Research Article

Effect of Saffron (Fan Hong Hua) On the Readiness of The Uterine Cervix In Term Pregnancy: A Placebo-Controlled Randomized Trial

Roghaieh Sadi,[1] Sakineh Mohammad-Alizadeh-Charandabi,[2,*] Mojgan Mirghafourvand,[3] Yousef

Javadzadeh,[4] and Afkham Ahmadi-Bonabi[5]

[1]Students' Research Committee, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, IR Iran
[2]Department of Midwifery, Social Determinants of Health Research Center, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, IR Iran
[3]Midwifery Department, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, IR Iran
[4]Pharmaceutics Department, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, IR Iran
[5]Gynecologist, Shohada Hospital, Bonab, East Azerbaijan, IR Iran

Corresponding author: Sakineh Mohammad-Alizadeh-Charandabi, Associate Professor, PhD in Reproductive Health, Department of Midwifery, Social Determinants of Health Research Center, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, IR Iran. Tel: +98-09143136276, Fax: +98-4134796969, E-mail: alizades@tbzmed.ac.ir, mhammadalizadehs@gmail.com

Abstract

Background: Readiness of the cervix is required for successful induction of labor, and there are a number of ways in which this can be achieved.

Objectives: The aim of the present study was to assess whether taking saffron orally could have an effect on the cervical readiness (primary outcome) and some delivery and neonatal outcomes (secondary outcomes) in women in the stage of term pregnancy.

Patients and Methods: In this double-blind trial, 50 women with a gestational age of 39 to 41 weeks, no indication of cesarean section, a Bishop's score of less than 4, who had plan to have vaginal delivery at Shohada hospital of Bonab, Iran were randomized into two groups receiving three 250mg saffron or placebo pills in 24 hours. The readiness of the cervix was assessed using the Bishop's score. The Mann-Whitney U test was used to compare the scores between the groups.

Results: There were no significant differences between the groups in terms of the Bishop's score at the baseline (P = 0.792) and 10-12 hours after starting the intervention (P = 0.159). The Bishop's score was significantly higher in the saffron group 20 - 24 hours after the intervention was started (P = 0.029) and just after onset of active uterine contractions (P = 0.003). In the saffron group, there was no cesarean section and 1 meconium staining of the fetus, but 3 and 4, respectively, in the placebo group. There was no statistically significant difference between the groups in terms of the timing of the onset of spontaneous active uterine contractions, the duration of the first and second stages of labor, the need for delivery augmentation, and the first and fifth minutes of neonatal Apgar (P > 0.05). No adverse event was reported in any of the groups.

Conclusions: Saffron can increase the readiness of the cervix in term pregnancies. However, the study limitations do not allow for any definite conclusions for its use in clinical practice, and more research is needed to assess its effect on delivery and neonatal outcomes.

Keywords: Saffron, Readiness, Cervix, Term Pregnancy, Bishop's Score, Herbal Medicine

1. Background

Labor is induced for a variety of reasons, such as preventing prolongation of pregnancy (1), rupture of membranes in the absence of labor, and diseases that threaten the mother or fetus (2). The readiness of the cervix is important for successfully inducing labor and reducing the need for assisted birth and cesarean section (1, 3, 4). Hence, significant attention has been focused on finding appropriate methods to prepare the cervix before inducing labor (3, 5).

Recently, prostaglandins or mechanical techniques have been used for ripening the cervix, but these methods have some limitations. For instance, prostaglandins should be used in the labor room or a place where it is possible to monitor the uterus activity and the fetal heart rate; in case of uterine tachysystolic activity, they should be immediately removed. Furthermore, intracervical gels, vaginal inserts, and mechanical techniques cannot be used if membranes are ruptured; if oxytocin is required, it should be provided at least 6-12 hours after administering prostaglandins (1, 3, 5).

Experiences of the past few decades have shown that chemical medications have adverse effects despite their efficacy, so herbal medications have become more attractive

(6, 7). Saffron, scientifically known as Crocus Sativus L, is a stemless herb found in compounds such as essential oil (containing trepenes), picrocrocin, and crocin (8, 9). It is traditionally used to accelerate labor with no prescription or sometimes as prescribed by traditional healthcare workers.

