Labor induction with combined low-dose oral misoprostol and Foley catheter vs oral misoprostol alone at term gestation—a randomized study

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BACKGROUND: The ideal method for induction of labor is still not clearly defined. Recent reports in literature have shown that oral administration of low-dose misoprostol is as effective as vaginal administration for induction of labor. The use of vaginal misoprostol in combination with Foley catheter has been shown to shorten the period of induction. However, there are limited reports on the use of oral misoprostol in combination with Foley catheter. Given the convenience of oral administration, improved compliance relative to other methods is probable. This study proposed that the combination of oral misoprostol and Foley catheter would be a better means of inducing labor.

OBJECTIVE: To compare the efficacy of combined low-dose oral misoprostol and Foley catheter with oral misoprostol alone for induction of labor at term gestation. The efficacy was compared in terms of the induction-to-delivery interval and the number of women delivering vaginally within 24 hours. The second objective was to document adverse events, if any, of the 2 protocols.

STUDY DESIGN: The study was conducted at a tertiary care center and included 200 patients with indication for induction, randomly allotted to either of the 2 groups: group A (a combination of Foley catheter and 25-μg misoprostol every 2 hours orally) and group B (only 25-μg misoprostol every 2 hours orally), using computer-generated random number sequence. The obstetrical and neonatal outcomes were recorded and compared between the 2 groups. Quantitative variables were compared using unpaired and paired *t*-tests within the groups across follow-ups.

RESULTS: Group A had significantly shorter mean induction-to-active-labor interval (10.67±1.75 vs 16.28±1.69 hours), mean induction-to-full-dilation interval (11.49 vs 19.00 hours), and mean induction-to-delivery interval (16.85 vs 21.90 hours). The proportion of women delivering vaginally within 24 hours was higher in group A (76 vs 57 women). In comparing maternal side effects, the only significant difference between the 2 groups was found in postpartum hemorrhage. A 5-minute Apgar score <7 was significantly more frequent in group B.

CONCLUSION: The combination of oral misoprostol with transcervical Foley catheter reduced the induction-to-delivery interval significantly (*P*=.001). In addition, the proportion of women delivering vaginally within 24 hours was significantly higher. Hence, the use of oral misoprostol with Foley catheter for induction of labor would be beneficial for patients.

Key words: Foley catheter, labor induction, misoprostol, term pregnancy

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Informed consent was obtained in local language from all patients before inclusion in the study.

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Introduction

Labor induction is the most common obstetrical intervention. In developed countries, up to 25% of term deliveries involve induction of labor, compared with approximately 9.6% in developing countries. Various means are used for induction, including mechanical, medical, surgical, and combined. Medical methods are currently most commonly used, and among them, prostaglandins are considered to be the most effective for induction. Misoprostol prostaglandin E1 is the cheapest prostaglandin and has been proven to be more effective than prostaglandin E2. Misoprostol can be administered by various routes, including oral, vaginal, and sublingual. The search for the best route and best protocol is ongoing.

A meta−analysis reported that vaginal misoprostol was the most effective cervical ripening method to achieve vaginal delivery within 24 hours, but had the highest incidence of uterine hyperstimulation with fetal heart rate (FHR) changes. The use of Foley catheter alone was associated with the lowest rate of uterine hyperstimulation accompanied by FHR changes. The cesarean delivery rate was lowest with the use of oral misoprostol for the induction of labor.[1]

A combination approach of using Foley catheter with misoprostol has been proposed, suggesting that both ripening agents act independently rather than synergistically.[2] Intravaginal misoprostol has been reported as more effective in improving the scores of cervical length and consistency, and transcervical Foley catheter as better at improving the cervical os dilatation score at preinduction cervical ripening; thus, the 2 improve different parameters.[3]

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Why was this study conducted?

The ideal method of induction of labor is still not clearly defined. Although the combination of vaginal misoprostol and Foley catheter has been widely explored, there are limited studies using oral misoprostol in combination with Foley catheter, hence the need for this study.

