

# The Impact of Equisetum arvense Vaginal Cream On Premature Rupture of Membranes in Primiparous Women with Striae Gravidarum: A Triple-Blind Randomized Controlled Trial

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ARTICLE INFO	ABSTRACT
Article type: Original article	<b>Background &amp; aim:</b> One of the risk factors of premature rupture of membranes (PROM) is striae gravidarum, which occurs in 50-90% of pregnancies due to poor skin elasticity. It was found that Equisetum arvense is a medicinal plant containing silicic acid, which can increase tissue elasticity, strength and resistance by stimulating collagen synthesis. Therefore, this study examined the effect of Equisetum arvense vaginal cream on PROM in primiparous women with striae gravidarum.
Article History: Received: 22-Jan-2022 Accepted: 06-May-2020	<b>Methods:</b> This triple-blind randomized controlled trial was performed on 90 pregnant women with gestational age of 37-38 weeks who had moderate and severe striae gravidarum, referred to the prenatal governmental and private clinics in Mashhad, Iran, between 2020 and 2021. Intervention and placebo groups, who were randomly assigned using quadruple blocks, smeared every night the beginning of the vagina with a knuckle of 3% Equisetum arvense vaginal cream or placebo from the beginning of 37-38 weeks until delivery. The occurrence of PROM was confirmed in case amniotic fluid leaks two hours before the onset of uterine contractions. Data were analyzed using independent t-test and Mann-Whitney.
<b>Key words:</b> Premature Rupture of Membranes Striae Gravidarum Equisetum arvense Primiparous Women	<b>Results:</b> The subjects in the two groups were homogeneous in terms of demographic and obstetric variables. The rate of PROM in the intervention group (13.0%) was significantly lower than the placebo group (38.6%) ( $p = 0.005$ ). <b>Conclusion:</b> Equisetum arvense vaginal cream is effective in preventing PROM. Therefore, its use is recommended to prevent PROM in women with moderate and severe striae gravidarum.

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## Introduction

Premature rupture of membranes (PROM) refers to the rupture of membranes before the onset of regular and spontaneous uterine contractions that can occur at any gestational age (1, 2). PROM is divided into preterm and

term, which occur before and after 37 weeks of gestation, respectively (1,3). The rate of preterm rupture of membranes is reported to be 2-3% in the United States which is responsible for more than one-third of preterm deliveries (3).

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Rupture of membranes at term pregnancy also occurs in approximately 8% of pregnancies (1). In Iran, the prevalence of PROM in the study of Kariman et al. (2012) was reported to be 7%, which is considered as the cause of 21.4% of perinatal morbidity and 18-20% of perinatal mortality (4).

PROM is associated with maternal, neonatal and perinatal morbidity and mortality (2, 5). PROM increases neonatal hospitalization rates in NICU and also increases the treatment costs and is associated with maternal outcomes such as chorioamnionitis, endometritis, and increased cases of emergency cesarean section following labor induction (1,4). Maternal intrauterine infection, sepsis, placental abruption, fetal distress, and fetal death following umbilical cord compression due to oligohydramnios are other complications of PROM (6,7).

Predisposing factors for PROM include primiparity, low socioeconomic status, history of PROM in previous pregnancies, history of abortion, smoking, urinary tract infection and vaginal infection (5, 8-10). Another risk factor for PROM is striae gravidarum, the severity of which is assessed by Atwal tool through simple observation (10,11). Striae gravidarum is defined as reddish streaks that commonly occur on the skin of the abdomen and sometimes on the skin of the breasts and thighs (1). These streaks, which occur in 50-90% of pregnancies, are a sign of poor skin elasticity (12-14).

