Advances in Nursing and Midwifery Original Article
Autumn 2020, Volume 29, Issue 3 (33-40)

Comparison Effects of Vaginal Misoprostol with Vaginal Evening Primrose on Ripening Cervix in Nulliparous Women

Narges Mirzadeh [1], Zohre Sheikhan [2,*], Masoumeh Simbar [3], Yasamin Mehrolhasani [4], Azam Saffar [5], Zohreh Yeganeh [6]

[1] Student Research Committee, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Midwifery and Reproductive Health Research Center, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Department of Obstetrics and Gynecology, Faculty of Medicine, Bam University of Medical Sciences, Bam, Iran
[5] Department of Biostatistics, Faculty of Paramedics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6] Department of Midwifery, Faculty of Nursing and Midwifery, Kermanshah University of Medical Sciences, Kermanshah, Iran

**Corresponding author: Zohre Sheikhan, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: zsheikhan@sbmu.ac.ir*

DOI: 10.29252/anm-30286

Submitted: 04 Feb 2020
Accepted: 14 May 2020
Published: 15 Jul 2020

Keywords:
Cervical Ripening
Evening Primrose
Misoprostol
Bishop Score

How to cite:
Mirzadeh N, Sheikhan Z, Simbar M, Mehrolhasani Y, Saffar A, Yeganeh Z. Comparison Effects of Vaginal Misoprostol with Vaginal Evening Primrose on Ripening Cervix in Nulliparous Women. *Adv Nurs Midwifery*. 2020;29(**3**):33-40. doi: 10.29252/anm-30286

Abstract

Introduction: Childbirth requires several changes in the function of the uterus and cervix. Today, various methods are used to prepare the cervix. Ripening of the cervix is one of the most factors in a successful delivery. This study aims to compare the effects of vaginal misoprostol tablet with vaginal evening primrose capsule on cervical ripening in nulliparous women with term pregnancy.

Methods: This study was a randomized clinical trial of a sokor conducted on 100 nulliparous women referred to Pasteur Hospital and Prenatal Clinic of University of Medical Sciences of Bam, 40 weeks to 40 weeks±6 days gestational age with Bishop Score less than 4. The women were selected by convenient sampling based on random numbers divided into two groups, evening primrose (1000 mg vaginal evening primrose capsules) and misoprostol (25 micrograms of vaginal misoprostol tablets). The data was collected by demographic and midwifery questionnaire, follow-up form, Bishop's checklist, fetal movement registration form, and daily record. Data were analyzed by SPSS20 software, independent t-test, Mann-Whitney, Chi-square, and Linear by Linear. In all of the tests, $P < 0.05$ was considered.

Results: Bishop's score at admission in the evening primrose group was 1.84 ± 0.88 versus 0.78 ± 0.66 in the misoprostol group ($P < 0.001$). The two groups had significant differences in terms of dilatation and cervical consistency during admission. The dilatation in the evening primrose group significantly increased, and cervical consistency was considerably softer in the misoprostol group ($P < 0.05$).

Conclusions: It seems that evening primrose is more effective on cervical ripening and dilatation.

INTRODUCTION

A strong predictor for successful and uncomplicated delivery is a cervix with a high bishop score [1]. Cervical ripening is one of the central labor stages in the final weeks of pregnancy when the cervix begins to soften [2]. Termination of pregnancy in cervical Incompatibility cases results in increased adverse outcomes such as

prolonged labor, fetal distress, and increased cesarean section [3]. Increased fetal death, post maturity, metabolic acidosis, low Apgar score, meconium aspiration syndrome, and prolonged labor are complications of pregnancy that persist for more than 42 weeks [1].

Different mechanical and pharmaceutical methods are currently used for cervical ripening [3-5]. There are many drugs available for the preparation of the cervix, which has a variety of prostaglandins. One of these is vaginal misoprostol tablets [6]. The systemic biological ability of vaginal misoprostol is more than twice that of its oral form [7]. Cervical susceptibility to misoprostol is increased during pregnancy, so that misoprostol is effective at 25-50 micrograms in late pregnancy and the early pregnancy with 400-800 micrograms [8]. Misoprostol is prescribed for pregnancy termination, especially in the third trimester, due to its high efficacy, excellent safety, reasonable price, ease of use, and easy maintenance at room temperature [9]. Side effects of this product have been reported in 8 - 34% [10]. In one study, vaginal misoprostol compared with other forms of it, although facilitating delivery within the first 24 hours, also caused the highest fetal heart rate changes [11]. Many studies have shown that vaginal misoprostol is a safe drug for the cervix's preparation [12, 13].

