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Effect of Crocus sativus (Saffron) on Cervical Ripening and Progress of Labor in Primiparous Term Women: A Randomized Double-Blind Placebo-Controlled Trial

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Abstract

Background: Saffron is a perennial plant native to Iran which has been traditionally prescribed to facilitate labor. We aimed to investigate the effect of *Crocus sativus* (Saffron) on cervical ripening and progress of labor in a sample of primiparous term Iranian women.

Materials and Methods: This randomized double-blinded study, was conducted on 60 primiparous women whose gestational age was 40 weeks or longer and who had referred to Hazrat Zahra Marzieh hospital in Isfahan, Iran. Inclusion criteria were: singleton pregnancy, cephalic presentation of the fetus, lack of uterine contractions, intact amniotic sac and having a low-risk pregnancy. The intervention (n=30), and control groups (n=30) respectively received one saffron capsule (250 mg, the content of total flavonoid in each saffron capsule was calculated 0.13-0.18 mg), and one placebo capsule for 3 consecutive nights. Bishop scores of the samples were recorded before and after the intervention.

Results: The mean Bishop score before inclusion in the study did not show significant difference between two groups (P>0.05). However, on third day of study, this score in saffron group was higher than the placebo (Saffron: 3.93±1.10 vs. placebo: 2.52±1.57) (P=0.001). Further, the mean Bishop score in saffron group was higher on third day of study compared to before their inclusion in the study (before: 2.42±1.19 vs after: 3.93±1.10) (P=0.001). But the placebo group did not show a significant difference before and after inclusion in the study (P=0.16). The average length of first and second stages of labor in saffron group was shorter than in the placebo (P>0.05).

Conclusion: It seems consumption of oral saffron capsules, affects cervical softening and ripening, and progress of labor.

Key Words: Cervical Ripening, Obstetric labor, Saffron.

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1- INTRODUCTION

Labor induction is common in the provision of healthcare for pregnant mothers (1). This is the artificial start of labor before its spontaneous onset, aimed to accomplish the safe delivery of the placenta and the baby (2). Cervical readiness is effective in a successful induction (3). That is why cervical readiness has attracted special attention (4). Cervical changes to prepare for labor include soft tissue alterations commonly known as cervical ripening and are considered one of the main stages of the onset of delivery (4). To measure the level of ripening or readiness of the cervix, Bishop Score can be used, which is obtained by vaginal examination.

In this scoring system, the position and consistency of the cervix, the position of the fetal head (station), the cervical effacement and dilation are used for grading. In Bishop's scores above 4, the probability of induction's success is higher and the chance of cesarean section is lower (5). In post-term pregnancies, some interventions are accomplished before the desirable ripening of the cervix. In these interventions, the uterus is prepared to respond better to the induction of labor. In case the desirable ripening is not achieved it may cause unfavorable outcomes such as prolonged delivery, cesarean section, and postpartum hemorrhage.

If the cervix is ready and suitable, labor induction is usually performed using oxytocin or via artificial rupture of extra-embryonic membranes; but if the cervix is in an undesirable condition, Prostaglandin gel or tablet is inserted into the vagina or the cervix to help ripen the cervix and then, uterine contractions begin (3). The experience of recent decades shows that chemical drugs, with all their effectiveness, have side effects. Also, people's awareness of the healing properties of medicinal plants and traditional medicine is increasing (6, 7). Today, people are more interested in taking herbal medicines which may arise from women's concern about the side-effects of chemical medications on the fetus (8). Previous studies have indicated the effect of some nonmedical products such as *Matricaria recutita*, *Sisymbrium consumption*, and *Peganeum harmala* smoke on the onset or progress of labor (9). *Crocus sativus*, commonly known as "saffron" is a species of flowering plant in the Iridaceae family and has long been used as a spice with pharmacological activity in many cultures.

