Original Article

Maintenance Therapy by Vaginal Progesterone after Threatened Idiopathic Preterm Labor: A Randomized Placebo-Controlled Double-blind Trial

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Abstract

Background: Patients with arrested preterm labor (PTL) are at increased risk for recurrence of preterm birth (PTB). Maintenance tocolysis after arrest of acute PTL is of questionable value. The objective of this study was to evaluate the efficacy of 200 mg vaginal progesterone in order to prevent PTB in women with episodes of threatened PTL.

Materials and Methods: This is a randomized double blind clinical trial study.Women with singleton pregnancies between 28-36 weeks of gestation, who were hospitalized for PTL were included. A total of 173 pregnant patients were randomly allocated to receive 200 mg vaginal progesterone suppositories (n=86) or placebo (n=87) daily until the 36th gestational week. The two groups were compared relative to demographic characteristics, incidence of PTB before 34 and 37 weeks, and maternal and neonatal complications. Data were analyzed by chi-square and Fisher's exact tests.

Results: Mean latency until delivery in the cases was longer than the control group (23.88 ± 18.01 vs. 16.67 ± 12.9; p=0.004).Treatment with progesterone was not associated with a reduction in the rate of PTB before 34 weeks [cases: 9 (10.8%) vs. controls: 8 (10%)] and 37 weeks [cases: 45 (54.2%) vs. controls: 33 (41.2%)]. Log rank analysis revealed a significant difference for mean time to delivery between the two groups (p=0.028). There were no significant differences for neonatal and maternal complications in the two groups.

Conclusion: Prophylactic administration of 200 mg vaginal progesterone suppositories after successful tocolysis in patients with threatened idiopathic PTL is associated with a longer latency to delivery, but failed to reduce the rate of PTB (Registeration Number: IRCT138706051096N1).

Keywords: Preterm Labor, Preterm Birth, Vaginal Tablet, Progesterone

Introduction

Worldwide, preterm birth (PTB) is estimated to affect approximately 13 million births annually (1). Around 10% of all births are premature and the rate of PTB has steadily increased over the past two decades (2). The incidence of PTB in developing countries is higher (3) and it is the main cause of neonatal mortality, morbidity and long term sequelae (4).

The prevention of preterm labor (PTL) has become one of the major objectives of perinatal medicine. The cause of PTL in most cases remains unclear. Additionally, despite the identification of PTL risk factors; to date, no intervention has been associated with a decrease in PTL rates. Thus, early detection of women at high risk for PTL and prophylactic treatment could be one of the best ways to prevent PTB (5, 6).

The effectiveness of progesterone on reducing PTB in high risk groups of women has been confirmed in recent studies (7-10). In 2003, two double-blind trials; one with daily vaginal progesterone suppositories and the other that utilized weekly intramuscular injections of 17 α-hydroxy-progesterone claimed that the treatments effectively reduced the incidence of PTB in women at risk for spontaneous PTL (7, 11).

Progesterone and its receptors are key mediators for the initiation of labor (12). Progesterone is required for implantation and pregnancy develop-

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ment. A lack of progesterone in the first trimester leads to abortion (4). Furthermore, labor can be induced by anti-progesterones at any stage of pregnancy (13). Progesterone has an important role in maintaining uterine quiescence and is thought to act by suppressing smooth muscle activity in the uterus (14-16). Progesterone is also known to have anti-inflammatory properties (17) and affect the immunological status in the vagina and cervix in addition to protecting against bacterial infections that can prevent PTL (18). Patients with arrested PTL are at increased risk for PTL recurrence; however maintenance tocolysis after the arrest of acute PTL is questionable (19). Recently, one study has shown that treatment with 17 α-hydroxy-progesterone did not reduce the rate of PTB in women with twin pregnancies (20).

There are numerous controversies regarding progesterone administration for the prevention of PTL. The ideal progesterone formulation, dosage, duration and route of administration are unknown.

The objective of this study was to evaluate whether the prophylactic administration of 200 mg progesterone suppositories in women who presented with symptoms of threatened preterm labor PTL could reduce the incidence of PTB. We choose patients with a threatened PTL because they are at particularly high risk for PTB.

Materials and Methods

A placebo-controlled, double-blinded randomized clinical trial was performed at Alzahra Hospital, Guilan University of Medical Sciences between June 2007 and May 2009. The study was approved by the Institutional Review Board and the trial registered at IRCT. IR. All women with singleton pregnancies with gestational ages between 28-36 weeks who were admitted for threatened PTL were eligible for the study. Gestational age was calculated on the basis of the patient's last menstrual period with regular cycles or the first trimester ultrasound. Preterm delivery was determined by uterine contractions (equal or more than six contractions within 30 minutes, that lasted for 30 seconds as registered by an external tochodynamometer) and cervical changes including: softening, at least 50% shortening and less than 2 cm dilatation with intact membranes.