A review of the literature did not yield any human studies on the effects of saffron on labor induction. Meanwhile, studies on rats showed that oral consumption of saffron can induce premature labor and abortion (10-12). Descriptive studies suggest that it may have an effect on human abortion (13-15). Furthermore, clinical trials reported the effects of saffron on reducing symptoms of premenstrual syndrome (16), primary dysmenorrhea (17), mild-to-moderate (18) and major depression (19), with no significant side effects in human subjects.

Some traditional medical textbooks mention that saffron has inducing effects on the smooth muscles of the uterus, and Chinese medicine recommends it be used for menorrhagia, difficult labor, and postpartum hemorrhage (20). However, it is believed that saffron can harm the fetus in the first trimester during organogenesis. Still, moderate consumption (0.5 - 2 g per day) after the first trimester can promote the elasticity of uterine tissue and facilitate labor (9, 21, 22).

2. Objectives

The present study aimed at investigating the effects of the oral consumption of saffron on cervical ripening (primary outcome), and certain delivery and fetal outcomes (secondary outcomes) in full-term pregnant women (at gestational weeks 39 - 41) without indications of requiring cesarean section.

3. Patients and Methods

3.1. Design, Setting, and Participants

The study was conducted as a randomized, double-blind, placebo-controlled trial. Fifty singleton pregnant women with zero to two parity and a gestational age of 39 to 41 weeks were recruited among outpatients presenting to two private offices and a clinic in Shohada hospital for prenatal care. Each of the women had intact amniotic sac, no active uterine contractions, a Bishop's score of less than 4, a reactive non-stress test, a normal fetus with estimated weight of 2500 to 4000 in cephalic presentation, and plans to have a vaginal delivery at Shohada hospital of Bonab, Iran. Women with the following criteria were excluded: (1) no access to a phone line; (2) illiterate or only primary education; (3) a history of cesarean section or any possible

indication that cesarean section would be required for the current pregnancy; (4) a history of cryotherapy or cauterization on the cervix; (5) a known chronic and systematic disease; or (6) smokers, alcohol drinkers, or drug abusers.

Shohada hospital is the only center for delivery in Bonab (a city with a population of 129,795) (23). It is a public center affiliated with Tabriz University of Medical Sciences which has maternity and pediatric wards and is responsible for the care of people living in Bonab and some of the small cities and villages surrounding the city. Almost all vaginal deliveries (about 150 per month), which comprise about half of all deliveries at the hospital, are facilitated by 20 midwives under the indirect supervision of 4 obstetricians.

The research protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Code 91219) and registered at the Iranian registry of clinical trials (Iranian registry of clinical trials (IRCT) 201212233706N19) on 17 March 2013 before starting participant recruitment.

3.2. Random Assignment and Blinding

The allocation sequence was determined using a computerized program using block randomization with block sizes of 4 and 6 and an allocation ratio of 1:1 and stratified according to a history of previous delivery (Yes/No). Sequentially numbered sealed opaque envelopes containing three saffron or three placebo pills were used for the allocation concealment. The allocation sequence and the packages were prepared by a person not involved in the recruitment, data collection, or analysis. The participants and other people involved in the recruitment, data collection, or analysis were not aware of the type of intervention for each participant.

3.3. Interventions

Participants in the intervention group received saffron in the form of 3 pills (250 mg in each pill) and participants in the control group received a placebo 3 times in 24 hours (one every eight hours). They took the first pill immediately after enrolling in the study under the supervision of the investigator. They were instructed orally and in writing on how to take the two other pills at home.

The saffron pills and the placebos were produced in the industrial pharmacy laboratory of the Tabriz University of Medical Sciences and under direct supervision of the pharmacist from our research team. Before preparation of the pills, the purchased active ingredient was identified and controlled for quality and safety by the Herbarium of the faculty of pharmacy at the Tabriz University of Medical Sciences. Saffron produced by Bahraman Co., Iran was purchased from a grocery. The company purchases saffron

from farms in Khorasan province and performs tests on the humidity percentage, acid insoluble ash, crocin (responsible for the color), picrocin (responsible for bitterness and taste), and saffranel (responsible for the aroma) using a spectrophotometer at wavelengths of 257, 330, and 440 nm, and microbial tests to monitor contamination and to safety of the product before packaging (24).

