

## SAFFRON AND CHILDBIRTH; A TRIPLE BLIND CLINICAL TRIAL

((Recibido 05-06-2017. Aprobado el 07-09-2017))

### Sediqueh Ahmadi

*MSc. of Midwifery, Iranian Social Security Organization (Torbat-Heidarieh, Razi Hospital), a graduate of the University of Medical Sciences, Mashhad, Iran*

### Maryam Aradmehr

*MSc of Midwifery, Department of Midwifery, School of Nursing and Midwifery, Sabzevar University of Medical Sciences, Sabzevar, Iran.*

### Sediqueh Azhari

*Instructor of Midwifery. Evidence-base Care Research Center, School of Nursing, Mashhad University of Medical Science Iran.*

*E-mail: maryam.aradmehr@yahoo.com*

**Abstract.** Background and objective: For many women, childbirth remains to be the most painful experience of their life. Coping with pain and shortening the course of childbirth are among the important aspects of healthcare. In Traditional Medicine, the pain-relief effects of saffron have been reported to facilitate childbirth. Therefore, the present study aimed to determine the effect of oral consumption of saffron on the severity of pain, anxiety and the length of the first and second stages of labor. Material and methods: This triple blind clinical trial was conducted on 60 women at first childbirth who were qualified for the study at 17Shahrivar Hospital in Mashhad during 2013-2014. The study units were randomly selected using available sampling method who were assigned into two intervention groups; experimental (250 mg saffron capsule) and control (placebo capsules) groups. With the onset of the active phase of labor, one saffron capsule was received by the study unit. Pain severity and anxiety were measured at the beginning of the study and then for every hour until the end of the active phase of labor using visual analogue scale of pain severity. The active phase length of the first and second stages of labor were measured through a vaginal examination by the researcher. The dosage was repeated, if needed, every 2 hours and up to three dosages, taking into account the possible side effects. The data were analyzed using SPSS 11.5, and descriptive and analytical statistics. Findings: The mean score for total pain severity at the active phase of the first stage of labor was  $85.9 \pm 4$  for the group who received saffron capsule and  $97.4 \pm 2.9$  for the placebo group, indicating a significant difference ( $p < 0.001$ ). The mean score for the length of the active phase of the first stage of labor was shorter for the group who receive saffron capsules compared to the placebo ( $63.6 \pm 13.8$ ), which indicates a significant difference between the two groups ( $p = 0.002$ ). The mean score for the length of second stage of labor were  $34.8 \pm 17.6$  and  $64.3 \pm 23.6$  for the saffron group and the placebo, respectively, indicating a significant difference between the two groups ( $p = 0.000$ ). The mean score for anxiety was for the saffron group ( $26.16 \pm 1.4$ ) was less than that of the placebo group ( $43.18 \pm 9.8$ ) ( $p = 0.000$ ). In addition, the mean score for fatigue in saffron group ( $57.20 \pm 7.9$ ) was significantly less than that of the placebo group ( $p = 0.004$ ). No maternal and neonatal complications were observed in the study units.

Conclusion: Given to the significantly reduced pain severity and anxiety, and thereby the reduced length of active phase of the first and second stage of labor for the group who received saffron capsule with no subsequent complication, the saffron can be used as a mild pain killer facilitating the process of childbirth.

**Keywords:** Saffron, Labor Pain, Active Phase of Labor

## 1. INTRODUCCIÓN

Pain during labor and delivery as well as its long duration are one the most important factors leading pregnant woman to caesarean delivery, and the abnormal fear of labor pain have become a new reason for women to prefer cesarean delivery (1) which, in addition to maternal complications (e.g., infection, bleeding), anesthesia complication and neonatal complications, requires more specialized and costly care (2).

Severe pain on mother can exacerbates the fear and anxiety during labor, stimulates sympathetic nervous system, and increases the release of epinephrine, norepinephrine and cortisol and by inhibiting oxytocin secretion leads to slow down the course of labor, prolong the sever pain on mother and increase the fetal and neonatal complications (3-5). Secondary skeletal muscle contraction due to pain and fear can cause the reactive contraction in pelvic floor muscles and consequently leads to prolong the course of labor (6,7). By prolonging the course of labor, the mortality rate associated to the birth are increased to 3.5% and can cause the prevalence of endometritis, fetal distress, abnormal contractions in the womb and the increased risk of post-traumatic bleeding (2). This is the reason for the maternal mortality up to 8% in developing countries (8).

Coping with pain and shortening the course of labor, having the least complication for the mother and the fetus, are among the important aspects of health care. Nowadays, various pharmaceutical methods are used to relieve pain and shorten the course of labor, all of which are associated with morbidity and even mortality (9, 10, 11, 12 & 13). Therefore, the search for the medicine that, in addition to pain-relief effects and its effectiveness in the progression of labor, can cause joyful and sedative effects for the mother. This can be an ideal in the field of midwifery.

According to the current study conducted on medicinal herbs and its various uses in traditional medicine seems to be a good alternative in this regard. Saffron is among these plants which has been mentioned in traditional medicine facilitating the process of labor and has pain-relief properties (14). Avicenna, in his book "The Canon of Medicine" points out to saffron as a sedative and joyful medicine and states that saffron can be used orally for women who suffers from labor pain in order to facilitate and accelerate childbirth (15, 16). Rhazes has prescribed 2 Dirham (dosage) of

saffron for accelerating and facilitating labor in several cases (17). Aghili Alavi states that "One mithqal of saffron is effective in facilitating childbirth (18). Ibn al-Nafis describes saffron as a facilitator for childbirth (19).