Key findings

We found statistically significant reduction in the duration of the first stage of labor. The number of women delivering vaginally within 24 hours was significantly higher statistically.

What does this add to what is known?

The combination of low-dose oral misoprostol and Foley catheter is a safe and efficacious option and is better than oral misoprostol alone.

Various studies that explored the advantages of combining misoprostol with use of Foley catheter have used vaginal misoprostol.[4–8] A meta-analysis of randomized trials showed that the combination resulted in shorter induction-to-delivery intervals.[9]

Low-dose oral misoprostol is considered as effective[10] and easier to administer than vaginal misoprostol. We propose that the combination of oral misoprostol and Foley catheter would be a better alternative. There is limited literature on the topic, hence the need for this study.

Aims and Objectives

We aimed to compare the efficacy of labor induction with combined low-dose oral misoprostol and Foley catheter with that of oral misoprostol alone at term gestation. The efficacy was compared in terms of the induction-to-delivery interval and the number of women delivering vaginally within 24 hours. Secondly, we sought to compare the 2 protocols in terms of safety.

Materials and Methods

This randomized case–control trial was conducted to compare labor induction with combined oral misoprostol and transcervical Foley catheter with oral misoprostol alone at term gestation at a tertiary care center, over a period of 1 year (June 2018–July 2019). The study was approved by the institutional scientific and ethical committee of the Dr. Baba Saheb Ambedkar Medical College and Hospital (NBE Reg. No-125-20110-181-218921).

Sample size

Sample size calculation was based on a randomized controlled trial by Husain et al,[6] which compared misoprostol alone with the combination of misoprostol and Foley catheter in 335 women. The minimum required sample size with 80% power of study and 5% level of significance was calculated as 85 patients in each group. We took a sample of 100 patients in each group.

Eligibility criteria

Inclusion criteria selected for pregnant women with single live pregnancies at ≥37 weeks' gestation with valid indication for induction, cephalic presentation, Bishop's score ≤4, and no fetal compromise. Exclusion criteria were absence of consent to the study, history of cesarean delivery or other uterine surgery, chorioamnionitis, and any contraindications to the use of misoprostol and /or vaginal delivery.

Methodology

Demographic data including name, age, religion, socioeconomic status, number of antenatal visits, obstetrical history, menstrual history, personal history, and any surgical and medical history were recorded for each patient. General physical and systematic examination was performed. Gestational age was confirmed by last menstrual period and early-trimester ultrasonography (USG) or available USG. Per abdomen examination was performed to ascertain period of gestation, lie, presentation, and auscultated fetal heart sounds. Bishop's score was assessed and antenatal records were reviewed. Informed consent to inclusion in the study was obtained after counseling about the modalities of induction of labor.

Definitions used

Fetal growth restriction: expected birthweight <10th centile with abnormal Doppler.

Fetal distress: nonreassuring or abnormal cardiotocography (CTG) readings.

Fever: temperature >100.4°F at any time.

Hyperstimulation: presence of >5 contractions in 10 minutes or a contraction exceeding 2 minutes.

Postpartum hemorrhage: any amount of blood loss causing signs or symptoms of hypovolemia.

CTG abnormalities: abnormal CTG patterns as per the American College of Obstetricians and Gynecologists guidelines.

Meconium-stained liquor: dark green or pea soup amniotic fluid that is thick, tenacious, and contains lumps of meconium.

Randomization

A computer-generated randomization scheme was generated by the researcher with equal number of allocations for each arm of the study: (1) Group "A" (n=100): oral misoprostol and Foley catheter combination group; (2) Group "B" (n=100): oral misoprostol alone group.

Interventions

Group A. Patients in this group received low-dose oral misoprostol of 25 μg every 2 hours for a maximum of 8 doses and intracervical 16–18 French Foley catheter, which was introduced at the first dose of misoprostol. Foley balloon was inflated with 60 mL of normal saline. The external end of the catheter was taped to the inner side of the thigh with gentle traction.