Patients with intrauterine infection, vaginal bleeding, pre-eclampsia, urinary tract infection established by clinical and laboratory exam, intrauterine growth retardation as established by ultrasound, chronic diseases such as hypertension and heart disease, in addition to dilatation ≥ 2 cm, fetal distress and fetal abnormalities, were not included in this study.

Additional exclusion criteria were the lack of access to patients for follow-up information.

At admission, all women were submitted to uterine contraction monitoring by external tochodynamometer followed by vaginal examination. Women with identified PTL were initially hydrated with 500 mL of Ringer's lactate and administered intramuscular Meperidine 0.75 mg/kg. If, after one hour the contractions continued, tocolysis was done by intravenous magnesium sulfate. After PTL was arrested, the women were referred to a high risk pregnancy unit for inclusion into the study.

The eligible women were given an informed consent and adequate information before enrollment into the study. The women who consented to participate were subsequently randomized into two groups using the random block allocation method. Patients who were enrolled as cases each received daily 200 mg vaginal progesterone suppositories. The remaining patients received vaginal placebo suppositories. The placebo consisted of stearate (H_{15}) and was similar to the study drug. Both drug and placebo were manufactured and labeled by Aboureihan Pharmaceutical Company. The suppositories were inserted into the vagina by a gynecologic resident after which uterine contractions were monitored for two hours. All patients received 12 mg betamethasone for two days to help with fetal pulmonary maturation. All patients received an antibiotic prophylaxis of intravenous ampicillin (2 g dose every six hours) during the period of hospitalization. The vaginal suppositories were inserted and uterine contractions monitored with an external tochodynamometer for 30 minutes. Both patients and physician were blinded to the type of suppositories.

If, after 48 hours, the subjects were stable and did not deliver they were discharged. Patients were instructed to limit their physical activity and continue with the insertion of vaginal suppositories until 36 weeks gestation. In cases with recurrent uterine contractions, patients were instructed to return to the hospital, otherwise they were assessed each two weeks wherein they were dispensed additional vaginal suppositories.

The primary outcome measures were the time until delivery (latency time) and PTB before 34 and 37 weeks of gestation.

PTL was defined as six or more regular uterine contractions in 30 minutes, that was associated with cervical changes as mentioned previously.

Secondary outcome measures were selected maternal and neonatal outcomes including nausea,

headache, pre-eclampsia, premature rupture of membranes (PROM), chorioamnionitis, post-partum hemorrhage for maternal complications and birth weight, Apgar score, admission to the NICU, fetal death, neonatal death, respiratory distress syndrome (RDS), sepsis, and intraventricular hemorrhage (IVH) for neonatal complications.
Data were analyzed using χ^2 or Fisher exact test and student's t-test. Kaplan-Meier survival analysis was performed to determine the relationship between vaginal progesterone and time to delivery. The log-rank χ^2 test was used to compare the time to delivery in the two study groups. Statistical analysis was performed using SPSS version 14. P-value <0.05 was considered statistically significant.

Ethical considerations

For all patients, routine management of PTL was performed according to the Parkland Hospital Protocol with progesterone or placebo added as an additional step. Patients gave informed consent before being included in the study.

Results

In total, 270 pregnant women admitted to Alzahra Hospital were identified as eligible participants. Of these, 97 (35.9%) delivered within 48 hours. The remaining 173 women were randomly assigned to the study and control groups. In the study group, 86 women received vaginal progesterone suppositories and 87 women received placebo as the control group.
There were 6 women in the progesterone group and 4 women in the control group who were lost to follow-up. Thus, 80 participants in the progesterone and 83 in the control groups were analyzed (Fig 1).
The baseline characteristics of the two study groups are listed in table 1.

Table 1: Baseline characteristics of the study participants

Characteristics	Placebo group (N=83)	Progesterone group (N=80)
Age (year)	24.06 ± 4.76	24.6 ± 5.58
Gestational age at admission (weeks)	33.95 ± 1.49	33.47 ± 1.84
Illiteracy	16 ± 21.6	20 ± 26.0
Nulliparous	53 ± 63.9	55 ± 68.8
Previous preterm delivery	3 ± 3.7	1 ± 1.3

As shown, there are no differences between the two groups with regards to age, gestational age at admission, illiteracy, parity and previous preterm delivery rate.

