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Comparison of dydrogesterone tablet and progesterone suppository effects on the outcome of pregnancy in pregnant women with threatened abortion: A Randomized Clinical Trial

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ABSTRACT

The aim of this study was to compare the effects of oral and suppository of Progesterone in pregnant women lower than 12th weeks of gestation with threatened abortion to prevent miscarriage. This random clinical trial study was conducted on 200 pregnant women with threatened abortion and gestational age ≤ 12 weeks who were referred to Kosar obstetrics and gynecology clinic in Shahid Motahari hospital affiliated to Urmia University of Medical Sciences, 2014. All study population was randomly divided into two equal groups considering the amount of vaginal bleeding (mild to moderate). Group I (received Dydrogesterone tablet) and group II (received Progesterone suppository). The participants' data such as age, gestational age, history for vaginal bleeding in previous pregnancies, the amount of vaginal bleeding were collected in the researcher- made questionnaire. The mean gestational age at the first ultrasound assessment in the group I and II was 9.28 ± 2.68 weeks and 9.41 ± 3.45 weeks, respectively (P = 0.76). In the group I, 53 (53%) of patients had mild vaginal bleeding and 47 (47%) of them had moderate vaginal bleeding. These figures in the group II were 46 (46%) and 54 (54%) respectively (P = 0.19). In the group I, 74 (74%) of pregnancies ended in birth while 26 (26%) of pregnancies were aborted. In the group II 78 (78%) of women had full- term pregnancy and 22 (22%) of them had abortion (P = 0.31). In the current study, no significant difference was found between the two groups in terms of continuing the pregnancy. But because of using oral Dydrogesterone are more convenient for patients as compare as vaginal Progesterone,and it is suggested that Dydrogesterone tablets are more prescribed for threatened abortion patients.

Key words: Pregnancy, Threatened abortion, Dydrogesterone tablet, Progesterone suppository

1. INTRODUCTION

Abortion is the most common complication of pregnancy (1). Although abortion is not associated with high mortality and morbidity, but it causes a lot of emotional and psychological effects on pregnant women (2). Threatened abortion is diagnosed when a vaginal bleeding appears in the presence of a viable fetus and a closed cervical os before 20 weeks of gestational age (3). While threatened abortion occurs in about 20% of pregnancies in the first trimester 50% of that lead to complete abortion (4, 5). It is worth noting that the risk of abortion doubles in pregnant women who have mild vaginal bleeding than women without bleeding during pregnancy, and this possibility will be increased to four times in the presence of heavy vaginal bleeding (4). Among women who experienced vaginal bleeding in the first trimester of pregnancy without complete abortion; so the risk of antepartum hemorrhage, preterm labor and low birth weight will be increased (3). Several risk factors can increase the rate of complete abortion such as older women, increased pre-pregnancy maternal body mass index (BMI), maternal serum Progesterone levels and living habits (like caffeine, some exercises, stress, smoking and alcohol consumption) (6). In the case of threatened abortion, the following measures are necessary; a pelvic exam to check the inevitable abortion, ultrasound to prove the presence of live fetus and laboratory testing to evaluate of fetal growth (7). Threatened abortion may occur for many reasons such as placental dysfunction (which can lead to preterm delivery, preeclampsia, placenta previa and IUGR), ineffective vascularization and chronic decidual inflammation (8). The outcome of threatened abortion can be predicted by some biochemical markers including serum β hCG, Progesterone, pregnancy-associated plasma