The medicinal parts of this plant include the three-branched stigma and the distal end of a carpel (style). Crocin, crocetin, and safranal are the main active constituents in saffron (10). This plant has been used as an herbal medicine for many years and has been used in cooking as a spice, coloring, and flavoring. Common places of cultivation for this plant are Turkey, Central Asia, Iran, India, China, Algeria, and parts of Europe. Iranian saffron is cultivated in South Khorasan province (11). In the sources of traditional medicine, the benefits of saffron are mentioned. Avicenna has pointed out several advantages of saffron such as its antidepressant, hypnotic, anti-inflammatory, hepatoprotective, and Bronchodilator properties along with induction of menstruation and labor (12).

Likewise, in traditional Chinese medicine, saffron had applications in the treatment of amenorrhea, menorrhagia, and high-risk pregnancies (10). According to evidence from modern pharmacological studies, bioactive compounds of saffron reduce or prevent the occurrence of some health problems like cardiovascular diseases, gastric problems, insulin resistance, premenstrual syndrome, depression, anxiety, and insomnia (13). A case-control study concerning the effect of saffron on the occurrence of miscarriage investigated a group of female workers on saffron

farms along with a control group and indicated that miscarriage rate was significantly higher among women who had contact with saffron compared to the control group (14). Prescription of saffron for pregnant rats also stimulated their uterine contractions that led to preterm labor and birth (15, 16). Generally, based on the scientific literature we can conclude that one of the most important effects of saffron is its potent oxytocic activity which traditionally has made it a useful herb to be prescribed for facilitated labor (11). Based on the previous literature, the effect of this herb to end unwanted pregnancy and abortion has been reported (17). Also, it has traditionally been used to induce labor in some areas of Iran by mothers. Accordingly, the current research aimed to investigate the effect of saffron on cervical ripening and the progress of labor in a sample of Iranian primiparous term women.

2- MATERIALS AND METHODS

2-1. Study design and population

This randomized double-blind placebo-controlled, parallel-group trial was conducted from August 2016 to February 2017. Study participants were primiparous term women whose gestational age was 40 weeks or longer and who had referred to Hazrat Zahra Marzieh hospital in Isfahan, Iran. The sample size was specified based on a statistical formula that is mentioned below:

For calculating the means difference considering α=0.05 and β= 0.20, the observed effect size was 0.70 and with a statistical test power of 0.80, by which 30 subjects were assigned to either intervention or placebo group.

$$n \geq 2\frac{\left(z_{\alpha/2}+z_{\beta}\right)^2\sigma^2}{\left(\mu_1-\mu_2\right)^2}$$

Sampling was accomplished by conven ience sampling for 7 months from among the qualified people with inclusion criteria and then, after getting the participants' informed written consent, the random allocation was performed in both groups using random number generator in Excel software. We used simple randomization and we assigned subjects to two groups A and B randomly for every assignment. In this method, we have a list of two groups A and B in column1, and then we inserted a new column next to the list of two groups (intervention, control groups) that we want to randomize.

In the first cell of the inserted column, enter the RAND formula: =RAND (18), and copy the formula down the column. In the last step, we sorted the column filled with random numbers in ascending order. Each sample received a packet of drugs to her inclusion in each group. The packets were numbered to 60 and contained saffron or placebo capsules and were placed on the physician's desk and the samples were selected and the packets were picked randomly. The numbers were random so that some numbers were assigned to saffron users and some to the placebo users. The physician, researcher, and the mothers were not informed about the type of the drug or placebo in each packet. The packets were supplied by the same pharmaceutical company that had produced the saffron and placebo capsules.

2-2. Measuring tools

The questionnaires of the study included: **1**. Patient demographic information form including 6 items: age, level of education, occupation, spouse's education, spouse's occupation, and monthly income. **2**. Obstetric patient record with 7 items: pregnancy rate, the first day of the last menstrual cycle, gestational age based on the first day of the last menstrual cycle, gestational age based on the ultrasound in the first trimester, presence or absence of pregnancy care, if the answer is positive, how many times, and pregnancy category (wanted or unwanted). **3**. A form for

Bishop Scoring system with 8 items: date and time of the patient's referral, dilatation, effacement, fetal station (-3 to +3), cervical consistency, cervical position and Bishop Score of the cervix before inclusion in the study as well as when the mother was admitted in the maternity ward. **4**. Daily drug record form (days 1, 2, 3, 4, 5, and 6. with 8 items: date and time of administration of saffron capsule, the symptoms after taking the saffron capsule, the number of fetal movements after each main meal, contraction, contraction intervals (minutes), number of contractions within 30 minutes, spotting and amniotic fluid leakage.

