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The Effects of Oral and Vaginal Administration of Evening Primrose Oil on Cervical Ripening and Birth Outcomes: A Systematic Review and Meta-Analysis

Azin Niazi[1], Vahid Ghavami[2], Forough Beiranvandi [3], Roya Partovi Golshan[4], Maryam Nouravaran Feizabadi[5], Ensieh Fooladi[6], Maryam Moradi[7*]

Abstract

Background: Given the conflicting results of three previous systematic reviews, drawing definitive conclusions about the effect of primrose oil on cervical ripening remains challenging.

Aim: This meta-analysis aimed to identify and evaluate studies that have examined the effects of oral and/or vaginal evening primrose oil on cervical ripening and birth outcomes.

Method: A comprehensive search of English and Persian articles from May 1990-March 2023 was performed in the PubMed, Web of Science, Cochrane Library, Scopus, SID and Magiran databases to identify randomized, placebo, controlled trials (RCTs) of primrose oil.

Results: In the review of 16 RCTs, the results revealed a significant difference in the duration of the second phase of labor in the oral EPO capsule (mean difference (MD) = -9.68, 95% confidence interval (CI): -17.23, -2.14, I2 = 0%). Three studies reported significantly higher Bishop scores for the vaginal capsule in the EPO group than in the placebo group (MD=1.81, 95% CI: 0.24; 3.38, I2=100%). Three studies reported significant improvements in 5-minute Apgar scores with the use of the EPO vaginal capsule (MD = 0.60; 95% CI: 0.49, 0.71). Cesarean section rates were significantly lower in the group given vaginal EPO (odds ratio (OR) = 0.62; 95% CI: 0.40–0.96; I2 = 0.1%).

Implications for Practice: Oral EPO shortens the duration of the second phase of labor and reduces cesarean section rates but does not yield a noteworthy increase in the Bishop score. Vaginal EPO seems to affect cervical ripening, reduce cesarean section rates, and improve 5-minute Apgar scores.

Keywords: Cervical Ripening, Evening Primrose Oil, Labor, Oral Administration, Pregnancy Outcome, Vaginal Administration

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1. MSC Midwife, Department of Midwifery, AsadAbad School of Medical Sciences, AsadAbad, Iran
2. Assistant Professor in Biostatistics, Department of Biostatistics, School of Heath, Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3. Assistant Professor, Department of obstetrics and gynecology, School of medicine, Lorestan University of Medical Sciences, Lorestan, Iran
4. MSc of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran
5. Master of Epidemiology, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
6. PhD, Monash Nursing and Midwifery, Monash University, Melbourne, VIC, Australia
7. PhD, Global and Women's Health, School of Public Health and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia

* Corresponding Author Email: maryam.moradi@monash.edu

Introduction

Induction of labor (IOL) is an intervention designed to artificially trigger uterine contractions (1). Globally, labor induction rates vary significantly across countries. A recent study indicated that the rates of IOL are 23.4% in the United States, 22.1% in the United Kingdom, 12.1% in Asia, 11.4% in Latin America and 4.4% in Africa (2). IOL is recommended when the benefits of delivery exceed the risks associated with continuing the pregnancy (3, 4). Indications for IOL include maternal health conditions, pregnancy-related hypertension, post term pregnancy, premature rupture of membranes (PROM), and intrauterine fetal death (IUFD) (5). If the cervix is not prepared, induction will be unsuccessful (6). for patients with an unfavorable cervix, cervical ripening is the initial step in the labor induction process (7). An unripe cervix raises the risk of cesarean section and prolonged labor (8). An extended duration of the second stage of labor is associated with various maternal and neonatal complications, including third- and fourth-degree tears, postpartum hemorrhage, low Apgar scores and sepsis (9). Consequently, a favorable cervical assessment is crucial in clinical obstetrics (10).

Cervical ripeness is evaluated using the Bishop scoring system (11). The Bishop score is determined on the basis of dilatation, effacement, station, cervical consistency, and position (12). Higher Bishop scores (≥6) are associated with successful labor induction and vaginal deliveries, while lower scores (<6) correlate with increased rates of failed inductions and cesarean deliveries (13). Research indicates that an increase in the Bishop score leads to decreased oxytocin usage, particularly during the latent phase of labor, a reduction in the duration of both the latent and active phases, and a rise in the incidence of vaginal births, underscoring the advantages of cervical ripening (14, 15). Cervical ripening methods encompass pharmacological options, such as misoprostol and dinoprostone, as well as mechanical methods like single or double balloon catheters (16). Mechanical techniques include trans cervical catheters, hygroscopic dilators, membrane stripping, artificial rupture of membranes, and extra-amniotic saline infusion, while medical methods involve agents like prostaglandins E1 and E2 (16, 17). However, both medicinal and surgical cervical ripening can lead to adverse outcomes, including bleeding during and after delivery, prolonged labor, fetal distress and injury, uterine rupture, chorioamnionitis, and increased mortality (17). Notably, pharmacological methods tend to produce more rapid uterine contractions, which may result in fetal heart rate abnormalities and necessitate more intensive neonatal care compared to mechanical methods (18). Recent studies suggest that no single cervical ripening method stands out in terms of safety and efficacy (19).

Meanwhile, the use of complementary medicine, particularly herbal remedies, for cervical ripening has become increasing popularity (20). Evening primrose oil (EPO) is mentioned in some midwifery literature as a treatment for post-term pregnancy, with over 60% of nurse-midwives in the United States reportedly prescribing it during late pregnancy (21). EPO is rich in polyunsaturated fatty acids (PUFAs), and gamma-linolenic acid (GLA), a potent converter of PUFAs to prostaglandins, is abundant in this oil. Thus, evening primrose oil may serve as an effective labor inducer. Given its general tolerability, there are no significant restrictions on its use during pregnancy, as it does not compromise fetal monitoring safety via biophysical profiles and non-stress tests (22, 23). However, one study found that EPO was linked to an increased incidence of prolonged rupture of membranes, higher oxytocin usage, and greater reliance on vacuum assistance during delivery (24).

