EFFECT OF ORAL EVENING PRIMROSE CAPSULES ON RIPENING OF THE CERVIX IN NULLIPAROUS IRANIAN PREGNANT WOMEN (A RANDOMIZED TRIAL)

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ABSTRACT

***Introduction**: Ripening of the cervix and uterine contractions are two basic factors of a successful delivery. Lack of ripening of the cervix is considered to be one of the problems of delivery. Thus, the present research was designed to determine the effect of oral evening primrose capsules on the ripening of cervix in nulliparous women.*

***Materials and methods**: This research has been conducted with the triple-blind randomized trial method on 80 nulliparous women in the 40th week of pregnancy (6th day + 40 weeks) visiting the prenatal clinic Prenatal clinic Shahid Akbarabadi educational and medical center of Iran University of Medical Sciences in 2015. Samples were divided into two equal groups of medicine and placebo with the randomized allocation method. Each of the participants took a bottle containing 14 1000mg oral evening primrose capsules (2 capsules per day, each 12 twelve hours for a week) or the placebo containing 14 1000mg oral capsules of paraffin in similar bottles. Data collecting tools include: demographic specifications questionnaire and the form of the records of the examinations. Data was analyzed through statistical tests and SPSS software version 16 using descriptive inferential statistic.*

***Findings**: Similarity of the two groups in terms of individual specifications and Bishop Score before the intervention were reviewed in the two groups and no significant statistical difference was seen between the two groups. The mean of the Bishop score for those who had taken 10 or more capsules after the intervention did not show a statistically significant difference (p=0.110).*

***Conclusion**: Consumption of evening primrose did not show a considerable improvement in the score. It is recommended to do more comparative studies in this field in later weeks of pregnancy due to the conflicts of the studies.*

***Key words**: Ripening of the Cervix, Evening primrose, Pregnancy.*

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Introduction

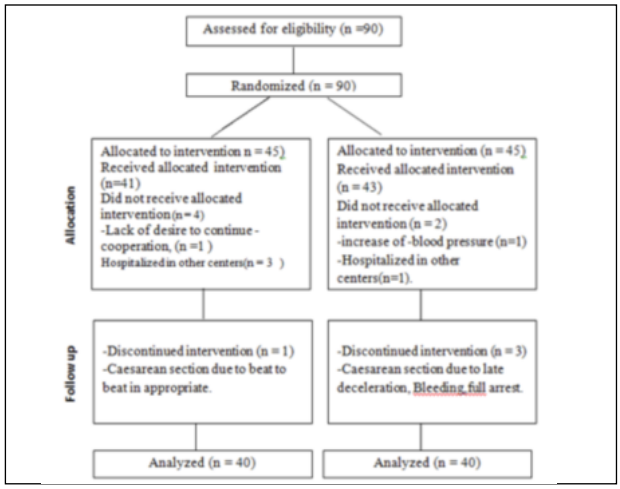
Firmness and closeness of the cervix are necessary throughout the whole pregnancy except for the few last weeks for the maintenance of pregnancy[1]; whereas the improvement of natural childbirth depends on the ripening of the cervix[2]. The most common method of evaluation of the ripening of the cervix was firstly recommended by Bishop in 1964 as the Bishop Scoring method based on scoring including 5 components (dilation, effacement, condition and strength of the cervix and display station of the organ)[3]. Currently, the Bishop score evaluation method is widely used as the most accurate and valuable of evaluating ripening of the cervix[4]. In other words, the higher the Bishop score is, the more ready the cervix will be and the probability of vaginal delivery increases and the probability of caesarean section decreases[5, 9]. The results obtained from the studies indicate that low bishop score brings pain, long delivery, and the risk of increasing the prevalence of C-sections[5] and its side effects are complications of anesthesia, bleeding, infection and repeated C-sections[6].

Length of the pain of delivery is also followed by complications such as mother's tiredness, increase of fear and anxiety during the current and the next delivery and probability of increasing infection in the mother and the newborn during and after the delivery[7]. In addition, length of delivery and the intensity of its pain are among the basic causes of mothers' fear of delivery and their tendency towards c-section operations[8]. Beginning of delivery with an undesirable cervix is also an important factor for predicting the condition of newborns who require hospitalization after being born[9]. Bishop scores that are lower than or equal to 4 which are assigned to the cervix are considered undesirable and might be considered as the indications of preparation of the cervix[10].