5. Follow-up form with 28 items: date and time of admission to the maternity ward, the cause for referral, vital signs, fetal heart rate, vaginal examination (Bishop Score): the time of attendance in the maternity ward, amniotic sac status, date and time of the rupture of amniotic sac, hemorrhage, contraction records after entering the maternity ward, duration of the first and second stages of labor (minutes), delivery method, application of oxytocin, Apgar Score, the newborn's weight and gender, amniotic fluid contaminated with meconium, need for analgesics, pain relief methods, uterine contractions within the first hour after delivery, the degree of maternal hemorrhage during the first hour after delivery, perineal status during the second stage of labor, the research sample's view about the effect of saffron capsule, the effect of saffron capsule on commencement of labor, the research sample's consent on application of this method in her next deliveries, obstetric complications and problems during administration of capsules, and **6**. A form for labor process: This form was prepared based on a review of literature using Partograph form provided by Ministry of Health of Islamic Republic of Iran. Bishop Scoring system has been used in various studies in Iran (6, 19, 20). To validate the forms for demographic information, obstetric information, daily records, and follow-up, the content validity method was applied. Therefore, after a review of several books and articles and identification of the intervening variables, these forms were developed and reviewed by 10 respective professionals. Taking the technical vocabularies into consideration, their validities were verified. Reliability was not needed for these forms. The reliability of the Labor process form that was a checklist was verified using a reliability assessment among the evaluators, midwives working in the maternity ward, and the researcher.

2-3. Intervention

Saffron plants used in the formulation were supplied by herbal raw materials stock of Goldaru Pharmaceutical Company. To produce the capsules in Goldaru Pharmaceutical Company, 50 g of weighted pure saffron was powdered by a blade grinder and extracted (macerated) with alcohol 70% with a ratio of 5:1 (solvent to herbal powder ratio) for 72 hours. Then, the extract was condensed in a vacuum to full alcohol evaporation using a distiller. The condensed extract was fully dried at 40 °C. Next, the dried extract was powdered. To smooth and soften the resulting powder, it was mixed with 105 g of excipient and 0.52 g of magnesium stearate in an electric mixer. The resulting granules were inserted in a laboratory capsule filling machine and finally, 250 mg capsules were prepared. To eliminate bias for the control group, a placebo containing 250 mg of lactose powder was prepared. The standardization of capsules was carried out based on the total flavonoid content using spectrophotometry measurement. This highly precise method is also applied to determine saffron content in the products of Goldaru Co. (capsules and drops of aphrodite, menstrogen capsule). The content of the total flavonoid

in each saffron capsule was calculated 0.13-0.18 mg). Saffron and placebo were put into a similar capsule so that they were not different in their appearance in terms of size, color, and odor. Before starting the intervention, the Bishop score for all samples was calculated by the physician and the scores were assigned before the intervention. Each group of women with a gestational age of 40 weeks or longer whose pregnancies had exceeded their due date received a packet containing 3 saffron or placebo capsules along with directions for use and a sheet to record drug use at home. The capsules were taken by the mothers once a day for three days.

If no incidence requiring hospitalization was reported by the participants, each mother would be asked to refer to the maternity ward in the selected hospital after taking the capsules for 3 days to be examined by the physician, and finally, Bishop Score was calculated. If Bishop Score was not adequate, capsules had to be taken for 3 more days; however, none of the samples needed a second round of prescription. Both groups of saffron and placebo users received similar healthcare services in the maternity ward and all maternal and fetal care services during labor were recorded. Patient demographic information form, obstetric patient form, and follow-up form were completed based on the patient's medical record and during the labor.

