Comparison of the Effect of Vaginal Capsule of Evening Primrose Oil and Misoprostol on Cervical Ripening of Nulliparous Women with Post-term Pregnancy

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objective: The rates of perinatal mortality and neonatal morbidity are higher for post-term pregnancies than for term pregnancies. The present study was conducted to compare the effect of vaginal capsule of evening primrose oil and misoprostol on cervical ripening of nulliparous women with post-term pregnancy.

Materials and Methods: This one-blind randomized trial conducted on 130 pregnant women with post-term pregnancy visiting to the labor ward of Sanandaj Be’sat Hospital. Samples were divided into two groups of intervention and control with the randomized allocation method. The intervention
1. INTRODUCTION

Pregnancy based on the gestational age divided into three categories of preterm, term, and post-term [1]. Post-term pregnancy (longer than 42 weeks or 294 days) occurs in approximately 10% of all singleton gestations [2]. The most common causes of post-term pregnancy are the mistake in determining the gestational age [1,3], anencephaly, adrenal hypoplasia and unripe cervix [4].

The adverse outcomes of post-term pregnancy include psychological stress, physical injuries, postpartum hemorrhage, postpartum infection and long-term hospitalization [5]. For management of post-term pregnancy, two major approaches have been employed: elective induction of labor at 41-42 week, and expectant management with intermittent fetal monitoring (e.g. cardiotocography, biophysical profile) and elective induction of labor [6].

Factors that can predict the probability of induction include maternal factors (number of births, age and body mass index), fetal factors (birth weight and gestational age) and cervical status [7]. Induction of labor where the cervix is not ripe can reduce the success of normal delivery and increase the probability of cesarean section [8]. The most common method of evaluation of the ripening of the cervix was firstly recommended by bishop in 1964 as the bishop score method based on scoring including five components (dilatation, effacement, location and firmness of cervix and presentation station) [9,10].

So far, several methods have been proposed to help soften the cervix before induction of labor, which are mainly classified in two groups of mechanical and medical [11,12].

Mechanical methods such as trans-cervical catheter [13], hygroscopic dilators and stripping [14] and medical methods such as E1 and E2 prostaglandin. Misoprostol (E1) is both vaginal and oral, and it is widely used for induction of labor due to its favorable price and high effect [15]. However, Misoprostol has maternal and fetal complications [16].

Nowadays, in addition to using various medical methods to ripening the cervix, there are also some traditional methods such as using various forms of medicinal plants emphasizes on using herbal medicines due to severe side effects of the chemical ones. Among herbal medicines primrose oil are used to help prepare cervix [11].

Primrose is a wild Two-year plant with yellow flowers that grows in North America and some parts of Europe [17,18]. Evening primrose oil (EPO) is extracted from the seeds of plant including 50-70% of Linoleic acid, 7-10% of Gama Linoleic acid [19]. Two necessary fatty acids Linoleic acid and Gama Linoleic facilitate E2 prostaglandin synthesis [1,20].

Primrose is generally tolerated well by individuals but also causes a mild upset stomach and headache. Thus, since EPO is generally tolerated well there is no limit for using it during the pregnancy because it has no effect on the safety of the fetuses monitored by biophysical profile test and Non stress test [11,21]. There are controversial studies regarding the effect of evening primrose oil on cervical condition. Taherman et al reported that vaginal capsules of evening primrose oil are effective in cervical ripening, and this medication is available, inexpensive and has no significant side effects [18]. The use of vaginal capsule of evening primrose oil can be effective in

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**Keywords:** Vaginal evening primrose oil; misoprostol; cervical ripening; post-term pregnancy; bishop score.

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group received 500 mg vaginal evening primrose capsule and 25 micrograms of sublingual misoprostol, and the control group received a placebo-vaginal capsule and 25 micrograms of misoprostol sublingually. Data collecting tools include: demographic questionnaire and bishop checklist. Data was analyzed by SPSS software version 15 with using Chi-square, T-test, one-way ANOVA test.