Cervix preparation methods are divided into two methods: medical methods such as E1 and E2 prostaglandin and mechanical methods such as Foley catheter. The most common method of cervix preparation is using different types of prostaglandin. However, it also has numerous side effects including Tachysystole, Aaspiration, Hypertonicity and Hygroscopic along with undesirable impacts on the heartbeat of the fetus, fever, nausea, vomiting, diarrhea and neonatal adverse consequences. That is why these products shall only be used in the delivery room and when it is possible to monitor the activity of the uterus and the fetal heart rate[10]. Application of mechanical methods such as Foley catheter also requires hospitalizing and monitoring pregnant women and is followed by increase of c-sections, uterine infections, and unnecessary examinations at the time of hospitalization in the hospital[10, 11].

In addition to using various medical methods to make the cervix ready, there are also some traditional methods such as using various forms of medicinal plants[12] n emphasizes on using herbal medicines due to severe side effects of the chemical ones[13]. Among herbal medicines, primrose oil, castor oil and red raspberry leaf are among herbal medicines which are used in order to stimulate and accelerate delivery and prepare the cervix[14]. A study in this field was done by Gibson and McFarlane in 1991 with the purpose of documenting usage of herbal products to prepare, stimulate and reinforce labor by the midwives.

The study showed that they had used castor oil for 93%, blue cohosh for 64%, red raspberry leaf for 60%, Evening primrose oil for 60% and black cohosh for 45%. Thus, they stated that the most effective method is using Evening primrose oil for softening the cervix and that the most effective application of castor oil is for labor stimulation. Primrose is a wild two-year plant with yellow flowers that grows in North America and some parts of Europe. Evening primrose oil (EPO) is extracted from the seeds of this plant including 50-70% of Linoleic acid, 7-10% of Gamma Linoleic acid and a small rate of oleic, palmitic and stearic acids[15] (Graph 1).:



Graph 1: Research Method Diagram.

Two necessary fatty acids Linoleic acid, and Gamma Linoleic facilitate E2 prostaglandin synthesis[16]. Preparation of the cervix is related to some medium factors and E2 and F2α prostaglandin seem to be the ultimate medium in this process[10]. Using EPO is useful for different types of disorders including Atopic Dermatitis, Rheumatoid arthritis, Diabetic neuropathy, multiple sclerosis, many types of cancer, Raynaud's phenomenon, Ulcerative colitis, Preeclampsia, premenstrual syndrome, hot flashes during the menopause, cysts and pain in the breasts, Sjogren's syndrome, Schizophrenia and hyperactivity[17, 18, 19].

According to the opinion of the National Center for Complementary and Alternative Medicine, primrose is generally tolerated well by individuals but also causes a mild upset stomach and headache[22]. Thus, since EPO is generally tolerated well[20], there is no limit for using it during the pregnancy[19] because it has no effect on the safety of the fetuses monitored by the biophysical profile test and stress-free test[21] and its consumption as an oral capsule is easy and does not require hospitalization and constantly monitoring the fetus[22]. Iran is one of the most important areas in terms of proper weather, and cultivation of evening primrose[23].

Given that finding a non-invasive, non-pharmacological method with less side effects than that of the common mechanical and pharmacological methods in the preparation of cervix, according to the studies, will lead to the reduction of fatal and motherhood complications and reduction of the time spent by the pregnant woman, financial expenses imposed on a person and health system of the society, and using primrose capsule is a non-invasive and non-pharmacological method, it is recommended as the non-invasive non-pharmacological method with minimum complications. Also, given that very few studies have been done in this regard in the world, and especially no documents have been recorded yet in the field above in Iran, researchers attempted to conduct a research with the purpose of determining the effect of this medicinal plant on the ripening and softening of the cervix so that if the research hypotheses are confirmed, the researchers will be able to recommend this natural, non-invasive method for an easier labor with less risks.

Materials and methods

This research has been conducted with the triple-blind randomized trial method with two groups of medicine and placebo from August to December of 2015 after being authorized by the Ethics Committee of Iran University of Medical Sciences and registering with the number (IRCT201507022248N17) in IRCT in Prenatal clinic Shahid Akbarabadi educational and medical center by getting the permission of the beneficiary references. Research units included 90 nulliparous women visiting the prenatal infirmary of Prenatal clinic Shahid Akbarabadi educational and medical center.