Systematic meta-analysis of nine studies (five on oral EPO capsules and four on vaginal capsules) indicated that evening primrose oil positively affects cervical ripening, reduces cesarean section rates, and shortens labor duration. Due to the considerable heterogeneity among studies, further research utilizing standardized tools based on the CONSORT statement has been recommended (25). Another meta-analysis demonstrated that EPO use significantly improved Bishop Scores. However, a separate analysis (four studies on oral EPO capsules and three on vaginal capsules) found no significant differences between groups concerning 1-minute Apgar scores and the duration of the second phase of labor (26). Additionally, a meta-analysis by Moradi et al. (2021) concluded that evening primrose oil had no effect on cervical ripening (27). Given the conflicting findings from these systematic reviews, reaching definitive conclusions about the impact of EPO on cervical ripening remains challenging. Therefore, this systematic review and meta-analysis, encompassing a larger number of articles and outcomes, aims to evaluate the effects of EPO on cervical ripening and birth outcomes.

Methods

This study was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Checklist (PRISMA) for Systematic Reviews (28). The protocol of this systematic review and meta-analysis was registered in PROSPERO with the reference number CRD42023481763. A comprehensive search of articles in English and Persian from May 1990 to March 2023 was performed in the PubMed, Web of Science, Cochrane Library, Scopus, SID and Magiran databases, as well as in the reference lists of the included articles. The search keywords and MeSH terms used included the following: Bishop score, cervical ripening, labor induction, evening primrose oil, labor induction, cervix preparation, post-term pregnancy, and pregnancy, and all possible combinations of these words (both in Persian and English) applying Boolean operators (OR, AND) were searched. The search strategy for the databases is presented in Table 1.

Table 1: Searching strategy results on randomized controlled trials of evening primrose oil for labor induction and cervical ripening

PubMed (560)	#1. ("Oenothera biennis"(tw) OR "Evening Primrose Oil "(Supplementary Concept) OR "Evening Primrose essential oil"(tw) OR "Evening Primrose Oil "(tw) OR colpermin(tw) OR "oil of Evening Primrose "(tw)) #2. ("Bishop score"(mh) OR "cervical ripening"(tw) OR "labor induction"(tw) OR "postterm "(tw) OR "pregnancy"(tw) OR "cervical"(tw) OR "ripening"(tw) OR "induction"(tw) OR "labor"(tw)) #3. #1 AND #2
Embase (293)	#1. ('Oenothera biennis'/exp OR 'Evening Primrose Oil':ti, ab OR ' Evening Primrose essential essential oil':ti, ab OR colpermin:ti, ab OR ' of Evening Primrose oil ':ti, ab. #2. ('Bishopscore'/exp OR 'cervical ripening':ti, ab OR ' labor induction ':ti, ab OR 'postterm ':ti, ab OR 'pregnancy':ti, ab OR 'cervical':ti, ab OR ' ripening':ti, ab OR ' induction':ti, ab OR 'labor ':ti, ab #3. #1 AND #2
Web of Science (209)	#1 ts=("Oenothera biennis" OR "Evening Primrose Oil" OR "Evening Primrose essential oil"OR "Evening Primrose Oil" OR colpermin OR "oil of Evening Primrose") #2 ts=("Bishopscore" OR "cervical ripening" OR "labor induction" OR "postterm " OR "pregnancy" OR "cervical" OR "ripening" OR "induction" OR "labor") #3. #1 AND #2
Cochrane Library (100)	#1 MeSH descriptor: (Irritable cervical ripening) explode all trees #2 " labor induction " or " Bishopscore " or " cervical ripening " or " postterm " or " pregnancy " or " cervical " or " ripening " or " induction " or " labor ":ti, ab, kw #3 #1 or #2 #4 " Oenothera biennis "OR "Evening Primrose Oil " OR "Evening Primrose essential oil"OR "Evening Primrose Oil " OR colpermin OR "oil of Evening Primrose "):ti, ab, kw #5 #3 and #4
SID (300)	#1 ts=("Oenothera biennis" OR "Evening Primrose Oil" OR "Evening Primrose essential oil" OR "Evening Primrose Oil" OR colpermin OR "oil of Evening Primrose") #2 ts=("Bishopscore" OR "cervical ripening" OR "labor induction" OR "postterm " OR "pregnancy" OR "cervical" OR "ripening" OR "induction" OR "labor") #3. #1 AND #2

The study utilizes the PICO framework to explore the following question:

- Population (P): Women who are nullipara with term or post term pregnancy.
- Intervention (I): Evening primrose oil administered orally and vaginally.
- Comparison (C): An alternative or control intervention.
- Outcome (O): Effects on Bishop scores, duration of the active phase, duration of the second phase, cesarean rate, and Apgar scores at 1 and 5 minutes.

The main selection criterion for this structured review was randomized clinical studies. Trials involving human participants were published in Persian or English and studied evening primrose oil for its ability to induce labor and birth outcomes. Exclusion criteria included unrelated studies, duplication, lack of access to the full text, failure to meet study objectives, studies where sample sizes were not reported, and studies where intervention outcomes were not reported (29). The process of selecting articles and the reasons for their exclusion are shown in Figure 1. Article selection was performed by screening titles and abstracts to identify studies containing the desired keywords. Two independent researchers (A.N. and M.M.) carried out the screening, and any discrepancies were resolved through consultation with a third researcher (M.N.). Quality assessment began with an initial review of abstracts, during which irrelevant and duplicate articles were removed. The included studies were then evaluated for selection bias, implementation bias, diagnostic bias, sample dropout, and reporting bias using Cochrane's Risk of Bias tool.