In the past, saffron has been used to relieve cramp, menstrual disorders and has been used a sedative medicine, pain killer, sexual stimulation, antidepressants, anti-inflammation, childbirth facilitator, anti-bacterial and anti-cancer medicine in traditional medicine using herbs (15, 20-23). In today's study, many pharmaceutical applications of saffron have been investigated (i.e., Anti-Alzheimer (24), anticonvulsant (25, 26), anti-inflammatory (27, 29), anti-depressant (30 – 33), antioxidant (34 – 37), cancer treatment (38 – 41), improvement of premenstrual syndrome (42), dysmenorrhea (43, 44) and postpartum pain (45), Anti-anxiety (46 – 84) and pain killer properties (28, 29, 46, 49 & 51). In the study of Hosseinzadeh and Nuraei (2005) reported that the aqueous extract of saffron at low dosage has anti-anxiety properties and at high dosage can cause imbalance, muscle relaxation and drowsiness (46). Saffron and its active ingredients have numerous beneficial effects in the treatment of different types of neurological pain, both of them having pain-relief and hypnosis effect (46, 51). The possible mechanism of the analgesic effect of the aqueous extract is through the inhibition of releasing prostaglandins and the presence of anthocyanins and flavonoids (mainly crocin and crocetin) (52, 53), having an analgesic effect (54, 55). The saffron having anti-oxidant properties (flavonoids and carotenoids) and anti-inflammatory effects of anthocyanins, flavonoids, tannin and saponin, can be considered as a medicine with analgesic effect(54).

In the study of Agha Hosseini et al., (2008), saffron capsule of 30 mg was administered twice a day during menstrual cycles, which has been shown to reduce the symptoms of premenstrual syndrome (42). In the study of Zinli et al., (2009), different extracts of saffron were administered to pregnant female rats resulted in preterm delivery in rats due to the stimulation of uterine contractions (56). Fukui (2011) in his study on 35 women indicated that smelling saffron for 20 minutes, by reducing cortisol level and increasing 17-beta estradiol level, can be effective in the treatment of premenstrual syndrome, painful menstruation and irregular menstrual cycles (57).

The anti-spasmodic and muscle relaxant properties of saffron are described in traditional medicine (16) and the effects of saffron has been investigated in

today's various study (25, 26, 58 & 59). Hosseinzadeh et al., by examining the anti-anxiety and narcolepsy effect of the aqueous extract of saffron on rats, have argued that saffron, like diazepam, has an anti-anxiety, pain-relief and muscle relaxant properties (29, 47, 60, 61). Chang et al., (1964) in their study stated that different extract of saffron on rats and guinea pigs can induce estrogenic and stimulatory effects on uterine contractions (62) which seems to be involved in neurogenic and myogenic mechanisms (35, 85). Probably there are some substances in saffron that can increase the spontaneous contractions of the uterus (63).

Given to the valuable properties of saffron, the present study aimed to examine the effect of oral consumption of saffron on the course of labor, pain severity and the mother's anxiety.

## 2. MATERIAL AND METHODS

This study is a triple blind randomized clinical trial which was conducted in 2013-14 on pregnant women who were taken in labor condition to maternity department of "17 Shahrivar" Hospital in Mashhad and were also qualified for the research, was performed. The sample size based on the preliminary study was on 20 subjects, with a confidence level of 95% and test power of 80% and by using of means comparison formula, 30 patients in each group were determined.

$$N = \frac{(Z1 - \alpha / 2 + Z1 - \beta)^2 (S1^2 + S2^2)}{(m1 - m2)^2}$$

Standard Saffron which was purchased from "Mashhad Noovin Saffron" company, under the supervision of a consultant pharmacist, was prepared as capsules containing 250 mg of powder of dried saffron stigmas. Placebo capsules also contained 250 mg of inert material which was prepared under the supervision of a pharmacist.

Convenience was conducted from those who referred to the research unit when the researcher was present there. Assigning randomly the subjects into two groups "saffron and placebo capsules" was made by removing one of the two codes about each qualified visitor. The subjects were nulliparous women who had spontaneous uterine contractions and cervical dilatation with 3 to 4 cm, age of 18-35 years; body mass index of 19.5-30; gestational age of 37-42 weeks; having no history of pregnancy more than 20 weeks of gestation; singleton pregnancy; cervical dilatation of 3-4 cm; cephalic presentation. Exclusion criteria: using any herbal drug during the past 48 hours; addiction or using a variety of tobacco and

alcohol; maternal pregnancy complications (preeclampsia, bleeding during pregnancy, threat to abortion, premature rupture of fetus membranes more than 12 hours before admission), having or history of any systemic disease (diabetes, hypertension, heart and kidney disease, etc), history of mental disorder, speaking, hearing and mental disorder, disproportion of maternal pelvic with fetal head; estimated fetal weight less than 2500 g and more than 4000 g (according to Johnson rules); fetal heart rate abnormalities; any abnormalities in the fetus (based on sonography); obstetric problems; multiple pregnancy; previous surgery on the uterus; cervix and delivery canal; cesarean indication; allergic reaction to the saffron, the person was not taken part in this study.

Exclusion criteria during the research consisted of lapse from continuing research, signs of fetal distress (tachycardia, bradycardia, late or severe variable deceleration of fetal heart rate, meconium repel), disorder during delivery (based on labor partograph which is available in Ministry of Health), Hypertonic uterus, abruption of placenta, bleeding more than a sign of labor (show), the use of pain relief medication, the use of the medicine in the first stage of labor and the need to emergency cesarean.

