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Effect of vaginal progesterone suppository (200 mg) on preventing preterm labor after the inhibition of uterine contractions: A randomized clinical trial

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ABSTRACT

Preterm labor implies a childbirth before the completion of 37 weeks, and accounts for the majority of infant mortalities. Finding proper medications is essential in the treatment procedure. The present research aimed to investigate the effect of vaginal progesterone suppository (200 mg) on the prevention of preterm labor after inhibiting uterine contractions. Participants were patients hospitalized in Shariati Hospital of Bandar Abbas in 2014-15. As a randomized clinical trial, the present research focused on all pregnant women who referred to Shariati Hospital in Bandar Abbas due to preterm uterine contractions in 2014-15. The inclusion criteria were: pregnancy with a singleton and passing one's 26th-34th week of pregnancy. Through convenient sampling method, 200 women were selected to enter the study. According to the table obtained from Random Allocation software, they were randomly divided into two groups, each comprised of 100 subjects. They were monitored for 48 hours in terms of uterine contractions and then if there were no contractions and change of dilatation or cervical effacement, they were discharged. They were asked to return for a revisit one week later in their 34th week of pregnancy. SPSS (version 17) was used to analyze the data through Man-Whitney U-test, Fisher's exact test, t-test and chi-squared test. P-value of significance was set at ≤.05. A statistically significant difference was found between the two groups in terms of the frequency of term and preterm labors (P<0.05). The Apgar score of infants in the intervention group was higher than the control (P<0.05). The rate of respiratory problems in the intervention group was significantly lower than the control (P<0.001). The rate of septicemia in the infants of the intervention group was 8% as compared to the control group 20%. The weight of infants in the intervention group was significantly higher than the control (P<0.05). Prescribing vaginal progesterone suppository (200 mg) can probably help to prevent preterm labor and fetal complications such as respiratory problems, need for artificial ventilation, septicemia, low birth weight and low Apgar score.

Keywords: preterm labor, progesterone suppository (200 mg), birth weight, respiratory distress, Apgar

INTRODUCTION

Preterm labor is the main cause of infant mortality worldwide [1]. It implies a childbirth before the completion of 37 weeks [2, 3]. In 2001 in the U.S., preterm labor was reported to account for the death of about two-third of all infants in their first year of life [4].

Infant morbidity is primarily influenced by the age of pregnancy and accordingly the fetal growth, and less by the birth weight. Infant morbidity is directly influenced by the age of pregnancy and the time of delivery. The rate of morbidity before 32 weeks of fetal life is 70 times as high as term infants [5]. Overall, preterm labor accounts for 75% of infant mortalities [6].

Preterm labor accounts for about 50% of child blindness and one-third of cerebral palsy. It also raises the risk of heart disease in adulthood [7, 8]. Infant morbidities are prevalent before 26 weeks. Before 24 weeks, it is seen among all infants. Therefore, the most serious problems for midwifery healthcare providers occur in the 23rd to 25th week of pregnancy [9]. The rate of fetal morbidities can be decreased with a timely diagnosis of preterm labor, interventions to delay preterm labor, prescription of corticosteroids and similar drugs and infantile healthcare provision [10]. No certain cause has been identified for preterm labor. In the majority of cases maintaining the infant inside the uterus is preferable to preterm labor [9]. Preterm labor is diagnosed based on regular and painful uterine contractions along with effacement [11]. Although interventions to limit uterine contractions do not always prevent preterm labor, they help to achieve a series of medical goals such as delaying the labor and creating a chance for prescribing corticosteroids [12]. The next goal of treating preterm labor is to provide sufficient time for performing an optimal surgery, caring for mother's health and providing all equipment required for taking care of the preterm infant [13, 14]. A myriad of pharmacologic factors are recognized which prevent preterm labor. However, the effect of none have been yet known. Since the most prevalent predictive factor of preterm birth is uterine contraction, stopping these contractions is the common point of all treatments [9]. A clinical trial was conducted by Edurado et al. (2007) in the UK and aimed to investigate the correlation of vaginal progesterone suppository (200 mg) and the risk of preterm labor among women with short cervix. 25,000 women at their 24th to 33rd+6(d) week of pregnancy were explored and it was concluded that vaginal progesterone suppository was effective in reducing preterm labor [15].

