

# The Effect of Progesterone Suppositories on Threatened Abortion: A Randomized Clinical Trial

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## Abstract

**Background:** Threatened abortion is a common complication of pregnancy. In order to prevent miscarriage in the cases with threatened abortion, this study was conducted to determine whether progesterone suppository is effective in allowing pregnancy to proceed beyond week 20 in women with threatened abortion.

**Methods:** This single-blind clinical trial study was done on 60 pregnant women with threatened abortion. Pregnant women, who had vaginal bleeding until 20 weeks of their pregnancy, were assessed for inclusion. Participants were divided into two groups by random allocation; the control group, which did not undergo any treatment and the case group. The case group was given 400 mg of vaginal progesterone suppository (Cyclogest) each day until their bleeding stopped in less than one week. Participants were followed up until the end of their pregnancy. The treatment was considered successful if pregnancy continued beyond 20 weeks of gestation. Qualitative and quantitative variables were analyzed statistically by Chi Square and T- test respectively. The p-values of less than 0.05 were considered significant.

**Results:** There was no statistically significant difference between the case and the control groups in terms of background variables. The number of abortions in the case group (6 cases, 20%) was lower than the control group which had 10 abortions (33.3%).

**Conclusion:** The study demonstrated that the rate of abortion was reduced in women treated with progesterone suppositories. However, the difference was not statistically significant.

**Keywords:** Progesterone suppository, Threatened abortion.

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## Introduction

Abortion is the spontaneous loss of the fetus before twenty weeks of gestation. It is a traumatic event that can have psychological consequences for the couples (1). Threatened abortion, as demonstrated by vaginal bleeding with or without abdominal cramps, is a common complication of pregnancy. It occurs in 20 percent of women during early gestation and approximately half of these pregnancies will abort (2, 3). Even

if abortion does not follow early bleeding, these fetuses are at increased risk for preterm delivery, low birth weight and prenatal death (4). A number of recent studies suggest that progesterone can reduce pregnancy loss in women with threatened abortion (5-10). By progression of pregnancy, the role of insufficient progesterone level declines and uterine structural malformation with or without cervical incompetency is responsible more than

hormonal deficit. In this case, some approaches like cervical cerclage can be effective more than medical interventions (11). Progesterone plays a crucial role in the maintenance of pregnancy. In the presence of sufficient progesterone levels during pregnancy, lymphocytes synthesize a mediator called progesterone induced blocking factor (PIBF), which is anti-abortive in mice (12, 13). Besides inducing secretory changes in the endometrium and supporting early pregnancy, it modulates the maternal immune response to prevent fetal rejection and relaxes the uterine smooth muscles (14). Despite this physiological evidence, which has led to progestogens being used in management of threatened abortion for many years, there is little data available to support their routine use in this issue (15). The aim of this study was to determine whether progesterone is effective in allowing pregnancy to proceed beyond week 20 in women with threatened abortion.

### Methods

This clinical trial study was done on 60 pregnant women with threatened abortion from April 2009 to March 2012 at Taleghani Hospital affiliated to Shahid Beheshti University of Medical Sciences. This trial was a single-blind study, in which the researchers did not have any placebos for the control group and were unaware which patient had received progesterone. The study was approved by the bioethics committee (400.11199/30 May 2012) of Shahid Beheshti University of Medical Sciences after the approval of the research group in the obstetrics and gynecology department. Verbal consent of all the pregnant women participating in the trial study was received as well. Pregnant women, who had vaginal bleeding until 20 weeks of their pregnancy, were assessed for inclusion. Participants underwent a general and pelvic examination, a pelvic ultrasound and a complete measurement of their blood count. In order to be included in the study, the women were required to have no systemic disease or fever and no loss of conception tissue. The presence of singleton pregnancy and detection of fetal heart activity, besides gestational age of less than 20 weeks was verified by ultrasound. Women were excluded if they had reaction to Cyclogest, multiple gestation, absence of fetus or fetal heart tone, uterine anomaly or fetal anomaly. Participants were divided into two groups; the control group, which did not undergo any treatment and the case group. The case group was given 400 mg of vaginal progesterone sup-

pository (Cyclogest, Actavis, UK) each day until their bleeding stop-ped for several days, mostly less than one week. Progesterone in suppository and injection form and in a short time usage did not have any adverse effect on mother or fetus (4, 6). Those who had slight vaginal bleeding received progesterone sup-pository only for 2 days. However, for those with moderate or severe vaginal bleeding, it continued up to one week. The sample size was 60 based on  $p_1=80\%$ ,  $p_2=50\%$  expected rate of abortion in threatened abortions,  $\alpha=0.05$  and  $\beta=20\%$ . Each group was selected by random allocation based on included criteria. Both groups consisted of 30 participants and were kept under standard care in terms of hydration and rest. Participants were followed up until the end of their pregnancy. The treatment was considered successful if pregnancy continued beyond 20 weeks of gestation.

**Statistical analysis:** Data analysis was performed by SPSS software version 18. Qualitative and quantitative variables were analyzed statistically by Chi Square and T-test respectively. The p-values of less than 0.05 were considered significant.

### Results

A total number of 60 pregnant women, with threatened miscarriage, participated in the study. All of them were referred to the Department of Obstetrics and Gynecology at Taleghani Hospital. The total age range was from 18 to 37 years with a mean value of  $27\pm 4$ . There was no statistically significant difference between the case group and the control group in terms of mothers' ages, gestational ages and parity score. The mean value of mothers' ages was  $27\pm 4$  years in the case group and  $27\pm 5$  years in the control group. Average gestational age was 9 weeks $\pm 3$  days in the case group and 10 weeks $\pm 3$  days in the control groups. Moreover, there were 20 nulliparous women in the case group and 18 in the control group, with the rest being multiparous. Repeated abortions were excluded. Five patients in the case group and nine patients in the control group had moderate to heavy uterine bleeding. Overall, 9 patients in the case group and 7 patients in the control had abdominal cramp with vaginal bleeding, but the outcome of ongoing pregnancy or abortion did not differ in both groups. The number of abortions in the case group was lower than the control group (6 cases, 20% against 10 cases, 33.3% respectively). However, the difference was not statistically significant.