The research tools used in the study included interview form, examination and observation, visual analogue scale of pain severity, visual analogue scale of anxiety, sonikde, chronometer, barometer (Mercury pressure gauge), tocodynamometer and medical thermometer.

To determine the validity of interview forms and forms of examination and observation (selection of samples, data from the examination of the vagina and pelvic, demographic, obstetric history, maternal care form first, second and third stage of labor, delivery and infant data) the content validity were used. So the forms were prepared after reading the latest books and articles, and then they were handed over to 10 members of Mashhad University of Medical Sciences and after their comments and amendment on them, they were used. Partograph labor form is a valid tool to monitor the progress of labor and it is approved by WHO. Reliability of interview forms and forms of examination and observation were determined by evaluators' agreement. Thus, in the preliminary (pilot) study on 10 subjects, forms completed separately at the same time by the investigator and the person who was in same level of science, and was confirmed with a correlation coefficient  $r = 0.83$ ,  $r = 0.87$ ,  $r = 0.91$ .

The validity and reliability of the visual analogue scale of pain severity and anxiety have been

confirmed in various studies. Azhari et al., (2012) have also confirmed the validity and reliability of the tool (64). In this research the reliability was determined with a reliability coefficient of  $r=0.81$ . The researcher started sampling after receiving written permission from the Ethics Committee of Mashhad university, No. 45/3/911184, written introduction letter from the Faculty of Nursing and Midwifery of Mashhad University and presenting them to the head of the hospital. After a brief explanation about the research and its methods to the mothers and the completion of the written consent form by the mother, the forms regarding to the Entry and Exit Criteria were completed by the researcher.

In order to determine pain severity before the intervention (the beginning of the active phase of the first stage of labor), visual analogue scale of pain severity was used. The forms related to the assessment of the anxiety level, fatigue and hunger were completed at the beginning of the study. The mother entered to the Labor room, the intravenous (IV) route of administration can be used for injections or infusions. Then, one saffron capsule (either saffron or placebo marked with the code) was administered orally by the researcher to the units of the study. Pain severity and anxiety were measured at the beginning of the study and then for every hour until the end of the active phase of labor using visual analogue scale of pain severity. The forms related to visual analogue scale for hunger, fatigue and anxiety were completed at intervals of 2 hours (from the reception to the end of the active phase of the first phase of the labor).

Uterine contractions pattern (intensity and frequency and duration of contractions), was determined and recorded in relevant form by tocodinamometer device which put every 30 minutes for 10 minutes on top of the uterus womb and also by touching the top of the uterus via hand . Vaginal examination to determine the length of active phase of labor, every 2 hours, and according to the requirements of every mother (duration and intensity of uterine contractions, etc.), was carried out by researcher. Maternal vital signs monitoring, fetal heart rate and uterine contractions also was performed by the researcher respectively, every one hour ,every 15 minutes, every 30 minutes, according to Health Ministry protocol in Mother-friendly hospitals(65). Given the pattern of uterine contractions (so that the contractions from active phase to 7 cm dilatation of uterus cervical, every 2 to 3 minutes, with 50- 60 seconds length, in 8 to 10 cm dilatation the contractions of uterus cervical every 2 to 3 minutes, with duration of 60 to 90 seconds to be maintained), the pattern of fetal heart

rate and the mother's vital signs, repetition of medicine dose , taking into account the possible side effects of the drug, and up to three doses were performed every 2 hours. The poor progress of labor (based on labor partograph), intervention was made based on the Ministry of Health protocol on mother-friendly hospitals, and research object was removed. In case of no well respond to non-pharmacological treatments to reduce pain and the need for reducing the pain by using of any of the medicinal pain reduction methods ,appropriate management was carried out and sample was excluded from the research. All information about the course of labor and delivery in the interview forms, examination and observation were completed and recorded by the researcher. The codes for placebo and saffron were only available to the drug manufacturer and the study units, the researcher and those who performed the statistical analysis were unaware of the codes. After completing the analysis, the codes for saffron capsules and the placebo were obtained from the manufacturer, and therefore a triple blind clinical trial was maintained.

Data using SPSS software version 11.5 was transferred to the computer. After ensuring the accuracy of data entry, analysis using descriptive statistics such as mean and standard deviation and analytical statistics included chi-square tests, t-test , manvitni, analysis of variance was made. To confirm normal distribution of the research quantitative variables, Kolmogroph- Smirnof and Shapiro Wilk test, was used. Confidence intervals was considered %95.

### 3. FINDINGS

The majority of participants (65%) ( $n = 39$ ), aged 18 to 25 years (mean age  $23/7 \pm 4/7$ ), secondary education (56/7%) ( $n =34$ ), housewives (98/3%) ( $n =59$ ) and urban (95%) ( $n =57$ ). Chi-square and T-tests showed that the two groups regarding these variables and job variables, body mass index, gestational age, number of prenatal care, the number of class attendance to prepare for labor, did not have significant differences and were homogeneous ( $P >0/05$ ). Also the two groups intervening variables at the beginning of the study (pre-intervention), such as pain, anxiety, fatigue, pattern of uterine contractions (duration, intensity and number of contractions), the situation and conditions of presenting part and fetus membranes ,were homogeneous ( $P >0/05$ ).