Group B. Oral misoprostol of 25 μg was given every 2 hours for a maximum of 8 doses. If the patient did not develop moderate contractions after the 8 doses, a standard low-dose oxytocin regimen of 1 to 2 mU per minute, increased incrementally by 1 to 2 mU in 30-minute intervals, was used for augmentation.

Outcome

Progression of labor was assessed every 4 hours. Foley expulsion was checked every 15 minutes and time of expulsion was recorded when expulsion was reported by the patient or healthcare provider. Induction-to-active-labor (5-cm dilatation), active-labor-to-delivery, and induction-to-delivery intervals were noted. Need for oxytocin was noted. The mode of delivery and neonatal outcomes including Apgar score at 5 minutes, neonatal intensive care unit (NICU) admission, and need for resuscitation were noted. The indications for operative delivery were as per the standard criteria for maternal and fetal distress. Side effects and complications were recorded, and the outcomes of the 2 groups were compared.

Statistical analysis

Categorical variables were presented in numbers and percentages. Continuous variables were presented as mean±standard deviation. Normality of data was tested by the Kolmogorov–Smirnov test. Quantitative variables were compared using the unpaired *t*-test and Mann–Whitney test (when the data sets were not normally distributed) between the 2 groups and paired *t*-test and Wilcoxon test within the groups. Qualitative variables were compared using chi square and Fisher exact tests. A *P* value of <.05 was considered statistically significant. The data were entered into a Microsoft Excel spreadsheet (for Microsoft Excel) and analyzed with IBM SPSS Statistics, version 21.0 (IBM Corp, Armonk, NY).

Observations and Results

We screened 230 women for inclusion into the study (Figure). Demographic

FIGURE
Flow Diagram of Participants.