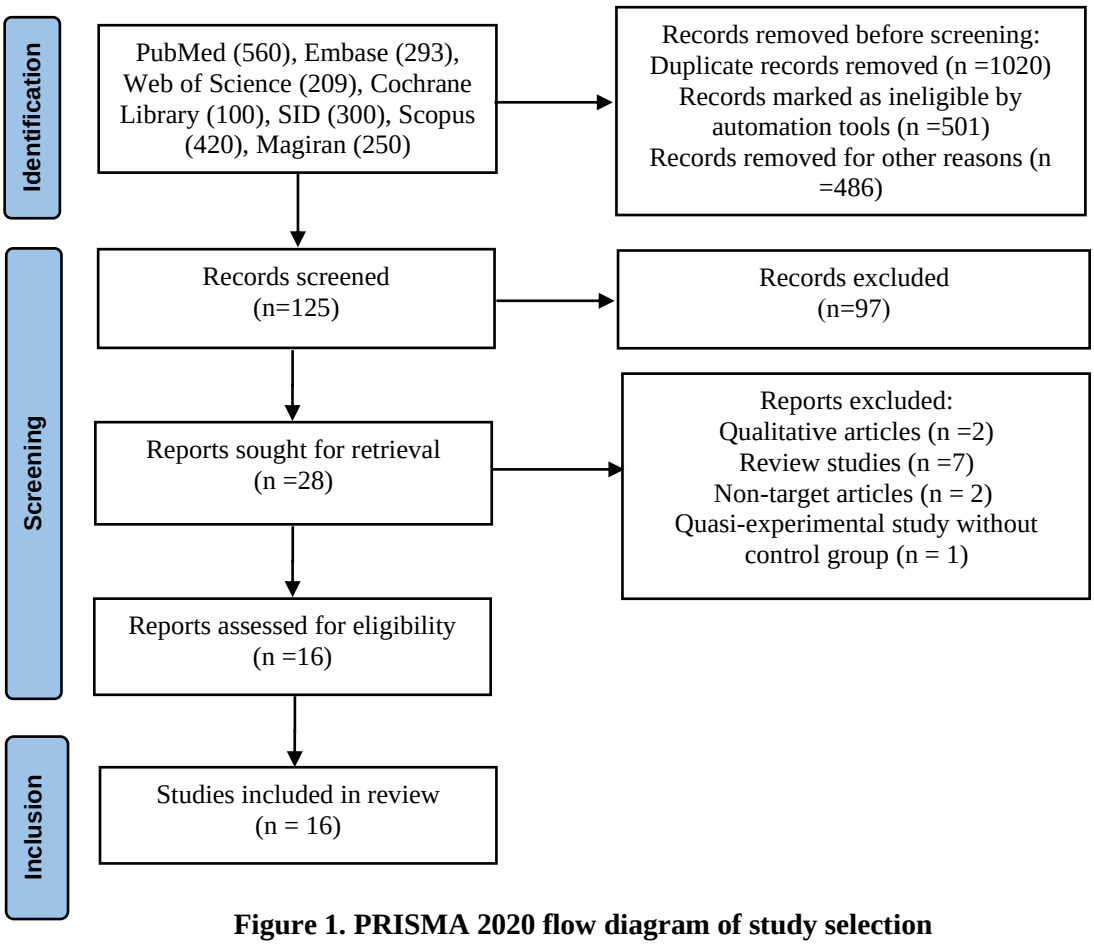

Figure 1. PRISMA 2020 flow diagram of study selection

The meta-analysis was performed via R software version 4.2.1 via the meta and dmetar packages (30). For the purpose of comparing the Bishop scores of the intervention group with those of the control group, we conducted a meta-analysis on the basis of the mean differences between the two groups. Since the studies separately reported baseline and endpoint data for each group, we calculated the mean and standard deviation (SD) of the change from baseline to the endpoint for each group. The formula used to calculate the SD in this case was as follows:

Mean change = Mean (endpoint) – Mean (baseline) (1)

SD (change)=√((SD(baseline))^2+(SD(endpoint))^2-2*r*SD(baseline)*SD(endpoint)), (2)

where r represents the correlation coefficient. As a conservative estimation, r was assumed to be 0.4 in this study. After the mean and SD changes in each group were calculated, the mean change difference (MCD) was defined as the mean change in the intervention group ($\bar{x}_1$) minus the mean change in the placebo group ($\bar{x}_2$):

MCD = $\bar{x}_1 - \bar{x}_2$. (3)

The standard error of the MCD can be obtained via the following formula:

$$SE_{MCD} = S_{pooled}\sqrt{\frac{1}{n1}+\frac{1}{n2}} \quad (4)$$

In the formula, $n1$ represents the sample size in the intervention group, $n2$ represents the sample size in the placebo group, and the pooled standard deviation of both groups is pooled. Using the standard deviations that were calculated on the basis of (2) for each of the intervention groups, s_1, and the placebo group, s_2, the value of Spooled can be calculated in this way:

$$s_{pooled} = \sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{(n_1-1)+(n_2-1)}} \quad (5)$$

For the duration of the active phase of labor, duration of the second phase of labor and Apgar score at minutes 1 and 5, we employed formulas (3) to (5), where $\bar{x}_1$, $\bar{x}_2$, and s_1 *and* s_2 are the means and standard deviations of these measures.

For the purpose of comparing the intervention group with the control group regarding the status of caesarians, we calculated the pooled effect size on the basis of the odds ratio; in this situation, the pooled measure was determined as the inverse variance weighted mean of the natural logarithm of the OR with 95% CI.

Heterogeneity across studies was evaluated by Cochran's Q test and I2 (31). I2 score values ranging from 0% to 40% were considered not important (29). On the basis of the results of Cochran's Q test and I2, the effect sizes were pooled by using a fixed or random effects model.

Owing to the limited number of studies, we were unable to assess publication bias via Egger's (4) and Begg's models (32, 33).