Other variables that might have been influenced the delivery process, such as the rupture of membranes, dilation and effacement of the cervix and fetal head station at the time of rupture of

membranes, duration of horizontal and upright positions of the mother, duration of massage and information about the baby also were examined in both groups and they were homogeneous ( $P > 0/05$ ) (table 1)

*Table 1. The mean and Standard deviation some quantitative variables During the active phase of labor According to saffron and placebo groups.*

Variable	Saffron group		Placebo group		Test
	±SD Mean	N	Mean ±SD	N	
Duration of horizontal positions during the active (Minutes in ) phase hour	18±6/0 /4	30	20/1±4/4	30	t-test t=1/2 df= 58 p= 0/237
Duration of Upright positions during the active phase (Minutes in hour)	41±5/1 /5	30	39/9±3/2	30	t-test t=1/4 df = 58 p= 0/281
Duration of massage (Minutes in hour)	13±4/5 /8	30	11/8±3/6	30	t-test t=1/8 df = 58 p= 0/066
Duration of acupressure (Minutes in hour)	9±2/9 9	30	10/6±3/8	30	t-test t=0/8 df = 58 p = 0/402

*Table 2. Mean and standard deviation for pain severity in two groups of saffron capsules and placebo*

variable	group				test
	Saffron capsules		placebo		
	Sd±M	N	Sd±M	N	
Pain severity before intervention	68.0±15.1	30	69.9±11.9	30	T -test t= -0.4 p= 0.64
Pain severity after intervention	85.9±8.4	30	97.4±2.9	30	T -test t= -0.1 p<0.001
Score difference of the pain severity before and after intervention	18.3±14.2	30	27.7±10.3	30	T -test t= -2.9 p= 0.00
Intragroup comparison	Paired T -test t=-6.3 p=0.000		Paired T -test t= -14.7 p=0.000		

The mean score for cervical dilatation rate and the mean score for the descent speed of Fetal Presenting Parts during the active phase of the first stage were significantly higher for the saffron group compared to the placebo ( $p=0.000$ ) (Table 3). In addition, the mean length of the active phase of the first stage of the labor in saffron group was shorter than that of the placebo ( $63.6±13.8$ ). According to the results of the independent t-test, there was a significant difference in terms of the

mean length of active phase between two groups ( $p=0.002$ ) (Table 3).

*Table 3. Mean score for cervical dilatation rate, the descent speed and the length of the active phase of the first stage for saffron and placebo groups*

	saffron		placebo		Test
	Sd±M	N	Sd±M	N	
Mean score for cervical dilatation rate (cm/h)	2.0±0.7	30	1.4±0.4	30	t-test t=3.8 df=58 p=0.000
the descent speed of Fetal Presenting Parts (cm/h)	1.4±0.4	30	0.7±0.2	30	Mann-Whitney Z=8.5/ P=0.000
the length of the active phase of the first stage (cm/h)	199.6±67.4	30	263.2±81.2	30	T-test T=-3.29 P=0.002

The mean score for the length of the second stage of the labor was  $34.8±17.6$  for saffron group and  $64.3±23.6$  for the placebo that according to Mann-Whitney test, there was a significant difference in terms of the variables between two groups.

*Table 4. Mean and standard deviation for the length of the second stage of the labor in saffron and placebo groups.*

Variable	Group				Test
	saffron		placebo		
	Sd±M	N	Sd±M	N	
Length of the second stage of the labor	34.8±17.6	30	64.3±23.6	30	Mann-Whitney Z=1.5/ P=0.000

The mean score for the anxiety in the saffron group was significantly less than the placebo ( $P<0.054$ ) (Table 5).

*Table 5. Comparison of mean and standard deviation for anxiety and fatigue before and after intervention in saffron and placebo groups*

variable	group				test
	saffron		placebo		
	$\bar{X} \pm SD$	N	$\bar{X} \pm SD$	N	
Anxiety before intervention	74.1±22.7	30	72.9±20.0	30	T-test t=0.22 P=0.824
Anxiety after intervention	26.4±16.7	30	46.5±18.9	30	T-test t=-4.32 P<0.001
Fatigue before intervention	38.8±26.9	30	45.6±32.4	30	T-test t=-0.88 P=0.382

Fatigue after intervention	60.6±21.7	30	72.7±24.8	30	T-test t=-1.97 P=0.054
----------------------------	-----------	----	-----------	----	------------------------------

There was no significant difference between the two groups in terms of the information associated to the infant. In both groups 2 infants (7.6%) needed to be resuscitated. Most of the research units in saffron groups (96.7%) and placebo (86.7%) had normal vaginal delivery. According to Fisher's exact test, there was no significant difference between two groups in terms of this variable ( $p=0.418$ ).

#### 4. DISCUSSION

In the present study aimed to determine to determine the effect of oral consumption of saffron on the severity of pain, anxiety and the length of the first and second stages of labor, it was observed that the mean score for pain severity of the labor and anxiety was significantly less than the placebo. In addition, the mean score for the length of the first and second stages of the labor in saffron group was significantly shorter compared to the placebo.

In animal studies, the analgesic effect of these components has been investigated, in a sense that Nasri et al., (2011) in their study conducted on the saffron and its components (crocin and safranal) indicated that two both the neurogenic and inflammatory phase of formalin test was affected and reduced by the alcoholic extract of saffron, and concluded that the ethanolic extract of saffron has the ability to inhibit the acute phase of pain due to formalin, and this effect is partly due to safranal. The prolonged stimulation of the pathways dependent on opioid receptors, glutamate NMDA receptor and nitric oxide are involved in inhibiting chronic and acute phase of pain. In addition, alcoholic extract, safranal and crocin were able to inhibit inflammation and also inhibited the second phase of formalin test, which is a completely inflammatory phase and is associated with inflammatory processes. Prostaglandin (anti-inflammatory) anti-inflammatory medicines are well able to inhibit this phase. Therefore, the researchers stated that the inhibition of inflammation and the pain caused by the second phase of formalin test using alcoholic extract and important components of saffron may be due to one of the reasons: the inhibition of the cyclooxygenase enzyme which is the main enzyme producing prostaglandin, and the effect of glucocorticoid hormones on the extract component and the stimulation for releasing hormones in the adrenal gland cortex (28).