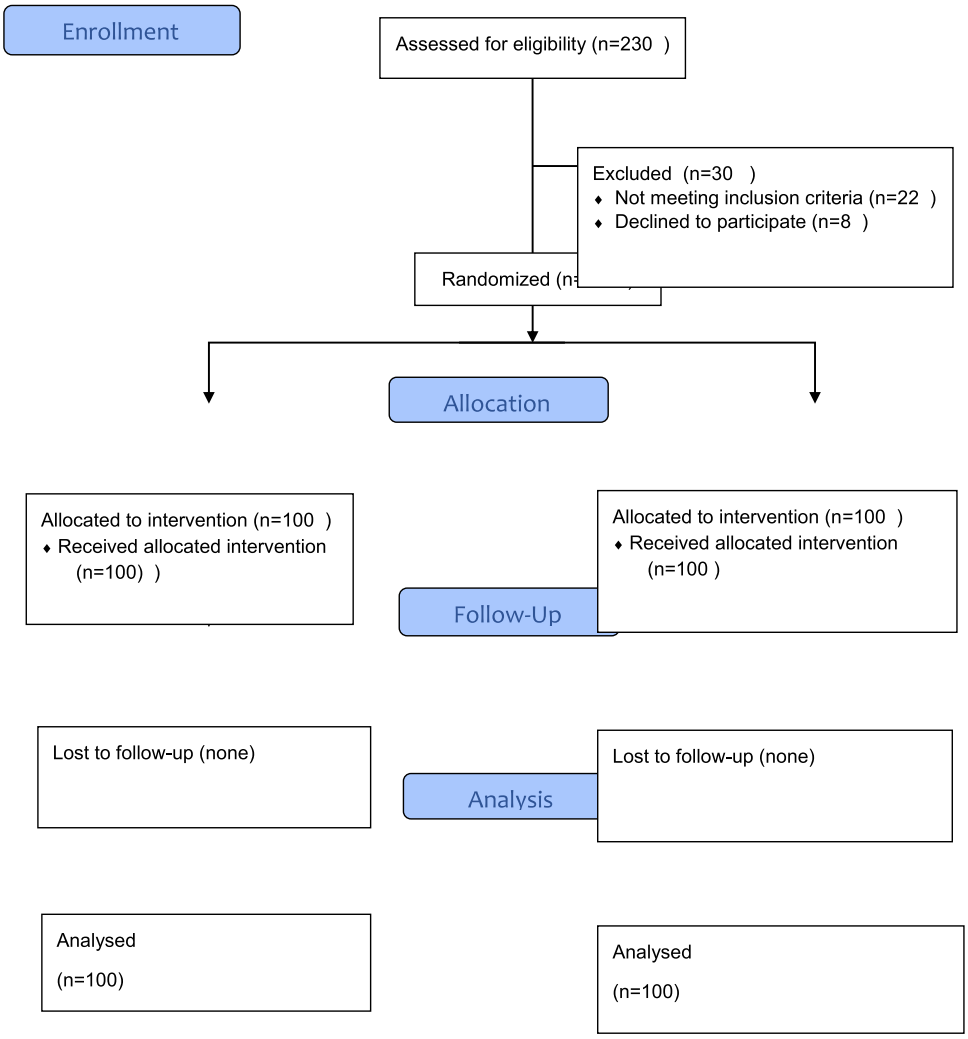

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TABLE 1
Clinical profile

Characteristic	Group A	Group B	*P* value
Age in y (mean±SD)	24.39±3.35	24.4±3.21	.98
Socioeconomic status			.46
Parity (mean±SD)	01.16±1.36	00.90±0.97	.24
Primigravidas (%)	57	59	
Second gravidas (%)	22	23	
Multigravidas (%)	21	18	
Mean gestational age at induction in wk (mean±SD)	39.38±1.32	39.62±1.59	.22
Indication of induction (%)			
Postdates	52	60	
Preeclampsia	20	14	.8
PROM/oligohydramnios	19	18	
FGR	05	03	
GDM	04	05	

FGR, fetal growth rate; *GDM*, gestational diabetes mellitus; *PROM*, preterm rupture of membrane; *SD*, standard deviation.

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data were comparable between the 2 groups (Table 1). The mean age was 24.39 years (range=19−35 years) in group A and 24.40 years (range=18−34 years) in Group B. With regard to parity, there were 57% primiparas and 22% second paras in group A vs 59% primiparas and 23% second paras in group B.

Postdated pregnancy was the most common indication for induction in both groups. The difference in indications for induction between the 2 groups was found to be insignificant (*P*=.8).

The mean gestational age at induction was 39.38±1.32 weeks in group A and 39.62±1.59 weeks in group B. The difference in gestational age between the 2 groups was insignificant (*P*=.22).

The induction-to-Foley-expulsion interval in group A ranged from 4 to 11 hours. The mean induction-to-Foley-expulsion interval duration was 6.94±1.7 hours.

The comparison of labor progress of women delivering vaginally between the 2 groups is shown in Table 2. The mean induction-to-active-labor interval was 5 hours and 30 minutes shorter in group A. The mean induction-to-full-dilation interval duration was 7 hours and 30 minutes shorter in group A. The difference in both intervals between group A and B was statistically significant. The interval from active labor to delivery was shortened in group A by approximately 25 minutes only, but this was statistically significant. In terms of the mean induction-to-delivery interval, group A delivered approximately 5 hours earlier (*P*=.001).

Table 3 depicts the induction outcomes in the 2 groups. There were 87% of women who delivered vaginally in group A and 76% in group B, with the difference being statistically insignificant (*P*=.16). Of the women who delivered within 24 hours, 76 were from group A and 57 from group B. This difference was statistically significant (*P*=.02).