Ethical Consideration

Ethical Consideration Approval was obtained from the Mashhad University of Medical Sciences with the code of ethics committee of IR.MUMS.NURSE.REC.1398.047. Consent to participate is not applicable.

Results

After removing duplicates from an initial search of 402 articles, a total of 125 articles were found, 28 of which were excluded, including two qualitative articles (34, 35) seven review papers (21, 25-27, 35-37), two nontargeted articles (38, 39), and one quasi-experimental cross-sectional study (40). Finally, 16 studies with final number of 1662 people were examined (22, 24, 41-53) (Figure 1). All the studies assessed Bishop's score except two studies (24, 51), 11 studies examined the effect of evening primrose oil on the cesarean rate (41, 43, 44, 46-51, 53, 54), five studies examined the effect of evening primrose oil on the duration of the second phase of labor (42, 46, 47, 49, 53), five studies examined the effect of evening primrose oil on the duration of the active phase (44, 46, 49, 51, 53), and eight studies examined the effect of evening primrose oil on the Apgar score (24, 42, 46, 47, 49, 50, 52, 53). The characteristics of the studies included in this systematic review are presented in Table 2.

Table 2: Characteristics of studies entered in the systematic review (n=16)

Author/year (reference number)	Place of study	Type of clinical trial	Participants	Interventions and control group (Dosage)	Interventions (Duration of treatment)	Complications	Primary outcome	Secondary outcome	Consequence
Zahran et al., 2009 (41)	Egypt	Randomized trial double-blind	EG :58 CG: 65 Primiparous pregnant women at 40 to 40 weeks and six days of gestation	EG :1000 µg oral capsule of primrose CG: Oral capsule placebo	every 12 hours for 10 days	No complications	Bishop score	Cesarean rate	Oral consumption of primrose had no impact on cervical ripening and induction of labor.
Jahdi et al., 2016 (22)	Iran	Randomized trial triple-blind	EG :45 CG: 45 Primiparous women with 40 to 40 weeks and six days of gestation	EG :1000 mg oral capsule of primrose every CG: Placebo tablet (500 mg paraffin)	2 capsules per day, each 12 hours for a week	Exclusion of one of the members in the intervention group due to the bit-to-bit disorder	Bishop score	-	Oral consumption of primrose had no impact on the increase of the Bishop score.
Kalati et al., 2018 (42)	Iran	Randomized trial triple-blind	EG :40 CG: 40 primiparous women at 40 weeks of gestation	EG :1000 mg oral capsule of primrose CG: Placebo tablet 500 mg paraffin	every 12 hours for seven days	No complications	Bishop score	Duration of second phase Apgar score minute 1and 5	Oral consumption of primrose had no impact on the increase of the Bishop score.

Ty-torredes et al., 2006 (43)	Philippine	Randomized trial double-blind	EG :38 CG: 33 primiparous women at 40 weeks of gestation	EG: oral capsule EPO 1500 mg CG: oral capsule placebo	three times daily for 1 week	No complications	Bishop score	- Cesarean rate	Oral consumption of primrose increased the Bishop score and cervical ripening.
Shahali et al., 2018 (44)	Iran	Randomized trial single-blind	EG :30 CG: 30 primiparous pregnant women at 41 to 41 weeks and six days of gestation	EG:1000 mg vaginal capsule of primrose with oxytocin induction CG: Application of gelatin capsule with oxytocin induction	Single dose during labor	No complications	Bishop score	- Cesarean rate -Duration of the active phase	Vaginal primrose oil reduced the duration of latent phase and had a positive effect on cervical ripening criteria.
Bahmani et al., (45, 52, 54, 58)	Iran	Randomized trial single-blind	EG :۶۵ CG: ۶۵ primiparous women with post-term pregnancy (40 weeks and 6 days)	EG : 500 mg vaginal evening primrose capsule and 25 micrograms of sublingual misoprostol, CG: placebo-vaginal capsule and 25 micrograms of misoprostol sublingually application of evening	up to a maximum of two doses within a 6-hour interval	No complications reported	Bishop score	-Cesarean rate - Apgar score minute 1 and 5	Vaginal use of primrose oil had a positive effect on cervical ripening criteria and increase of the Bishop score.
Najafi et al., 2019 (46)	Iran	Randomized trial double-blind	EG :43 CG: 43 primiparous women with gestational age of 38 week	EG : 1000 mg soft capsules of Evening primrose CG: 1000 mg soft capsules containing edible paraffin	vaginal capsule daily dose from the 38th week of pregnancy until the time of delivery	No complications reported	Bishop score	-Duration of the active phase - Duration of the second phase -Cesarean rate - Apgar score minute 1 and 5	Vaginal Evening primrose is useful to ripen the cervix of term nulliparous women
Hoseinipour et al., 2022 (53)	Iran	Randomized trial triple-blind	EG :57 CG: 57 primiparous women with gestational age of 38 week or more	EG : Two capsules of 1000 mg oral evening primrose oil CG: ٦ capsules of 1000 mg oral Castor oil	Single dose simultaneously with induction using ١٠ units of oxytocin	No complications reported	Bishop score	-Duration of the active phase - Duration of the second phase -Cesarean rate - Apgar score minute 1 and 5	Vaginal Evening primrose is useful to ripen the cervix of term nulliparous women
Heydari et al., 2022 (47)	Iran	Randomized trial single-blind	EG vaginal :43 CG: 42 EG oral :39 primiparous women with a gestational age of 39 weeks	EG vaginal : thirty 1000-mg evening primrose oil capsule EG oral: thirty 1000-mg evening primrose oil capsule CG: Placebo	one capsule per twelve hours for one whole week	No complications reported	Bishop score	-Cesarean rate - Duration of the second phase - Apgar score minute 1 and 5	Vaginal and oral evening primrose oil administrations significantly positively affect cervical ripening. The Bishop score and vaginal evening