The results of some studies indicate that the reduction of collagen synthesis plays an essential role in the development of striae (15,16). Also, in the study which investigated the relationship between PROM at term pregnancy and the amount of membranes' collagen, the results showed that the amount of collagen in the ruptured membranes was lower than in intact membranes (17). Connective tissue defects and decreased collagen synthesis seem to be a common mechanism in the development of striae and PROM (10). According to the results of the studies, the severity of striae gravidarum is associated with PROM and the rate of PROM is higher in women with severe striae (10).

Studies on the effect of vitamin C supplementation on the prevention of PROM

have reported contradictory results (18,19). In recent years, the tendency of people, especially pregnant women, to use medicinal plants, which is a branch of complementary medicine, for the prevention and treatment of diseases has increased (20, 21). *Equisetum arvense* is one of the oldest medicinal plants which belongs to the category of Pteridophyte and is seen in Iran as self-growth (22, 23). The most important compounds of this plant include silicic acid, flavonoids, alkaloids, linoleic acid, oleic acid, stearic acid and linolenic acid (24). *Equisetum arvense* is used as an anti-inflammatory, antispasmodic, antimicrobial, antifungal and also for wound healing (22, 24). According to the studies, the extract of this plant has an inhibitory effect on a wide range of gram-positive and gram-negative bacteria (25). Silicic acid in this plant can increase tissue elasticity, strength and resistance by stimulating collagen synthesis, strengthening collagen fibers and connective tissue (22,24,26).

Therefore, considering the importance of maternal and neonatal complications caused by PROM and collagen-producing properties, strengthening the tissue and anti-fungal and anti-bacterial properties of *Equisetum arvense* and the availability of this plant, and lack of a study to prevent PROM in primiparous women with striae who are at risk of PROM, the present study was performed to examine the effect of *Equisetum arvense* vaginal cream on the rate of PROM in primiparous women with striae gravidarum.

## Materials and Methods

This two-group triple-blind randomized controlled trial was performed between 2020 and 2021 on 90 primiparous pregnant women referring to the prenatal clinic of Omm Al-Banin Hospital and private clinics in Mashhad, Iran. Inclusion criteria were primiparity, age of 18-35 years, gestational age of 37-38 weeks, body mass index of 18.5-30 kg/m<sup>2</sup>, moderate and severe striae gravidarum (total striae score above 9 based on Atwal tool), singleton pregnancy, cephalic presentation, absence of medical disease and obstetric complications, no urinary tract and vaginal infections and no dependence on cigarettes and drugs. Exclusion criteria were withdrawal from the study, allergy to the cream, no proper and regular use of the

cream, and cream use for less than 2 weeks. The sample size was calculated based on the pilot study with 95% confidence interval and 80% test power and using the ratio comparison formula ( $N = (Z_{1-\alpha} / 2 + Z_{1-\beta})^2 (p_1 (p_1(1-p_1) + p_2 (1-p_2) / (p_1-p_2)^2)$ ). The final sample size was estimated 42 subjects in each group and considering 20% possible dropout, a total of 103 people were entered the study.

The tools used in this study included a demographic and midwifery information questionnaire, a checklist for recording daily cream use and possible complications, delivery information form, and Atwal tool (to calculate the Total Striae Score (TSS)). The validity of tools was determined by content validity method. In this study, TSS was calculated using Atwal scoring system. Based on this tool, the skin of four areas of the body (abdomen, thighs, breasts and buttocks) is evaluated in terms of color and number of striae, and 6 points are assigned to each area. The sum of the obtained scores is interpreted as follows: 0-3 (without striae), 4-9 (mild striae), 10-15 (moderate striae) and more than 15 (severe striae). The validity and reliability of this tool has been confirmed by Atwal et al. (2006) and in Iran by Omid et al. (2018) with a correlation coefficient of 0.8 (10, 11). The reliability of Atwal tool in the present study was also confirmed by the method of inter-rater agreement with a correlation coefficient of 0.72.