**Table 1.** The effect of progesterone suppositories on threatened abortion based on maternal and perinatal characteristics

|                               | Case Group | Control    | Total      | Chi-Square | df | p-value |
|-------------------------------|------------|------------|------------|------------|----|---------|
| Miscarriage                   | 6 (20%)    | 10 (33.3%) | 16 (26.7%) | 1.364      | 1  | 0.243   |
| Successful delivery           | 24 (80%)   | 20 (66.7%) | 44 (73.3%) |            |    |         |
| <b>Parity</b>                 |            |            |            |            |    |         |
| Nulliparous                   | 20 (66.7%) | 18 (60%)   | 38 (63.3%) | 0.287      | 1  | 0.592   |
| Multiparous                   | 10 (33.3%) | 12 (40%)   | 22 (36.7%) |            |    |         |
| <b>Pain</b>                   |            |            |            |            |    |         |
| No                            | 21 (70%)   | 23 (76.7%) | 44 (73.3%) | 0.341      | 1  | 0.559   |
| Yes                           | 9 (30%)    | 7 (23.3%)  | 16 (26.7%) |            |    |         |
| <b>Vaginal bleeding</b>       |            |            |            |            |    |         |
| vaginal bleeding (moderate)   | 5 (16.7%)  | 9 (30%)    | 14 (23.3%) | 1.491      | 1  | 0.222   |
| Vaginal spotting              | 25 (83.3%) | 21 (70%)   | 46 (76.7%) |            |    |         |
| <b>Gestational age (week)</b> |            |            |            |            |    |         |
| age <8                        | 5 (16.7%)  | 6 (20%)    | 11 (18.3%) | 0.424      | 2  | 0.809   |
| 8<age<16                      | 23 (76.7%) | 23 (76.7%) | 46 (76.7%) |            |    |         |
| age >16                       | 2 (6.7%)   | 1 (3.3%)   | 3 (5%)     |            |    |         |

As demonstrated in table 1, 80% of women in the case group and 66.7% of women in the control group had a successful term pregnancy. This difference was not statistically significant ( $p=0.243$ ). Approximately 66.7% of patients with successful delivery in the case group and 60% in the control group were nulliparous ( $p=0.592$ ). Moreover, 70% of the patients with successful delivery in the case group and 76.7% of them in the control group had no abdominal cramp ( $p=0.559$ ). Accordingly, neither parity nor abdominal cramp had any effect on the outcome of pregnancy.

### Discussion

This study was conducted in order to assist pregnant women with threatened abortion, since miscarriage is a deeply distressing condition for couples (1). The study demonstrated that the rate of abortion was reduced clinically but not statistically in women treated with progesterone suppository as compared to women who received only supportive care. These findings support recent studies on women with threatened abortion that have shown a reduction in pregnancy loss with progesterone treatment (3, 7-10, 21).

Pro-inflammatory cytokines associated with miscarriage and progesterone-induced blocking factor (PIBF) had inhibitory effect on immune reaction and shifting of cytokines from type 1 to type 2 cytokines caused an increase in the production of cytokines type 2 (22). Pregnancy is often hampered by immunological factors, luteinic and neu-

roendocrine deficiencies and myometrial hypercontractility. This may explain the reduction in abortion in women treated with prophylactic progesterone (3, 6, 9, 19).

There are some studies, however, that show insufficient data on the effect of progestogens on threatened miscarriage (2, 5, 6, 15).

According to one study from El-Zibdeh, miscarriage rates were significantly lower in the group treated with dydrogesterone as compared to the untreated group (16). Progestogens also have a direct pharmacologic effect by reducing the synthesis of prostaglandins, thereby relaxing uterine smooth musculature and preventing inappropriate contractions that may result in miscarriage and preterm labor pain (5, 18-20). Some pregnant women have lower abdominal pain followed by missed period, but if lower abdominal pain is associated with uterine bleeding, it may predict impending abortion. In this study, however, most of the pregnant women had no abdominal pain in either the case group or the control group and the difference between two groups was not statistically significant.

A study has shown that the use of progesterone is effective in both pain relief and decreasing the frequency of uterine contractions after 5 days of progesterone usage (8).

Effect of progesterone on different gestational ages was also evaluated in this study. In gestational age of 8 weeks or less, 80% of participants in the case group and 50% of participants in the

control group had successful delivery. In gestational age of 8 to 16 weeks, 80% of pregnant women treated with progesterone had successful delivery as compared to the 60% in the control group. In gestational age of more than 16 weeks, 80% of pregnant women treated with progesterone and 50% of women in the control group had successful delivery. The difference between the two groups was not statistically significant. In previous studies, there has been no report of comparison between case and control groups with respect to different gestational ages. There are some studies which have reported some problems during the course of pregnancy in women with threatened abortion (4, 16). However, in this study, all pregnant women who passed their course of threatened abortion had normal term pregnancies.

### Conclusion

The study demonstrated that the rate of abortion was reduced in women treated with progesterone, irrespective of their gestational age. Nevertheless, its effect on prevention of abortion was not statistically meaningful, which may be due to the study's small sample size. The use of large sample sizes, double-blind and randomized controlled trials are recommended for future studies on this issue.

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### Conflict of Interest

This article is extracted from the obstetrics and gynecology resident thesis in Shahid Beheshti University of Medical Sciences.

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