**Results:** The results showed that the mean bishop score of the subjects in the intervention group were significantly higher than the control group (p <0.05). There was no significant difference in uterine contractions, fetal heart rate and vital signs between two groups (p > 0.05).

**Conclusion:** The results of the present study showed that vaginal capsule of evening primrose oil with misoprostol on the cervical ripening in post-term pregnancies was more effective than misoprostol alone.

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improving cervical profile and its ripening before applying genealogy [22]. A retrospective study reported that oral administration of evening primrose oil from 37 weeks of gestation until the beginning of labor did not only reduction the length of pregnancy and labor, but also it caused a slight increase in the prevalence of prolonged rupture of membranes, uterine abnormal contractions, stopping the fetus from descending and the use of vacuum [23]. According to the results of Jahdi et al. [11] study, the use of evening primrose oil capsules did not change the bishop score significantly.

The present clinical trial study was conducted on 130 pregnant women with post-term pregnancy referring to the labor ward of Be’sat Hospital in Sanandaj in 2018.

2. MATERIALS AND METHODS

The present randomized, one-blind clinical trial was conducted on all nulliparous women with post-term pregnancy admitting to labor ward of Be’sat Hospital in Sanandaj in 2018. The inclusion criteria were nulliparous, willingness to participate in the study, being healthy, lack of contraindications for the use of evening primrose oil and misoprostol, no structural cervical anomalies, 40 weeks and 6 days of gestational age based on the date of the first day of the last menstruation or the first trimester ultrasonography, single-pregnancy, live fetus, vertex fetal presentation, normal fetal heart rate, absence of uterine contractions, bishop score lower than or equal to 4, Intact membranes, normal non stress test, mothers’ height of more than 150 cm, lack of drug abuse, an estimated weight of fetus between 2500-4000 grams.

Exclusion criteria were using enema or laxative, using herbal medication prior to study, mother’s unwillingness to continue cooperation in the research, the need for cesarean section during study, the development of possible side effects of the medication such as headache, nausea, diarrhea, fever, shortness of breath, abnormal contractions of uterus and pattern of fetal heart rate.

The researcher referred to the maternity ward of the center and selected 130 nulliparous women with post-term pregnancy that had the criteria for entering the study. In order to observe ethical considerations, after giving explanations about the objective and process of the study to the pregnant mothers, their written consent informed was obtained. The subjects were randomly closed envelops divided into two groups of intervention (evening primrose oil and Misoprostol) and control (Misoprostol and placebo). Required data was collected using a three-part questionnaire. The first part was related to the demographic characteristics of the mother (age, education, occupation, place of residence), the second part was related to the obstetric characteristics (BMI, abortion, gestational age, bishop score, estimated fetal weight). The third part was completed to record bishop score, evaluate uterine contractions, fetal heart rate and vital signs of the mother. The demographic information questionnaire was completed and a preliminary clinical examination including maternal vital signs, uterine contractions, non-stress test and bishop score, was performed by the research collaborator for all samples. The initial bishop score was recorded in the relevant table by the researcher.