Nowadays, complementary medicine, especially herbal remedies for cervical ripening, has been increasing [14, 15]. Some herbs have been considered and may be useful in cervical ripening. The evening primrose plant is from the Onagraceae family, scientifically named Oenothera biennis [16]. This plant extract contains two essential fatty acids (50-75% linoleic acid, 7-10% gamma-linoleic acid) and a small amount of oleic, palmitic, and stearic acid. These two essential fatty acids facilitate prostaglandin E2 synthesis [17, 18].

Some studies confirm the effects of evening primrose on cervical ripening [19, 20], but one study found that evening primrose did not affect cervical development [21]. The use of this plant has no restrictions on pregnancy [22], research has shown that its use has no adverse effects on fetal health [23], but can it affect cervical ripening? Due to the contradictory results regarding the effects of evening primrose on cervical development, the present study aimed to compare the impact of vaginal misoprostol tablet with vaginal evening primrose capsule on cervical ripening in primiparous women referred to Pasteur Hospital in Bam 2018.

METHODS

This single-blind randomized clinical trial study was performed on 100 nulliparous women with term pregnancy. Bishop scores less than 4, referred to Pasteur Hospital and Prenatal Clinic affiliated with University of Medical Sciences Bam, Iran. It was done from April to November 2018. The sample size was based on the study's overall objective, probability of first type error of 0.05%, test power of 0.1%, with 15% sample loss per group consisted of 55 patients (110 patients in total). Inclusion criteria included: 18-30 years of age, first and single pregnancy, cephalic fetus presentation, live fetus, gestational age 40 weeks to 40 weeks and six days based on the first day of last menstrual and first-trimester ultrasound, no uterine contractions, Bishop Score less than four, Intact amniotic sac, estimated fetal weight of 2500-4000 grams, low-risk pregnancy (no known internal and surgical diseases and pregnancy complications such as previa, placental abruption, preeclampsia, and no known fetal problems), no vaginal examination during the 24 hours before the study, there was no sexual intercourse and herbal medicines. If they had any issues requiring emergency action such as fetal failure, maternal bleeding, etc., receiving any herbal medication during the study, possible drug-related complications, and withdrawal from participation in the task at each stage were excluded. Required explanations about the research and its aims were given to the women, and then informed consent was obtained from those who met the inclusion criteria. The women in the study were first available, and then they were randomly divided into two groups based on a random number table. One hundred ten envelopes were placed in a box. Each envelope was assigned to one of the two groups of misoprostol and the evening primrose based on a table of random numbers. The first ones took envelope number 1, and the next ones took the envelopes in order of their number and were in the assigned groups. Finally, 100 patients, 45 were in the evening primrose group (4 were excluded due to sexual intercourse during the study and six were excluded due to the lack of complete referral for placement of the evening primrose capsule), and 55 were assigned to the misoprostol group(Figure 1). The women in both groups were unaware of the type of medication used.

In the evening primrose group, the researcher referred to the prenatal clinic and examination room of Pasteur Hospital and women whose gestational age was 40 weeks and had a Bishop examination of less than four, after justifying the goals and written consent were given 1000 mg vaginal evening primrose capsule manufactured by Amin Drug Company for seven days. The women were instructed over a week until the next referral in case of labor pain, spotting or bleeding, leakage, decreased fetal movement, or any other problems during a telephone contact with the researcher to refer to the hospital's emergency clinic. In the misoprostol group, women referred to Pasteur Hospital with a gestational age of more than 40 weeks were selected as candidates for 25 micrograms (one eighth

200 micrograms) vaginal misoprostol tablets manufactured by Samisaz Mashhad Company. After taking misoprostol, the woman and her fetus were monitored. The researcher followed up with both groups until admission. The vaginal examination and Bishop Score were assessed in both groups by a researcher (experienced midwifery expert). Samples were also provided with the researcher's telephone number to contact the researcher at any time of the day if any problems or questions arose. At each stage of the onset of labor symptoms or hospitalization for any reason, the patient was followed up by the researcher from hospitalization to the end of delivery.

