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The Effect of Oral Progesterone on Deceasing Preterm Labor in Patients with a History of Preterm Labor

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Abstract

Background

Preterm birth with a prevalence of about 10% causes 75-95% of prenatal mortality, and one of the effective factors of it is hormonal factors. This study aimed to investigate the effect of oral medroxy progesterone on reducing preterm labor in women with a history of preterm labor.

Materials and Methods

This double-blinded clinical trial was performed on 214 pregnant women with the history of at least one preterm labor referred to midwifery clinic of Fatemieh Hospital, Shiraz, Iran, during 2017 to 2018. One hundred and seven women underwent treatment with oral medroxy progesterone (100 mg per day), and 107 individuals were prescribed placebo, and prenatal care was performed routinely. Recent pregnancy course and delivery time were compared in two groups. Data were analyzed by SPSS software version 16.0.

Results

Gestational age with a mean of 30 ± 3.89 and 36± 2.11 weeks, respectively in control and intervention groups differed significantly (P <0.05). The number of referrals to hospital due to preterm labor, the age of patients at first referral due to preterm labor, and age of delivery in both groups of receiving progesterone and placebo were significantly different (P <0.05).

Conclusion

Based on the results of the current study using 100 mg oral progesterone per day in weeks 16-36 of pregnancy was effective in reduction of preterm labor, and caused improved gestational age in mothers.

Key Words: Oral Medroxy Progesterone, Pregnant women, Preterm Labor.

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1- INTRODUCTION

Preterm labor is referred to birth before 37th week of pregnancy, its prevalence in developed countries varies between 6-12%, and in developing countries this prevalence is 22-26%, and is also one of the reasons for prenatal mortality (1-5). The chance for survival of premature fetuses increases with increasing gestational age. In addition to mortality, premature infant is susceptible to physical and intelligence disorders, and the cost of caring for these infants in intensive care units is high (6-9). Etiology of preterm labor is unclear but risk factors related to maternal aspects, infections, mothers' life-style, chronic diseases in mother, hereditary factors, and hormonal factors are known; one of the important risk factors is history of previous preterm labor as the risk of later preterm labor will be increased by each time of previous preterm labor (10).

Despite many progresses in treatment of preterm labor, its prevalence has not been decreased in the last decades (11). Progesterone, one of the hormones secreted by the placenta, is essential for maintaining pregnancy survival. Weekly injection of 17-alpha hydroxyprogesterone caproate or using daily progesterone suppository causes decrease in the number of preterm labors in high-risk women with the history of preterm labors (12-14). Various clinical trials investigated the effect of 17-hydroxyprogesterone and vaginal progesterone in patients with history of preterm labor (15-17).

On the other hand O'Brien et al., found that using progesterone gel is not effective in reducing preterm labor in comparison to placebo (18). Several studies showed that using progesterone prevents preterm labor (12-17). The medication commonly used in the studies was 17-hydroxyprogesterone. Using 17-hydroxyprogesterone has shown promising results but intramuscular injection is painful and requires somebody to help inject it. Micronized progesterone has been used orally and vaginally in defects of luteal phase and loss of early stages of pregnancy. However, vaginal route is not acceptable by most of the patients, since it causes increase in vaginal secretions that bothers the patient. Therefore, since the oral progesterone to prevent preterm labor has not been investigated, the aim of the current study is to investigate efficacy, safety and the effects of oral progesterone (Medroxyprogesterone) to prevent preterm labor in mothers with history of preterm labor.

2- MATERIALS AND METHODS

2-1. Study design and population

This study was a clinical trial performed on pregnant women aged 18-35 years with history of preterm labor referred to midwifery clinic of Fatemieh Hospital, Shiraz, Iran (covered by Shiraz University of Medical Sciences) in the second half of year 2018 and first half of year 2019. Two hundred and fourteen pregnant women were selected randomly, all of which had history of preterm labor. Then the participants were allocated in two equal groups (107 patients in case group and 107 patients in control group). Both groups were matched based on age of mother, partum, and history of preterm labor. For all of the patients a questionnaire consisted of age, gravity, abortion history, preterm labor history, the underlying reason for preterm labor, the type of previous labor (vaginal or cesarean section) and the weight of previous child was filled.