Tocolyticsae used today in treating preterm labor but do not enjoy a high chance of success [16]. Therefore, finding an effective remedy is essential in the treatment procedure of the disease. Consequently, the present study intended to explore the effect of vaginal progesterone suppository (200 mg) on preventing preterm labor after inhibiting uterine contractions among patients hospitalized in Shariati Hospital of Bandar Abbas in 2014-15.

MATERIALS AND METHODS

Subjects

The present research was a randomized clinical trial. The target population consisted of all pregnant women who referred to Shariati Hospital due to preterm uterine contractions within 2014-15. Inclusion criteria were: pregnancy with a singleton, 26th-34th week of pregnancy. Exclusion criteria were: preterm rupture of membranes, chorioamnionitis, antepartum hemorrhage, placental abruption, placenta previa, concomitant systemic diseases (pre-eclampsia, pregnancy diabetes, overt diabetes, cardiovascular diseases, renal diseases, asthma, hyperthyroid, etc.), fetal anomalies (only if accompanied by an obstetric ultrasonography), signs of infection in urinalysis, cervical dilatation ≥3 cm, Polyhydramnios, IUGR.

Sample size

200 patients were selected to enter the study through convenient sampling method. Base on the inclusion and exclusion criteria of this research as well as the table output of Random Allocation software, these subjects were randomly assigned to either a treatment (intervention) group or a control each comprised of 100 members.

Research protocol

After the reception procedure, all subjects had a vaginal examination using a sterile speculum. Fern test was applied to make sure of the health of membranes. Urinalysis helped to diagnose any signs of urinary infection. After the urine culture test if there was any infection found, antibiotics were prescribed and the subjects were excluded from the study. In the case of negative fern test result and at least 4 uterine contractions every 20 minutes along with cervical changes in the form of dilatation or effacement found through manual examination, the subjects were diagnosed with preterm labor with healthy fetal membranes and entered the study. Subjects were initially treated with 500 ml of Ringer's solution and 75 mg of intramuscular pethidine. In case the contractions continued an hour after the solution and pethidine, the next step was the use of venous magnesium sulfate (4 g) at a rate of 1 g/min followed by consistent venous infusion of magnesium sulfate (2g/h) if the contractions still continued within 12 hours.

All subjects received antibiotic prophylaxis and venous ampicillin (2 g) every 6 hours for a total of 48 hours. Patients were given two doses (12 mg) of betamethasone in 24-hour intervals for fetal lung growth. 48 hours after the contractions stopped, the abovementioned patients were allocated to either the treatment or the control group based on the Random Allocation table.

All patient's information including age, weight, gravidity, parity, occupation, education, history of prior pre-term labor, age of pregnancy based on a reliable LMP, ultrasound of the first trimester, vital signs, examination upon reception, contact number. The treatment group received a daily vaginal progesterone suppository (200 mg). They were advised to continue the treatment until their 36th week of pregnancy at home. The control group received no such treatment and were only followed up. The treatment group were requested not to reveal to anyone that they were receiving a particular treatment procedure. Therefore, the control group were expected to be unaware of the treatment applied in the other group.

After 48 hours of being monitored in advance to discharge, patients were examined by the researcher. They were discharged in case there was no more contraction, change of dilatation or effacement. These patients were asked to revisit a week later at their 34th week of pregnancy. The acquired data were recorded and coded by the researcher. In each visit, uterine contractions, dilatation and effacement were examined. The data obtained were later compared between the two groups. According to the age of pregnancy, subjects were divided into four groups (26-27 weeks and 6 days, 28-29 weeks and 6 days, 30-31 weeks and 6 days, 32-33 weeks and 6 days). To remove the age of pregnancy as a confounding factor, the treatment group and the control were compared and contrasted in the same age groups.

Statistical procedure

The collected data entered SPSS (version 17). Mean, standard deviation and percentage were used to describe the data. Man-Whitney U-test, Fisher's exact test, T-test and chi-squared test were used to compare the groups. The level of significance was set at $\leq$.05.

RESULTS

In this study, mothers who were received the treatment were compared with a control group. All mothers were divided into 4 groups in terms of the age of pregnancy (table 1). Their demographic features in the two groups were also compared which showed no statistically significant divergence (table 2).

A comparison of the frequency of term and preterm labor in the four groups, a significant difference was found in 26-28 w, 28-30 w and 30-32 w groups ($p<0.05$). However, this difference was not significant in the 32-34 w group ($p>0.05$). Concerning Apgar score, infants whose mothers received vaginal progesterone suppository (200 mg) at a lower age were in a better condition than others, as compared to the control group. This difference was statistically significant in the 26-28 w (0.029) and 28-30 w (0.037) groups. In the other two groups, the difference between the control and treatment groups was not statistically significant (table 3).

