Outpatient Cervical Ripening With Misoprostol to Prevent Post-Term Pregnancy: A Double-Blind Randomized Clinical Trial

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Abstract- Outpatient use of misoprostol is assessed in a few studies and usually in low doses and vaginal routes. This study aimed to evaluate cervical ripening by outpatient administration of misoprostol to prevent post-term pregnancy. This randomized clinical trial study was performed on 140 patients that were randomly allocated into two groups: 25 µg sublingual SL (group A) and 50 µg PO misoprostol (group B). The patients were primigravid with a gestational age of 40 weeks, with an amniotic fluid index (AFI) of ≥5 cm, a reactive non-stress test (NST) with no evident uterine contraction, Bishop Score of <8, and no notable past medical history. Patients who had a normal vaginal delivery before 41 weeks were considered successful delivery. Maternal age, the number of misoprostol doses, vaginal examination, type of interventions before delivery, the indication of hospitalization, delivery route, the indication of cesarean section, delivery complications, and neonatal outcomes were compared using SPSS software. $P<0.05$ was considered statistically significant. group A had mean age of 23.27±4.03 years and Group B had a mean age of 24.61±5.46 years with no significant difference ($P=0.223$). The number of misoprostol doses ($P=0.001$), extra misoprostol, and oxytocin application were significantly lower in group B ($P=0.003$). Maternal and neonatal complications showed no significant difference between the two groups ($P>0.05$). Outpatient cervical ripening with misoprostol appears to be an optimal method. More prospective studies with higher sample sizes are required to ensure its safety for routine recommendations for cervical ripening to prevent post-term pregnancy.

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Keywords: Outpatient; Cervical ripening; Misoprostol; Post-term pregnancy

Introduction

Post-term pregnancy is defined as a gestational age of more than 42 weeks and occurs in 3 to 12 percent of pregnancies (1). This condition is associated with several neonatal and maternal morbidities and even mortality. Studies have reported a higher incidence of stillbirth and early neonatal deaths. Moreover, a greater number of low Apgar score infants, meconium aspiration, neonatal acidemia, macrosomia, and subsequent birth injury (2). Several maternal problems can also happen in post-term pregnancy including severe perineal lacerations, postpartum hemorrhage, chorioamnionitis, endometritis, and higher rates of cesarean sections (3). Furthermore, the condition poses a heavy emotional burden to the patients, too (4). Although the risk of the above-mentioned complications is usually highest after the gestational age of 42 weeks, they can also happen at a high rate at the age of 40 to 42 weeks; thus the termination of the pregnancy should be considered in this gestational age (5).

Moreover, although the cervix should be firm and closed during the whole period of pregnancy, cervical ripening should be developed within the last weeks of pregnancy, to have a normal vaginal delivery (6). This ripening is usually assessed with Bishop Score and patients with scores ≤4 should be considered to have an intervention (7). Usually, this ripening is conducted by medical or mechanical methods. The patients that underwent mechanical methods such as Foley catheter

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insertion should be hospitalized and monitored (8). In the case of medical intervention usually, E1 and E2 prostaglandins such as misoprostol and it is advisable to use this method in the delivery room, to monitor neonatal and maternal complications. However, the administration of prostaglandins is a usual inpatient method for labor-inducing (9).

Misoprostol is a potential induction drug in an outpatient setting. It is believed that 25 μg of vaginal misoprostol does not impose uterine hyperstimulation on the mother and can be used as an outpatient method for cervical ripening (10). However, this medication was not assessed in higher doses and sublingual and oral routes. This study aimed to evaluate cervical ripening by outpatient administration of misoprostol to prevent post-term pregnancy.