Arbabiyani et al., (2009) in their study The effect of aqueous extract of saffron on the chronic pain induced by formalin test in female mice investigated the potential mechanisms of the extract in reducing chronic pain and stated that saffron is effective in reducing pain through inhibiting nitric oxide enzyme (66).

One of the mechanisms of saffron in reducing pain is associated to its antioxidant properties. Other components of saffron such as flavonoids and carotenoids, have an antioxidant effect and, by trapping free radicals (55), inhibit the production of prostaglandins (67). Among the variables that can affect the labor pain is the mother's anxiety. In the present study, the mean score for anxiety in saffron group was less than that of the placebo ( $p=0.000$ ). The fear and anxiety during labor can cause muscle stiffness and increased sensitivity to pain initiating the defective ring of pain, fear and muscle stiffness (69, 68).

Hosseinzadeh et al., (2009) in their study indicated that the aqueous extract of saffron reduced the level of anxiety in rats (46). The anti-spasmodic and muscle relaxant properties of saffron are expressed in traditional medicine books (16) and have been observed in various studies of the present day (59, 70, 71) and it is has been argued that the effect of saffron is much similar to that of diazepam, and like diazepam, as a benzodiazepine, has an anxiolytic, analgesic, and muscle relaxant effect (47, 61). In the present study, it was observed that the saffron can be effective in reducing anxiety and has the muscle relaxation effect can reduce the labor pain.

In a study conducted by Hosseinzadeh et al., (2009), dosage of 0.56 gram per kilograms of saffron increased the total sleep and indicated that the aqueous-alcoholic extract and safranal had hypnagogic and anti-anxiety effect (46). Tiran and et al., (2004) stated that aromatherapy can cause relaxation and sleep and increases the secretion of endorphins, thereby increasing the mother's ability to cope with painful stimuli (52). In the present study, this effect (hypnagogic) can be considered as one of the mechanisms involved in reducing labor pain.

The average duration of the active phase of labor in saffron consumer group was 63/7 minutes shorter than the placebo consumer group and on the basis of statistical analysis, the difference between the two groups was significant ( $p=0/002$ ). This result confirms the saffron facilitate effect which Abo Ali Sina was stated in the "Qanoon" book (16). "Zeinali" et al. (2009) in their study showed that administration of different saffron essences to pregnant mice, caused premature birth in mice

through stimulating uterine contractions(56). "Chang" et al(1964) stated in their study that different saffron essences on mice and Indian pigs induced estrogenic effects and had the stimulatory effect on uterine contractions that seemed neurological and myogenical mechanism to be involved (62). "Sadraee"" et al (2003) in their study concluded, saffron Hydro-alcoholic essence at a dose of 200-1600 micrograms / cc , increases spontaneous rhythmic contractions induced by potassium chloride in the isolated rat uterus. But does not affect the contractions induced by acetylcholine and stated that there may be substances in saffron, which can increase the spontaneous contractions of the uterus (63).

Stiffness in the pelvic floor muscles that is because of pain and fear, leads Disorder in fetal descent and rotation of fetus presenting part and it causes disruption to the progress of labor (7, 73). In this research , the saffron has been able to reduce labor pain and anxiety. Saffron may have been effective in shortening the active phase of labor by reducing the anxiety and labor pain.

As mentioned saffron was used in traditional medicine as an elimination of muscle cramp and in different studies, the effect of this plant on muscle relaxant is shown. In our study, according to the pattern of uterine contractions during labor, can be said that Saffron did not have muscle relaxant effect on the smooth muscle of the uterus, and due to the study Sadraee, saffron increases rhythmic contractions of the uterus(63). Saffron relaxant effect might be limited to skeletal muscle especially pelvic floor muscles and diminished the stiffness of these muscles . So probably Saffron has a relative relaxant effect on the above muscles as well as the effect which has on pain relief (75), leads to reduce stiffness pelvic floor muscles and by facilitating the descent trend of the fetus presenting part during labor, reduced the delivery period . As in this study, the average speed of descent of the fetus presenting part during the active phase of labor in saffron consumer group was significantly more than the group taking placebo. Reducing the length of the second stage of labor in the saffron consumption group in this study can also be confirmed this content. It was said that spasmolytic drugs also are effective in improving cervical spasm and facilitate uterus cervical dilatation during labor (76 , 77). In this study, the mean rate of uterus cervical dilatation during the active phase of labor in saffron consumer group was significantly more than the group taking placebo (p =0/000). This finding can be due to saffron relaxant effect on uterus cervical tissue and contributes to its dilatation, and also its

effect on uterine smooth muscle contractions and helps to improve the delivery process .

Saffron has been used in traditional as oral medicine for women who suffer from labor, to facilitate and accelerate the delivery (16- 12). The use of the word "facilitate" delivery, with literally meaning “facilitate”, probably refers to the pain of labor. The findings of this research are consistent with the contents of known traditional medicine books, including “Qanoon “and state the obvious effect of saffron in shortening the delivery process .