									primrose oil significantly positively affect the length of the second stage of labor.
Azad et al., 2022 (49)	Iran	Randomized trial double-blind	EG :88 CG: 87 primiparous women with gestational age≥ 41 weeks	EG: two soft capsules containing 500 mg of EPO CG: Placebo	soft capsules into the posterior vaginal fornix 6 hours before oxytocin induction of labor	No complications reported	Bishop score	-Cesarean rate -Duration of the active phase - Duration of the second phase - Apgar score minute 1 and 5	Vaginal application of EPO at a single dose of 1000 mg at 41 weeks gestation improved Bishop score and reduced parturition time in post-term pregnancies.
Mirzadeh et al., 2020 (48)	Iran	Randomized trial single-blind	EG :45 CG: 55 primiparous women with gestational age 40 weeks to 40 weeks and six days	EG :1000 mg vaginal evening primrose capsules CG: 25 micrograms of vaginal misoprostol tablets	Daily for seven days	No complications reported	Bishop score	-Cesarean rate	This study showed that a vaginal evening primrose capsule could effective on cervical ripening and dilatation
Moghimi et al., 2022 (51)	Iran	Randomized trial single-blind	EG :101 CG: 99 primiparous women with Term or post-term pregnancy	EG: 500 mg evening primrose vaginal capsule CG: 25 micrograms of vaginal misoprostol tablets	to induce labor and repeated every three hours until reaching the bishop score > 4	- Apgar score of less than seven - Neonatal pH of blood cord sample -Meconium extraction - Maternal headache -	-	-Cesarean rate - Duration of the active phase	Evening primrose capsules can be used to induce labor
Danesh Shahrak et al., 2023 (50)	Iran	Randomized trial double-blind	EG :55 CG: 55 prim gravid pregnant women with a gestational age of ≥40 weeks	EG :1,000 mg Pearl of primrose oil CG: 25 µg misoprostol tablets	If the first dose did not elicit any response, it was repeated 6 hours later With the same dose as before for a maximum of four times	-	Bishop score	-Cesarean rate - Apgar score minute 5	Primrose oil resulted in significantly better Bishop Scores and fewer cesarean sections compared to misoprostol in pregnancy 40 weeks and more
Dove et al., 1999 (24)	United States	Randomized trial double-blind	EG :54 CG: 54 primiparous women with gestational age of 38 week	EG :٥٠٠ mg orally primrose oil CG: Oral capsule placebo	three times daily for ١ week	protracted active phase, arrest of descent, and vacuum extractor utilization		- Apgar score minute 1 and 5	Use of orally administered evening primrose oil does not shorten gestation or decrease the overall length of labor. There was no significant difference between groups according to Apgar score.

Eight control groups were given placebo (22, 41-43, 46, 47, 49), one control group received a placebo capsule with oxytocin (44), three control groups received a placebo capsule with 25 micrograms of misoprostol sublingually (45, 52, 54), one control group received capsules of 1000 mg oral castor oil (53), and three studies received misoprostol (48, 50, 51). The dose of evening primrose oil ranges between 500 and 4500 mg daily. EPO was used in the form of a vaginal suppository in ten trials (44-52, 54). In seven studies, the dosage ranged from 500 to 1000 mg during labor (44, 45, 49-52, 54), and in three studies, it ranged from one week until the onset of labor, and doses of 1000 (46, 48)) and 2000 (47) mg were prescribed. Oral capsules of EPO were used in six trials (24, 41-43, 47, 55). In 4 studies, it was 2000 mg per day (22, 41, 42, 47); in one study, it was 1500 mg per day (24); and in one study, it was 4500 mg per day (43) for one week to 10 days. The quality of the studies was evaluated using the Cochrane risk of bias tool summarized in Figures 2 and 3.