Demographic and midwifery questionnaire, observation and examination, follow up form, daily registration form, and Bishop Checklist were used for data collection. Data were analyzed using SPSS 20 software. Kolmogorov-Smirnov test was used to ensure normal distribution of data. Independent t-test and Mann-Whitney test were used for normal distribution of data. Chi-square tests were used to compare qualitative and nominal data. Linear by Linear association was also used for data analysis. A P-value less than 0.05 was considered significant. The Ethics Committee approved the present study of Shahid Beheshti University of Medical Sciences under IR. SBMU.PHNM.1396.851 and also registered in clinical trial site IRCT20180101038176N1.

RESULTS

This study was conducted on 100 women (55 women in the misoprostol group and 45 women in the primrose group) that showed in Figure 1, and their demographic details are presented in Table 1. The findings are as follows: The two groups were matched for maternal age and body mass index after analyzing data. Mean and standard deviation of gestational age in the evening primrose group at the first day of last menstruation and first-trimester ultrasound were respectively 40 weeks and 1.44 ± 1.23 days and 40 weeks and 1 ± 1.3 days, and in misoprostol group were 40 weeks and 2.45 ± 1.63 days and 40 weeks and 2.38 ± 1.95 days. The two groups were similar in gestational age on the first day of the last menstrual and first-trimester ultrasound. Still, they were significantly different in the number of gestational days (on the first day of previous menstrual P = 0.001), (on the first-trimester ultrasound P<0.001). Gestational age based on the first day of last menstruation and first-trimester ultrasound was significantly higher in the misoprostol group (Table 1).

The most common cause of hospitalization in the evening primrose group, 18 patients (40%), was the pain. In the misoprostol group, 41 (74.5%) had the time of delivery. At the time of admission, 23 (51.1%) in the evening primrose group had an Intact amniotic sac, while in the misoprostol group, all women had an Intact amniotic sac. There was no significant difference between fetal heart rate at the beginning of the study and admission and fetal heart rate status during the study. There was a statistically significant difference between the two groups in terms of bleeding at admission, of which 5 (11.1%) in the evening primrose group and in the misoprostol group had 1 (1.8) patients with low bleeding. At admission, 40 (88.9%) of the evening primrose group women with uterine contraction and 54 (98.2%) of the misoprostol group had no uterine contraction. At least one uterine contraction within 10 minutes at the onset of contractions during maternity hospitalization was observed in 23 (52.3%) women. In the evening primrose group, 20 women were given one dose on the first day, 23 women two doses in two days, and two women three doses of 1000 mg capsules in three days vaginally on the first day. The misoprostol group received only one dose of 25 micrograms intravaginal. The type of delivery was the majority vaginal, 41 (91.1%) in the evening primrose group and 49 (89.1%) in the misoprostol group. No significant difference was observed. There was no significant difference between the two groups in terms of duration of labor phases. 32 (72.3%) women in the evening primrose group and 41 (74.5%) in the misoprostol group used oxytocin. Hyoscine was the most commonly used drug during labor in the evening primrose group of 6 patients (50%) and the misoprostol group 6 patients (60%). There was no statistically significant difference between the two groups. There was a statistically significant difference in the incidence of side effects between the two groups in terms of nausea and vomiting, with nausea and vomiting higher in the misoprostol group (12 (26.7%) in the evening primrose group and 36(65.5%) in the misoprostol group (P<0.001). There was no significant difference between the two groups in terms of meconium-stained amniotic fluid, fetal heart rate changes, diarrhea, and bleeding. None of the women studied had a fever and a contraction more significant than 6 in 10 minutes.

There was a significant difference between the two groups regarding Bishop Score at admission, and this score was significantly higher in the evening primrose group (p <0.001) (Table 2). There was a significant difference between the two groups at the entrance in terms of cervical dilatation and consistency. Dilatation was significantly higher in women of the evening primrose group (P < 0.001), but the cervical texture was softer in the misoprostol group (P < 0.001) (Table 3).

