. 2).

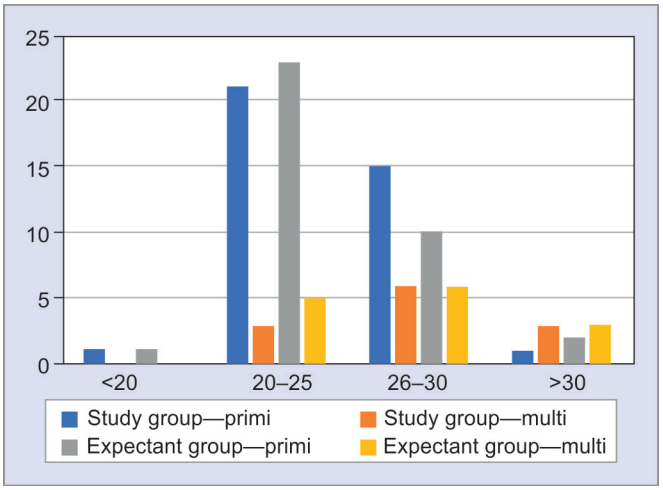

Fig. 1: Age and parity distribution among study group vs expectant group

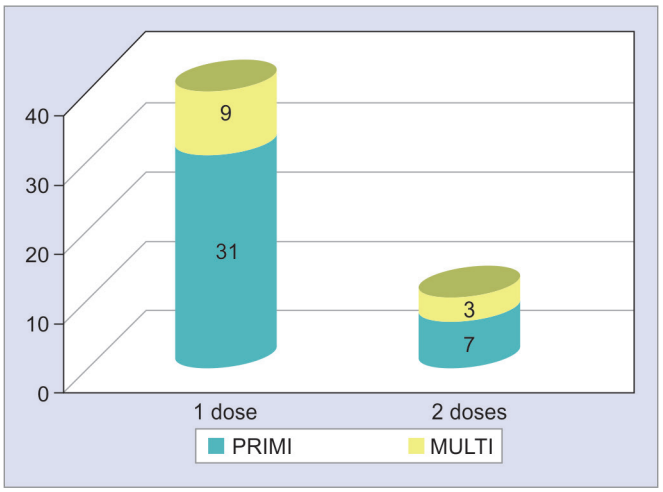

Fig. 2: Number of doses of oral mifepristone required in study group

As in Table 1, at the end of 24 hours of oral mifepristone, of the 50 women in the study group, 40 (80%) had a favorable modified Bishop score of 6, whereas, at the end of 24 hours of expectant management, three (6%) had a favorable modified Bishop score of 6.

At the end of 48 hours, after two doses of oral mifepristone 200 mg each, all 10 women (100%) in the study group had a favorable modified Bishop score of 6.

After 48 hours of expectant management, of the 47 women in the expectant group, 45 (92.5%) had an unfavorable modified Bishop score of <6 and 2 (7.5%) had a favorable modified Bishop score of 6.

As shown in Table 2, the mean modified Bishop score at admission in the study group was 4.02 and in the expectant group was 4.08. The difference is not statistically significant with a *p*-value of 0.634.

After 24 hours, the mean modified Bishop score in the study group (after one dose of oral mifepristone) was 7.34 and in the expectant group was 4.28 which is statistically significant with a *p*-value of <0.001.

Table 1: Change of modified Bishop score in the study group and expectant groups

Modified Bishop score at the end of 24 hours	*Study group (N = 50) After one dose of oral mifepristone*			*Expectant group (N = 50)*		
	Primi	*Multi*	*Total*	*Primi*	*Multi*	*Total*
<6	7 (14%)	3 (6%)	10 (20%)	35 (70%)	12 (24%)	47 (94%)
≥6	31 (62%)	9 (18%)	40 (80%)	1 (2%)	2 (4%)	3 (6%)
Modified Bishop score at the end of 48 hours	*Study group (N = 10) After two doses of oral mifepristone*			*Expectant group (N = 47)*		
	Primi	*Multi*	*Total*	*Primi*	*Multi*	*Total*
<6	—	—	—	32 (80%)	5 (12.5%)	45 (92.5%)
≥6	7 (70%)	3 (30%)	10 (100%)	0	3 (7.5%)	2 (7.5%)

Table 2: Mean difference of modified Bishop score in the study group and expectant groups

	Group	*N*	*Mean*	*Std. deviation*	*Std. error mean*	*p value*
Modified Bishop score at admission	Study	50	4.02	0.654	0.093	0.634
	Expectant	50	4.08	0.601	0.085	
Modified Bishop score after 24 hours	Study	50	7.34	1.533	0.217	<0.001
	Expectant	50	4.28	1.179	0.167	
Modified Bishop score after 48 hours	Study	10	7.50	0.527	0.167	<0.001
	Expectant	47	4.28	1.155	0.169	