Criteria of entering the study include: healthy pregnant women originally from Iran who are not at risk that much (lack of surgical diseases or known surgeries or pregnancy complications such as paranoia, placental abruption, preeclampsia and lack of fetal problems) and pregnancy age (40 week) to (6th day + 40 weeks) based on the latest day of period and sonogram of the first three month, live fetus, cephalic fetal presentation, natural pattern of fetal heart rate, lack of uterine contractions, Bishop score of less than 4, healthy membrane, mother's height of more than 150cm, lack of drug abuse, natural modified biophysical profile testing at the time of entering the study, having a sonogram in terms of placental grading, an estimated weight of fetus between 2500 and 4000 grams based on a manual examination of the abdomen or sonogram, avoiding using enema, no intercourse, consumption of laxatives, herbal and chemical medicines or traditional methods for the beginning of the pain of labor, lack of vaginal examination from hours before the beginning of the study to the end.

Criteria of exiting the study: consuming less than two capsules per day, c-section due to any reason and probable side effects related to medicine such as headache, nausea, diarrhea and other items. Given the sample volume, by using an available similar research in the field of effect of EPO capsule on the Bishop score by considering the confidence level of 95% and a test power of 80% and by assuming that the rate of impact of intervention (impact of EPO capsule on the Bishop score) in comparison with the control group is at least d=1, after placing the values in the formula, each group was estimated to include 40 persons. By calculating the probability of the elimination of the components of the sample, ultimately 45 persons were put in each group that makes a total of 90 persons.

The sampling method was as such that firstly, 90 women with the criteria of entering the study who agreed to participate in the study, after getting a written consent, were cautiously put in one of the two groups of using the primrose capsule or the placebo; in such way that the names of each of the two groups were written as codes A and B on paper and were put inside separate envelops. The first sample that entered the study picked out one of the envelops and the next person went to the other group and the same was done for the third person and the fourth person went to the second group so that all of the individuals in the sample volume would enter one of the two groups of the study either consuming EPO capsules (45 persons) or placebo (45 persons).

The tools use in this research include a two-form questionnaire and a sheet of the records of the hours of drug consumption, sheet of recording and reviewing the unwanted complications of the Ministry of Health and Medical Education of Iran and department of food and drug. In order to determine the validity of the questionnaire, appearance and content validity method was used; in such way that firstly the valid articles were studied, the data gathering tools were selected and then in order for the ultimate review, they were given to 10 of the faculty members of the department of nursing and

midwifery of Iran University of Medical Sciences. Ultimately, the questionnaire was arranged and used. For the Bishop score to be reliable, firstly 10 examinations were done by the researcher and they were controlled by another fellow midwife at the same rank and its correlation was more than 0.99 and that is how its reliability was confirmed. All of the capsules had the same shape and color and were coded A and B by the pharmacist in similar packages.

The research samples and groups and statistical analyzers did not know what the capsules contained; thus the present research was a triple-blind one. Demographic specification questionnaires and record of preliminary examinations included the mother's vital signs, conditions of fatal heart rate, uterine contradictions, and cervix Bishop score and were filled out in the infirmary. Then each of the participants took a bottle containing 14 1000mg oral evening primrose capsules (2 capsules per day, each 12 twelve hours for a week) or the placebo containing 14 1000mg oral capsules of paraffin in similar bottles A o B. The safe dose of EPO, according to the studies, is at most 2-16 500mg capsules per day(17). Also, dose of 3g EPO is 3 capsules per day (2*500gm capsules or 1*1000mg capsules)[24]. About the instruction of consuming the capsules, the required information was given to the studied individuals. Throughout the research, the researcher kept in touch with the participants by phone in order to get information about the samples or the probability of the occurrence of complications related to the consumption of capsules. After the capsules are all taken, or in case of presence of warning symptoms including a runny nose, bleeding, reduction of fetal movement, severe abdominal pain, the pregnant women shall visit a hospital. And the researcher went to the hospital and recorded all of the information and determined examinations in the questionnaire and the form of examinations. At the time of the visit, the examinations were done in order to calculate the Bishop score and they were recorded in the form of examinations. It is necessary to mention that the rate of elimination of the sample was 10% in the present research. During the process of the research, out of the 90 samples, ultimately, 5 persons were eliminated from the EPO capsule group (40 persons) and 5 persons were eliminated from the placebo group; in such way that out of the 6 persons eliminated in the allocation stage in the placebo group, one person was eliminated due to the increase of blood pressure (blood pressure during pregnancy) and a person for being hospitalized in other centers, and in the medicine group one person was eliminated due to lack of tendency towards continuing to cooperate and three persons were eliminated for being hospitalized in other centers. Also, in the Follow Up stage, four persons were eliminated for c-section, one person in the medicine group was eliminated due to improper bit to bit and three persons in the placebo group were eliminated due to late drop of heart rate and bleeding. And ultimately, in total, 80 persons participated in the research (graph 1). At the end, after analyzing the information and getting the final results, type of each medicine and the pharmacist was asked about the code related to it and finally the results were discussed for the last time. Data analysis was done in two stages. In the first stage, in order to describe demographic specifications, the descriptive statistical tests including relative and absolute frequency of mean and standard deviations were used and in the next stage, in order to compare the means, the accurate Fisher test, Chi-square and independent statistical T-tests were used. Ultimately, in order to analyze the data, SPSS software ver.16 was used.