Sampling was performed in the prenatal clinic of Omm Al-Banin Hospital and private clinics in Mashhad, Iran using the available method based on inclusion and exclusion criteria. After stating the objectives of the study and obtaining written consent from the subjects, taking into account the privacy of the pregnant women, four areas of the abdomen, thighs, breasts and buttocks were examined in terms of color and number of striae to calculate TSS. Women who scored above 9 on the Atwal tool were entered into the study, then a checklist for selecting the subjects and a demographic and midwifery information questionnaire were completed. Pregnant mothers were divided into intervention and placebo groups based on a random allocation sequence with a quadruple block kept in

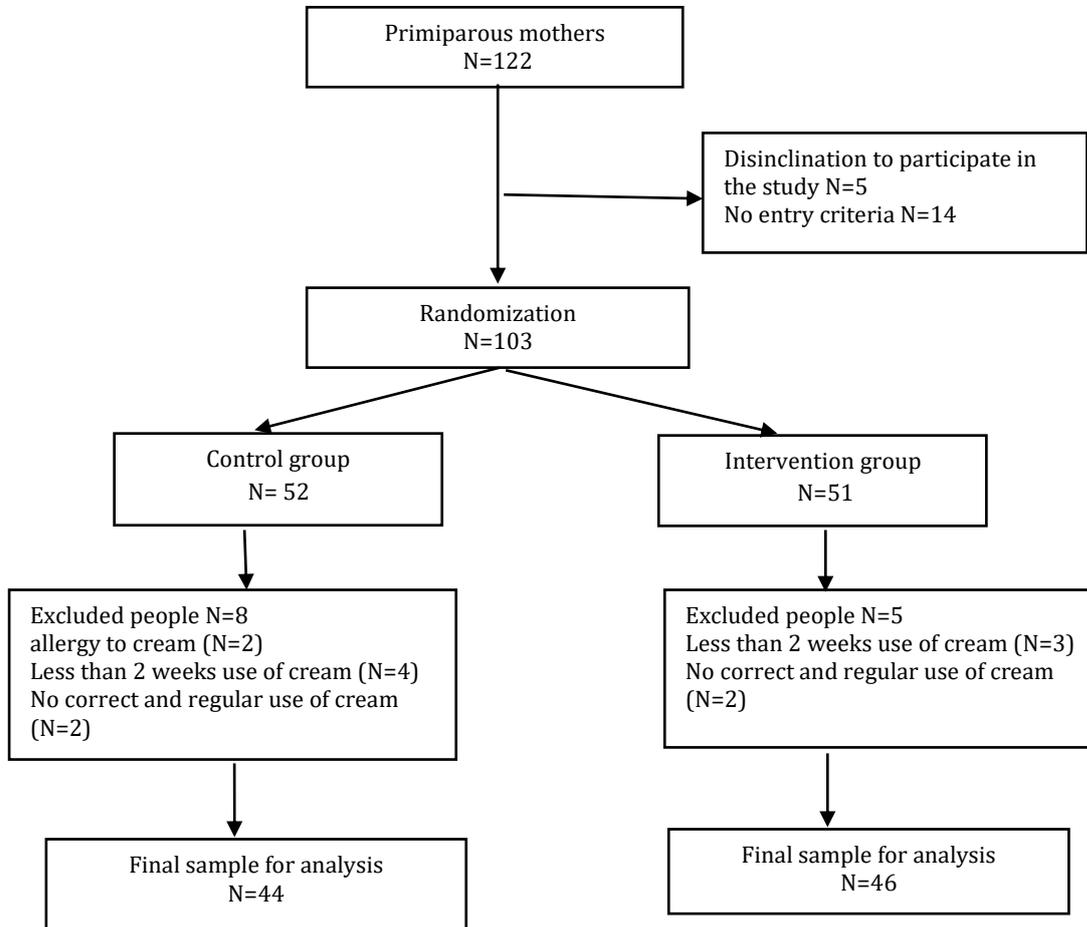
closed envelopes. Equisetum arvense cream and placebo cream tubes had exactly the same appearance and label. The coding was done by a respected pharmacist consulting professor and a code was assigned to each tube. Until the end of the study, researcher, the subjects and statistical analyst were not informed about the codes related to Equisetum arvense cream and placebo.