Respiratory problems were significantly lower in the infants of the treatment group than the control (0.001). Only 9% of the infants of mothers in the treatment group had respiratory problems which needed hospitalization and artificial ventilation (0.001). Septicemia in the mothers of the treatment group was 8%, whereas the 20% in the control group (about 3 times as high). This divergence was statistically significant (0.003). Examining the infants' birth weight revealed that those whose mothers had received the treatment had an overall higher birth weight (0.001). Examination of Apgar scores revealed that the infants whose mothers belonged to the treatment group were in a better condition than the control group. The difference between the two research groups was significant with this regard (0.004) (table 4).

Table 1. Frequency distribution across pregnancy age groups

Sub-variables of Gestetional age (weeks)	Treatment group	Control group
	F	F
[26-28)	21	20
[28-30)	26	24
[30-32)	24	26
[32-43)	29	30
Total	100	100

A comparison of infants' birth weight indicated that the newborns in the treatment group had a higher birth weight than those in the control group. This difference was found to be statistically significant ($p<0.05$). Only in the 32-34 w group, this divergence was not significant (0.08). Moreover, mothers who had received the progesterone treatment at a lower age of pregnancy were found to have the lowest frequency of stunted pregnancy. This difference was

statistically significant in the 26-28 w (0.039) and 28-30 w (0.010) groups. No statistically significant divergence was observed in mothers at a higher age of pregnancy (30-34 w) (table 5).

Table 2.Comparison of mothers' demographic features

variable	Treatment group	Control group	p-value
	Mean ±SD	Mean±SD	
Mother's age(years)	26.23 ± 5.13	25.98 ± 5.76	0.05<
Mother's weight(Kg)	58.11 ± 8.4	60.02 ± 8.1	0.05<
Gravidity	2.1 ± 1.1	2.15 ± 1.2	0.05<
Parity	0.41 ± 0.57	0.64 ± 0.75	0.05<

Table 3. Comparison of labor and Apgar in infants in the treatment and control groups in terms of pregnancy age

variable	Sub-variables of Gestetional age	Variable sub-group	Treatment group	Control group	total	p-value
labor	[26-28)	Term	17(80.96%)	8(40%)	25(60.97%)	0.05>
		Preterm	4(19.04%)	12(60%)	16(39.03%)	
		total	21(100%)	20(100%)	41(100%)	
	[28-30)	Term	22(84.62%)	11(45.83%)	33(66%)	0.05>
		Preterm	4(15.38%)	13(54.17%)	17(34%)	
		total	26(100%)	24(100%)	50(100%)	
	[30-32)	Term	17(70.83%)	12(46.15%)	29(58%)	0.05>
		Preterm	7(29.17%)	14(53.85%)	21(42%)	
		total	24(100%)	26(100%)	50(100%)	
	[32-43)	Term	24(82.76%)	21(70%)	45(76.27%)	0.05<
		Preterm	5(17.24%)	9(30%)	14(23.73%)	
		total	29(100%)	30(100%)	59(100%)	
Infant Apgar	[26-28)	7>	3(14.28%)	9(45%)	12(29.27%)	0.029
		7≤	18(85.72%)	11(55%)	29(70.73%)	
		total	21(100%)	20(100%)	41(100%)	
	[28-30)	7>	4(15.38%)	10(41.66%)	14(28%)	0.037
		7≤	22(84.62%)	14(58.34%)	36(72%)	
		total	26(100%)	24(100%)	50(100%)	
	[30-32)	7>	6(25%)	10(38.46%)	16(32%)	0.201
		7≤	18(75%)	16(61.54%)	34(68%)	
		total	24(100%)	26(100%)	50(100%)	
	[32-43)	7>	3(10.34%)	6(20%)	9(15.25%)	0.653
		7≤	26(89.66%)	24(80%)	50(84.75%)	
		total	29(100%)	30(100%)	59(100%)	

Table 4.Comparison of infants' demographic information in the treatment and control groups