Table 3: Requirement of PGE2 gel in the study group and expectant groups

	Study group (N = 50)			*Expectant group (N = 50)*		
Number of PGE2 gels required	*Total*	*Primi*	*Multi*	*Total*	*Primi*	*Multi*
0	12 (24%)	7	5	4 (8%)	0	4
1	16 (32%)	11	5	3 (6%)	1	2
2	12 (24%)	10	2	11 (22%)	9	2
3	10 (20%)	10	0	32 (64%)	26	6

Table 4: Augmentation with oxytocin in active labor in the study and expectant groups

	Study group (N = 50)			*Expectant group (N = 50)*		
Oxytocin augmentation	*Total*	*Primi*	*Multi*	*Total*	*Primi*	*Multi*
Required	30 (60%)	26	4	43 (86%)	34	9
Not required	20 (40%)	12	8	7 (14%)	2	5

Table 5: First dose of mifepristone-to-delivery interval in the study group

	Study group (N = 50)		
Time (hours)	*Total*	*Primi*	*Multi*
Within 24 hours	12 (24%)	7	5
32–36	20 (40%)	15	5
37–40	7 (14%)	6	1
41–44	8 (16%)	7	1
45–48	3 (6%)	3	0
Total	50 (100%)	38 (76%)	12 (24%)

After 48 hours of expectant management in the expectant group and after two doses of oral mifepristone 200 mg orally in the study group, the mean modified Bishop score was 4.28 and 7.50, respectively, which is statistically significant with a *p*-value of <0.001.

Requirement of PGE2 Gel and Oxytocin in Study Group vs Expectant Group

As depicted in Table 3, in this study, the requirement of PGE2 gel in the study group vs the expectant group was significantly less, with a *p*-value of <0.001.

The need for augmentation with oxytocin in active labor was lesser in the study group compared to the expectant group which was statistically significant with a *p*-value of 0.003 (Table 4).

"Mifepristone-to-delivery" Interval in Study Group vs Expectant Group

As shown in Table 5, in the study group out of the 50 women, 12 women (24%) delivered within 24 hours of the first dose of oral mifepristone. This group did not require a PGE2 gel.

Seven women (14%) delivered between 37 and 40 hours of the first dose of oral mifepristone.

Eight women (16%) delivered between 41 and 44 hours of the first dose of oral mifepristone.

Three women (6%) delivered between 45 and 48 hours of the first dose of oral mifepristone 200 mg.

The mean duration of "mifepristone-to-delivery" interval in the study group was 31.66 hours.

"PGE2 Gel-to-delivery" Interval in Study Group vs Expectant Group

The mean duration between the initiation of PGE2 gel induction and delivery is 13.45 hours in the study group and 20.41 hours in the expectant group which was significantly short with a *p*-value of <0.001.

Intrapartum Fetal Heart Monitoring in Study Group vs Expectant Group

In the study group, 6% had fetal heart abnormalities and 8% had grade III meconium-stained labor (MSL). In the expectant group, 12% had fetal heart abnormalities and 6% had grade III MSL. There was no significant difference between the two groups.

Mode of Delivery in the Study Group vs Expectant Group

In the study group, 82% delivered by spontaneous vaginal delivery with episiotomy and 18% underwent emergency lower-segment cesarean section (LSCS). In the expectant group, 80% delivered by spontaneous vaginal delivery with episiotomy and 20% underwent emergency LSCS. The difference between the two groups is not statistically significant, with a *p*-value of 0.799.

There were no instrumental deliveries in both groups.

Indications for LSCS in the Study Group vs Expectant Group

There were nine cesareans in the study group and 10 cesareans in the expectant group. There were three cases of fetal distress in each group. Grade III meconium in early labor was seen in four cases of the study group and three cases of the expectant group. Failed induction was an indication in one case of the study group and four cases of the expectant group. One cesarean was done for the arrest of dilatation in the study group.

The rate of failed induction was lesser in the study group compared to the expectant group. This was not statistically significant with a *p*-value of 0.565.

Neonatal Outcome in Study Group vs Expectant Group

The majority of the babies had a birth weight of >2.5 kg (94% in the study group and 92% in the expectant group). None of the neonates had an Apgar score less than 7 in both groups. Neonatal intensive care unit (NICU) admission (>72 hours) was 4% in the expectant group and nil in the study group. Respiratory distress was equal in both groups (2%).