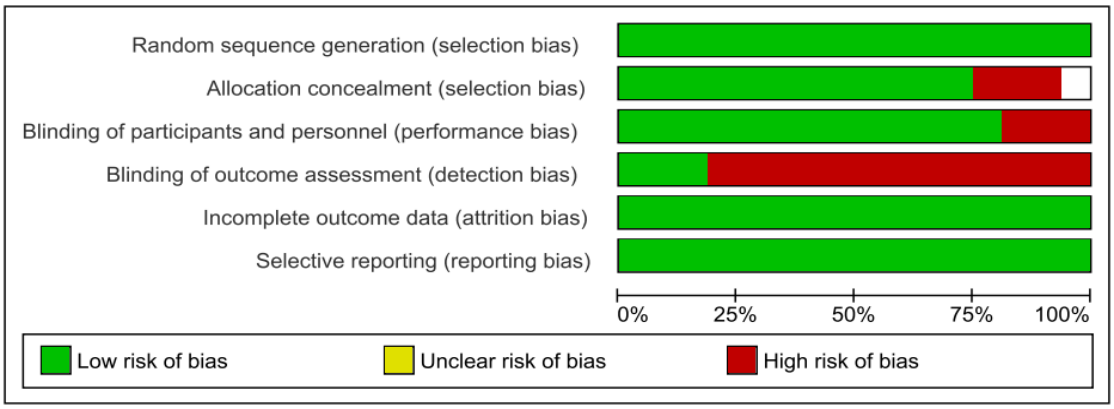

Figure 2: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

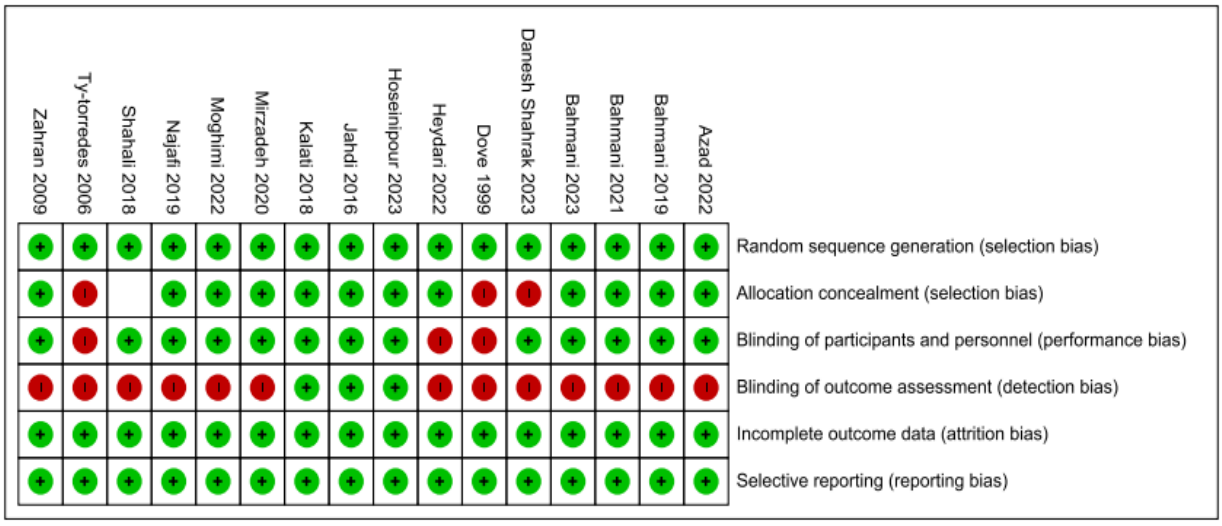

Figure 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Random Sequence Generation:
Vague Reporting: Four studies lacked clear explanations of their randomization processes (24, 43, 44, 50). Low Risk: Twelve studies provided adequate methods for random sequence generation, indicating low selection bias (22, 41, 42, 45-49, 51-54). Allocation Concealment: Low Risk: Nine studies had appropriate measures for allocation concealment (41, 42, 46, 48-51, 53, 55). Blinding Methods: Six studies employed two-sided blinding (24, 41, 43, 46, 49, 50). Three studies utilized three-sided blinding (42, 53, 55). Seven studies had one-sided blinding (44, 45, 47, 48, 51, 52, 54). Participant Blinding: Eight studies reported low risk of bias regarding participant blinding (41, 42, 46, 48-51, 53, 55), while five studies exhibited high risk (24, 43-45, 47, 52, 54). Blinding of Analyzers: Three articles ensured blinding of the analysts reviewing the allocations (22, 42, 53). Overall Risk: Thirteen articles were assessed to have high risk of bias after evaluation (24, 41, 43-52, 54). Sampling Bias: Sixteen studies maintained participant consistency from randomization through result analysis, indicating low sampling bias (22, 24, 41-54). Reporting Bias: All sixteen articles reported all expected outcomes, suggesting low reporting bias. Effects of Interventions: The section on the effects of interventions has not been detailed in the provided text. Thus, these studies had a low level of bias in terms of sampling shedding bias. In terms of reporting bias, all 16 articles contained all the expected outcomes.
The meta-analysis findings of five studies revealed that the bishop score change (compared with that at baseline) in the oral capsules of the EPO group was not significantly different from that in the placebo group (mean difference (MD) = -0.02, 95% confidence interval (CI): -0.99-0.94, I2 = 100%) (Figure 4). However, there was a significant difference in the duration of the second phase of labor in the Oral capsules of the EPO group (MD = -9.68, 95% CI: -17.23 -2.14, I^2 = 0%) (Figure 5). The results of the meta-analysis of three studies (24, 42, 47) indicated that the oral capsules in the EPO group did not have a significant effect on the 1-min Apgar score (MD = -0.03, 95% CI: -0.16--0.10) (Figure 6). The overall outcome of the meta-analysis involving three studies (24, 42, 47)) demonstrated that the 5-min Apgar scores in the oral capsules of the EPO group were not significantly different (MD = 0.18, 95% CI: -0.91 - 1.26, I^2 = 100%) (Figure 6). The cesarean section rate was significantly greater in the group receiving oral EPO capsules than in the control group (odds ratio (OR) = 0.68; 95% CI: 0.41–1.15; I2 = 0.13%).The meta-analysis of three studies revealed a significantly greater bishop score in the vaginal capsules of the EPO group than in those of the placebo group (mean difference (MD) =1.81, 95% confidence interval (CI): 0.24-- 3.38, I2=100%). However, the same meta-analysis revealed that there was no significant difference in the bishop score between the vaginal capsules of the EPO group and the misoprostol group (MD=0.43, 95% CI: -1.50--2.37, I2=100%) (Figure 7). Furthermore, the duration of the active phase of labor in the vaginal capsules of the EPO group did not significantly differ (MD=0.34, 95% CI: -0.50; 1.17, I2=67%).

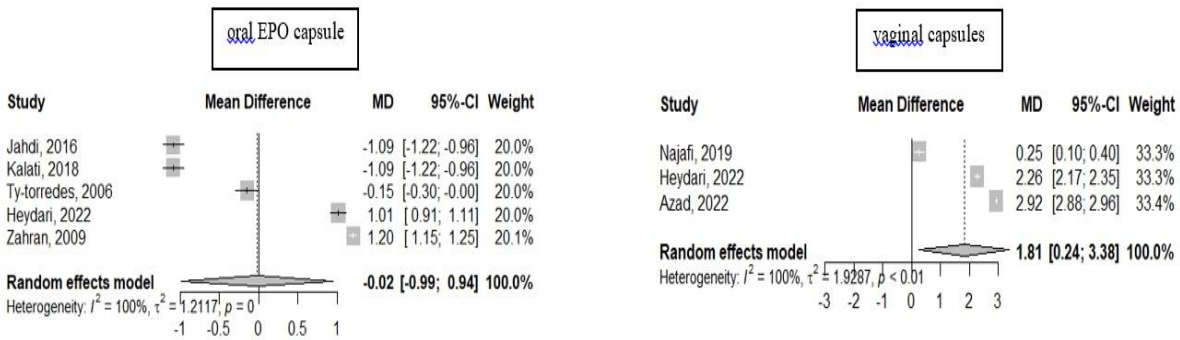

Figure 4: Forest plot of mean difference pooling of Bishop Scores for oral EPO and vaginal capsule groups compared to placebo