2-4. Ethical consideration

Current research with a code of ethics IR.SBMU.RAM.REC.1395.53 was registered at the Ethics Committee of Shahid Beheshti University of Medical Sciences and in Iranian Registry of Clinical Trials with registration code IRCT201603243860N24.

2-5. Inclusion and exclusion criteria

Inclusion criteria were as follows: primiparous women aged 18-35, singleton pregnancy, cephalic presentation of the fetus, gestational age of full 40-41 weeks based on the first day of the woman's last menstrual cycle and the pregnancy ultrasound for the first trimester, lack of uterine contractions, a Bishop score lower than or equal to 4, an intact amniotic sac, a normal fetal heart rate, a normal non-stress test (NST), an estimated fetal weight of 2500-4000 g, having a low-risk pregnancy (lack of internal diseases or recognized surgery or pregnancy complications such as preeclampsia and placental abruption and lack of recognized fetal problems) which was detected based on the absence of risk symptoms and reports in the prenatal care record and admission report consisting of any risky symptoms like bleeding, lack of narrow pelvic outlet and not being under herbal therapy or taking any other medication before the intervention. Exclusion criteria included abnormal fetal heart rate, lack of fetal movement, and high-risk pregnancy (such as some obstetric issues needing emergency actions like severe bleeding).

2-6. Data Analyses

Data were analyzed using SPSS (version 18, SPSS Inc., Chicago, IL). Data normality was measured by the Kolmogorov-Smirnov test, and parametric tests were used if the normality condition was met and if not, nonparametric tests were used. Data were analyzed by Independent and Paired t-test, Chi-square, Mann-Whitney, Fisher's exact test. The significance level of all tests was considered 0.05.

3- RESULTS

The participants' inclusion and exclusion processes are presented in **Figure.1**. In placebo group one woman due to unusual increased Fetal Movement, and in Saffron group 3 women due to weakness, lethargy and erythema (n=1) and palpitations and nausea (n=2) were excluded. Demographic characteristics of study participants are mentioned in

Table.1. Chi-square test demonstrated that frequency of walking, use of castor oil, sexual intercourse and oral administration of misoprostol before delivery was not significantly different between the two groups (P>0.05). Fisher's exact test indicated that frequency of saffron nectar intake before delivery did not show a significant difference between the two groups (P> 0.05). Chi-square test suggested that frequency distribution for cause of referral to hospital was not significantly different between the two groups (P>0.05). Chi-square test also indicated that frequency distributions for delivery category and cause of cesarean section were not significantly different between the two groups (P>0.05).

Table-1: Baseline characteristics of study participants.

Variables		Saffron group	Placebo groups	P- value	Test statistics
		Mean ± SD	Mean ± SD		
Maternal age		26.60±3.71	26.71±3.30	0.97*	t=0.04
Gestational age (Week based on LMP)		40.70±0.92	40.59±1.01	0.78*	t=0.29
Gestational age (Week based on first trimester sonography)		40.90±1.17	41.02±0.69	0.64*	t=0.46
		Frequency (%)	Frequency (%)		
Mother's job	Work from home	4(13.3)	1(3.3)	0.27**	X^2=2.59
	Housewife	24(80)	25(83.3)		
	Employee	2(6.7)	4(13.4)		
Spouses' jobs	Unemployed	2(6.7)	1(3.3)	0.66**	X^2=1.57
	Worker	7(23.3)	7(23.3)		
	Self employed	13(43.3)	17(56.7)		
	Employee	8(26.7)	5(16.7)		
Mother's educational level	Primary school	1(3.3)	1(3.3)	0.33***	Z= 0.98
	Middle school	3(10)	2(6.7)		
	High school	8(26.7)	14(46.7)		
	University education	18(60)	13(43.3)		
Spouses' educational level	Primary school	3(10)	2(6.7)	0.13***	Z= 1.51
	Middle school	3(10)	7(23.3)		
	High school	12(40)	14(46.7)		
	University education	12(40)	7(23.3)		
Family monthly income	Less than enough	6(20)	6(20.7)	0.51***	Z= 0.66
	Enough	22(73.3)	24(80)		
	More than enough	2(6.7)	0(0)		

*Independent t-test. **Chi-square test. ***Mann-Whitney test. SD: Standard deviation.