Variable	Sub-variable	Treatment group	Control group	Total	p-value
Respiratory problems	Yes	7	26	33(16.5%)	0.001
	No	93	74	167(83.5%)	
	Total	100	100	200(100%)	
Need for artificial ventilation	Yes	9	27	36(18%)	0.001
	No	91	73	164(82%)	
	Total	100	100	200(100%)	
septicemia	Yes	8	20	28(14%)	0.003
	No	92	80	172(86%)	
	Total	100	100	200(100%)	
Birth weight(g)	<2500 g	20	41	61(30.5%)	0.001
	≥2500 g	80	59	139(69.5%)	
	Total	100	100	200(100%)	
Infant Apgar	7>	16	35	51(25.5%)	0.004
	7≤	84	65	149(74.5%)	
	Total	100	100	200(100%)	

Table 5. Comparison of infants' mean of birth weight and the number of stunted pregnancy in the treatment and control groups in terms of pregnancy age

variable	Sub-variables of Gestetional age	Treatment group Mean ± SD	Control group Mean ± SD	P-value
Mean birth weight (g)	[26-28)	2981.71 ± 701.48	2174.34 ± 931.33	0.007
	[28-30)	3081.12 ± 581.19	2441.21 ± 768.20	0.005
	[30-32)	3011.11 ± 543.23	2776.21 ± 613.63	0.020
	[32-43)	32.89.45 ± 312.23	3151.13 ± 251.00	0.080
Mean stunted pregnancy(days)	[26-28)	68.72 ± 21.40	45.57 ± 30.18	0.039
	[28-30)	69.18 ± 57.12	40.03 ± 24.46	0.010
	[30-32)	41.75 ± 17.49	34.45 ± 18.13	0.081
	[32-43)	34.10 ± 11.48	31.88 ± 8.87	0.259

DISCUSSION

The present research indicated that the prescription of vaginal progesterone suppository (200 mg) can probably help to prevent preterm labor and such complications as respiratory problems, need for artificial ventilation, septicemia, low birth weight and low Apgar score. In an examination of the frequency of stunted pregnancy (in days), it was revealed that mothers who had received the treatment at a lower age of pregnancy had a higher rate of stunted pregnancy than their counterparts.

In a review article which perused the 1983-2012 literature, Vincenzo et al. in the UK observed that the receivers of vaginal progesterone suppository (200 mg) had a 44%, 37% and 43% reduction of preterm labor. However, this treatment had no evident effect on reducing such complications as hospitalization in NICU and RDS. Moreover, in five studies reviewed the reduction of preterm labor below 37 weeks had been confirmed in mothers treated with vaginal progesterone suppository (200 mg). This reduction was estimated to be statistically significant [17].

In their investigation of women at their 24^{th}-34^{th} week of pregnancy, Eduardo et al. found a significant 50% reduction of preterm labor in the group treated with vaginal progesterone suppository (200 mg) [15].

Roberto et al. investigated the need for artificial ventilation in the infants of 775 mothers. The findings of this research approved the positive effect of the treatment on reducing the need for artificial ventilation for 51% [18]. Similarly, in the present research the respiratory problems of infants in two groups were examined. Respiratory problems were found to be significantly lower in the infants of mothers who had received vaginal progesterone suppository (200 mg). Only 9%of these mothers had respiratory problems and needed artificial ventilation. In the control group, this percentage was about 3 times as high.

With regard to infant's birth weight, the present research revealed that the infants of mothers who received the treatment had significantly a higher birth weight than others. The number of infants weighing less than 1500 g was reduced for 45%. Similarly, Hassan et al. witnessed a 53% reduction in low birth weight as a result of vaginal progesterone suppository treatment, which is consistent with the finding of the present research [19].

Examination of infants' Apgar scores revealed that the progesterone treatment had managed to create a more desirable condition concerning this variable. In the light of further groupings based on the age of pregnancy, infants whose mothers had been treated at a lower age of pregnancy showed a more optimal Apgar score than the control.
In the present research, septicemia was estimated to be 8% in the treatment group while it was 20% in the control. This attests to the occurrence of about 2.5 times as compared to the intervention group.

Among the limitations of this research is that it was conducted only in one hospital. The quality of services varies across hospitals. Cultural, economic status and life-style of the patients of Shariati Hospital might have affected the results.

This study suggests further investigations of the effectiveness of vaginal progesterone suppository in different doses in preventing preterm labor. It suggests a measurement of the serum level of progesterone in blood across groups and comparing the effect of vaginal progesterone suppository on women with a history of pre-term labor and cervical length of $\leq$35 mm with a cervical cerclage.

CONCLUSION

Considering the findings of the present research, prescribing vaginal progesterone suppository (200 mg) can probably help to prevent preterm labor. It can also prevent such complications as respiratory problems, need for artificial ventilation, sepsis and low Apgar.

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