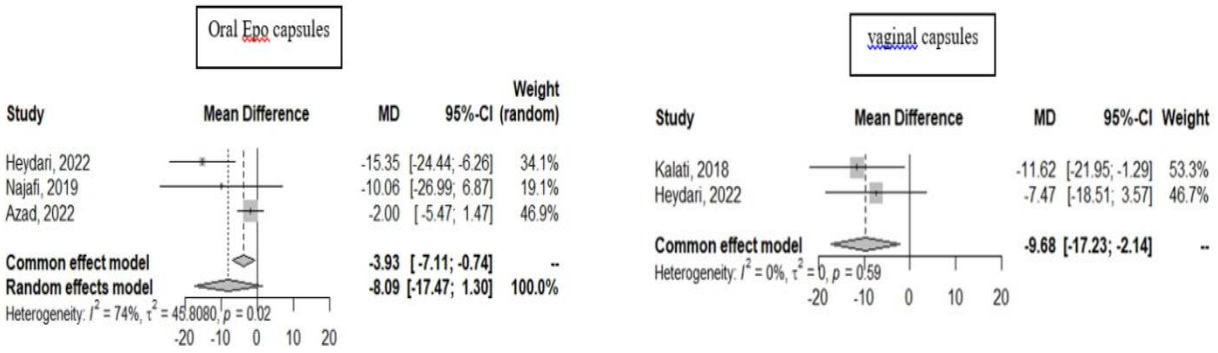

Figure 5: Forest plot of mean difference pooling of duration of second stage of labor for oral EPO and vaginal capsule groups compared to placebo

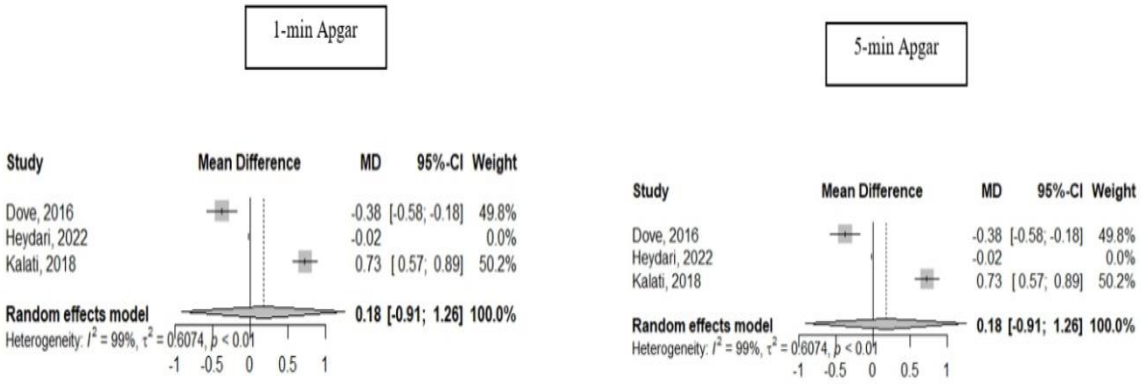

Figure 6: Forest plot of mean difference pooling of 1-min and 5-min Apgar score for oral EPO capsule groups compared to placebo

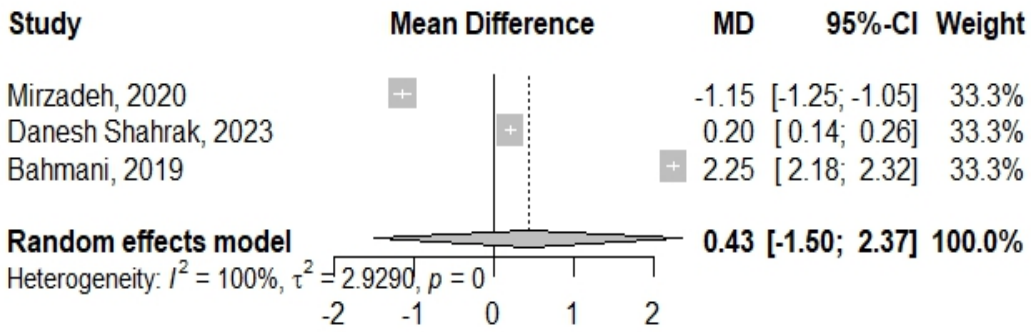

Figure 7: Forest plot of mean difference pooling of Bishop scores of vaginal capsules in EPO groups compared to misoprostol

The results of the meta-analysis of the three studies (46, 47, 49) revealed no statistically significant effect of administering vaginal capsules of evening primrose oil on the 1-minute Apgar score (mean difference (MD) = -0.12; 95% confidence interval (CI): (-0.27, 0.04)) (Figure 8). The overall outcome of the meta-analysis, which included three studies (46, 47, 49), indicated a significant improvement in the 5-minute Apgar score when vaginal capsules of EPO were used (MD = 0.60; 95% CI: 0.49, 0.71) (Figure 8). However, the duration of the second phase of labor in the group receiving vaginal suppositories of EPO did not significantly differ (MD = -8.09; 95% CI: -17.47, 1.30; I2 = 0%). Compared with the control group (placebo or misoprostol), the rate of cesarean section was significantly lower in the group receiving vaginal capsules of EPO (odds ratio (OR) = 0.62; 95% CI: 0.40–0.96; I2 = 0.1%) and (OR = 0.47; 95% CI: 0.25–0.89; I2 = 54%), respectively.