in the intervention group 500-mg capsule of evening primrose oil [11,24] was pierced by a sterilized needle and implanted vaginally into posterior fornix [22]. After the insertion, the woman was advised to stay on bed for 30 minutes, sleep on the left side and not leave the bed. At the same time, 25-micrograms of misoprostol was given to the mother by sublingually. The fetal heart rate was recorded every 15 minutes after the implantation of the capsule. After 6 hours, the bishop score was evaluated again by a collaborator research who was not aware of the classification of the subjects, and the obtained value was recorded by the researcher in the relevant table. If the bishop score was less than 9 and Uterine contractions were ineffective (less than 3 contractions with 40 seconds duration), and the heart rate was normal, a maximum of two other doses (500-mg evening primrose oil vaginal capsule with 25-micrograms sublingual misoprostol) was repeated every 6 hours and the Bishop score was evaluated. After the second dose, if the Bishop score increased or uterine contractions started, the third dose would get cancelled and the intervention would end. Subjects in the control group were given 25-micrograms misoprostol sublingually by a researcher and an empty capsule (placebo) was placed vaginally in the posterior fornix. After the insertion, the woman was advised to stay on bed for 30 minutes, sleep on the left side and not leave the bed. At the first hour after the administration of misoprostol, the fetal heart rate was evaluated and recorded by the researcher every 15 minutes. Then, 6 hours after the
intervention, the bishop score was re-evaluated by a collaborator research and recorded in the relevant table. If the bishop score was less than 9 and uterine contractions were ineffective (less than 3 contractions were not initiated with 40 seconds duration) and the fetal heart rate was normal, two other doses were repeated every 6 hours, and the bishop score was evaluated and recorded again. After the second dose, if bishop score increased or uterine contractions started, the third dose would get cancelled and the intervention would end. Finally, the collected data was analyzed with SPSS 15 with using Chi-square test, independent t-test, covariance analysis, one-way ANOVA, and repeated measures. This study was approved by Ethics Committee of Kurdistan University of Medical Sciences with ethics code of (ir.muk.rec.1396 / 36) and registering the proposal in the IRCT.ir system with the code (IRCT20180224038846N1).

3. FINDING

According to the results of the present study, the age average in the intervention and control group was respectively 27.81±5.64 and 28.13±5.35 years. About 36.9% of the researched units in the intervention group and 40% in the control group had diploma. Most of them (93.8%) were housewives and mostly (70%) lived in the urban. About 13.8% of the subjects in the intervention group and 4.5% in the control group had history of abortion, and 4.5% of the intervention group and 3.8% of the control group reported curettage history. The mean estimated fetal weight was 3441 grams in the intervention group and 3480 grams in the control group (Table 1).

The statistical independent t-test indicated that the mean of the bishop score in the two reviewed groups before the intervention did not had a significant statistical difference, and both groups were homogeneous (p = 0.73). However, result showed significant statistical difference between the two groups after intervention (p <0.05) (Table 2 and Fig. 1).

The results of the study did not show a significant difference between two groups in regard with fetal heart rate (p = 0.57) (Table 3). The mean and standard deviation of uterine contractions was 3.45±0.72 in the intervention group and 3.39±0.87 in the control group, which was not statistically significant (p = 0.67).

The findings showed that there was no significant difference between the two groups in regard with vital signs of blood pressure (p=0.16), pulse (p=0.6), breathing (p=0.15), and temperature (p = 0.10).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency and percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1(1.5)</td>
</tr>
<tr>
<td>20-24</td>
<td>20(30.9)</td>
</tr>
<tr>
<td>25-29</td>
<td>19(29.3)</td>
</tr>
<tr>
<td>30-34</td>
<td>17(26.1)</td>
</tr>
<tr>
<td>≥35</td>
<td>8(12.2)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>2(3.1)</td>
</tr>
<tr>
<td>Primary school</td>
<td>19(29.2)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>16(24.6)</td>
</tr>
<tr>
<td>Diploma</td>
<td>24(36.9)</td>
</tr>
<tr>
<td>Academic education</td>
<td>4(6.2)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>62(95.4)</td>
</tr>
<tr>
<td>Employed</td>
<td>3(4.6)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>40(61.5)</td>
</tr>
<tr>
<td>Rural</td>
<td>25(38.5)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>≥40±6</td>
</tr>
<tr>
<td></td>
<td>40.89</td>
</tr>
<tr>
<td>History of abortion</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>18(27.7)</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>47(72.3)</td>
</tr>
<tr>
<td>Curettage history</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>7(10.8)</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>58(89.2)</td>
</tr>
</tbody>
</table>
Table 2. Comparison of the mean and SD of Bishop Score of the two groups under study