Materials and Methods

A double-blind placebo randomized controlled trial was conducted in an outpatient clinic of the academic hospitals of Mashhad University of Medical Sciences, Mashhad, Iran, for ten months from October 2019 to June 2020. The study was approved by the Ethics Committee of Mashhad University of Medical Sciences code number 971899 and was registered in the Iranian registry system of randomized clinical trials (IRCT20191208045653N1). Forty weeks singleton primigravid women (according to the first-trimester sonography) with an age range of 18 to 40 years old and without any notable past medical or obstetric history (diabetes, preeclampsia, stillbirth,) were included in the study. Inclusion criteria included Mothers' sonography should have the cephalic presentation and normal amniotic fluid index (AFI) (≥5 cm). Moreover, the cases should have a Bishop Score of <8 and a reactive non-stress test (NST) with no evidence of uterine contraction. Exclusion criteria were the development of preeclampsia after enrollment in the study or the arbitrary use of uterotonic drugs.

According to the two previous studies (11,12), a sample size of 70 people was calculated for each of the study groups using Cochran's formula. All the patients were enrolled in the study after they were provided with an informed consent. The patients' demographic data including mothers' age, gestational age, and education level (Elementary, Junior, high school, and university) were randomized into two groups with equal numbers and similar demographics. Group A received 25 μg sublingual (SL) misoprostol and Group B received 50 μg oral (PO) misoprostol, commercially named as Misoglandin. Researchers were blinded to the treatment allocation and a double-blind approach was used. Before administrating misoprostol in each of the groups, the mother and the fetus were monitored for 20 minutes, and in the presence of reactive NST and absence of uterine contraction, misoprostol was administered. If the fetus had reactive NST, the severe signs including labor pain, vaginal bleeding, and amniotic fluid leakage) was educated to the mother and she was advised to return for examination, 24 hours after misoprostol administration. If the patient had a Bishop Score of <8, another dose of misoprostol was administered. This process should be done repetitively for a maximum of seven days. The primary outcome was defined as successful vaginal delivery before a gestational age of 41 weeks and those who failed were hospitalized to induce delivery in an inpatient setting. Secondarily, neonatal and maternal complications were assessed.

All the gathered data were entered in SPSS software version 17 (SPSS Inc, Chicago, IL, USA) and were analyzed. The number of misoprostol doses, vaginal examination, type of interventions before delivery, the indication of hospitalization, delivery route, the indication of cesarean section, delivery complications, and neonatal outcomes were compared using the chi-square test and exact Fisher's test when needed. Moreover, mothers' mean age, mean gestational age and mean duration of the second stage of labor were compared by Mann–Whitney or t-test. $P<0.05$ was considered statistically significant.

Results

A total of 140 patients were included in the study in two seventy-number groups. Table 1 compares demographic data including the mother's mean age, gestational age, and education level between the two study groups that showed no significant difference.

Table 1 also compares the number of misoprostol doses and interventions before delivery between the two study groups. The number of misoprostol applications was significantly lower in the group B ($P=0.001$); for example 44% of the patients in group B and 20% of the patients in group A were hospitalized for normal vaginal delivery, due to various indications after the first dose of misoprostol. In the case of interventions before delivery, 51.4% of the cases in Group B and 34.3% in Group A need no intervention before delivery. Indeed, more interventions including extra misoprostol (10.0% vs. 7.1%) and oxytocin (54.3% vs 30%) were needed in group A. This difference was statistically significant

(*P*=0.003).

The hospitalization to second-stage labor time was significantly lower in group A compared to group B (*P*=0.01). Table 3 shows other details.

Table 1. Comparing demographic data including the mother's mean age, gestational age, and education level were compared between the two study groups

Feature		25 µg misoprostol SL Group A (%)	50 µg misoprostol PO Group B (%)	*P*
Mother's age year (mean±SD)		23.27±4.03	24.61±5.46	0.223
Gestational age days (mean±SD)		280.00±0.00	280.00±0.00	-
Education level N (%)	Elementary school	10 (12.9)	4 (5.7)	0.466
	Junior school	25 (35.7)	29 (41.4)	
	High school	34 (50.0)	35 (50.0)	
	University	1 (1.4)	2 (2.9)	

Table 2. Comparing the number of misoprostol doses and interventions before delivery between the two study groups