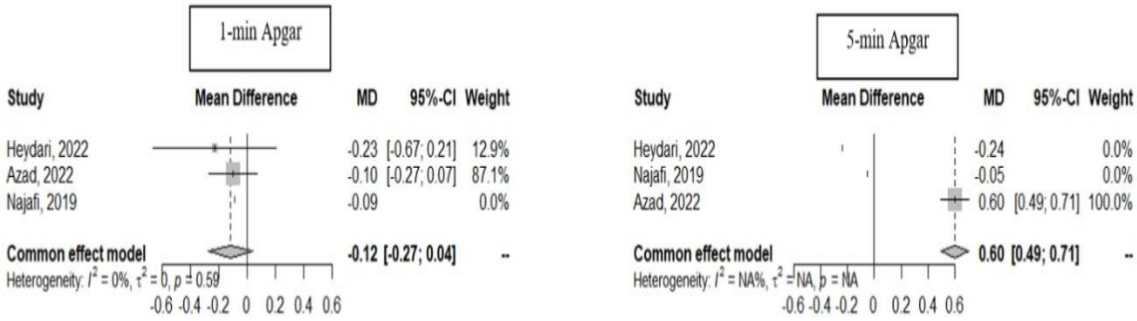

Figure 8: Forest plot of the mean difference pooling for1-min and 5-min Apgar in the vaginal capsules of EPO groups compared to placebo

Discussion

The purpose of this study was to investigate the effects of oral and vaginal capsules of EPO on cervical ripening and birth outcomes. The results of five studies included in this extensive analysis demonstrated that oral capsule EPO did not yield a noteworthy enhancement in the Bishop score (22, 41-43, 47). In accordance with the present study, Moradi et al.'s (2021) meta-analysis revealed that the oral administration of evening primrose oil did not seem to be beneficial for cervical ripening (27); however, conversely, the outcomes revealed that, compared with the control, vaginal capsule EPO effectively improved the Bishop score (46, 47, 49). Nevertheless, it did not have a significant effect compared with misoprostol (45, 48, 50). The discrepant outcomes of these investigations may be due to variations in the method or frequency of EPO administration. In the vaginal type, the results were effective. It can be said that the simultaneous use of oxytocin and misoprostol, along with evening primrose oil, has increased the effects. Additionally, in the vaginal type, the medication was typically administered during labor, whereas in the oral type, it was taken one week to ten days prior to the onset of labor. Gamma-linolenic acid, present in EPO, serves as a forerunner to prostaglandin E2. Prostaglandin E2 enhances cervical ripening by augmenting submucosal fluid, altering collagen binding and glycosaminoglycans, and increasing myometrium sensitivity to oxytocin (56, 57). However, due to high variation between studies, further clinical trials of high methodological quality are needed to obtain certain results. In this study, the results of six studies evaluating the effectiveness of vaginal capsules with EPO indicated that the efficacy of EPO improved cervical ripening. However, the current meta-analysis did not reveal a significant difference in terms of effectiveness between the misoprostol and EPO groups. The vaginal form of this oil is more effective than the oral form in improving cervical ripening.

The present meta-analysis of the effects of EPO on labor contraction revealed that the oral consumption of 1000 mg of EPO every twelve hours for seven days reduced the duration of the

second stag phase and labor. In the study conducted by Kalati et al. (2018), the duration of the second phase of labor was 45 minutes in the experimental group of EPO, whereas in the control group, it was 57 minutes (42). Another study conducted by Heydari et al. (2022) revealed that the duration of the second phase of labor was 48 minutes within the EPO group, whereas the control group experienced a duration of 56 minutes (47). The substantial impacts of EPO on the duration of the second phase of labor are presumed to result from its prostaglandin-like influences, which enhance the effectiveness of uterine contractions and the circulation of blood within the pelvic region (42, 47). However, vaginal administration did not have any effect on the active phase of labor (44, 46, 49) or the length of the second phase of labor (46, 47, 49). The lack of effect of EPO on the duration of the first and second stages of labor could be related to the fact that the impact of any medication depends on the timing of its administration. The higher dosage of consumption in the EPO group is likely the reason for the effectiveness of EPO on uterine contractions in the second phase of labor.

Compared with that in the control group, the cesarean delivery rate in both the oral consumption group and the vaginal EPO group decreased. Nonette et al. (2017) reported that establishing a direct link between EPO use and cesarean delivery was impossible (40). The results of Hemetzadeh's systematic review and meta-analysis revealed that the cesarean section rate in the EPO group was significantly lower than that in the control group (placebo or dinoprostone) (OR=0.61; 95% CI: 0.43–0.86; p=0.004), which is in line with the results of the present study. The results of the present study were not consistent. Despite generally good methodologies, 13 studies showed high bias, particularly due to a lack of blinding in outcome assessments. This poses a limitation to the findings and underscores the need for studies with stronger methodologies regarding diagnostic blinding. Given the high heterogeneity among studies, further research is recommended to determine the optimal EPO dosage for enhancing cervical ripening and improving birth outcomes.

Implications for practice

Oral EPO shortens the duration of the second phase of labor and reduces cesarean section rates but does not yield a noteworthy increase in the Bishop score. Vaginal EPO seems to affect cervical ripening, reduce cesarean section rates, and improve 5-minute Apgar scores. Given the high degree of heterogeneity between studies, the researchers recommend further research into the best dose of EPO to improve cervical preparation rates and birth outcomes.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Authors' Contributions

A.N., M.M., V.G., F.S., R.P.G. and M.N. jointly contributed to the study design and interpretation of the data. A.N. and M.M. conducted the search. V.G.: Performed the analysis. M.M., A.N. and R.P.G.: Drafted the manuscript. A.N., V.G., M.M and E.N: Critically reviewed and revised the manuscript. All the authors approved the final manuscript.

AI Statement

Artificial intelligence was not used in writing the manuscript.

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