In group A, 13 women had cesarean delivery, which was significantly lower than in group B, in which 24 women had cesarean delivery. When indications for lower-segment cesarean delivery (LSCD) were compared, LSCD for fetal indication was performed in 23% and 37.5% of cases in group A and B, respectively. Failure of progress of labor was the indication in 77% and 62.5% of cases in group A and B, respectively.

The mean dose of misoprostol required in group A was 4.66, with a range of 3 to 8 doses. The mean dose of misoprostol required in group B was 5.99, with a range of 4 to 8 doses (*P*=.001). The need for additional oxytocin was 9% in group A and 15% in group B. No statistical difference in the need for additional oxytocin between the 2 groups was found (*P*=.16).

In the comparison of maternal side effects, the only significant difference was found in postpartum hemorrhage, which was higher in group A, although mild (Table 4). The comparison of perinatal outcomes between the 2 groups is shown in Table 5. A 5-minute Apgar score <7 was found in a significantly greater number of neonates in group B. However, the mean Apgar score at 5 minutes was not statistically different between the 2 groups (*P*=.77).

The visual analog scale score for the induction process was evaluated in both

TABLE 2
Progress of labor in 2 groups

	Group A		Group B		
Interval Studied	Range	Mean±SD	Range	Mean±SD	*P* value
Induction-to-active-labor-interval (in h)	7.10−14.10	10.67±1.75	11.5−21.20	16.28±1.69	.001
Induction-to-full-dilation interval (h)	7.50−16.55	11.49±2.67	16.15−22.55	19.00±1.27	.001
Active-labor-to-delivery interval	3.00−6.10	4.36±0.98	3.00−7.05	4.79±0.81	.002
Induction-to-delivery interval (in h)	12.2−28.05	16.85±3.80	17.2−28.15	21.91±2.54	.001

SD, standard deviation.

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TABLE 3
Outcome of labor in 2 groups

Outcome studied	Group A	Group B	*P* value
Successful outcome (delivery within 24 h)	76 (87.4%)	57 (75.0%)	.02
Vaginal delivery after 24 h of induction	11 (12.6 %)	19 (25.0%)	.49
Total vaginal delivery	87	76	.16
LSCD	13	24	.04
Fetal distress	3 (23%)	9 (37.5%)	
Failed progress of labor	10 (77%)	15 (62.5%)	
Instrumental delivery	3	2	.56

LSCD, lower-segment cesarean delivery.

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TABLE 4
Maternal side effects in 2 groups

Side effect	Group A N	Group B N	*P* value
Fever	3	2	.56
Vomiting	10	9	.79
Hyperstimulation	7	5	.11
Postpartum hemorrhage	7	4	.01

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TABLE 5
Perinatal outcomes in 2 groups

Outcome Parameter	Group A N	Group B N	*P* value
Neonatal resuscitation needed	10	14	.05
CTG abnormalities	3	2	.57
NICU admission	13	18	.06
MSL	8	5	.22
Apgar <7 at 5 min	10	30	.01

CTG, cardiotocography; *MSL*, meconium-stained liquor; *NICU*, neonatal intensive care unit.

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groups. The score was ≥7 in both groups, without statistically significant difference (*P*=.16).

Discussion

Principal findings

Induction of labor is a commonly practiced procedure in obstetrics to artificially initiate labor. Recently, there have been guidelines for routine induction of labor at 39 weeks' gestation in low-risk pregnancy. The means of induction of labor are evolving with the aim of improving efficacy and safety. Studies using Foley catheter in combination with oral misoprostol are limited, although it is considered to be safe, efficacious, and easy to use for obstetrical patients.[11]

Our observation suggests that the mean induction-to-active-labor interval is significantly reduced by the combined use of Foley catheter and oral misoprostol (*P*=.001) in comparison with oral misoprostol alone. Similarly, the mean induction-to-full-dilatation interval was also significantly reduced (*P*=.001) by the combination.