Feature		25 µg misoprostol SL Group A N (%)	50 µg misoprostol PO Group B N (%)	*P*
Number of outpatient misoprostol applications N (%)	1 dose	14 (20)	31 (44.3)	0.001
	2 dose	25 (35.7)	11 (15.7)	
	3 dose	17 (24.3)	22 (31.4)	
	4 dose	13 (18.6)	4 (5.7)	
	5 dose	0 (0.0)	0 (0.0)	
	6 dose	0 (0.0)	0 (0.0)	
	7 dose	1 (1.4)	1 (1.4)	
	Extra misoprostol	7 (10.0)	5 (7.1)	
Interventions before delivery N (%)	Oxytocin	38 (54.3)	21 (30.0)	0.003
	Misoprostol+ Oxytocin	1 (1.4)	8 (11.4)	
	Without any intervention	24 (34.3)	36 (51.4)	

Table 3. Comparing variables related to the timings of delivery

Feature	25 µg misoprostol SL Group A	50 µg misoprostol PO Group B	*P*
Intervention to delivery time (hour) (mean±SD)	2.49±1.15	2.2±1.6	0.075
Hospitalization to the second stage of labor time (hour) (mean±SD)	8.22±6.14	10.52±7.22	0.01
Duration of the second stage of labor (hour) (mean±SD)	0.85±0.34	0.89±0.34	0.639

Assessment of the indications of hospitalization showed that totally the most common hospitalization indications were labor contractions, rupture of the membranes, and reduced fetal movement. Group A cases had more frequent contraction compared to group B (85.7% vs 61.41%), while group B had more frequent rupture of the membranes (23.3% vs. 10.0%) and higher reduced fetal movement rate (12.9% vs. 2.9%) with significant difference (*P*=0.01). No vaginal bleeding, abnormal biophysical profile, or amniotic fluid reduction case was found in this regard. About 90% of the patients had a normal vaginal delivery in both groups, and 4.3% of the cases in group A had vacuum-assisted delivery; however, no cases of vacuum-assisted delivery were found in group B. Moreover, both groups had an incidence of cesarean section (7.1%). Delivery type (*P*=0.215) and indications of cesarean section (>0.999) showed no significant difference between the two groups. In case of neonatal complications, one neonate in each study group needed NICU and was hospitalized for 7 days. These two neonates were born from two mothers with postpartum hemorrhage, who received 7 doses of outpatient misoprostol. Maternal and neonatal outcomes showed no significant difference between the two groups. Table 4 shows more details.

Table 4. Comparing indication of hospitalization, delivery, an indication of cesarean, delivery route, and maternal, and neonatal outcomes between the two study groups

Feature		25 µg misoprostol SL Group A	50 µg misoprostol PO Group B	*P*
Indication of hospitalization N (%)	Contraction	60 (85.7)	43 (61.41)	0.01
	Vaginal bleeding	0 (0.0)	0 (0.0)	
	Rupture of the membranes	7 (10)	17 (23.3)	
	Fetal low Apgar score and gestational age of ≥41 weeks	1 (1.4)	1 (1.4)	
	decreased fetal movements	2 (2.9)	9 (12.9)	
	Decreased amniotic fluid	0 (0.0)	0 (0.0)	
	Abnormal biophysical profile	0 (0.0)	0 (0.0)	
Delivery route N (%)	Normal vaginal	62 (88.6)	65 (92.9)	0.215
	Vacuum-assisted delivery	3 (4.3)	0 (0.0)	
	Cesarean section	5 (7.1)	5 (7.1)	
Indication of cesarean N (%)	Fetal distress	1 (20.0)	1 (20.0)	>0.999
	Lack of labor progress	4 (80.0)	4 (80.0)	
	Dystocia	0 (0.0)	0 (0.0)	
Maternal and neonatal outcome N (%)	Post-partum hemorrhage	1 (1.4)	1 (1.4)	>0.999
	Packed-cell transfusion	1 (1.4)	1 (1.4)	
	3^{d} or 4th-degree perineal tear	0 (0.0)	0 (0.0)	
	Uterine tachysystole	0 (0.0)	0 (0.0)	
Neonatal outcome N (%)	First minute Apgar (mean±SD)	8.97±0.17	8.97±0.17	1.000
	Fifth minute Apgar (mean±SD)	9.99±1.2	9.96±0.2	0.312
	Birth weight	3305.87±396.98	3378.29±368.2	0.270
	Meconium-stained AF N (%)	3 (4.3)	7 (10.0)	-
	Admission in NICU N (%)	0 (0.0)	2 (2.9)	-