<table>
<thead>
<tr>
<th>Score</th>
<th>Group</th>
<th>Intervention</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td>0.41±0.51</td>
<td>0.66±0.65</td>
<td>0.73</td>
</tr>
<tr>
<td>6 hours after intervention</td>
<td></td>
<td>2.75±1.28</td>
<td>1.41±0.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>12 hours after intervention</td>
<td></td>
<td>5.08±1.62</td>
<td>3.08±1.72</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Fig. 1. The progression of bishop scores in two groups during time

Group 1. Intervention group, Group 2. Control group

Table 3. Comparison of mean and standard deviation of fetal heart rate in the studied groups

<table>
<thead>
<tr>
<th>Fetal heart rate</th>
<th>Intervention</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 15 minutes</td>
<td>139.24±6.05</td>
<td>138.50±6.59</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>First 30 minutes</td>
<td>138.56±8.02</td>
<td>140.26±8.01</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>First 45 minutes</td>
<td>139.50±10.05</td>
<td>142.12±8.5</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>First 60 minutes</td>
<td>159.61±15.9</td>
<td>144.73±9.58</td>
<td>P&gt;0.05</td>
</tr>
</tbody>
</table>

4. DISCUSSION

The present study was conducted to compare the effect of vaginal capsule of evening primrose oil and misoprostol on cervical ripening of nulliparous women with post-term pregnancy. Based on statistical analysis, there was no significant difference between two groups in bishop score before the intervention. However, the mean bishop score of the intervention group was significantly higher than the control group after the intervention.

According to the results of Khatami et al. [24] study, entitled “The effect of vaginal consumption of evening primrose oil on cervical preparation in nulliparous women with post-term pregnancy”, vaginal administration of evening primrose oil reduced the duration of the latent phase and had a positive effect on cervical ripening. Also, the results of TY-Torredes et al. [25] study, the administration of 3 capsules of oral primrose oil a day for one week show that there was effective on the bishop score and cervical length of pregnant women in term labor. These two studies are consistent with the results of the present study.

Tahermanesh et al. [18] study assessed the effect of evening primrose oil on cervical ripening and dilation of the cervix before hysteroscopy operation. 28 women received EPO gel and 22 women received placebo 6-8 hours before the Hysteroscopy operation in posterior vaginal fornix. Total time of the dilation of cervix among individuals who received EPO was less than that of those who had received placebo and came to the conclusion that primrose affects the ripening of the cervix before the Hysteroscopy operation and has no serious side effects. Also,
Rossini et al. [22] study investigated the effects of evening primrose oil on cervical ripening prior to gynecologic procedures. In the end, it was concluded that receiving 4 capsules of evening primrose oil before applying gynecology could be effective in improving the cervical profile and its achievement. Aquino et al. [26] study investigated the ease of cervical dilation in postmenopausal women and nulliparous premenopausal women who received vaginal evening primrose oil prior to hysteroscopy operation. In this study, 2 capsules (1000 mg) of evening primrose oil were inserted into the posterior fornix of the vagina at 4-6 hours prior to hysteroscopy operation, and the cervical dilation rate was assessed using a Hegar dilator. The results indicated that cervical dilation was significantly facilitated in all patients who received evening primrose oil.

The results of these three studies are consistent with the results of the current study and show the positive impact of evening primrose oil on the amount of cervical ripening. This medication is also available, inexpensive, and has no significant side effects. The Bishop score of participants in the intervention group was significantly higher than the control group, indicating the effectiveness of the drug in ripening the cervix. Further more, the results indicated that vaginal administration of evening primrose oil had no significant effect on fetal heart rate, uterine contractions and vital signs of the mother.