Mean induction-to-delivery interval was reduced by 5 hours when oral misoprostol was used in combination with Foley catheter. In our study, a greater number of women in group A (87%) delivered vaginally, but this was found to be statistically insignificant (*P*=.16). However, the difference in the proportion of women delivering vaginally within 24 hours (higher in group A) was statistically significant (*P*=.02).

Results explained and their implications

The combination of Foley catheter with low-dose misoprostol in our study reduced the time needed by the women to reach active labor and full dilatation, and subsequently to deliver. Thus, the first stage of labor was reduced by approximately 7 hours, implying that the duration spent in the labor room was reduced, easing the process for both women and the medical team.

In a study done by Graham,[8] the mean induction-to-onset-of-active-labor interval duration was significantly shorter (by 151 minutes) in the combination group, but the mean induction-to-full-dilation interval was found to be similar. This could be because the management of active labor was decided by the obstetrician. Balamurugan et al[7] reported that the mean induction-to-active-labor interval was significantly lower in the combination group than in the oral misoprostol group (9 vs 18 hours; *P*=.002). However, these studies used 50 μg or higher misoprostol protocols. Lower but frequent doses are expected to maintain the blood levels better as per the pharmacologic properties of misoprostol.

Husain et al[6] and Balamurugan et al[7] reported a similar reduction in the induction-to-delivery interval in the combination group.[6,7] Graham[8] and Adhikari et al[5] did not find any difference. The former allowed active labor management as per obstetrician's judgment and later used 2 doses of 100 μg. This results in poorly sustained blood levels of misoprostol. We did not stop the misoprostol doses once the contractions were established until there was hyperstimulation or fetal distress, whereas most studies using 50-μg protocols stopped the doses once contractions were established.

The LSCD rate was found to be significantly lower in the combination group. In contrast, the study done by Husain et al[6] found statistically significant differences in mode of delivery, with 91.9% of women delivering vaginally and 8.1% via LSCD in the combination group, and 79% of women delivering vaginally and 21% via LSCD in the misoprostol alone group. However, other authors reported no significant difference in mode of delivery between the 2 groups.[5,8]

We found statistically significant (P=.02) differences in the proportion of women delivering vaginally within 24 hours. A study reported that the proportion of women failing to achieve vaginal delivery within 24 hours in the combination group was lower (11.8% vs 28.7%, P=.001). When they stratified the groups on the basis of parity, the difference was statistically significant for parous women.[5] Graham[8] reported no statistically significant difference.

In some studies, no significant difference was found in the incidence of maternal or neonatal complications.[5,8] We found higher incidence of postpartum hemorrhage in the combination group, but it was mild with no significant morbidity. A cluster-randomized trial reported that induction of labor at term in gravid women with intact membranes using oral misoprostol and Foley bulb did not result in a higher vaginal delivery rate, but did result in more clinical chorioamnionitis compared with the use of oral misoprostol alone.[5] There were no cases of chorioamnionitis in our study. In a meta-analysis reported by McMaster et al,[12] transcervical catheters were not associated with higher rates of maternal or fetal infection.

In our study, we found that 5-minute Apgar scores <7 were more frequent in group B than in group A. Another author reported higher NICU admission rates in neonates of patients treated with oral misoprostol alone.[6]

Clinical and research implications

We found that the combined regimen was effective, easy to use, and provided a reduction in labor duration significant enough to consider it in routine practice. We consider that broadening its application by obstetricians may be beneficial. It would be more appropriate to infer the results from multicentric studies and studies in which routine induction at 39 weeks' gestation is practiced. We suggest that the fetal and neonatal outcomes be studied in greater detail by future researchers to establish this combination further with regard to safety.