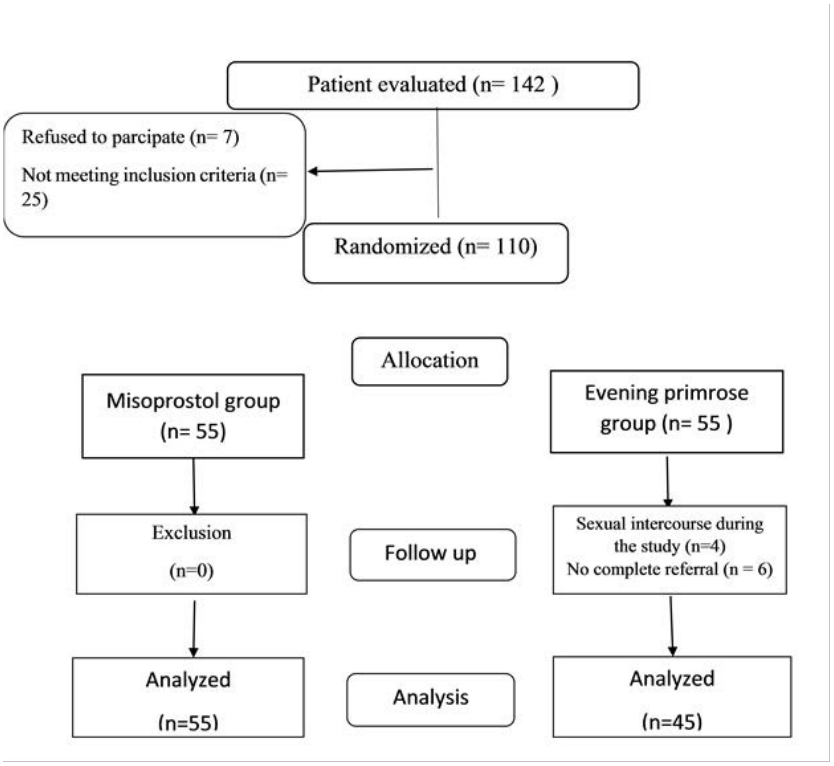

Figure 1. The Consort Flowchart

Table 1. Comparing of Demographic Data of the Women in the Two Groups of Evening Primrose and Misoprostol.

Variable	Evening primrose group N=45	Misoprostol Group N=55	P-Value
Mother's age	22.29 ± 4.04a	22.49 ± 3.37	0.786*
Mother weight	61.84 ± 9.96	60.82 ± 7.75	0.757**
BMI	23.1 ± 2.89	22.87 ± 2.38	0.658*
First day of last menstruation	40w&1.44 ± 1.23	40w&2.45 ± 1.63	0.001**
First trimester ultrasound	40w&1± 1.3	40w&2.38 ± 1.95	<0.001**
Maternal education			0.621***
Elementary	6(13.3)b	5(9.1)	
Secondary school	7(15.6)	10(18.2)	
High school	21(46.7)	21(38.2)	
Academic	11(24.4)	19(34.5)	
Employment status of the mother			0.088***
Housewife	42(93.3)	45(81.8)	
Employee	3(6.7)	10(18.2)	
Attend delivery preparation classes			0.296***
Yes	9(20)	15(27.28)	
No	36(80)	40(72.72)	
Prenatal exercise			0.805***
Yes	5(11.1)	7(12.7)	
No	40(88.9)	48(87.3)	
Number of prenatal care sessions			0.293**
1-3 sessions	1(2.2)	1(1.8)	
3-5 sessions	4(8.9)	7(12.7)	
More than 5 sessions	40(88.9)	47(85.5)	

* Independent t-test, ** Mann-Whitney test, *** Chi-square test
Data in the table are presented as Mean ± SD or No. (%)

Table 2. Comparing of Bishop's Score at Different Times in the Women in the Two Groups of Evening Primrose and Misoprostol.

Bishop's Score at Different Times	Evening Primrose Group, N = 45	Misoprostol, Group, N = 55	P-Value
Before starting the study	0.95 ± 0.75	0.78 ± 0.66	0.259*
At admission	1.84 ± 0.88	0.78 ± 0.66	< 0.001*
At the beginning of the active phase	5.38 ± 0.93	5.19 ± 1.114	0.272*
2 hours after active phase	9.24 ± 1.88	9.33 ± 1.9	0.796*
4 hours after active phase	11.65 ± 0.9	11.81 ± 0.654	0.784*

* Mann-Whitney test
Data in the table are presented as Mean ± SD

Table 3. Comparing of Components of Bishop's Scoring System at the Time of Admission of the Women in the Two Groups of Evening Primrose and Misoprostol.