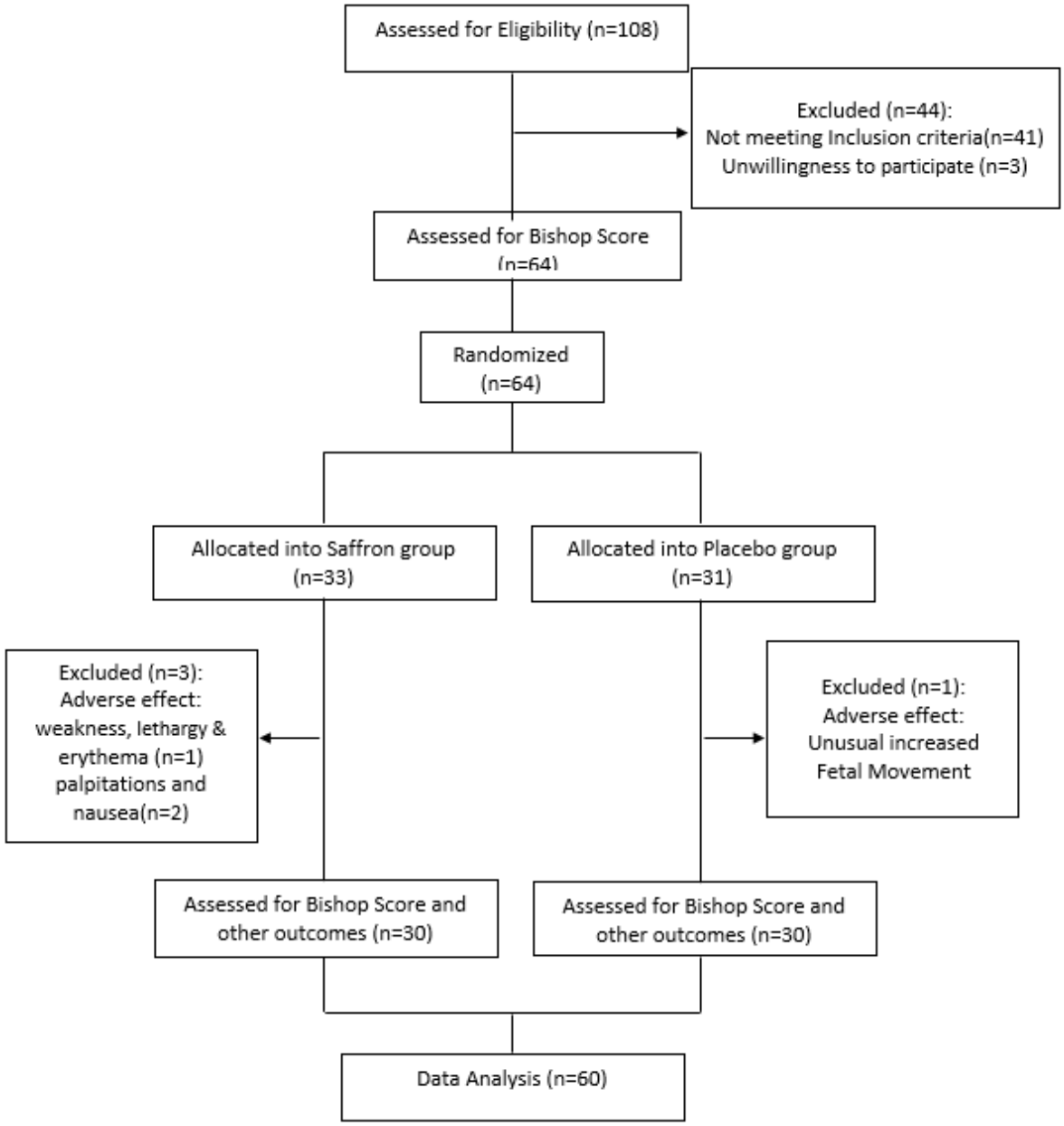

Fig.1: Study Flowchart.