In order to prepare the creams, Equisetum arvense was prepared from the northern regions of Iran by the staff of the school of Pharmacy and approved with Herbarium Code of Equisetum arvense 13515 in the school of Pharmacy of Mashhad University of Medical Sciences. The dried aerial parts of this plant were soaked in water and alcohol solvent 70% for 72 hours after pulverization with an electric mill. The hydraulic extract of Equisetum arvense, which was prepared after filtering and removing the solvent, was placed at a rate of 3% in the cold cream purchased from Farabi Pharmaceutical Company and was thoroughly mixed. It was then poured under sterile conditions and under a laminar hood (sterile hood) into 45 g aluminum tubes (empty tubes were sterilized under high temperature) and sealed. The placebo cream also contained 45 grams of cold cream of the same color and shape of the Equisetum arvense cream.

Subjects from 37-38 weeks of gestation to delivery, once a night before sleeping, smeared the beginning of the vagina with a knuckle (equivalent to 2.5 cm) of Equisetum arvense cream or placebo using the thumb finger, so that the first 3-4 cm of the vagina was completely soaked in the cream. An educational pamphlet on how to use the cream and a checklist to record daily use of cream and possible side effects were also provided to the subject. During the study, the researcher communicated with the subjects every three days through phone calls and short messages and asked about the use of cream and possible side effects, and emphasized that if there were any signs of labor onset, they should go to the hospital and inform the researcher.

In the case of amniotic fluid leakage two hours before the onset of labor contractions, which was confirmed by placing a sterile

Figure 1. CONSORT Flowchart



speculum and observing amniotic fluid leaking from the cervix or a two-finger examination after wearing sterile gloves and using nitrazine test, PROM was confirmed. If the patient reported a history of amniotic fluid leakage, but the examination and nitrazine test were negative, an ultrasound examination was performed to determine the amniotic fluid index (AFI). After delivery, delivery information form including gestational age at hospitalization, cause of hospitalization, time of rupture of membranes and its color, time of onset of uterine contractions, mode of delivery and baby characteristics including birth weight, sex and fifth minute Apgar score were completed by the researcher. Data were analyzed using SPSS software (version 25) and statistical tests of Chi-square, Exact Chi-square, independent t-test and

Mann-Whitney.  $P < 0.05$  was considered statistically significant.

## Results

In the present study, 103 primiparous pregnant women with moderate and severe striae were included in the study, of which 7 women due to less than two weeks of cream use (1 in the intervention group and 3 in the placebo group due to the rupture of membranes and 2 in the intervention group and 1 in the placebo group due to the onset of labor contractions), 4 women due to no correct and regular use of the cream (2 in each group) and 2 women due to allergy to the cream in the placebo group were excluded from the study and finally the data of 90 (46 in the intervention group and 44 in the placebo group) were analyzed (Figure 1).

The two groups were not significantly different in terms of demographic characteristics including age, education level, family income, weight at the beginning of pregnancy and weight at the time of enrollment in the study, Body Mass Index (BMI), pregnancy weight gain, food group share and fluid intake, duration of walking and other sports exercises per week ( $P>0.05$ ). Also, the two groups were

homogeneous in terms of midwifery variables including receiving maternity care, taking pregnancy supplements, history of abortion, gestational age at the time of entering the study, TSS and the striae score in the abdomen, thighs, breasts and buttocks areas, and gestational age at admission in the maternity ward ( $P>0.05$ ) (Table 1, 2).