Findings

The age average in the medicine and placebo group was respectively 24.00 and 24.85 years. 57.5 percent of the researched units in the medicine group and 60 percent in the placebo unit had graduated high school and had a diploma. All of the mothers in the placebo group and 95% of those in the medicine group were housewives. The average body mass index has been respectively 23.46 and 23.35 in the medicine and placebo group. According to the results of this study, the two groups have been similar in terms of age average of the mother and her husband (independent statistical t-test), mother's level of education (chi-square test), fathers' level of education and occupation of the mother and the father (accurate Fisher test), mother's body mass index (independent t-test) and statistical tests did not show a significant statistical difference between the groups (P>0.05). Also, the two groups did not have a significant statistical different in terms of pregnancy based on the first day of the latest period or the sonogram of the first three months (table 1).

The statistical independent t-test indicated that the mean of the Bishop score in the two reviewed groups before the intervention does not have a sig-

nificant statistical difference compared to after it. The average of the Bishop score in the medicine and placebo groups, before the intervention, was respectively equal to 1.05±1.17 AND 1.25±1.08.

Group Individual specifications		Group 1	Group 2	Test results
Mother's age		24.00±4.01	24.85±4.22	t=0.923 df=78 P-value = 0.359
Body mass index		23.46±3.71	23.35±3.53	t=0.135 df=78 P-value = 0.893
Spouse's age		28.30±4.71	28.77±4.61	t=0.456 df=78 P-value = 0.650
Mother's level of education	Elementary and guidance school	11(27.5%)	11(27.5%)	χ^2=0.112/0 df=2 p-value = 0.945
	High school and diploma	23(5.5%)	24(60.0%)	
	University	6(15.0%)	5(12.5%)	
Mother's occupation status	Housewife	38(95.0%)	40(100.0%)	p-value=0.494
		(0/5%)2	(0/0%)0	
Spouse's level of education	Illiterate	1(25%)	2(5.0%)	p-value=0.893
	Elementary and guidance school	16(40.0%)	16(40.0%)	
	High school and diploma	17(42.5%)	18(45.0%)	
	University	6(15.0%)	4(10.0%)	
Spouse's occupation status	Employee	6(15.0%)	4(10.0%)	χ^2=0.459 df=2 p-value=0.795
	Worker	14(35.0%)	15(37.5%)	
	free	20(50.0%)	21(52.5%)	

Table 1: Distribution of frequency of individual specifications of the researched units.
**Independent t-test*
***Chi-square test*

Group Variable			Medicine	Placebo	Total
Capsule	5 >	Number	8	6	14
		Percentage	20.50%	15.00%	17.70%
	(5, 9)	Number	13	17	30
		Percentage	33.30%	42.50%	38.00%
	(10, 13)	Number	7	7	14
		Percentage	18%	17.50%	17.70%
	14	Number	11	10	21
		Percentage	28.20%	25.00%	26.60%
Total		Number	39	40	79
		Percentage	100.00%	100.00%	100.00%

Table 2: Distribution of absolute and relative frequency of the studied units based on the number of the consumed medicines.

In addition, the findings showed that the majority of the studied units did not have cervix ripening in the medicine group (90%) and in the placebo group (80%) (P=0.110). Standard deviation of the average of the Bishop score has obtained to be equal to 3.60±1.75 and 4.35±2.34 in the medicine and placebo groups, respectively, after the intervention. The results of the independent t-test also showed lack of a significant statistical difference between the two groups (P=0.431) (Table 4).