Discussion

One of the popular medical ways of cervical ripening for normal vaginal delivery is misoprostol consumption as a synthetic prostaglandin E1 analog (13); but due to several adverse effects including tachysystole, meconium aspiration, and hypertonicity, misoprostol usually is prescribed in an inpatient condition (14). As post-term pregnancy has some complications for both mother and neonate that should be considered for terminating a pregnancy, it seems that ripening of the cervix with outpatient use of misoprostol can be a reasonable intervention to lower the post-term pregnancy complications (15).

We found that outpatient misoprostol can also be used as an alternative method to ripen the cervix for normal vaginal delivery without significant neonatal or maternal complications. As a significant finding about 90% of our studied mothers had normal vaginal delivery. Also, the incidence of cesarean section was similar in both study groups. Moreover, we had no cases of dystocia and 3^{d} or 4th-degree perineal tear as complications of post-term pregnancy. Moreover, no case of tachysystole was found as a side effect of misoprostol.

In the case of comparing 25 µg misoprostol SL and 50µg misoprostol PO, we found superiority for 50 µg misoprostol PO in cervical ripening. As these cases needed a lesser number of misoprostol applications during the whole study period and needed lesser oxytocin and misoprostol during hospitalization for delivery compared to the 25 µg misoprostol SL. The vaginal examination further proved the superiority of 50 µg misoprostol PO.

Few studies have addressed the outpatient use of misoprostol for cervical ripening (10,16,17). Outpatient application of 25 µg misoprostol was assessed by Malar *et al*., (10); however, this application was in the vaginal route and along with stripping of the membranes as a mechanical intervention. They reported that patients who received 25 µg misoprostol had a shorter intervention to delivery interval compared to the placebo group; moreover, they had a lower rate of cesarean section. These vulnerable results happened in the absence of severe maternal complications including postpartum hemorrhage, uterine rupture, and septicemia. Only one case of chorioamnionitis was found. Moreover, there was no considerable neonatal complication. We also had only one case of postpartum hemorrhage in each study group that their neonates were hospitalized in NICU for 7 days. These two cases received 7 doses of misoprostol, which seems to be high

and may be a cause of maternal and neonatal complications. There were no other serious maternal or neonatal complications in these patients.

Another study similarly assessed the outpatient use of misoprostol without mechanical intervention in 40 weeks women with a Bishop's score of lower than eight. They reported that the outpatient use of misoprostol significantly lowered the time to delivery, shorter duration of active labor, and earlier gestational age at delivery. This study presented no significant neonatal complications such as low Apgar score, fetal distress, or other side effects (16). Our study only showed two cases of low Apgar scores and two cases of fetal distress. It seems that higher oral doses of misoprostol can cause a bit more neonatal side effects.

Our study had a novelty, which was the comparison of oral and sublingual misoprostol with different doses that were not addressed in many other similar studies. We had no cases of tachysystole and this can be addressed as another powerful point of our study. Moreover, the studies in the case of outpatient use of misoprostol are very few and our study further helps to improve the existing evidence in this regard. Furthermore, it would be better to compare our findings for oral and sublingual misoprostol with vaginal doses and even mechanical interventions. Thus, future studies should focus on these limitations.

Outpatient cervical ripening with misoprostol appears to be an optimal method, but more prospective studies with higher sample sizes are required to ensure its safety for routine recommendations for cervical ripening to prevent post-term pregnancy.

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