**Table 1.** Demographic characteristics of subjects in two groups of Equisetum arvense and placebo cream

Variable	Group		Test results
	Equisetum arvense cream (n=46)	Placebo (n=44)	
	Mean±SD	Mean±SD	
Age (years)	23.9 ± 4.0	23.1 ± 3.7	*P=0.324, t=-0.9, df=88
BMI (kg/m <sup>2</sup> )	23.9 ± 3.4	22.9 ± 3.4	*P=0.199, t=-1.2, df=87
Total Striae Score (TSS)	12.5 ± 2.8	13.0 ± 3.1	*P=0.519, t=0.6, df=88
Education	N (%)	N (%)	
Elementary	2 (4.3)	2 (4.5)	
Secondary	4 (8.7)	8 (18.2)	**P=0.126, Z=-1.5
High school	13 (28.3)	15 (34.1)	
College	27 (58.7)	19 (43.2)	
Family Income level			
Less than enough	1 (2.2)	5 (11.4)	
Enough	41 (89.1)	37 (84.1)	**P=0.085, Z=-1.7
More than enough	4 (8.7)	2 (4.5)	

\* Independent T \*\* Mann Whitney

The rate of PROM in the intervention group was significantly lower than the placebo group ( $P=0.005$ ). The number of women who referred to the maternity with a complaint of spontaneous onset of labor contractions was significantly higher in the intervention group than the placebo group ( $P=0.040$ ). The number of cesarean deliveries was lower in the intervention group than the placebo group (21.7% vs. 40.9%), but the result of Chi-square test showed no significant difference ( $P=0.050$ ) (Table 2). The mean of infant's weight and fifth minute Apgar score were not significantly different between the two groups ( $P>0.05$ ) (Table 2).

In the evaluation of PROM based on the severity of striae gravidarum in moderate and severe striae subgroups, the results showed that the rate of PROM in women with moderate severity of striae in the intervention group was significantly lower than the placebo group ( $P=0.021$ ), but in the subgroup of severe striae, this difference was not significant due to the small sample size ( $P=0.072$ ) (Table 3). No side effects were reported in the intervention group, but in the placebo group, 2 people reported burning and itching following the use of the cream.

**Table 2.** Comparison of delivery outcomes and neonatal characteristics of subjects in the two groups of Equisetum arvense and placebo cream

Variable	Group		Test's results
	Equisetum arvense cream (n=46)	Placebo (n=44)	
	N (%)	N (%)	
premature rupture of membranes			
Yes	6 (13.0)	17 (38.6)	* P=0.005, Chi <sup>2</sup> =7.7, df=1
No	40 (87.0)	27 (61.4)	
Color of amniotic fluid			
Clear	43 (93.5)	37 (84.1)	**P=0.087, Chi <sup>2</sup> =4.1, df=2
light meconium	2 (4.3)	7 (15.9)	
Bloody	1 (2.2)	0 (0.0)	
Mode of delivery			
Vaginal delivery	36 (78.3)	26 (59.1)	*P=0.050, Chi <sup>2</sup> =3.8, df=1
Cesarean section	10 (21.7)	18 (40.9)	
Cause of hospitalization in maternity ward			
Onset of labor contractions	31 (67.4)	19 (43.2)	*P=0.040, Chi <sup>2</sup> =8.2, df=3
Rupture of membranes	6 (13.0)	17 (38.6)	
Post date	5 (10.9)	4 (9.1)	
Decreased fetal movements	4 (8.7)	4 (9.1)	
Sex of neonate			
Female	22 (47.8)	22 (50.0)	*P=0.837, Chi <sup>2</sup> =0.0, df=1
Male	24 (52.2)	22 (50.0)	
	<b>Mean±SD</b>	<b>Mean±SD</b>	
Birthweight	3371.3 ± 347.4	3340.9 ± 432.9	***P=0.718, t=-0.3, df=85
5 <sup>th</sup> minute Apgar score	9.9 ± 0.1	9.9 ± 0.2	****P=0.288, Z=-1.0
Gestational age at admission in maternity ward (week)	39.8 ± 0.7	39.7 ± 0.7	***P=0.479, t=-0.7, df=85
Cervical dilatation at admission	2.6 ± 1.5	2.0 ± 1.7	****P=0.039, Z=-2.0