Discussion

Over the past several decades, the incidence of labor induction has increased owing to increased fetal and maternal risk factors. Successful induction of labor, which culminates in a vaginal delivery, needs many favorable factors. Mifepristone is an antiprogestin that sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

This study conducted at Sri Ramachandra Institute of Higher Education and Research had 50 participants in the study group who received one or two doses of oral mifepristone 200 mg 24 hours apart and 50 participants in the expectant group who had expectant management.

Like in many other studies, there were no significant differences in age, parity, gestational age, or modified Bishop score at admission between the study and expectant groups.[1–6]

In the present study, 200 mg of mifepristone was given orally in the study group at admission and repeated after 24 hours if the cervix is unfavorable (modified Bishop score <6) which is also similar to Frydman et al. and Oleg et al. study.[4,6]

The mean modified Bishop score after 24 hours of oral mifepristone 200 mg in the study group was 7.34 ± 1.533 which was statistically significant when compared to the expectant group (4.28 ± 1.179) *p* <0.001. Other authors reported similar results.[3,4,6,7]

The mean modified Bishop score after 48 hours of oral mifepristone (two doses) was 7.50 ± 0.57 in the study group which was statistically significant when compared to the expectant group (4.28 ± 1.155) *p* <0.001. Similar observations were made by Oleg et al.[4]

In the study group, 80% had a favorable modified Bishop score of >6 at the end of 24 hours of oral mifepristone and 100% had a favorable modified Bishop score of 6 at the end of 48 hours after two doses of oral mifepristone 200 mg each. These findings are similar to Li et al. study done in Beijing who reported a cervical ripening ratio of 100%.[8]

The requirement for further inducing agents (number of PGE2 gels) has also been significantly less in the study group compared to the expectant group with a *p*-value of <0.001 which is consistent with studies done by Wing et al. and Yelikar et al.[1,3,4]

In the study group, 24% went into spontaneous labor within 24 hours of the first dose of oral mifepristone. They did not require a PGE2 gel. This observation is comparable to the study done by Oleg et al., where 20% went into spontaneous labor within 24 hours of the first dose of oral mifepristone.[1,3,4]

In our study, 60% in the study group and 86% in the expectant group required augmentation with oxytocin in active labor. The need for augmentation with oxytocin in active labor is lesser in the study group compared to the expectant group which is statistically significant with a *p*-value of 0.003. These findings are comparable to Wing et al. study, where 45.4% of the mifepristone-treated women required oxytocin augmentation.[1,3,9]

In the present study, the mean duration between the initiation of PGE2 gel induction and delivery was 13.45 ± 4.536 hours in the study group and 20.41 ± 3.896 hours in the expectant group. The induction-to-delivery interval is significantly shorter in the study group compared to the expectant group in the present study (*p*-value of <0.001). Yelikar et al.[3] and Wing et al.[1] reported similar findings.

In a study conducted by Wing et al., with 200 mg of oral mifepristone, 87% of the women delivered by spontaneous vaginal delivery which was consistent with the present study where 82% in the study group delivered by spontaneous vaginal delivery with episiotomy. Similar results were also seen in Giacalone et al. study.[1–3]

In the present study, 82% of the study group and 80% of the expectant group delivered vaginally. Hence, the mode of delivery is almost comparable in both groups with a *p*-value of 0.799. There were no instrumental deliveries in both groups.

The results of Hapangama and Neilson study[9] reported that mifepristone-treated women were less likely to undergo cesarean section as a result of failure to induce labor which was consistent

with the present study. In the present study, 2% in the study group underwent cesarean section due to failed induction, whereas, in the expectant group, 8% underwent cesarean section due to failed induction. This was not statistically significant in our study with a *p*-value of 0.565.

Hyperstimulation of uterine activity was not observed in both study and expectant groups. Wing et al. study also had a similar observation.[1]

The occurrence of MSL was not significantly different in the two groups (8% of the study group and 6% of the expectant group).

In the present study, fetal heart rate abnormalities were seen in 6% of the study group and 12% of the expectant group, whereas, in Wing et al. study, it was 5% in the study group and 7% in the expectant group.[4]

Neonatal outcomes were similar in the study and expectant groups. This finding was consistent with other studies.[3,4]

Conclusion

Oral mifepristone given for preinduction cervical ripening was found to be effective and safe with a reduction in the need for additional prostaglandins and oxytocin and shorter induction-to-delivery interval with no serious maternal or fetal adverse effects. The mode of delivery did not differ significantly between the two groups. Though the rate of cesarean section due to failed induction was lesser in mifepristone-treated women, it was not statistically significant.

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