Each saffron pill had dried saffron stigma (250 mg), microcrystalline cellulose (filler), sodium stearate glycolate of 3% (disintegrant), and magnesium stearate 1% (lubricant). The placebo pills had the same materials except for the saffron stigma and were identical to the saffron pills in terms of color and size.

3.4. Outcome Measures

The primary outcome was readiness of cervix assessed by the Bishop's score at 10 - 12 and 20 - 24 hours after initiation of intervention, and just after onset of uterine active contractions. The Bishop's score is a quantifiable method used to predict outcomes of labor induction involving 5 components, including dilatation, effacement, fetal station, cervical consistency, and position, each of which has been described by Bishop (1964). The possible score ranges from 0 to 13; the higher score, the better the readiness of the cervix (2).

Secondary outcomes included delivery-related variables such as the interval between starting the intervention and the onset of active uterine contractions, the duration of the first and second stages of delivery, the frequency of vaginal delivery, and hemorrhage assessed by measuring hemoglobin and hematocrit at the admission to the hospital and 12 - 24 hours after delivery. Fetal and neonatal outcomes such as the Apgar score measured at the first and fifth minutes, meconium staining, and the need for admission into the neonatal ward were also considered.

3.5. Recruitment and Data Collection

To recruit participants, potentially eligible women were examined using abdominal palpation in 10 minutes to rule out active uterine contractions, and a non-stress test conducted in 20 minutes to rule out any fetal distress. The eligibility criteria was assessed by a midwife and confirmed by an obstetrician.

After obtaining informed written consent from eligible women and assessing their baseline characteristics, the women were given pre-prepared packages containing the pills to the participants in their recruitment order into the study. They were also provided with a diary to record the times when the pills were taken and to report any side events. It was emphasized that they needed to immediately report any complications including hemorrhage, decrease in fetal movement, perforation of the amniotic sac,

or any other serious adverse events by calling the investigator or referring to the hospital.

The women were also instructed on how to count fetal movements and to notice the start of active contractions (tightening of abdominal muscles three or more times in ten minutes). It was also emphasized that the participants were to come back for follow-up assessment 10 - 12 and 20 - 24 hours after taking the first pill, and also whenever active uterine contractions had started. Furthermore, the participants were called every 3 - 4 hours during the day, and before and after a 6 hour interval during the night within the first 24 hours to remind them about the instructions.

Delivery progress was assessed using a partograph. Any other interventions, including using misoprostol or oxytocin for augmentation or induction, were recorded. After delivery, the first and fifth Apgar scores and weight of the infants were checked by the investigators. Also, any procedure used for neonatal resuscitation was recorded.

All women were monitored at least for two hours after delivery. Hospital records of the women and their infants were checked for any intervention that may have been administered. At time of admission to the hospital and 12 - 24 hours after delivery, blood samples were taken from the women to measure hemoglobin and hematocrit levels.

3.6. Sample Size and Statistical Analysis

The initial sample size included 20 people in each group based on the guidelines of Pirdadeh et al.'s study (25), where M1 = 2.50 (Bishop's mean score), Sd1 = 1.29, M2 = 3.75 (a 50% increase in Bishop's mean score), Sd1 = Sd2 = 1.29, $\alpha = 0.05$ and ß = 0.1. Considering the possible dropout rate, 25 people were ultimately selected for each group.

Some imputation was done before data analysis. For participants who did not attend the 10 - 12 hours follow-up, if the Bishop's scores at the baseline and at the 20 - 24 hours assessment were the same, the same score was also used for the 10 - 12 hours assessment score. If the two values were not the same, the participant was omitted from the analysis at the time-point with no recorded information. For any participants who delivered before 20 hours after intervention, the maximum Bishop's score was used for the 20 - 24 hour score after intervention. Any person who had a cesarean section before the follow-up score assessments prior to starting active uterine contractions was omitted from the bishop score analysis.