The rate of PTB before 37 weeks was not significantly different between the two groups (vaginal progesterone: 41.2% and placebo: 54.2%). There was also no significance difference in the two study groups for PTB before 34 weeks gestation. The study progesterone group demonstrated a statistical significantly longer mean latency until delivery date (23.88 ± 18.01 vs. 16.67 ± 12.09, p=0.004).

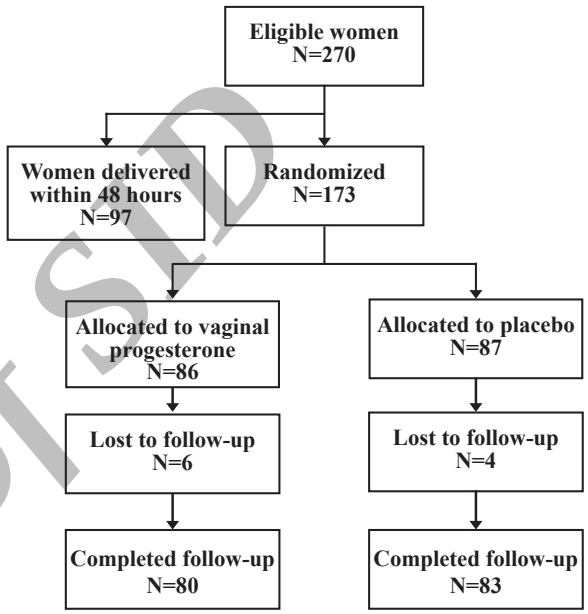

Fig 1: Flow diagram of the study

The mean gestational age at delivery was 36.31 ± 1.82 weeks in the placebo group and 36.89 ± 2.27 weeks in the progesterone group (Table 2).
The time until delivery in the two groups was compared using survival analysis to determine the relationship between vaginal progesterone and PTB. The mean latency time to delivery for the placebo group was 24.69 ± 2.26 days and for the progesterone group was 44.58 ± 4.01 days. The log rank analysis revealed a significance difference for mean time to delivery in the two groups (p=0.028) (Fig 2).

Table 2: Primary outcomes based on the study groups

Outcomes	Placebo group (N=83)	Progesterone group (N=80)	pvalue
Gestational age at delivery (weeks)	36.31 ± 1.82	36.89 ± 2.27	0.074
Latency (days)	16.67 ± 12.9	23.88 ± 18.01	0.004
Preterm birth before 37 weeks	45 ± 54.2	33 ± 41.2	0.098
Preterm birth before 34 weeks	9 ± 10.8	8 ± 10	0.86

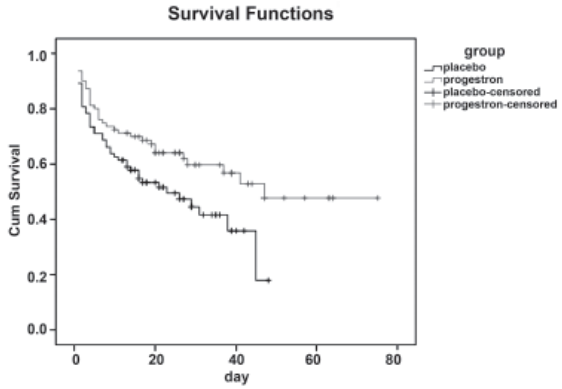

Fig 2: Cumulative survival of undelivered women by progesterone and placebo groups. Log rank χ^2 =4.81, p=0.028.

As illustrated in table 3, there were no significant differences for secondary outcomes including neonatal and maternal complications between the two groups.

Table 3: Secondary outcomes (neonatal and maternal) based on the study groups

Outcomes	Placebo group (N=83)	Progesterone group (N=80)
Birthweight (g)	3025.9(494.31)	2996.56 (578.67)
Apgar less than 7	4	1
Admission in NICU	2	3
RDS	10	7
Sepsis	3	0
Neonatal death	6	1
Nausea	0	1
Headache	0	1
Pre-eclampsia	1	4
PROM	10	5

Discussion

The results of this placebo-controlled double-blind trial which estimated the efficacy of maintenance 200 mg vaginal progesterone therapy in patients with threatened PTL revealed that progesterone could delay delivery for just seven days (p=0.004). It could not reduce the rate of PTB prior to 34 and 37 weeks of gestation.