Bishop System Components	Evening Primrose Group, N=45	Misoprostol Group, N=55	P Value
Cervical dilatation			<0.001*
Closed	2(4.5)	29(52.7)	
1-2	41(91.1)	26(47.3)	
3-4	2 (4.4)	0	
Cervical consistency			<0.001**
Firm	43(95.6)	35(63.6)	
Medium	2(4.4)	20(36.4)	
Soft	0	0	
Cervical Status			0.182*
Posterior	33(73.3)	34(61.8)	
Middle	12(26.7)	20(36.4)	
Anterior	0	1(1.8)	
Cervical effacement			
0-30	45(100)	55(100)	
40-50	0	0	
60-70	0	0	
80=<	0	0	
Station of the fetal head			
-3	45(100)	55(100)	
-2	0	0	
-1	0	0	
+1,+2	0	0	

* Linear by Linear Association, ** Chi-square test
Data in the table are presented as No. (%)

DISCUSSION

This single-blind randomized clinical trial study was performed on 100 nulliparous women with term pregnancy. Bishop scores less than 4, referred to Pasteur Hospital and Prenatal Clinic affiliated with University of Medical Sciences Bam, Iran. The study aims to compare the effects of vaginal misoprostol tablet with vaginal evening primrose capsule on cervical ripening in nulliparous women with term pregnancy. The finding of the current research, Bishop's score at admission in the evening primrose group, is higher than the misoprostol group. The dilatation in the evening primrose group significantly increased, and cervical consistency was considerably softer in the misoprostol group. Cervix ripening is one of the success factors in labor and delivery. According to the present study's findings, Bishop's score at admission, despite not having a statistically significant difference at the beginning of the research in the two groups, was significantly higher in women of the evening primrose group. Ty-Torredes et al. (2006) [23] and Bahmani et al. (2019) [20] have shown in their studies that the evening primrose capsule increases Bishop's score effectively and significantly. It is noteworthy that in the study of Bahmani et al. (2019), in the intervention group, vaginal evening primrose capsule combined with sublingual misoprostol tablets could be used up to two doses, which may be due to the positive effect of Bishop Score sublingual misoprostol [20], In the present study, however, the impact of vaginal evening primrose capsule alone in the evening primrose group on cervix ripening was assessed. Vahdat et al. (2015) also showed that evening primrose capsules could also affect cervical ripening in non-pregnant women [19]. But Jahdi et al. (2016) [21] and Kalati et al. (2018) [24] showed that oral evening primrose capsules did not affect Bishop Score increase. Perhaps the reason for the differences in the results of studies is using different evening primrose capsules doses and how to use it. In this study, a vaginal evening primrose capsule was used once daily, but Jahdi et al. (2016) [21] and Kalati et al. (2018) [24] used an oral evening primrose capsule twice daily. Some researchers have reported that oral evening primrose capsules during pregnancy and prolonged lactation labor increased prolonged rupture of membranes, the arrest of descent, oxytocin use, and vacuum delivery [25]. The Natural Medicines Comprehensive Database states that oral evening primrose capsules may be avoided during pregnancy due to possible pregnancy-related complications [26]. These side effects may be due to the use of extended and long-term doses of evening primrose capsules. Batukan et al. (2008), in their study, identified one of the possible mechanisms of effective absorption of vaginal misoprostol, its direct transfer from the vagina to the uterus [27]. Possibly the vaginal evening primrose capsule with the same mechanism localized absorption. One of the results of this study is the effect of evening primrose capsules on cervical dilatation. In their research, Vahdat et al. (2015) showed that evening primrose is useful on cervical dilatation [19]. In the study by Aquino et al. (2011), the evening primrose capsule effect on cervical dilatation was evident, but the researchers used 2000 mg evening primrose capsule [28]. Linoleic acid from the evening primrose converts to arachidonic acid during a number of enzymatic processes. Finally, arachidonic acid by

cyclooxygenase facilitates the synthesis of prostaglandin E2 from the evening primrose capsule [17, 29]. Prostaglandin E2 physiologically increases cervical readiness by increasing water under the cervical mucosa and altering collagen bands [30]. It is worth noting that cervix is composed mainly of fibroblast cells and connective tissue composed of collagen and glucose aminoglycans. Cervix preparation is an active biochemical process in which a series of extensive collagenase reactions occur. In the collagenase process, type 1 and 8 metalloproteinase are essential. Type1 metalloproteinase are produced by fibroblast cells and type 8 by predominantly neutrophils (leukocytes). Studies have shown that prostaglandin E2 has a direct effect on stimulating the activity of type 1 metalloproteinase [31, 32] and that prostaglandins can increase the level of type 8 metalloproteinase by adsorption of neutrophils into the cervix [33]. This leads to increased collagenase activity and further softening of the cervix. Therefore, it can be considered as a positive effect of evening primrose capsule on cervical readiness by increasing prostaglandin E2.