## CONCLUSION

According to the findings of the study, saffron seemed to be a good medicine in reducing pain severity and shortening the length of the labor without having complication on mother and fetus. it is recommended that more studies should be done with change in medicine dose, way of consumption and time of consumption to determine the mechanism effect of saffron and other effects. One of strength point in this research was triple blind clinical trial. The limitations of this study were: individual differences, genetic and psychological state of participants which have effect on their respond to questionnaires that are all out of researcher's full control .But we tried to eliminate these differences by randomization as much as possible.

## ACKNOWLEDGMENT

The study is the part of the approved master's thesis in Mashhad University of Medical Sciences under registration number 45/3/911184 and was registrated in Clinical Trials Registry Center under this registration number IRCT201205229830N1. Hereby I express my gratitude to honourable deputy minister of Mashhad University of Medical Sciences, Managing Director of Social Security Organization of Khorasan Razavi, obstetric department of Mashhad “17 Shahrivar Hospital “as well as Torbat-Heidariye Razi Hospital staff, Novin Saffron Mashhad company Managing Director, mothers who took part in this project and all those who we helped us to conduct this project.

## REFERENCES

Derenzo G. A new indication for cesarean delivery? Journal of Maternal-Fetal & Neonatal Medicine. 2003; 13(4): 217.

- Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Williams obstetrics. 23 ed. New York: McGraw-Hill 2014.
- Murray SH. Foundation of maternal newborn nursing. New York: St. Louis; 2002: 365-366.
- Tork Zahrani Sh, Honarjoo M, Jannesari Sh, Alavi Majd H. The effect of massage on intensity of pain during first stage of labor. J Shaheed Beheshti Univ Med Sci 2008;32 (2):141-5.(Persian)
- Keshavarz M, Dadgary A, Miri F. Evaluation of short form Maccgill pain questionnaire in nuliparouse women who referred to Fatemiye hospital. Knowledge Health 2007;2(2):34-7. (Persian).
- Simkin P, Ancheta R. The Labor Progress Handbook: Early Interventions to Prevent and Treat Dystocia. Translated by: Kodi M, Golmakani A, Seyed Alavi Gh. Mashhad University of Medical Sciences; 2005:100-15(Persian).
- Jabarzadeh Ganjeh S. The effect of intradermal injection of strilled water on the severity of back pain in childbirth. [Midwifery Master's thesis]. Iran. School of Nursing and Midwifery of Mashhad University of Medical Sciences;1994.(Persian)
- Abasi Z, Abedian Z, Fadaii A. The effect of massage on the duration of first stage labor. Arak University Journal (Rahavard Danesh). 2008;11:63-71. [Persian]
- Reddy B, Edwards T. Management of acute pain: a practical guide. Translated by: Sharifi M, Ordookhani A. 1st ed: World Association of pain; 2002: 105 - 106.
- Mirhaghjoo N, Faramarzi M. Manual of Clinical Problems in Medicine. Gilan: Research Publications 1379; 178.
- Likis FE, Likis FE, Andrews JC, Collins MR, Lewis RM, Seroogy JJ, et al. Nitrous oxide for the management of labor pain: a systematic review. Anesth Analg. 2014;118(1):153-67.
- Lind JN, Perrine CG, Li R. Relationship between Use of Labor Pain Medications and Delayed Onset of Lactation. J Hum Lact. 2014 : 22.
- Myles M, Ruth B, Linda B. Myles Textbook for Midwives. 16th ed. London: Churchill Livingstone ; 2010: 458-463.
- Hosseinzadeh H. Saffron herbal medicine of the third millennium - the anti-cancer effects of Cancer (Volume I). First published Smbhlh Mashhad; 2009.
- Anonymous. Al-Qanun fil-Tibb, (Arabic) Book, (original Author-Avicenna), Vol: 1. Al-kotob Al-ilmiyah Publication: Lebanon; 1999: 548.
- Hosseinzadeh H, Nassiri-Asl M. Avicenna's (Ibn Sina) the Canon of Medicine and Saffron (Crocus sativus): A Review. PHYTOTHERAPY RESEARCH 2012.
- Anonymous .Al-havy (Arabic) Book, (original Author- Muhammad ibn Zakariya Razi), Vol: 20 . Regulation of translation and research by: Afshari Poor S. Nezhat pub 1384;324 - 325.
- Aghili Alavi S.M.H. Makhzan-al-adviyeh: 433.
- Anonymous .Al-mojez fi-teb (Arabic) Book, (original Author- Ibn Nafis);1986; 94 , 260.
- Schmidt M, Betti G, Hensel A. Saffron in phytotherapy: pharmacology and clinical uses. Wien Med Wochenschr 2007; 157: 315–319.
- Zargari A. Medical plants. 6 ed. Tehran University Press 1990; 574-578. (Persian)
- Bhargava VK. Medicinal uses and pharmacological properties of crocus sativus L. (saffron). Int J Pharm Pharm Sci 2011; 3: 22–26.
- Osbaldeston TA, Wood RPA. Dioscorides, De Materia Medica. IBIDIS Press: Johannesburg, South Africa, Vol 1, 2000; 29–30.
- Khalili M, Hamzeh F. Effects of Active Constituents of Crocus sativus L., Crocin on Streptozocin-Induced Model of Sporadic Alzheimer's Disease in Male Rats. Iranian