Data were analyzed using SPSS Version 16. The normality of the distribution of the quantitative variables according to study group was assessed using the Kolmogorov–Smirnov test. Bishop's scores, along with their log10 and Ln, had no normal distribution. Therefore, a Mann-Whitney U test was used to compare the groups in terms of the primary outcome and also for in terms of the Bishop's

test components. An independent T-test was used for the other quantitative outcomes which had normal distribution. Pearson Chi-square, Linear-by-Linear, or Fisher's exact tests were used for comparison of the groups in terms of the qualitative outcomes. P < 0.05 was considered as a significant level.

4. Results

Participant recruitment was carried out from May 23 until July 17, and follow-up ended on July 29, 2013. All women randomized into the groups (25 women in each group) were followed up on until discharge from the hospital after delivery. Two participants from the placebo group did not take the second and third pills due to opposition from their husbands. Two participants from each group did not attend the 10 - 12 hour follow-ups. Only one participant from the placebo group did not report for the 20 - 24 hour follow-up. One person from the placebo group had a cesarean section at 13 hours after intervention before starting active uterine contractions due to meconium staining of the fetus. The hemoglobin and hematocrit of 1 person could not be measured from the saffron group, and for 3 persons from the placebo group 12 - 24 hours after delivery (Figure 1).

The groups were similar in terms of demographic and fertility characteristics. About half (52%) of the women were aged 20 - 29 years. All but two were housewives. About half (46%) were having their first pregnancy. The gestational age of about three fourths (76%) was 273 - 280 days (Table 1).

The mean (SD) of the Bishop's score for the saffron group increased from 2.6 (0.6) at baseline to 3.0 (1.1) at 10 - 12 hours, to 5.2 (2.6) at 20 - 24 hours and to 7.2 (0.9) at just after starting active uterine contractions. The corresponding figures for the placebo group were 2.6 (0.6), 2.6 (0.6), 4.0 (2.4), and 6.2 (1.1), respectively. The difference between the groups was not statistically significant at the baseline (P = 0.792) and at 10 - 12 hours (P = 0.159). The score was significantly higher in the saffron group at 20-24 hours (P = 0.029) and at just after starting active uterine contractions (P = 0.003) (Table 2).

Comparing the groups in terms of the Bishop's components showed statistically significant differences only in terms of effacement at 10 - 12 hours (P = 0.019) and 20 - 24 hours (P = 0.023), and station (P = 0.003) and consistency (P = 0.006) at just after starting active uterine contractions (Table 3).

There was no cesarean section and only 1 labor augmentation in the saffron group. The corresponding figures were 3 and 3, respectively, in the placebo group. However, the differences were not statistically significant (P = 0.117

Table 1. Demographic and Fertility Characteristics of Participants by Study Group[a]

Characteristics	Saffron (n = 25)	Placebo (n = 25)	Statistical Results
Age (years)			t = 1.055, df = 48, P^b = 0.297
≤ 19	2 (8)	3 (12)	
29 - 20	16 (64)	10 (40)	
30 ≤	7 (28)	12 (48)	
Mean (SD)	25.9 (4.7)	27.6 (6.5)	
Academic education	5 (20)	2 (8)	x^2 trend = 0.360, df = 2, P^c = 0.549
Employed	0 (0)	2 (8)	P^d = 0.490
Primiparous	11 (44)	12 (48)	x^2 = 0.081, df = 1, p^e = 0.777
History of abortion	2 (8)	2 (8)	P^d = 1.0
Gestational age (273 - 279 days)	19 (76)	19 (76)	x^2 = 0.000, df = 1, P = ^{e}1.0
Birth weight (gr) Mean (SD)	3266 (430)	3272 (278)	t=0.059, df = 48, P^b = 0.954

[a] The values show number (percent) unless otherwise indicated.
[b] Results of independent T-test.
[c] Results of linear-by-linear Chi-square test.
[d] Results of Fisher's exact test.
[e] Results of Pearson Chi-square test.

and P = 0.609, respectively). Also, there was no statistically significant difference between the groups in terms of the timing of starting spontaneous active uterine contractions (P = 0.372), the duration of the first (P = 0.173) and second (P = 0.615) stages of labor, and hemoglobin (P = 0.854) and hematocrit (P = 0.878) levels at 12 hours after delivery (Table 2).