On the other hand, according to the results of Jahdi et al. [11] study, which was conducted on the effect of oral capsules of evening primrose oil on cervical dilation of pregnant women, oral administration of evening primrose oil in pregnant women with gestational age (40 weeks to 40 weeks and 6 days) did not change the Bishop score significantly. Also, In Dow and Johnson’s study [23], with the title review of the impact of primrose on the duration of pregnancy and consequences of pregnancy on 54 women who were in the 37th week of their pregnancy using 500mg EPO 3 times a day for the first week and then two capsules per day until the beginning of labor and 54 women who did not receive a medicine in the control group, was indicative of lack of a significant difference in terms of age, Apgar score and days of pregnancy. The inconsistency between the results of these studies and the current study can be due to differences in drug use patterns, in these studies using oral administration but the current study using vaginal administration of the evening primrose oil. This study was also performed at 40 weeks and 6 days and more of gestational age, while Jahdi's study was conducted at 40 weeks to 40 week and 6 days gestational age. In Dow's study, oral administration of evening primrose oil was performed from 37 weeks of pregnancy to delivery.

Several studies have been conducted on the effective dose of misoprostol, according to the results of which 25-micrograms every 4 to 6 hours is the best and most efficient dose [27], which is quite consistent with the results of the present study.

According to the results of Abedi Asl et al. study, which was conducted to compare the effect of vaginal misoprostol and intra-cervical Foley catheter on cervical ripening before induction. The total time of beginning of induction to labor was similar in both groups [28]. However, Same with Jadith’s study [29], Tachycardia, Excessive uterine stimulation and need for sedative (pethidine and promethazine) were observed in the misoprostol group. Additionally, the results of Sotoudenia et al study [30], which was conducted to compare the effect of vaginal misoprostol and oral castor oil on the induction of labor, indicated that abrupton, tachycardia, and the hospitalization of the infant in NICU were the main side effects of misoprostol, while nausea and diarrhea were the only side effects of castor oil.

In the end, the two groups were compared for duration of the active phase, type of delivery and Apgar score, and the results indicated that the duration of the active phase in the intervention group was lower than that of the control group. Also, the number of people who had given vaginal delivery in the intervention group was more than the control group and in cases of need for cesarean during the study, the participant was excluded from the study and another sample was replaced. And about Apgar score, result indicating there was no significant difference between the two groups in terms of Apgar score.

Also, According to the results of the present study, both groups did not show abnormalities in fetal heart rate, uterine contractions and vital signs of mother. Therefore, evening primrose is a safe flower and according to various studies, it is generally tolerated well there is no limit for using it during the pregnancy because it has no effect on the safety of the fetuses monitored by
biophysical profile test and Non stress test. Also evening primrose oil is quite cheaper than misoprostol and does not have misoprostol side effects include abruption, tachycardia, and the hospitalization of the infant in NICU [11,21]. Therefore it seems that the application of evening primrose oil is much more reasonable.

5. LIMITATIONS OF THE RESEARCH

The main limitations of the present study, Being conducted on nulliparous women and not considering women with multiple pregnancies. Therefore, it is suggested to conduct further studies to provide more comprehensive results and findings.

Since the use of herbal and complementary medicine is very important, using a larger sample size and comparison of herbal medicine and chemical drugs and the use of non-pharmaceutical methods is, also recommended.

6. CONCLUSION

The results of the present study showed that vaginal capsule of evening primrose oil is more effective than misoprostol in cervical ripening and bishop score. Also, it does not effect on the fetal heart rate, uterine contractions, and vital signs of the mother. Therefore, it can be used as an appropriate substitute for misoprostol for cervical ripening.

CONSENT

In order to observe ethical considerations, after giving explanations about the objective and process of the study to the pregnant mothers, their written consent informed consent was obtained.

ETHICAL APPROVAL

This study was approved by Ethics Committee of Kurdistan University of Medical Sciences with ethics code of (ir.muk.rec.1396 / 36) and registering the proposal in the IRCT.ir system with the code (IRCT20180224038846N1).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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