Another result of this study was the difference in cervical consistency. Misoprostol caused softness of the cervix. Oppegaard et al. (2010), Confess misoprostol can be used to soften the cervix [34]. The softening effect is due to its direct impact on the cervical tissue. Although its mechanism is unclear but, reducing the amount of cervical collagen and increasing its solubility and activity of collagen degrading enzymes may be one of the possible tools of this product [12]. However, its use (oral-vaginal) also be of interest. Perhaps the reason for the firm of the cervical consistency in women of the evening primrose group is the short duration of capsule use. Most of these women had been admitted to the hospital on the first day after capsule application.

Other findings of the study showed that the incidence of adverse events such as nausea and vomiting was significantly higher in women in the misoprostol group than in the evening primrose group. Still, Jahromi et al. (2016), in their study, showed no significant difference in adverse events except meconium-stained amniotic fluid and change in fetal heart rate [35]. The most common side effect of misoprostol is gastrointestinal side effects that are dose-dependent [8, 11]. In the study of Bahmani et al. (2019), no side effects were found in women using vaginal evening primrose [20].

In this study, the rate of bleeding at admission was higher in the evening primrose group due to the higher dilatation rate. Bloody show can be attributed to cervical dilatation. Also, some women in the evening primrose group had amniotic rupture sacs at the time of hospitalization. Perhaps this was due to the effect of the evening primrose on the cervix. As a result of uterine contractions, the amniotic sac's hydrostatic effect leads to the dilatation of the cervix [1]. Therefore, uterine contraction intensity can be a possible cause of amniotic sac rupture in this group.

Considering the effect of all Bishop Score components on the chance of vaginal delivery, although a related study can be stated, cervical dilatation is the most critical component of Bishop Score for cervical ripening in the successful prediction of labor induction [36].

CONCLUSIONS

This study showed that a vaginal evening primrose capsule could effective on cervical ripening and dilatation. However, various factors affect the bishop score. Researchers recommend considering this method as an affordable, inexpensive, and uncomplicated way to improve labor and delivery compared to other methods. Further studies and their effect on delivery outcomes are suggested to obtain more definitive results regarding the evening primrose capsule's efficacy on cervical ripening. The most vital point of the study is introducing a herbal material that facilitated childbirth with the least side effects. One of the limitations of this study is that it is a single-blind survey, repeated vaginal examinations of midwives in labor, and chemical drugs in work.

ACKNOWLEDGMENTS

We are grateful for the cooperation of Shahid Beheshti University of Medical Sciences, Bam University of Medical Sciences, gynecologists, midwives, and pregnant women participating in the study.

Conflict of Interests

All authors have no conflict of interest.

Funding

This article results from a thesis by MSc Narges Mirzadeh with the support of Shahid Beheshti University of Medical Sciences, which was performed in the Pastor Hospital and Clinic affiliated with Bam University of Medical Sciences.

Authors' Contribution

Zohre Sheikhan developed the original idea, study concept, and design and study supervision. Narges Mirzadeh had the leading role in the data collection, interpretation of data, and writing of the manuscript. Other authors: Masoumeh Simbar, Yasamin Mehrolhasani, and Zohreh Yeganeh study concept, critical revision of the manuscript; Azam Saffar analysis of data.

Ethical Consideration

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences under IR. SBMU.PHNM.1396.851 and also registered in clinical trial site IRCT20180101038176N1.