The average Bishop Scores before and after inclusion in the study in both saffron and placebo groups are presented in **Table.2**. The average length of each stage of labor (minutes) in saffron and placebo groups is given in **Table.3**. Independent t-test indicated that the average duration for administration of oxytocin in saffron group was significantly lower than in the placebo group ($P<0.05$). However, the average Apgar score at 1 and 5 minutes after birth was not significantly different between the two groups ($P>0.05$). Fisher's exact test demonstrated that maternal hemorrhage within the first hour after delivery among saffron users was significantly less than among placebo users ($P<0.05$). Chi-square test indicated that frequency distribution of perineal status in the second stage of labor was not significantly different between the two groups ($P>0.05$). Considering the side-effects of the administered medication, one

participant in the intervention group reported weakness, lethargy and redness in face and other organs. Two other participants also experienced heart beat and nausea; in the control group, one participant reported a sharp increase in fetal movements and was excluded from the study.

Table-2: The average Bishop Scores before and after inclusion in the study in both saffron and placebo groups.

Time	Saffron group	Placebo groups	P-value*	T-test
	Mean ± SD	Mean ± SD		
Before inclusion in the study	2.42±1.19	2.30±1.33	0.33	1
3 days after inclusion in the study	3.93±1.10	2.52±1.57	0.001	3.55
T-test	5.91	1.60		
P-value**	<0.001	0.16		

* Independent T Test. ** Paired T Test, SD: Standard deviation.

Table-3: The average length of each stage of labor (minutes) in saffron and placebo groups.

Stages	Saffron group	Placebo groups	P-value*	T-test.
	Mean ± SD	Mean ± SD		
First Stage	206.49±89.60	275.73±125.44	0.03	2.20
Second Stage	27.17±17.28	38.05±12.51	0.02	2.34
Third Stage	4.04±2.69	4.23±1.24	0.87	0.16

* Independent T-test, SD: Standard deviation..

4- DISCUSSION

The present study investigated the effect of Crocus sativus (Saffron) on cervical ripening and progress of labor in primiparous term women. According to the findings of the present study, the average Bishop Score before inclusion in the study did not show a significant difference between the two groups (P> 0.05), but on the third day of study, this score in the saffron group was higher than in the placebo group (P<0.05). The average Bishop Score on the third day of study in the saffron group was higher than before their inclusion in the study (P<0.05), but no significant difference was found between these two dates in the placebo group (P>0.05). In line with this finding, an interventional study on pregnant women at their gestational age of 39 to 41 weeks whose Bishop Score was less than 4, prescription of 3 saffron tablets (250 mg) for 24 hours (every 8 hours) for the intervention group and the same amount of placebo for the control group indicated that Bishop Scores within 20-24 hours after the intervention and at the time of commencement of uterine contractions in the saffron group were higher than in the placebo group (21). Therefore, despite the different methodologies applied in that study compared to our study, the results of both studies consistently suggest the positive effect of saffron on cervical readiness for delivery. Regarding different methods of administration between current study and the mentioned study in (21), further studies, are needed to investigate recommended administration method based on effects and side effects. The present study demonstrated that the average duration of delivery in the first and second stages of labor in the saffron group was shorter than in the placebo (P<0.05), but the average duration in the

third stage of labor did not show a significant difference between the two groups (P>0.05). The average duration of administration of oxytocin in the saffron group was shorter than in the placebo group (P<0.05). In a study on the effect of honey saffron syrup on the progress of labor, results showed that honey saffron syrup shortens the duration of the first stage (22). The findings of that research are consistent with the present study. The results of another study aimed at investigating the effect of Saffron with or without date sugar showed that it is effective in reducing pain intensity and duration of the active phase (23).