Strengths and limitations

To the best of our knowledge, ours is one of the very few studies that have used 25-μg oral misoprostol alone and in a combination protocol. Most available studies with oral misoprostol in the literature have used 50-μg or higher misoprostol protocols. In addition, we used 25-μg tablets, ensuring uniform and convenient dosing. In a recent Cochrane review,[10] it has been stated that oral misoprostol may result in lower vaginal birth rate within 24 hours (risk ratio [RR], 0.81) when compared with vaginal misoprostol, but less hyperstimulation and FHR variations (RR, 0.69) and thus fewer cesarean deliveries for fetal distress. They reported that up to 25 μg of oral misoprostol is better for induction than 50-μg doses, resulting in similar vaginal delivery rates to those reported with vaginal misoprostol, and also for reducing cesarean delivery rates because of hyperstimulation with fetal heart changes.

A major limitation of our study concerns neonatal outcomes. We did not use invasive fetal monitoring for predicting fetal outcomes, and the neonates with low Apgar scores at birth were not followed up. The neonatal outcome also depends on the indication for induction in high-risk pregnancies. Thus, fetal outcomes need to be studied in greater detail in future studies.

Conclusion

On the basis of our findings, we suggest oral misoprostol in combination with Foley catheter as an alternative choice for inducing labor, given that this combination reduces labor duration while providing good outcomes. ■

REFERENCES

1. Chen W, Xue J, Peprah MK, et al. A systematic review and network meta-analysis comparing the use of Foley catheters, misoprostol, and dinoprostone for cervical ripening in the induction of labour. BJOG 2016;123:346–54.
2. Lim SY, Kim YH, Kim CH, et al. The effect of a Foley catheter balloon on cervical ripening. J Obstet Gynaecol 2013;33:830–8.
3. Oliveira MV, Oberst PV, Leite GK, et al. [Cervical Foley catheter versus vaginal misoprostol for cervical ripening and induction of labor: a randomized clinical trial]. Rev Bras Ginecol Obstet 2010;32:346–51.
4. Carbone JF, Tuuli MG, Fogertey PJ, Roehl KA, Macones GA. Combination of Foley bulb and vaginal misoprostol compared with vaginal misoprostol alone for cervical ripening and labor induction: a randomized controlled trial. Obstet Gynecol 2013;121:247–52.
5. Adhikari EH, Nelson DB, McIntire DD, Leveno KJ. Foley bulb added to an oral misoprostol induction protocol: a cluster randomized trial. Obstet Gynecol 2020;136:953–61.
6. Husain S, Husain S, Izhar R. Oral misoprostol alone versus oral misoprostol and Foley's catheter for induction of labor: a randomized controlled trial. J Obstet Gynaecol Res 2017;43:1270–7.
7. Balamurugan V, Joseph K, Kurian R, Joseph T. Sivashannkari. Comparison of efficacy of PGE2 gel, Oral misoprostol and combination of Foleys bulb with Oral misoprostol in predicting the Outcome of induction of labour: a randomized controlled trial. Indian J Obstet Gynecol Res 2021;6:196–201.
8. Graham K, Nguyen M, Sit A, Morfin J, Garabedian M. 417: Oral misoprostol versus combination of foley bulb catheter and oral misoprostol alone for induction of labor: A randomized controlled trial. Am J Obstet Gynecol 2018;218:S254–5.
9. Ornat L, Alonso-Ventura V, Bueno-Notivol J, Chedraui P, Pérez-López FR. Health Outcomes and Systematic Analyses (HOUSSAY) Research Group. Misoprostol combined with cervical single or double balloon catheters versus misoprostol alone for labor induction of singleton pregnancies: a meta-analysis of randomized trials. J Matern Fetal Neonatal Med 2020;33:3453–68.
10. Kerr RS, Kumar N, Williams MJ, et al. Low-dose oral misoprostol for induction of labour. Cochrane Database Syst Rev 2021;6:CD014484.
11. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev 2014;6:CD001338. PMID: 16625542.
12. McMaster K, Sanchez-Ramos L, Kaunitz AM. Evaluation of a transcervical Foley catheter as a source of infection: a systematic review and meta-analysis. Obstet Gynecol 2015;126:539–51.