\*Chi-Square \*\* Exact Chi-Square \*\*\* Independent T \*\*\*\* Mann Whitney

**Table 3.** Frequency distribution of premature rupture of membranes based on the severity of striae gravidarum in the two groups of Equisetum arvense and placebo cream

severity of striae gravidarum	premature rupture of membranes	Group		Test's results
		Equisetum arvense cream (n=46)	Placebo (n=44)	
		N (%)	N (%)	
Moderate	Yes	6 (15.8)	14 (40.0)	*p=0.021, Chi <sup>2</sup> =5.3, df=1
	No	32 (84.2)	21 (60.0)	
	Total	38 (100.0)	35 (100.0)	
Severe	Yes	0 (0.0)	3 (33.3)	*p=0.072, Chi <sup>2</sup> =3.2, df=1
	No	8 (100.0)	6 (66.7)	
	Total	8 (100.0)	9 (100.0)	

\*Chi-square

## Discussion

In the present study, use of 3% Equisetum arvense vaginal cream for at least 2 weeks significantly reduced the incidence of PROM at term; so that the rate of premature rupture of

membranes in the Equisetum arvense cream group was 25.6% lower than the placebo group. Due to the presence of silicic acid, Equisetum arvense stimulates collagen synthesis, strengthens the collagen fibers, and due to its binding to protein molecules, increases the strength and resistance of

connective tissue (24,26). Due to its antibacterial, anti-fungal and anti-inflammatory properties, Equisetum arvense can be effective in reducing the rate of infection and inflammation, which is the most important and common cause of rupture of membranes (1,24). Bacteria reduce the strength of membranes and their elasticity by activating inflammatory mechanisms (1,27).

In the study of Saghafi et al. (2018), which examined cervical bacterial colonization in women with preterm premature rupture of membranes, the most common isolated microorganism was *E. coli* (24.2%) and other microorganisms were *Staphylococcus epidermidis* (14.7%), *Staphylococcus saprophyticus* (12.5%), *Candida* (11.7%), *Klebsiella pneumoniae* (8.8%), *Staphylococcus aureus* (2.9%) and *Pseudomonas aeruginosa* (2.2%) (28). Radulović et al. (2006) reported that Equisetum arvense has antimicrobial activity against a wide range of strains and its antimicrobial activity has been confirmed against bacteria such as *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Salmonella enteritidis* and fungi such as *Aspergillus niger* and *Candida albicans* (24, 29, 30).

Lamont et al. (2003) investigated the effect of clindamycin 2% vaginal cream in women with bacterial vaginosis on the number of preterm deliveries. The results showed a positive effect of clindamycin cream on reducing the rate of preterm deliveries (also including preterm premature rupture of membranes) and reducing the number of neonatal hospitalizations ( $P=0.030$ ) (31). In the study of Larson et al. (2006), the results showed that the rate of preterm delivery in the clindamycin cream group was lower than the control group, but this difference was not statistically significant ( $P>0.05$ ). Gestational age ( $P=0.024$ ) and neonatal birth weight ( $P=0.009$ ) in women with preterm delivery were significantly higher in the intervention group than the control group (32). The results of the present study are consistent with these two studies, with the difference that in these

two studies, the number of preterm deliveries has been studied.

In the study of Ghomian et al. (2013), daily consumption of 100 mg vitamin C from 14 to 37 weeks of pregnancy in women with history of at least one Preterm Premature Rupture of Membranes (PPROM), is effective in preventing premature rupture of membranes in both term and preterm delivery ( $P<0.001$ ) (19). The results of the present study are consistent with their study, with the difference that the present study was performed on the prevention of premature rupture of membranes in term deliveries. Equisetum arvense is a rich source of vitamins and minerals, so that one kilogram of Equisetum arvense contains 200-260 ml of vitamin C (22). Vitamin C plays an important role in collagen production and secretion, and serum depletion of vitamin C levels has been associated with PROM (19,33). Sourya et al. (2018) in a meta-analysis evaluated the role of vitamin C in the prevention of preterm and premature rupture of membranes and reported that vitamin C has no role in the prevention of PPRM and preterm delivery (18).