Mean neonatal weight was 3266 g (SD 430) in the saffron group and 3272 g (SD 278) in the placebo group (P = 0.954). There was a lower, but not statistically significant, frequency of meconium staining of the fetus (one vs. four, P = 0.110) and neonatal admission in the neonatal ward (1 vs. 6, P = 0.098) in the saffron group compared with the placebo group. Also, there was no statistically significant difference between the groups in terms of the first (P = 0.235) and fifth (P = 1.00) minute neonatal Apgar scores, with no Apgar scores of less than 7 among either of the groups. No adverse event was reported in either of the groups.
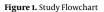
5. Discussion

This study is the first trial on full-term pregnant women that attempts to determine the effect of oral saf-
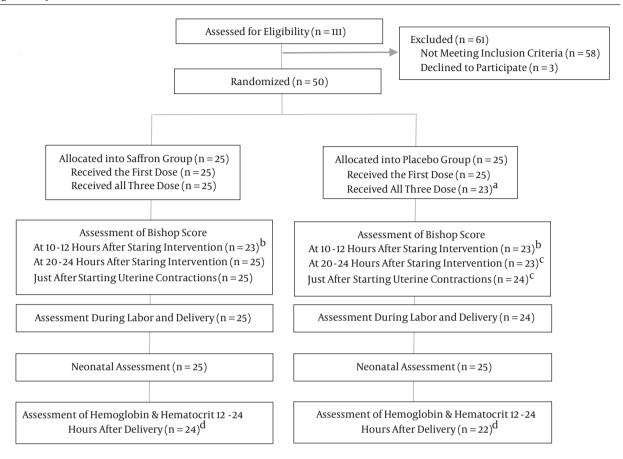
Figure 1. Study Flowchart

A,Two participants did not take the second and third pills due to husband opposition; B,Two participants from each groups did not report for the 10 - 12 hour follow-up.From the placebo group, for 1 person, the baseline and 20 - 24 hour Bishop's score assessments were the same, and the same score was considered for the 10 - 12 hour assessment score. One person in this group did not refer for both the 10-12 and 20 - 24 hour follow-ups and was omitted from the analysis at those points in time. For 2 participants from the intervention group who did not report for the 10 - 12 hour follow-up, and due to differences between baseline and 20 - 24 hours Bishop's score assessment, their results were omitted from the analysis; C, One person did not refer for the 20 - 24 hour follow-up and another had a cesarean section before onset of active uterine contractions 13 hours after intervention due to meconium staining of the fetus; D, Hemoglobin and hematocrit were not assessed for 1 person in the saffron group and for 3 in the placebo group due to their early discharge

fron tablets on cervical ripening in outpatients. The saffron pill recipients had a significant increase in the Bishop's mean score 20 - 24 hours after the intervention and onset of uterine contractions as compared with the placebo group, but the time of the onset of contractions was not significantly different between the two groups. The length of the first and second phases of labor was shorter, and fewer women required cesarean section or labor induction, but the differences were not statistically significant. Studies in rats indicate that saffron can stimulate the uterus, cause abortion, and preterm labor (10-12). Additional observations have shown an increased probability of abortion in

pregnant farmers who had been working in saffron farms during the first trimester of pregnancy (14, 15). These effects can be attributed to the prostaglandin-producing effects of saffron.

Examination of the Bishop's score components showed that saffron has the highest effect on effacement and cervical ripening. Considering that one of the causes of abortion in the first trimester is a reduced level of progesterone, and progesterone antagonists such as mifepristone play a role in cervical ripening at the end of pregnancy (2), saffron might therefore have an effect on abortion or premature labor as a progesterone antagonist.