- Biomedical Journa 2010; 1 14 (1 & 2): 59-65.
- Hosseinzadeh H, Khosravan, V. Anticonvulsant effects of aqueous and ethanolic extracts of *Crocus sativus* L. stigmas in mice. *Arch Irn Med.* 2002; 5(1):44- 47.
- Hosseinzadeh H, Sadeghnia HR. Protective effect of safranal on pentylenetetrazoleinduced seizures in the rat: involvement of GABAergic and opioids systems. *Phytomedicine.* 2007; 14: 256 - 62.
- Bathaie SZ, Mousavi SZ. New applications and mechanisms of action of saffron and its important ingredients. *Crit Rev Food Sci Nutr* 2010; 50: 761–86.
- Nasri S, Hosseini S. Y, Sahraei H, Zardoos H. Inhibition of pain and inflammation induced by formalin in male mice by ethanolic extract of saffron (*Crocus sativus*) and its constituents; crocin and safranal. *Kowsar Medical Journal* 2011; 15( 4): 189-195.
- Hosseinzadeh H, Younesi HM. Antinociceptive and anti-inflammatory effects of *Crocus sativus* L. stigma and petal extracts in mice. *BMC Pharmacol.* 2002;2: 7.
- Hosseinzadeh H, Karimi G, Niapoor M. Antidepressant effect of *Crocus sativus* L. stigma extracts and their constituents, crocin and safranal, in mice. *Acta Horticult.* 2004; 650: 435–445.
- Karimi G, Hosseinzadeh H, Khaleghpanah P. Study of antidepressant effect of aqueous and ethanolic extract of *Crocus sativus* in mice. *Iran J Basic Med Sci.* 2001; 4: 11–15.
- Wang Y, Han T, Zhu Y, Zheng C.J, Ming Q.L, Rahman KH, et al. Antidepressant properties of bioactive fractions from the extract of *Crocus sativus* L. *J Nat Med.* 2010; 64: 24–30.
- Noorbala AA, Akhondzadeh S, Tamacebi-Pour N, Jamshidi AH. Hydroalcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *J Ethnopharmacol.* 2005;97: 281–284.
- Assimopoulou AN, Sinakos Z, Papageorgiou. Radical scavenging activity of *Crocus sativus* L. extract and constituents. *Phytother. Res.* 2005; 19: 997 – 1000.
- Chen Y, Zhang H, Tian X, Zhao C, Cai L, Liu Y, Jia L, Yin HX and Chen C. Antioxidant potential of crocins and ethanol extracts of *Gardenia jasminoides* ELLIS and *Crocus sativus* L.: A relationship investigation between antioxidant activity and crocin contents. *Food Chem.* 2008; 109: 484-92.
- Kanakis CD, Tarantilis PA, Tajmir-Riahi HA, Polissiou MG. Crocetin, dimethylcrocetin and safranal bind human serum albumin: stability and antioxidative properties. *J. Agric. Food Chem.* 2007; 55 (3): 970 - 7its bioactive
- Verma SK and Bordia A. Antioxidant property of saffron in man. *Ind. J. Med. Sci* 1998; 52 (5):204 - 7.
- Bolhassani A, Khavari A, Bathaie S.Z. Saffron and natural carotenoids: Biochemical activities and anti-tumor effects: Review. *Biochimica et Biophysica Acta* ; 2014: 20–30.
- Abdullaev FI. Cancer Chemopreventive and tumoricidal properties of Saffron(*Crocus Sativus* L.). *Exp Biol Med* Maywood. 2002; 227: 20- 5.
- John P, Melnyk JP, Wang SN, Marccone MF. Chemical and biological properties of the world's most expensive spice saffron. *Food Res Int.* 2010; 43: 1981–1989.
- Betti G, Schmidt M . Valorization of saffron (*Crocus sativus*). 2nd Int. Symposium on Saffron Biology and Technology, Mashhad. 2006; 28–30.
- Agha-Hosseini M, Kashani L, Aleyaseen A, et al. *Crocus sativus* L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. *Br J Obstet Gynaecol* 2008;115: 515–519.
- Gout B, Bourges C, Paineau-Dubreuil S. Satiereal, a *Crocus sativus* L extract, reduces snacking and increases satiety in a randomized placebo-controlled study of mildly overweight, healthy women. *Nut Res* 2010; 30: 305–313.