The importance of progesterone in maintaining pregnancy has long been recognized. Progesterone is a multifaceted hormone with several functions during pregnancy; it supports uterine quiescence, suppresses contractile genes and prevents the rejection of the fetus by the mother through suppressing the cellular component of the immune system (12). An additional value of progesterone in prevention of PTL has been recently demonstrated by an experimental study in which progesterone increased the tocolytic effect of ritodrine by reducing 50% of the maximal response, amplitude and frequency of myometrial contractions (21). Despite the apparent benefits of progesterone in high risk populations, progesterone has been studied only as a prophylactic method in asymptomatic women, not as a tocolytic agent in women with symptoms of PTL. Recently, one study has shown that patients who remained undelivered after an episode of PTL underwent progressive cervical shortening during the three week observational period and treatment with a high dose progesterone was associated with both a lower cervical shortening as well as a reduced rate of PTB (10). In a recent trial, Borna and Colleagues have shown that in patients who were successfully treated for a PTL episode, maintenance tocolysis with 400 mg vaginal progesterone significantly prolonged pregnancy (8).

In their study, 70 women who presented with symptoms of threatened PTL, after arrest of uterine activity, were randomized to progesterone therapy (400 mg daily) until delivery. The control group received no treatment. The mean latency days until delivery were significantly different between the two groups (36.11 ± 17.9 study group vs. 24.52 ± 27.2 control group).

Their study had some limitations in that it was not a double blind study and there was no placebo for the control group. In the absence of a placebo and lack of blinding, one can not exclude the possibility that many of these women were not actually in labor and that the prolongation of pregnancy was not an effect of drug treatment. In addition, only 42 of 137 (29%) women delivered preterm, raising the question that many of the patients may not have been in true labor. Sample size and the power to detect clinically important outcomes were additional limiting factors.

The results of this study conform with the findings of one meta-analysis that showed progesterone therapy has no significant effectiveness when used to halt labor or as an adjunct to the use of other drugs to stop labor (12).

Fonseca et al. conducted a randomized placebo-controlled trial on 142 women; they reported the clinical usefulness of progesterone (100 mg vaginal suppository) by the decrease in the incidence of PTB from 28.5% in the placebo group to 13.8% in the progesterone group (7).

In the present study, despite the use of a higher dose of progesterone (200 mg), the rate of PTB did not differ significantly in the two groups which can be due to the different study design. Fonseca et al. evaluated women who were at high risk for

PTL (history of previous PTB, cervical cerclage and uterine malformations), but in this study we evaluated patients with symptoms of PTL who were successfully treated with tocolytic therapy. The patients with threatened PTL are at particularly high risk for recurrent PTL (19). Patients who have been treated successfully after a PTL episode are actually at risk because approximately 30% deliver preterm. The role of progesterone in prevention of fetal rejection through suppressing the cellular component of the immune system can explain why progesterone is effective if initiated prophylactically but fails to prevent delivery once labor is initiated (12, 22, 23).

All the successful trials benefited from initiated therapy relatively early in gestation in women who showed no symptoms of PTL. Trials of progesterone to aid in halting the progression of labor have not been successful and they suggest that the use of progesterone in women who have had symptoms or signs of labor should be discouraged (12).

In a previous study, 250 women who were identified as having a short cervix of less than 15 mm as seen with transvaginal sonography received either 200 mg intravaginal progesterone or placebo beginning from 24 to 33 weeks of gestation. The rate of PTL before 34 weeks was significantly lower in the progesterone group (p=0.007) (24). Facchinetti et al. showed that patients who were treated successfully for a PTL episode underwent a progressive shortening of the cervix that was attenuated by 17 α-hydroxy- progesterone treatment. Such an effect is associated with a reduction in the rate of PTD. They also determined that the latency period was significantly longer in the 17 α-hydroxy- progesterone group (35.3 ± 19.1 days) when compared with the observation group (25.5 ± 15.1 days; p=0.003) (25).

In the present study, the administration of 200 mg vaginal progesterone did not reduce the rate of PTB, but the latency period was longer in the progesterone group (p=0.04).

The different findings amongst various studies can be due to the effect of the route of progesterone administration, gestational age at commencement of therapy, or total cumulative dose of medication (25).

Thus the role of progesterone for women after presentation with threatened PTL remains uncertain. In addition, the combined sample size of the studies is small and underpowered to detect differences in both maternal and infant health outcomes (8, 10).

This study also did not have sufficient power to demonstrate a significant reduction in perinatal mortality and morbidity. The effect of progesterone on perinatal mortality and morbidity is uncertain. Treatment of women with progesterone should continue to be confined to women enrolled in well-designed randomized controlled trials (26).

Conclusion

Although the time is early to treat all women at risk for PTL with progesterone, it is not too soon to hope that these reports will be followed by further larger, randomized trials showing not only a decline in PTL but a reduction in perinatal mortality and morbidity. Thus, further studies are needed to evaluate the use of progesterone in larger populations with high risk obstetric factors for PTL.

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