The findings are consistent with the present study. This plant has long been prescribed in difficult labors due to its strong oxytocic effects (11). As it has been applied for high risk and difficult labors in traditional Chinese medicine (10), traditional medicine books have pointed to its inducing effect on uterine smooth muscle tissues (21). Concerning the effect of saffron on a pregnant uterus a study under the title "Increased miscarriage rate in female farmers working in Saffron fields" demonstrated that miscarriage rate among women working on saffron farms was significantly higher than among the control group (14). The effect of doses above 10 grams of saffron on the induction of abortion was proven. However, this study showed that milder exposure and even frequent exposure to saffron particles may cause miscarriage. Saffron also led to pre-term delivery through inducing uterine contractions in pregnant rats (15, 16).

In the study with brewed saffron, the length of pregnancy and number of babies showed a significant decrease in saffron-user rats compared to the control group which was likely due to abortion or fetal resorption (16). A study suggested that saffron hydroalcoholic extract caused an increased rhythmic uterine contraction in laboratory rats and could induce early uterine contractions during pregnancy (24). Also, the anti-anxiety and hypnotic effects of saffron water extract and its compounds, crossing, and safranal, have already been proven. For example, a reduction in metabolic and behavioral stress symptoms has been reported after the administration of saffron water extract in male rats (10). As we know, fear and anxiety during childbirth cause muscle stiffness and increase the sensitivity to pain, and initiate the vicious cycle of pain, fear, and muscle stiffness, and as a result, the lack of progress of the labor (25).

Therefore, we can suggest that the anti-anxiety effects of saffron may not be ineffective in improving the progress of labor -as a stressful process. Summing up the aforementioned effects of saffron on the occurrence of abortion, pre-term delivery, and cervical readiness, saffron may affect these as a progesterone antagonist because the reduction of progesterone level is one of the causes of miscarriage during the first trimester. On the other hand, progesterone antagonists such as mifepristone contribute to the process of cervical ripening at the end of pregnancy (21). In our study, we met some kinds of side effects in the saffron group such as lethargy and redness in the face and other organs, heartbeat, and nausea. However, prior similar studies had not reported such side-effects (21).

The strengths of the current study were that the samples and the researcher were uninformed about the contents of drug packets and consequently it was a double-blind research and its intervening variables were controlled by the inclusion criteria and statistical tests. Short-term interventions and dosage of saffron capsules were the limitations of present work. Therefore, it is suggested that future comparative studies focus on different doses of medication and compare the saffron effect with other methods effective in cervical readiness.

5- CONCLUSION

Consumption of oral saffron capsules for 3 days before delivery (250 mg per day, with the content of total flavonoid in each saffron capsule calculated as 0.13-0.18 mg), affects cervical softening and ripening and progress of labor. In general, the results of current work suggest the effective role of saffron capsules in speeding up cervical ripening, stimulation and intensification of uterine contractions, facilitation of labor, and lower use of oxytocin.

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7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. Hall HG, McKenna LG, Griffiths DL. Complementary and alternative medicine for induction of labour. Women and Birth. 2012;25(3):142-8.

2. Baloch R, Jabeen N, Zahiruddin S, Mawani MK. Induction of labor; efficacy and safety of intravaginal rostaglandin E2 pessary. Professional Med J. 2017;24(2):288-92.

3. Gulmezoglu AM, Crowther CA, Middleton P, Heatley E. Induction of labour for improving birth outcomes for women at or beyond term. The Cochrane database of systematic reviews. 2012(6):Cd004945.

4. Cunningham F, Leveno K, Bloom S, Hauth J, Rouse D, C. S. Williams obstetrics. 23 ed. New York: McGrow-Hill Medical; 2010.

5. Naghizadeh S, Fathnezhad Kazemi A, Hemmatzadeh S, Ebrahimpour M. The relationship between the Bishops score at admission and deliver outcomes in nulliparous women in 29 Bahman hospital, Tabriz. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2016;19(6):11-21.

6. Zahrani ST, Dasumi S, Tansaz M, Akbarzadeh AJMHJ. The effects of peganeum Harmala Smoke cervical ripening, initiation and outcome of labor. 2016;8(27):151-77.

7. Hossain A, Rahman MJ. Safety, Nutrition and Functionality of the Traditional Foods. Traditional Foods: Springer; 2019. pp. 219-38.