2-2. Inclusion criteria

Inclusion criteria were pregnant women aged 18-35 years with a history of spontaneous preterm labor between weeks 20-36 of gestation which had no contraindication for continuing their pregnancy.

2-3. Exclusion criteria

Exclusion criteria were women with fetal anomaly, vaginal bleeding during first semester of pregnancy, active hepatic disease, and the age lower than 18 years or more than 35 years.

2-4. Ethical consideration

After approval by ethical committee of Hamedan University (IR.UMSHA.REC.1395.377), firstly the protocol of the study was completely explained to the participants, and in case of agreement of mothers, they were entered to the study. Participating in the study and also exit from the study was voluntary. This study is registered at clinical trial site with the code of IRCT201710079014N192.

2-5. Intervention

After random allocation of mothers in two groups of intervention (mothers with a history of preterm labor treated by medroxyprogesterone), and control (placebo group), midwifery examination and systematical and physical were performed by gynecologist in first visit for both intervention and control groups. Gestational age was calculated based on last menstrual period (LMP), and crown-rump length before week 12, and also Biparietal diameter (BPD) diameter in second trimester was considered. Examination by speculum was done at first visit. Transabdominal sonography (TAS) between weeks 16-18 for serial biometry of fetus, placental location, fluid volume, and rejection of fetal anomalies were performed. TVS during first and second weeks was performed to measure cervix length and diameter of internal os, which cerclage is required for assessment. Patients in control group were prescribed placebo capsule (manufactured by Shiraz school of pharmacy and contained gelatin) twice daily and patients in intervention group were prescribed 100mg medroxyprogesterone (manufactured by Aboureihan Pharmaceutical Company, Iran) twice daily from week 16 of gestation to a maximum of 36^{th} week of gestation. This regimen was continued until 36^{th} week or until the time of labor (each happened sooner). Women were asked to refer for check-up every two weeks. Patients and physician were not aware of the dose and type of the prescribed medication until time of labor and end of the intervention. In the intervention group patients with preterm labor were treated based on protocol, and the study results were assessed based on gestational age, and classification was as follows: below 28 weeks, 28^{th} to 32^{nd} week, 32^{nd} to 34^{th} week, 34^{th} to 36^{th} week, and over 36^{th} week. For control group routine prenatal care was performed.

2-6. Data Analyses

Then pregnancy results in both groups were compared. Obtained results for both groups were analyzed by SPSS software (version 16.0). Frequency tables to describe data and Chi-square test and T-test to compare between case and control groups were used. P-value less than 0.05 were considered as significant. Normality of distribution was assessed by Kolmogrov-Smirnov

3- RESULTS

Two hundred and fourteen individuals participated in this study, of which 107 individuals were in control group and 107 individuals were in intervention group. There were no significant differences for age, educational level, and social class between two study groups ($P>0.05$). The total times of referral to hospital in two groups with a mean of 2.89 ± 1.04 times for control group and 2.61 ± 1.42 times for intervention group did not differ significantly ($P<0.05$). The first referral of mothers to hospital in the control group was at 26^{th} week of gestation and in the intervention group was 29^{th} week ($P<0.05$).

The number of referrals to hospital due to preterm labor was 0.59 ± 1.38 times in control group and 0.44± 1.23 times in intervention group (P<0.05). The total lost pregnancies, patient's age, and the number of gravidities were not significantly different (P>0.05). Gestational age was about 30 ± 3.89 weeks in control group and 36 ± 2.11 weeks in intervention group and this difference was significant between groups (P<0.05). There were no significant differences in regard to other outcomes of pregnancy such as infant death, infant infection, fetal death and number of abortions between groups receiving progesterone and placebo (P>0.05). The number of abortions in first trimester were not significantly different but the number of abortions in second trimester with a mean of 0.45 ± 1.17 in control group and 0.19 ± 1.67 in intervention group was significantly different.