REFERENCES

1. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams obstetrics, 24e: Mcgraw-hill2014.
2. Cohen WR, Friedman EA. Labor and delivery care: a practical guide: John Wiley & Sons; 2011.
3. Tenore JL. Methods for cervical ripening and induction of labor. Am fam phy. 2003;67(10):2123-8.
4. Fox NS, Saltzman DH, Roman AS, Klauser CK, Moshier E, Rebarber A. Intravaginal misoprostol versus Foley catheter for labour induction: a meta-analysis. BJOG. 2011;118(6):647-54. **doi:** 10.1111/j.1471-0528.2011.02905.x **pmid:** 21332637
5. Blackburn ST. Maternal, Fetal, & Neonatal Physiology4: Maternal, Fetal, & Neonatal Physiology: Elsevier Health Sciences; 2012.
6. Fernandez H, Alby JD, Tournoux C, Chauveaud-Lambling A, DeTayrac R, Frydman R, et al. Vaginal misoprostol for cervical ripening before operative hysteroscopy in pre-menopausal women: a double-blind, placebo-controlled trial with three dose regimens. Hum Reprod. 2004;19(7):1618-21. **doi:** 10.1093/humrep/deh302 **pmid:** 15155607
7. Rahman H, Pradhan A, Kharka L, Renjhen P, Kar S, Dutta S. Comparative evaluation of 50 microgram oral misoprostol and 25 microgram intravaginal misoprostol for induction of labour at term: a randomized trial. J Ob Gyn Canada. 2013;35(5):408-16. **doi:** 10.1016/S1701-2163(15)30931-2
8. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. N Engl J Med. 2001;344(1):38-47. **doi:** 10.1056/NEJM200101043440107 **pmid:** 11136959
9. Hill JB, Thigpen BD, Bofill JA, Magann E, Moore LE, Martin JN, Jr. A randomized clinical trial comparing vaginal misoprostol versus cervical Foley plus oral misoprostol for cervical ripening and labor induction. Am J Perinatol. 2009;26(1):33-8. **doi:** 10.1055/s-0028-1091396 **pmid:** 18850516
10. Nunes FP, Campos AP, Pedroso SR, Leite CF, Avillez TP, Rodrigues RD, et al. Intravaginal glyceryl trinitrate and dinoprostone for cervical ripening and induction of labor. Am J Obstet Gynecol. 2006;194(4):1022-6. **doi:** 10.1016/j.ajog.2005.10.814 **pmid:** 16580291
11. Chen W, Xue J, Peprah MK, Wen SW, Walker M, Gao Y, 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(3):346-54. **doi:** 10.1111/1471-0528.13456 **pmid:** 26538408
12. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet. 2007;99 Suppl 2:S160-7. **doi:** 10.1016/j.ijgo.2007.09.004 **pmid:** 17963768
13. Shakya R, Shrestha J, Thapa P. Safety and efficacy of misoprostol and dinoprostone as cervical ripening agents. J Nepal Med Associ. 2010;49(177):33-7. **doi:** 10.31729/jnma.132
14. Navidi A, Qasemi Soleymanie K. Encyclopedia of holistic medicine: traditional and modern medicine methods. Tehran: Cultural Institute Tymvrzadh publishers-publishing Physician; 2003.
15. Ozgoli G, Goli M, Simbar M. Effects of ginger capsules on pregnancy, nausea, and vomiting. J Altern Complement Med. 2009;15(3):243-6. **doi:** 10.1089/acm.2008.0406 **pmid:** 19250006
16. Kiss A, Derwińska M, Granica S. Quantitative analysis of biologically active polyphenols in evening primrose (Oenothera paradoxa) seeds aqueous extracts. Polish J food nutri sci. 2011;61(2):109-13. **doi:** 10.2478/v10222-011-0011-y
17. Ghasemnezhad A, Honermeier B. Yield, oil constituents, and protein content of evening primrose (Oenothera biennis L.) seeds depending on harvest time, harvest method and nitrogen application. Indus Crops Product. 2008;28(1):17-23. **doi:** 10.1016/j.indcrop.2007.12.006
18. Khan IA, Abourashed EA. Leung's encyclopedia of common natural ingredients: used in food, drugs and cosmetics: John Wiley & Sons; 2011.
19. Vahdat M, Tahermanesh K, Kashi AM, Ashouri M, Dodaran MS, Kashanian M. Evening primrose oil effect on the ease of cervical ripening and dilatation before operative hysteroscopy. Thrita. 2015;4(3):e29876. **doi:** 10.5812/thrita.29876
20. Bahmani S, Hesamy K, Shahgheibi S, Roshani D, Shahoei R. Comparison of the Effect of Vaginal Capsule of Evening Primrose Oil and Misoprostol on Cervical Ripening of Nulliparous Women with Post-term Pregnancy. Gynecol Infertilit. 2018;21(8):30-8.