8. Louik C, Gardiner P, Kelley K, Mitchell AA. Use of herbal treatments in pregnancy. American journal of obstetrics and gynecology. 2010;202(5):439.e1-.e10.

9. Ghasemi V, Rashidi Fakari F, Ebadi A, Ozgoli G, Kariman N, Saei Gharenaz M. Effective interventions for the induction of labor: A systematic review. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2018;21(1):90-104.

10. Al-Snafi AE. The pharmacology of Crocus sativus-A review. IOSR Journal of Pharmacy. 2016;6(6):8-38.

11. Javadi B, Sahebkar A, Emami SA. A survey on saffron in major Islamic traditional medicine books. Iran J Basic Med Sci. 2013;16(1):1-11.

12. Hosseinzadeh H, Nassiri-Asl M. Avicenna's (Ibn Sina) the canon of medicine and saffron (Crocus sativus): a review. Phytotherapy Research. 2013;27(4):475-83.

13. Melnyk JP, Wang S, Marcone MF. Chemical and biological properties of the world's most expensive spice: Saffron. Food Research International. 2010;43(8):1981-89.

14. Ajam M, Reyhani T, Roshanravan V, Zare Z. Increased Miscarriage Rate in Female

Farmers Working in Saffron Fields: A Possible Effect of Saffron Toxicity. Asia Pacific Journal of Medical Toxicology. 2014;3(2):73-5.

15. Zeinali F, Anvari M, Dashti RMH, Hosseini SM. The effects of different concentrations of saffron (Crocus sativus) decoction on preterm delivery in mice. Planta Med. 2009;75(09):PI29.

16. Dashti-Rahmatabadi M, Nahangi H, Oveisi M, Anvari M. The Effect of Saffron Decoction Consumption on Pregnant Mice and Their Offspring. The Journal of Shahid Sadoughi University of Medical Sciences. 2012;19(6):831-7.

17. Tafazoli M, Kermani T, Saadatjoo A. Effects of saffron on abortion and its side effect on mice balb/c. Quarterly of Horizon of Medical Sciences. 2004;10(3):53-5.

18. Mélard GJCs. On the accuracy of statistical procedures in Microsoft Excel 2010. 2014;29(5):1095-128.

19. Heydari A, Nasiri F, Kariman N. Effect of topical magnesium sulfate in latent phase on Bishop Score and latent phase duration in primiparous women %J The Iranian Journal of Obstetrics, Gynecology and Infertility. 2020;23(2):42-9.

20. D'Souza RDJO, Gynecology. Bishop Score as a Measurement Instrument [30H]. 2019;133:92S.

21. Sadi R, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Javadzadeh Y, Ahmadi-Bonabi A. Effect of Saffron (Fan Hong Hua) On the Readiness of The Uterine Cervix In Term Pregnancy: A Placebo-Controlled Randomized Trial. Iranian Red Crescent Medical Journal. 2016;18(10): e27241.

22. Ghaderi S, Zaheri F, Nouri B, Shahoei RJJoPRI. The Effect of Honey Saffron Syrup on Labor Progression in Nulliparous Women. 2019:1-8.

23. Mohammadierad R, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Fazil F. Effect of Saffron with or Without Date Sugar on Intensity of Pain and Anxiety During Labor in Primiparous Females: A Randomized, Controlled Trial. 2018;20(S1): e61289.

24. Sadraei H, Ghannadi A, Takei-bavani M. Effects of Zataria multiflora and Carum carvi essential oils and hydroalcoholic extracts of Passiflora incarnata, Berberis integerrima and Crocus sativus on rat isolated uterus contractions. International Journal of Aromatherapy. 2003;13(2):121-7.

25. Azhari S, Ahmadi S, Rakhshandeh H, Jafarzadeh H, Mazlom SR. Evaluation of the Effect of Oral Saffron Capsules on Pain Intensity during the Active Phase of Labor. Journal of Obstetrics Gynecology and Infertility. 2014;17(115):1-10.