Group Interval	Medicine		Placebo	
	Frequency	Percentage	Frequency	Percentage
Less than 3 days	10	25.6	9	22.5
3 to 5 days	11	28.2	14	35
5 days and more	18	46.2	17	42.5
Total	39	100	40	100
Standard deviation ± mean	4.39±1.98		4.45±1.84	
Results of the independent t-test	t=0.122 df=77 p-value=0.903			

Table 3: Distribution of absolute and relative frequency of the studied units based on the duration of consumption of the medicine till the beginning of labor.

According to table 2, the number of individuals who took 10 or more than 10 capsules, is 46.2% in the medicine group and 42.5% in the placebo group and 44.3% in total. And only 28.2% and 25% in the placebo group took all of the 14 capsules and also only 46.2% in the medicine group and 42.5% in the placebo group took the capsules for 5 days and more (table 3).

Bishop Score	Evening primrose	Placebo	
Group	Mean and standard deviation	Mean and standard deviation	Statistic
Before intervention	1.05±1.17	1.25±1.08	t=0.792 df=78 p-value=0.431
After intervention	3.60±1.75	4.35±2.34	t=1.619 df=72.12 p-value=0.11

Table 4: Comparing the mean of the Bishop score before and after intervention in both medicine and placebo groups.

Discussion

The research findings in the present study indicated that taking the one EPO capsule two times a day for a week does not have a considerable effect on the Bishop score.

In Dow and Johnson's study (1999), 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 laber 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 (P>0.05). This study is compatible with the present study in terms of lack of medicine's effect on other results of pregnancy and labor; whereas the results of the study of Ty-Torredes (2006).

This study was done in order to review the impact of edible EPO on the Bishop score and length of cervix during the pregnancy on 71 pregnant women in two groups containing 38 persons. In the test group, the members took one EPO capsule three times a day for a week and 33 persons were in the placebo group. A considerable improvement was seen in the Bishop score in the group consuming the primrose capsule compared to the group consuming the placebo (P=0.0001). Also, a considerable reduction was seen in the length of the cervix by the transvaginal ultrasound in the medicine and placebo groups (p=0.001).

The results of this study do not comply with the present study. One of the probable causes of this difference is that in Ty-Torredes's study, consumption of medicine has began in the 39th week by the research units; whereas the present research has been conducted in the 40th week and the probability of occurrence of the signs of labor before the capsules finish is more in the 40th week compared to previous weeks; in such way that only 28.2% in the medicine group and 25% in the placebo group have consumed the capsules completely. And also only less than half of the research units consumed the capsules for five days and more.

In fact, the beginning of the consumption of the capsules in the later weeks increases the probability of a more complete consumption of capsules. Thus, consumption of a different number of capsules in the present research can be the reason for which the research hypotheses are rejected. On the other hand, ripening of the cervix occurs gradually a few weeks before the beginning of labor and it seems that the effective factors on this ripening shall be reviewed during these weeks[25]. As it has been mentioned in the study of Dow and Johnson, application of EPO few weeks before labor might have a different effect on the results of pregnancy and around labor. In another study done by Vahdat, et al. in 2015 was done with the purpose of determining the effect of EPO on the dilation and ripening of the cervix before the Hysteroscopy operation. 28 women received EPO gel and 22 women received placebo 6-8 hourse 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 (p=0.003) and came to the conclusion that primrose affects the ripening of the cervix before the Hysteroscopy operation and has no serious side effect.

Although this study has been done before pregnancy for the ripening of cervix; but it has showed the effect of EPO capsule on the ripening of the cervix before the Hysteroscopy operation. It is probable that the cause of incompatibility of this study with the present study is using the gel in the posterior vaginal fornix and different tools such as different dilators for opening the cervix. For eliminating these conflicts and finding out the certain effect of evening primrose on the ripening of the cervix, it is required to do various studies with a strong methodology[26-27].

Conclusion

The results of the present study did not a significant statistical difference in the effect of the consumption of EPO on the preparation of the cervix, therefore it is recommended to do more studies in the later weeks of pregnancy and a higher sample volume due to the conflicts of the studies.

Limitations of the research

• Lack of an accurate and on time consumption of the medicine by the participants: by informing the participants and repeatedly calling them so that this would be prevented.

• Simultaneous consumption of another medicine by the participants of which the researcher does not have information: by giving information to the participants in the research this could be prevented.

• Visiting other centers for the labor by the participants: by making the participants informed about it, the occurrence of it can be prevented to some extent; but due to the long distance of the paths and presence of traffic, it was not controllable completely.

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