21. Jahdi F, Kalati M, Kashanian M, Naseri M, Haghani H. Effect of oral evening primrose capsules on ripening of the cervix in nulliparous Iranian pregnant women (a randomized trial). Acta Med Mediterrane. 2016;32(Specia):1273-9.
22. Stonemetz D. A review of the clinical efficacy of evening primrose. Holist Nurs Pract. 2008;22(3):171-4. **doi:** 10.1097/01.HNP.0000318026.45527.07 **pmid:** 18453897
23. Ty-Torredes KA. The effect of oral evening primrose oil on bishop score and cervical length among term gravidas. Am J Ob Gyn. 2006;195(6):S30. **doi:** 10.1016/j.ajog.2006.10.078
24. Kalati M, Kashanian M, Jahdi F, Naseri M, Haghani H, Sheikhansari N. Evening primrose oil and labour, is it effective? A randomised clinical trial. J Obstet Gynaecol. 2018;38(4):488-92. **doi:** 10.1080/01443615.2017.1386165 **pmid:** 29426270
25. Dove D, Johnson P. Oral evening primrose oil:: Its effect on length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women. J Nurse-Midwif. 1999;44(3):320-4. **doi:** 10.1016/S0091-2182(99)00055-5
26. Database NMC. Natural Medicines Comprehensive Database. Evening primrose oil 2007. Available from: http://www.naturaldatabase.com.
27. Batukan C, Ozgun MT, Ozcelik B, Aygen E, Sahin Y, Turkyilmaz C. Cervical ripening before operative hysteroscopy in premenopausal women: a randomized, double-blind, placebo-controlled comparison of vaginal and oral misoprostol. Fertil Steril. 2008;89(4):966-73. **doi:** 10.1016/j.fertnstert.2007.03.099 **pmid:** 17681307
28. Aquino P, Fernandez H, Garcia M, Barrientos M, Apepe E, Pichay R. Determining the Ease of Cervical Dilation in Patients Given Evening Primrose Oil (Eveprim®) Intravaginally before Hysteroscopy in Postmenopausal and Nulliparous, Premenopausal Women Ages 37-77 Years Old: A Pilot Study. J Minimally Invasive Gyn. 2011;18(6):S126-S7. **doi:** 10.1016/j.jmig.2011.08.518
29. Timoszuk M, Bielawska K, Skrzydlewska E. Evening Primrose (Oenothera biennis) Biological Activity Dependent on Chemical Composition. Antioxidants (Basel). 2018;7(8). **doi:** 10.3390/antiox7080108 **pmid:** 30110920
30. Church S, Van Meter A, Whitfield R. Dinoprostone compared with misoprostol for cervical ripening for induction of labor at term. J Midwifery Womens Health. 2009;54(5):405-11. **doi:** 10.1016/j.jmwh.2009.03.006 **pmid:** 19720343
31. Yoshida M, Sagawa N, Itoh H, Yura S, Takemura M, Wada Y, et al. Prostaglandin F(2alpha), cytokines and cyclic mechanical stretch augment matrix metalloproteinase-1 secretion from cultured human uterine cervical fibroblast cells. Mol Hum Reprod. 2002;8(7):681-7. **doi:** 10.1093/molehr/8.7.681 **pmid:** 12087084
32. Kelly RW. Inflammatory mediators and cervical ripening. J Reproduct Immun. 2002;57(1-2):217-24. **doi:** 10.1016/S0165-0378(02)00007-4
33. Osmers RG, Adelmann-Grill BC, Rath W, Stuhlsatz HW, Tschesche H, Kuhn W. Biochemical events in cervical ripening dilatation during pregnancy and parturition. J Obstet Gynaecol

(Tokyo 1995). 1995;21(2):185-94. **doi:** 10.1111/j.1447-0756.1995.tb01092.x **pmid:** 8556580

34. Oppegaard KS, Lieng M, Berg A, Istre O, Qvigstad E, Nesheim BI. A combination of misoprostol and estradiol for preoperative cervical ripening in postmenopausal women: a randomised controlled trial. BJOG. 2010;117(1):53-61. **doi:** 10.1111/j.1471-0528.2009.02435.x **pmid:** 20002369
35. Jahromi BN, Poorgholam F, Yousefi G, Salarian L. Sublingual versus vaginal misoprostol for the induction of labor at term: a randomized, triple-blind, placebo-controlled clinical trial. Iran J Med Sci. 2016;41(2):79.
36. Rane SM, Guirgis RR, Higgins B, Nicolaides KH. The value of ultrasound in the prediction of successful induction of labor. Ultrasound Obstet Gynecol. 2004;24(5):538-49. **doi:** 10.1002/uog.1100 **pmid:** 15386612