In the present study, due to the lower number of PROM cases in the intervention group than in the placebo group, the number of cases who referred to the maternity ward with a complaint of spontaneous onset of labor contractions was significantly higher in the intervention group than the placebo group. The mean cervical dilatation at the admission, which is an effective factor in predicting the success of vaginal delivery, was significantly higher in the intervention group. In the study of Haji Foghaha et al. (2008) who examined the effect of daily consumption of 100 mg of vitamin C from the beginning of 20<sup>th</sup> week of pregnancy on the rate of PROM, the rate of rupture of membranes was significantly lower in the intervention group than the control group ( $P<0.001$ ). Also, the number of cases in the intervention group who referred to the hospital due to the onset of labor contractions was higher than the placebo group ( $P<0.001$ ) (34), which is consistent with the results of the present study.

In the present study, there was no significant difference between the two groups in terms of mean gestational age at admission to the maternity ward and mean birth weight of newborns. In the study by Casanueva et al. (2005) that examined the effect of vitamin C intake from 20<sup>th</sup> week of pregnancy on rupture of membranes, the rate of rupture of membranes was significantly lower in the intervention group than the placebo group ( $P=0.018$ ). Also, in the study of Casanueva, gestational age at birth and birth weight were not significantly different between the two groups ( $P>0.05$ ) (35), which is consistent with the results of the present study. In the study of Ghomian et al. (2013), mean gestational age at admission to the maternity ward and mean birth weight were significantly higher in the intervention group than the placebo group ( $P<0.001$ ) (19) which are inconsistent with the results of the present study. This difference may be due to the fact that in the study of Ghomian et al., the intervention started at 14<sup>th</sup> weeks of pregnancy and the prevention of premature rupture of membranes and preterm delivery in the intervention group increased the gestational age and birth weight. The present study was conducted during at term pregnancy and the duration of the study was two to three weeks.

Omidi et al. (2018), who investigated the relationship between the severity of striae gravidarum and PROM, reported that women with severe striae were 2.6 times more likely at risk of rupture of membranes ( $P=0.010$ ) (10). In the present study, no case of PROM was observed in the intervention group who had severe striae; although the rate of PROM was higher in women with severe striae in the placebo group than in the intervention group, but due to the small number of samples in the subgroup of severe striae, this difference was not statistically significant.

One of the strengths of the present study was that *Equisetum arvense* vaginal cream for the first time was used to reduce the rate of PROM in pregnant women with striae who are at risk of PROM. Random allocation and triple-blindness are other strengths of this research. One of the limitations of the present study was the self-report of the subjects about use of the cream, which was partially controlled by making

a phone call and completing a daily checklist for cream use. Also, nutritional status and type of maternal tissue can affect the occurrence of rupture of membranes. In this study, the homogeneity of the two groups in terms of nutrition and income level was examined by asking nutrition questions and income level of subjects. Accurate control of urinary tract infections and vaginal infections was not possible due to the high cost of laboratory tests, but was relatively controlled by random allocation and exclusion criteria at the beginning and during the study.

## Conclusion

*Equisetum arvense* vaginal cream is effective in preventing premature rupture of membranes in primiparous women with striae gravidarum. Therefore, due to the increasing tendency of people, especially pregnant women to use medicinal plants and easy access to *Equisetum arvense* in this country, it is recommended to use *Equisetum arvense* vaginal cream to prevent PROM in women with striae gravidarum, who are at risk for PROM.

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## Conflicts of interest

Authors declared no conflicts of interest.

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