protein A (PAPP-A), inhibin A and activin A (9, 10). Progesterone is a steroid hormone that is secreted from ovarian granulosa cells; and it causes decidual changes in endometrial, and prepares the uterus and it causes decidual changes in endometrial and prepares the uterus for implantation of the blastocyst (9). Progesterone is secreted from the corpus luteum during pregnancy (11). This hormone inhibits the contraction of smooth muscle and production of prostaglandins, also blocks the mother's cellular immune responses (9). Progesterone stimulates the production of particular substance from the lymphocytes of mice that are known as the anti-abortion (11). One study concluded that Progesterone with a level more than 37.2 ng/ml, and 90% sensitivity with 75% negative predictive value and 92% specificity with 97% positive predictive value shows the pregnancy continues (9). In another study, the abortion rate was reduced by using of Progesterone suppository (12). Progesterone can be prescribed in different route; orally, vaginally, and intramuscularly (13). The intramuscular injection of Progesterone can be produced the highest blood levels, but it can be associated with possible complications of pain and abscess formation (14). Although vaginal effective dose can be provided by using the vaginal suppository, but in the presence of vaginal bleeding, its use is often difficult or even it may be washed out with severe vaginal bleeding (13). Oral administration of Progesterone does not have effective blood levels and also some side effects occur such as nausea, drowsiness and headaches (13-15). Dydrogesterone is structurally and pharmacologically similar to the natural Progesterone with higher bioavailability and fewer side-effects, so it can be used instead of Progesterone (13). Dydrogesterone has high specificity for Progesterone receptor and it is different with other synthetic Progesterone because it does not have androgenic and anabolic properties or hormonal effects like estrogen and corticoid. Numbers of recent studies have suggested that Dydrogesterone can reduce the abortion rate among women with bleeding-threatening. A study on 111 women under treated with Dydrogesterone showed acceptable results, and there were only 9 abortions (16). Some other studies compared Dydrogesterone therapy with conservative treatment in women with vaginal bleeding at 13th weeks of pregnancy; according to their results, abortion rate in the Dydrogesterone group is significantly lower than conservative group- including prescribed complete bed rest and Progesterone (17, 18). 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 routineuse in this issue (19). The purpose of the current study is to compare the effects of dydrogesterone and Progesterone in pregnant patients who were referred because of threatened abortion and also to evaluate and comparation between Dydrogesterone drug and Progesterone suppository in maintaining pregnancy in patients with threatened abortion.

2. MATERIALS AND METHODS

This randomized clinical trial study was performed on 200 pregnant women at gestational age ≤ 12 weeks who were referred due to threatened abortion to Kosar obstetrics and gynecology clinic in Shahid Motahari hospital affiliated to Urmia University of Medical Sciences, 2014. The study treatment conducted on non- hospitalized women, but in the case of long distance between patients' living locations to the hospital, they were hospitalized to follow-up treatment. All study population was randomly divided into two equal groups - considering the amount of vaginal bleeding (mild to moderate). Group I (received Dydrogesterone tablet) and group II (received Progesterone suppository). Inclusion criteria were singleton pregnant women at the first trimester with symptoms of threatened abortion, having an ultrasound report that confirmed a viable fetus, no history of uterine anomalies and mullerian defects, having a closed cervical os, and no history of smoking and alcohol. Exclusion criteria included the presence of underlying diseases such as hypertension, diabetes, severe hepatic impairment, antiphospholipid syndrome, fever, disorders of the cervix and cervical length are less than 3 cm, allergy to components of prescribed drug, severe bleeding, absence of a normal gestational sac in 5th week, the absence of fetus at the 6th weeks of gestation, and absence of heart activity in 7th weeks of pregnancy. After history-taking and preliminary examinations, an ultrasound examination was performed for confirming a live fetus in the uterus; then patients received their treatment protocol according to their group. The participants' data such as age, last menstruation age (LMP) and gestational age, history of previous pregnancies, the history for vaginal bleeding in previous pregnancies, the amount of vaginal bleeding, history of previous abortion, etc. were collected in the researcher-made questionnaire. For each patient BMI was assessed and reported in her questionnaire. Patients attending the clinic on Saturday, Monday or Wednesday were allocated to dydrogesterone and those attending on Sunday, Tuesday or Thursday were allocated to the Progesterone suppository group. Group I (Dydrogesterone group) received 40 mg Dydrogesterone stat followed by 10mg daily, (Duphaston®, Solvay Pharmaceuticals, USA.) which was continued one week after stopping bleeding. The group II (Progesterone group) was given vaginal Progesterone suppository 200 mg (Cyclogest, Actavis, UK)) each night and was continued until the end of vaginal bleeding. During treatment, patients were examined and evaluated weekly. Patients were re-examined and also re-evaluated by ultrasound after stopping vaginal bleeding. The obtained results from two groups were compared like the number of days of vaginal bleeding, the amount of bleeding, the number of hospitalization days, and continuation of pregnancy after 20 weeks of gestational age and the side effects of prescribed drug such as burning and vaginal discharge. The