The results showed that 4% (5 individuals) in control group experienced labor after 36th week and about 50% (50 individuals) in intervention group experienced labor after 36th labor. Twenty-seven individuals (25%) in control group delivered before 28th week of gestation, and none of the individuals in intervention group delivered before 28th week of gestation. Twenty individuals (18.7%) in control group and 1.9% (2 individuals) in intervention group delivered between 28th-32nd week of gestation. Forty-six individuals (43%) in control group and 11 individuals (10.3%) in intervention group delivered during weeks 32-34, and 9 individuals (8.4%) vs. 44 individuals (41%) in intervention group delivered between 34th-36th week of gestation.

4- DISCUSSION

The current study aimed to assess efficacy, safety, and the effects of oral progesterone for prevention of preterm labor in mothers with a history of preterm labor. Despite numerous clinical trials on preterm labor and many advances in midwifery science, the best therapeutic method is yet challenging. Unfortunately, in the last two decades no progress has been made in reducing preterm labor (19, 20). In the current study consumption of 100mg/day of progesterone from 16th week of gestation showed increased gestational age in group receiving progesterone in comparison to control group (P<0.05). A review study in 2006 reported that initiation of prescription of progesterone from second trimester might reduce the risk of preterm labor before 37th week of gestation (21). In the study by Bahadori et al., mean and standard deviation of gestational age at the labor time in the progesterone group and control group differed significantly (22). Spong et al., in their study in 2005 in America on women with preterm labor found that mean gestational age at labor time in intervention group with progesterone was significantly higher than control group (6).

Other studies also reported the effect of progesterone on reducing preterm labor (10, 15, 19, 23-26). In addition, some previous studies showed the lack of effectiveness of progesterone in reducing risk of preterm labor (27, 28). Senat et al., in a study in 2013 in France found that treatment with injectable progesterone causes significant change in the rate of preterm labor (29). In the study by Grobman et al., in 2012 in America, the rate of preterm labor was not significantly different between groups receiving progesterone and placebo (30). Salari performed a study in 2012 in Iran on 100 pregnant women with the symptoms of preterm labor, but he did not observe any significant difference between two groups receiving progesterone and isoxsuprine for the rate of preterm labor (31). Although mechanism of the effect of progesterone in prolongation of pregnancy is not yet understood, but according to studies performed up to date in this context,

progesterone relaxes myometrial smooth muscles, inhibits oxytocin, and inhibits formation of connections between myometrial cells of uterus which is essential for coordination of uterus muscles which results in labor (32). However, this point should be considered that prescribed progesterone doses in various studies were different. For example, Saghafi et al., used 250 progesterone vial weekly, intramuscular (19), and the progesterone dose of our study was 100mg per day. It seems that minimum prescribed progesterone is also effective in reducing preterm labor, and there is no need to prescribe higher doses of progesterone. On the other hand, oral progesterone was not used in any of the previous investigations. In this study for other outcomes of pregnancy such as neonatal death, neonatal infection, fetal death, and the number of abortions in two groups receiving progesterone and placebo, no significant difference was observed which is consistent with Briery et al.'s study (33). In the current study, frequency of labor before 32nd week in women treated by oral medroxyprogesterone in comparison to control group was significantly lower. Despite numerous studies in the context of the effect of progesterone for prevention of preterm labor, the effect of progesterone on mortality and complications before birth is controversial and further studies in this context are needed (34-36).

5- CONCLUSION

Based on the results of the current study using oral progesterone (100 mg per day from 16th week until 36th week of gestation) is effective in the rate of preterm labor and improves gestational age. Performing studies with larger sample size in order for better investigation of the role of oral progesterone in prevention of preterm labor are recommended. Since some factors such as high rate of previous lost pregnancies represents underlying problem of the patient, and there is no significant association for control and intervention group in this context. Therefore, it seems that correct selection of individuals who may take advantage of treatment with progesterone in order to prevent preterm labor is cost effective and causes reduction in unnecessary costs.

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7- CONFLICT OF INTEREST: None.

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