Table 2. Primary and Secondary Outcomes for Each Study Group

Outcomes	Saffron (n = 25)		Placebo (n = 25)		P Value
	Mean (SD)	Med (P25 - P75)	Mean (SD)	Med (P25 - P75)	
Primary Outcome					
Bishop's score (0-13)[a]					
Before intervention	2.6(0.6)	3.0 (2.0 - 3.0)	2.6 (0.6)	3.0 (2.0 - 3.0)	0.792[b]
10 - 12 hours after intervention	3.0 (1.1)	3.0 (2.0 - 3.0)	2.6 (0.6)	3.0 (2.0 - 3.0)	0.159[ab]
20 - 24 hours after intervention	5.2 (2.6)	5.0 (4.0 - 6.0)	4.0 (2.4)	3.0 (2.0 - 5.0)	0.029[b]
Just after starting uterine contractions	7.2 (0.9)	7.0 (6.0 - 8.0)	6.2 (1.06)	6.0 (6.0-7.0)	0.003[b]
Secondary Outcomes					
Interval between initiation of intervention and starting spontaneous uterine contractions (hour)	140 (119)	93 (49 - 225)	112 (96)	102 (31 - 173)	0.372[c]
Duration of first stage of labor (hour)	4.8 (2.5)	4.4 (3.1 - 5.5)	6.2 (4.3)	4.8 (3.8 - 7.4)	0.173[c]
Duration of second stage of labor (min)	26.0 (32.5)	15.0 (5.0 - 32.0)	30.2 (24.1)	25.0 (10.0 - 40.0)	0.615[c]
Labor augmentation	1 (4)[d]	-	3 (12)[d]	-	0.609[e]
Vaginal delivery	25 (100)[d]	-	22 (88)[d]	-	0.117[e]
Vaginal delivery not achieved within 24 hours	23 (92)[d]	-	24 (96)[d]	-	1.000[e]
Hemoglobin (g/dl)					
At admission to hospital	12.6 (1.2)	12.7 (11.5 – 13.6)	12.8 (0.7)	12.7 (12.3 - 13.2)	0.433[b]
12 hours after delivery	11.2 (1.5)	11.3 (10.1 – 12.2)	11.1(1.0)	11.3 (10.1 – 11.9)	0.854[b]
Hematocrit (%)					
At admission to hospital	36.6 (2.9)	36.6 (34.0 – 38.9)	37.4 (1.8)	36.7 (36.1 – 38.2)	0.268[b]
12 hours after delivery	32.5 (3.7)	32.4 (29.6 – 35.8)	32.3 (2.7)	32.7 (30.3 – 34.5)	0.878[b]

SD, standard deviation; Med (P25-P75): median (percentile 25-percentile 75).
[a]The higher the score, the more readiness.
[b]Results of the Mann–Whitney U test.
[c]Results of the independent T-test.
[d]Number (percent).
[e]Results of Fisher's exact test.

Furthermore, another study has revealed the effect of saffron on treating primary dysmenorrhea (17). The main cause of primary dysmenorrhea is prostaglandins and their effect on uterine contractions and narrowing of the cervical canal (24). Therefore, it is possible that saffron may improve primary dysmenorrhea and readiness of the cervix in term-pregnant women with similar mechanisms, i.e., cervical ripening, but further lab investigations and clinical trials are needed for additional support.

A review study by Gulmezoglu et al. (1) showed that cervical ripening before labor induction leads to shorter latent and active phases. Although the results of the present study showed shortening of the first and second phases of labor in the saffron group, the difference was not significant. This may be related to the small sample size in this study.

A major concern about using misoprostol and oxy-tocin for labor induction is extreme uterine contractions, and increased risk of the need for cesarean section as well as other side effects for the mother and the fetus (26-28). No abnormal uterine contractions occurred in the present study and the need for cesarean section and meconium staining were reduced, although the reductions were not statistically significant.

Furthermore, another major concern about medicinally intervening is the possibility of adverse side effects. Bollapragada et al. (26) used isosorbide mononitrate for labor induction in outpatients, of whom 66% complained of headache with different intensities, while there were no reports of similar such side effects in the present study. Another study that utilized saffron tablets for therapeutic and research purposes at higher doses than were used in the present study did not report a significant effect in clinical parameters or the occurrence of any side effects (17, 29).