amount of bleeding was evaluated by the number of pads consumption: 1-2 pads was as mild bleeding, 3-4 pads medium and more than 4 pads, or if there was blood clots was severe bleeding. All patients received standard supportive treatments include iron supplements, folic acid and multivitamins. For continuous variables, data were presented as means ± standard deviation (SD) and for categorical variables; as number with frequency. The comparisons of variables between the two groups were made using the Fisher's exact or Chi-square methods for categorical variables. The Mann-Whitney and t- test were used for the continuous variables. Statistical analysis was performed using SPSS version 20 and STATA 11, and data with P <0.05 were significant. Ethical Considerations - Our research approved by the ethics committee of Urmia University of Medical Sciences. Informed consent was obtained from all participants of this study.

3. RESULTS AND DISCUSSION

A total number of 200 pregnant women at gestational age ≤ 12 weeks with threatened miscarriage, participated in the study. The mean ages (± SD) in Dydrogesterone and Progesterone groups were 27.57 ± 5.63 and 27.68 ± 5.68 years, respectively. T-Test did not show significant difference between two groups (P = 0.89). The mean BMI in the Dydrogesterone group was 26.67 ± 2.29 kg /m^2 and in the Progesterone group 25.42 ± 2.46 kg /m^2. According to the T- test; there was no significant difference between study groups (P=0.21). The two groups were similar about history of previous pregnancy. While in Dydrogesterone group, 54 women (54%) had a history of previous pregnancy, this figure in Progesterone group was 52 women (52%). According to Fisher's Exact test; it was not observed significant difference between two groups regarding the history of previous pregnancy (P=0.44). In Dydrogesterone group, only 8 women (8%) had a history of vaginal bleeding in previous pregnancy, and in Progesterone group 7 women (7%). The two groups were also similar about history of vaginal bleeding in previous pregnancy. According to Fisher's Exact test; there was no significant difference between two groups about history of vaginal bleeding (P=0.50). The first ultrasound showed that the mean gestational age was 9.28 ± 2.68 and 9.41 ± 3.45 weeks in the Dydrogesterone and Progesterone groups, respectively. There was no significant difference between study groups, according to the T- test (P=0.76). The second ultrasound showed that the mean gestational age for Dydrogesterone group was 20.54 ± 5.43 weeks and for Progesterone group 20.47 ± 5.79 weeks after stopping vaginal bleeding and T- test showed P.value =0.2 (Table 1).

Table 1. Participants' features among two groups

Treatment group / Variables	Group I (Dydrogesterone tablet) N=100	Group II (Progesterone suppository) *N=100*	P.value
Age (years) (Mean±SD)	27.57±5.63	27.68±5.68	0.89
BMI (kg/m^2) (Mean±SD)	26.67±2.29	25.42±2.46	0.21
History of previous pregnancy (n,%)	54(54%)	52(52%)	0.44
History of previous vaginal bleeding (n,%)	8(8%)	7(7%)	0.50
gestational age at the first ultrasound(Mean±SD)	9.28±2.68	9.41±3.45	0.76
*The amount of vaginal bleeding: (n,%) - Mild (1-2 pad) - Moderate(3-4 pad)	 53 (53%) 46(46%)	 47 (47%) 54 (54%)	0.19
duration of vaginal bleeding(day) (Mean±SD)	2.91± 1.50	2.73 ±1.61	0.4
duration of hospitalization(day) (Mean±SD)	3 ± 1.73	4	0.56
gestational age at the second ultrasound(Mean±SD)	20.54±5.43	20.74±5.79	0.2
*Successful pregnancy: (n,%) -yes -no	 74 (74 %) 26 (26 %)	 78(78%) 22 (22%)	0.31
*The side effects of drugs: (n,%) -yes -no	 0(0%) 15(%)	 100(100%) 85(85%)	0.000