- Khodakrami N. The Effect of an Iranian Herbal Drug on Primary Dysmenorrhea: A Clinical Controlled Trial. *Journal of Midwifery & Women's Health*. 2009; 54( 5).
- Shadipour M, Simbar J, Salamzadeh N, Nasir A. comparative study on the effects of Menstrogol and Mefenamic acid on postpartum after-pain. University of Medical Sciences, Tehran.2011.
- Hosseinzadeh H, Noraei N.B. Anxiolytic and Hypnotic Effect of *Crocus sativus* Aqueous Extract and its Constituents, Crocin and Safranal, in Mice. *PHYTOTHERAPY RESEARCH*. 2009; 23: 498 – 503.
- Ai J, Dekermendjian K, Wang X, Nielsen M, Witt MR. 6-Methylflavone, a benzodiazepine receptor ligand with antagonistic properties on rat brain and human recombinant GABA(A) receptors in vitro. *Drug Dev Res* 1997;41: 99 –106 .
- Pitsikasa N, Boultradakisa A, Georgiadoua G, Tarantilisb P.A, Sakellaridis N. Effects of the active constituents of *Crocus sativus* L, crocins, in an animal model of anxiety. *Phytomedicine*. 2008; 15: 1135–1139
- Shams J, Molavi S, Marjani S, Kamalinejad M, Zardooz H, Sahraei H, et al. The aqueous extract of *Crocus sativus* stigma reduces morphine tolerance. *Physiol Pharmacol*. 2009;13(2):170-8. [Persian].
- Vahidi AR, Bashardost N, Akhondi H. The analgesic effect of saffron extract in rats as compared with morphine sulfate. *Planta Med*. 2007; 73: 995.
- Amin B, Hosseinzadeh H. Evaluation of aqueous and ethanolic extracts of saffron, *Crocus sativus* L., and its constituents, safranal and crocin in allodynia and hyperalgesia induced by chronic constriction injury model of neuropathic pain in rats. *Fitoterapia* 2012; 888–895.
- Abdullaev FL. Biological effects of saffron. *Biofactors* 1993;4:83-6.
- Ríos JL, Recio MC, Giner RM, Máñez S. An update review of saffron and its active constituents. *Phytother Res* 1996;10:189–93.
- Kubo I, Kinoshita H. Flavonols from saffron flower: tyrosine inhibitory activity and inhibition mechanism. *J Agric Food Chem* 1999;47(10):4121-5.
- Samuelsson G. *Drugs of natural origin*. 4th ed;1999. pp. 227-228, 341-342.
- 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: 1026–1026 [ Abstract].
- Fukui H, Toyoshima K, Komaki R. Psychological and neuroendocrinological effects of odor of saffron (*Crocus sativus*). *Phytomedicine* 2011; 18: 726–730.
- He sY, Qian Z, Tang FT. Effect of crocin on intracellular calcium concentration in cultured bovine aortic smooth muscle cells. *Xue. Bao*, 2004;39(10) 778- 781.
- Boskabady MH, Aslani MR. Relaxant effect of *Crocus sativus* (saffron) on guinea pig tracheal chains and its possible mechanisms. *J. Pharm. Pharmacol*. 2006; 58 (10): 1385 - 90.
- Vahdati Hassani F, Naseri V, Razavi BM, Mehri S, Abnous K, Hosseinzadeh H. Antidepressant effects of crocin and its effects on transcript and protein levels of CREB, BDNF, and VGF in rat hippocampus. *US National Library of Medicine National Institutes of Health* 2014; 22(1):16.
- Marder M, Estiu G, Blanch LB et al. Molecular modeling and QSAR analysis of the interaction of flavone derivatives with the benzodiazepine binding site of the GABA(A) receptor complex. *Bioorg Med Chem*. 2001;9: 323–335.
- Chang P.Y, Wang C.K, Liang CT, Kuo W. The pharmacological action of Zang Hong Hua (*Crocus sativus* L.). effects on the uterus and estrous cycle. *Yao Hsueh Hsueh Pao*, 1964; 61 ,2348(Abstr).
- Sadraei H, Ghannadi AR, Takei-bavan 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( 2–3): 121–127.
- Azhari S, Khalilian Movahed H, Tara F, Esmaili HA. Comparison of upright and bend at the second stage of labor on pain experienced during the second stage of labor in nulliparous women. *IJOGI* 2012; 15(33): 7-11. (persian).
- Guide state hospitals providing obstetric loving mother. Ministry of Health and Medical Education Department Bureau of Population, Family Health and Maternal Health., Second Edition. First reviewed;1390.
- Arbabian S and coworker. Effect of aqueous extract of saffron (*Crocus Sativus*) on formalin-induced pain of small laboratory rats. *Kowsar Medical Journal*.2009; 14(1): 11- 18.
- Fanton, J.C, Ward P.A, Rubin E, Farber J.L. *Inflammation In Pathology*. 2nd ed. Philadelphia: J.B. Lippicott Company; 1994. pp. 34-66.
- Simpson KR, Greehan PA. *Perinatal Nursing*. 2end ed. Philadelphia: Lippincot.2001; p: 73 ,312- 14,328-29.
- Otte T. *The Illustrated Guide to Pregnancy And Birth*. London: New Holland publishers(UK).1998; p: 53, 62, 77, 84.
- Hosseinzadeh H, Talebzadeh F. Anticonvulsant evaluation of safranal and crociri from *Crocus sativus* in mice, *Fitoterapia*. (2005); 76, 7-8, 722-724. From Pubmed. Abst: 16253437.
- Liu N, Yang Y, Mo S, Liao J and Jin J. Calcium antagonist effects of Chinese crude drugs: preliminary investigation and evaluation by <sup>45</sup>Ca. *Appl. Radiat. Isotopes*. 2005; 63 (2): 151 - 5.
- Tiran D, Chummun H. Complementary therapies to reduce physiological stress in pregnancy. *J. Complementary Therap NM*. 2004; 10: 162 - 7.
- Otte T. *The Illustrated Guide to Pregnancy and Birth*. London: New Holland(UK); 1998: 53, 62- 3, 77- 8.
- Jabarzadeh Ganjeh S. The effect of intradermal injection of strilled water on the severity of back pain in childbirth. [Midwifery Master's thesis].Iran. School of Nursing and Midwifery of Mashhad University of Medical Sciences;1994.(Persian)
- Azhari S, Ahmadi S, Jafarzadeh H, Rakhshandeh J, Mazlom R. The effect of oral capsules of saffron on pain intensity in the active phase of first stage of labor. *IJOGI*, Vol. 17, No. 115, pp. 1-10, Sep 2014
- Mishra SL, Toshniwal A, Banerjee R. Effect of drotaverine on cervical dilatation: A comparative study with epidosine. *J Obstet Gynecol Ind*. 2002; 52(3):76-79.
- Sirohiwal D, Dahiya K, DE M. Efficacy of hyoscine-N-butyl bromide (Buscopan) suppositories as a cervical spasmolytic agent in labour. *Aust N Z J Obstet Gynaecol*. 2005; 45(2):128-9