Table 3. Scores of Bishop's Components at Different Time Points for Each Study Group[a]

Bishop's components	Saffron (n = 25[b])			Placebo (n = 25[b])			P value[c]
	0	1	2 or 3	0	1	2 or 3	
Dilatation (0 - 3)							
10 - 12 hours after intervention	23 (92)	2 (8)	0	24 (100)	0	0	0.161
20 - 24 hours after intervention	15 (60)	8 (32)	2 (8)	15 (65)	6 (26)	2 (9)	0.754
Just after starting uterine contractions	1 (4)	22 (88)	2 (8)	2 (8)	16 (67)	6 (25)	0.309
Effacement (0 - 3)							
10 - 12 hours after intervention	19 (79)	5 (21)	0	24 (100)	0	0	0.019
20 - 24 hours after intervention	8 (32)	15 (60)	2 (8)	16 (70)	5 (22)	2 (8)	0.023
Just after starting uterine contractions	1 (4)	14 (56)	10 (40)	2 (8)	15 (63)	7 (29)	0.368
Station (0 - 3)							
10 - 12 hours after intervention	24 (100)	0	0	24 (100)	0	0	1.000
20 - 24 hours after intervention	23 (92)	0	2 (8)	21 (91)	1 (4)	1 (4)	0.966
Just after starting uterine contractions	9 (36)	16 (64)	0	19 (79)	5 (21)	0	0.003
Consistency (0 - 2)							
10 - 12 hours after intervention	21 (91)	2 (9)	0	24 (100)	0	0	0.144
20 - 24 hours after intervention	13 (52)	12 (48)	0	18 (78)	5 (22)	0	0.060
Just after starting uterine contractions	1 (4)	23 (92)	1 (4)	8 (33)	16 (67)	0	0.006
Position (0 - 2)							
10 - 12 hours after intervention	22 (96)	1 (4)	0	24 (100)	0	0	0.307
20 - 24 hours after intervention	13 (52)	12 (48)	0	18 (78)	5 (22)	0	0.060
Just after starting uterine contractions	12 (48)	13 (52)	0	14 (58)	10 (42)	0	0.473

[a] Data indicates number (percent).
[b] In 2 participants from the intervention group and 1 person from the control group who did not report for the 10-12 hour follow-up, the dilatation and station at the baseline and at 20-24 hours were the same, so the same score was considered for the 10 - 12 hour assessment score. In the control group, 1 person who had a cesarean section at 13 hours after intervention due to meconium staining of the fetus, and 1 person who did not report for the 10 - 12 and 20 - 24 hour follow-ups were omitted from the analysis. For 2 participants from the intervention group and 1 from the control group who delivered before 20 hours after intervention, the maximum Bishop's score was considered for the 20-24 hour score after intervention.
[c] Results of the Mann–Whitney U test for comparison of the two groups.

Performing outpatient interventions and having patients take the tablets themselves is a strength of this intervention. In their review study, Kelly et al. concluded that there is little available data on the efficacy or potential risks of labor induction in outpatients, so it is not possible to determine the applicability and safety of such labor induction at this particular time (30). On the contrary, Dowswell et al. (31) revealed in their review study that some medications and forms of acupuncture were safe to use for cervical ripening in low-risk pregnant women.

Because there were no interventional studies on the effect of saffron in pregnant women and considering its possible maternal and fetal side effects, the intervention was performed for a short time and at low doses in low-risk full-term women. Therefore, the results cannot be generalized for labor induction in other situations, particularly in post-

term and high-risk pregnancies. Moreover, further studies are required to determine the optimal dose, the most effective route of administration, and the optimal duration of performing such an intervention for cervical ripening and labor induction. Moreover, it will be useful to investigate the effect of this method along with other conventional methods of labor induction.

5.1. Conclusions

Given the results of the present study, it seems that oral saffron is effective for the cervical ripening of full-term pregnant women. Although the number of cesarean sections and the amount of meconium staining were lower in the saffron recipients, the difference was not significant. However, the study limitations, including the sample size, do not allow for any definite conclusion for the use of saf-

fron in clinical practice, and more research is needed to assess its effect on delivery and neonatal outcomes and its potential side effects.

Acknowledgments

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Footnote

Authors' Contribution: Roghaieh Sadi designed protocol, administered the intervention, collected the data, and prepared drafts of the manuscript. Sakineh Mohammad-Alizadeh-Charandabi and Mojgan Mirghafourvand designed and supervised the study, performed the statistical analyses, and read the drafts critically. Yousef Javadzadeh prepared the drug and its placebo. Afkham Ahmadi-Bonabi examined all participants, and confirmed their eligibility before their recruitment into the study. All authors read and approved the final version of the manuscript.

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