*Fisher Exact test

In this study, the amount of vaginal bleeding was evaluated according to the numbers of pad consumption. In Dydrogesterone group, 53 women (53%) were recorded in the mild vaginal bleeding group and 47 women (47%) in the medium group. In Progesterone group, these records were 46(46%) and 54 (54%), respectively. According to Fisher's Exact test; it was not observed significant difference between two groups regarding the amount of vaginal bleeding (P=0.19) (Table 1). The mean duration of vaginal bleeding in the first and second group was 2.91± 1.50 and 2.73 ±1.61 days, respectively. According to T-test; there was no significant difference between two groups about duration of bleeding (P=0.4). Among group I; three patients were hospitalized for 3 ± 1.73 days and in the group II only one woman was hospitalized but for 4 days. There was no significant difference between study

groups, according to Mann- Whitney test (P=0.56). In the first group, pregnancy was continued among 74 women (74 %) but in 26 women (26 %) was aborted. In the second group, these figures were 78(78%) and 22 (22%), respectively. According to Chi- square test; it was not observed significant difference between two groups regarding the continuation of pregnancy (P=0.31) (Table 1). The obtained results showed that, there was not any side effect of prescribed drug (Dydrogesterone oral tablet) in the group I. In the group II (Progesterone suppository) 15 women (15%) showed some side effects, while 85 women (85%) in this group did not have any side effects. Most patients in the group II complained from burning and itching of the vagina, and 1 woman complained from vaginal discharge. According to Fisher's Exact test; there was a significant difference between two groups regarding the side effect of prescribed drug (P=0.000). The aim of this study was to investigate compararative Dydrogesterone oral tablet with Progesterone suppository to prevent miscarriage in the cases of threatened abortion. According to our results in the two groups no significancy in pregnancy continiuation was reported (P=0.31). In a comparative study in women who were referred because of threatened abortion, the rate of continuing pregnancy by administered Dydrogesterone was more than control group who did not receive any medication (P< 0.05). This study showed no difference between the two groups regarding to preterm delivery, preeclampsia, low birth weight and congenital anomalies (20). The same results were reported in a study about Dydrogesterone administration in women with threatened abortion as compared to control group (21). In a systematic review study was indicated that the administration of Dydrogesterone reduced 47% of the miscarriage risk in women with threatened abortion (13). In the study based on Cochrane review was reported that, Progesterone administered decreased the risk of miscarriage in women with threatened abortion, without any impact on increasing the rate of congenital anomalies or pregnancy-induced hypertension as compared to control group (19). In two other studies were demonstrated that administration of Progesterone reduced the miscarriage rate in patients with recurrent spontaneous abortion (11, 22). In a randomized clinical trial study, was determined that Progesterone administration did not show any effect on pregnancy outcomes in threatened abortion women, but it significantly cause to decrease in interferon gamma (IFNγ) and increase in interleukin-10(IL-10) in endocervical secretion (23). A decline in the uterine contractions and pain was provided in women at the risk of threatened abortion with vaginal Progesterone consumption in a prospective, randomized, double-blind study (P < 0.005) (24). Other randomized clinical trial study also determined that administration of Progesterone reduced the miscarriage rate in patients with threatened abortion, although this rate was not statistically significant (P=0.243) (12). In a study showed that, administration of Dydrogesterone and Dihydrodydrogesterone had fewer androgenic effects on the fetus as compared to Progesterone (25). According to a randomized clinical trial study, Dydrogesterone tablets had similar effect with Progesterone vaginal suppository to support of luteal-phase in patients who were undergoing in vitro fertilization (IVF) (26).

4. CONCLUSION

The study demonstrated no significant differences were found between the two groups in terms of continuing the pregnancy. 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; But because of the use of oral Dydrogesterone are more convenient for patients than vaginal Progesterone, it is recommended that Dydrogesterone tablets are more prescribed for threatened abortion patients.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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