Effect of progesterone as maintenance tocolytic therapy on the prevention of recurrent preterm labor: a randomized clinical trial

Hajieh Borna [1] M.D., Sedigheh Borna [2] M.D., Soghra Khazardoust [2] M.D., Sedigheh Hantoushzadeh[2] M.D., Noshin Sahabi [3] M.D.

1 Mostafa Khomeini Hospital, Shahed University of Medicine, Tehran, Iran.
2 Department of Perinatology, Medical Sciences/ University of Tehran, Tehran, Iran.
3 Obstetrician and gynecologist.

Received April 2007; Revised and accepted July 2007.

Abstract

Objective: The study evaluated the efficacy and safety of vaginal progesterone on prevention of recurrent preterm labor.

Materials and methods: Total number of 70 patients with preterm labor treated with intravenous magnesium sulfate in perinatology department of valiasr hospital entered to a randomized clinical trial. Treatment group after inhibition of preterm labor with magnesium sulfate received progesterone suppository (400 mg) daily until delivery and control group received no treatment. Latency until delivery, recurrence of preterm labor and neonatal outcomes were studied. Statistical significance was defined as $p< 0.05$.

Results: Mean latency until delivery ($p< 0.05$), low birth weight ($p< 0.05$), birth weight ($p< 0.01$) were significantly different between the two groups. Recurrence of preterm labor was not significantly different between the groups.

Conclusions: The use of vaginal progesterone suppository after successful parenteral tocolysis associated with a longer latency preceding delivery but failed to reduce the incidence of recurrent preterm labor.

Key words: *preterm labor, maintenance tocolytic therapy, progesterone suppository*

Introduction

Approximately 65% of non-anomalous fetal and neonatal deaths are attributed to complications of prematurity (1) and in those infants who survive, preterm birth have a higher incidence as both acute and long-term health sequels (1, 2). Pharmacologic therapy with a variety of drugs of different categories has been the primary method of treating acute preterm labor (3).Patients with arrested preterm labor are at increased risk for recurrence, but to this point, continued tocolytic treatment with any agent after arrest of acute preterm labor is of questionable value in prolongation of pregnancy or improving outcome (3, 4). Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin F_2 α and α-adrenergic stimulation and therefore increases the α-adrenergic tocolytic response (5). Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain artificial progestins and β-mimetics (3).

Correspondence:
Sedigheh Borna,Vali-e-Asr Reproductive Health Research Center, Imam Hospital Complex, Keshavarz Blvd., Tehran 14194, Iran.
Tel: +98-2166937766 Fax: +98-2188718062
E.mail: SBorna@Tums.ac.ir

Progesterones for the prevention of preterm birth have a long history. In 2003, two widely published double-blind trials, one of daily vaginal progesterone suppositories and the other of weekly intramuscular injections of 17 alpha-hydroxyprogesterone, claimed that the treatments effectively reduce the incidence of preterm birth in women at risk of spontaneous preterm labor (5, 6).
No studies have demonstrated the efficacy of maintenance vaginal progesterone versus placebo or no treatment. We designed a randomized clinical trial to compare vaginal progesterone with no treatment to test the null hypothesis that maintenance tocolytic therapy with vaginal progesterone would not significantly delay delivery in patients successfully treated with intravenous magnesium sulfate for preterm labor. The purpose of this study was to determine if vaginal progesterone maintenance therapy after a successfully treated episode of acute preterm labor could increase latency period.

Materials and methods

This randomized clinical trial performed in the obstetrics ward of Vali-e-Asr university hospital in Tehran, Iran, from March 2004 to December 2005. The ethics committee of Tehran University of medical sciences approved this study.
Pregnant women admitted to the high-risk obstetric service at Vali-e-Asr hospital were considered eligible for the study if they had a gestational age of 24 to 34 weeks, a singleton gestation, intact amniotic membranes, no cerclage, diagnosis of arrested preterm labor, and a cervical dilatation of 4 cm or less. At admission, all patients had an ultrasonographic examination, which included confirmation of the estimated gestational age. Preterm labor was defined as progressive cervical dilatation or effacement associated with regular uterine contractions at a rate of at least four in 20 minutes or eight in 60 minutes. Arrested preterm labor was defined as a 12-hour contraction-free period after intravenous (IV) therapy had been discontinued. Exclusion criteria included clinical evidence of intra-amniotic infection or pyelonephritis, medical complications contraindicating tocolysis, evidence of fetal growth retardation, and sonographic evidence of congenital anomalies inconsistent with life. The women were initially hydrated with 500 mL of Ringer's lactate over a 30-minute period. All patients were given IV magnesium sulfate, with an initial bolus of 4–6 g followed by continuous infusion at a rate of 2–4 g per hour. All patients received antibiotic prophylaxis consisting of Ampicillin IV (2 gr every 6 hours) for 48 hours. All patients received a single course of Betamethasone, consisting of two 12 mg injections during the first 24 hours after admission.
After arrested preterm labor was diagnosed, the patient was counseled about the study and offered an institutional review board–approved informed consent document. Patients included in the study were randomized within 48 hours of arrest of labor. Computer-generated random number tables were used for randomization of the investigation. Group assignments were placed in sealed, opaque, sequentially numbered envelopes.
Both groups of pregnant women were randomly selected to receive the vaginal progesterone suppository (400 mg) or no treatment. If the subjects were stable and undelivered after a total of 48 hours, they were discharged for observation in the high-risk obstetric clinic. During the study period, no patient received oral tocolytics. All patients were observed weekly in the high-risk obstetrics clinic, if the patient complained of subjectively

increased uterine activity, the physician performed a digital exam.

We assumed an SD of 12 days on the basis of data from a previous trial evaluating oral terbutaline for maintenance tocolysis (7). Significance level was set at 5% and power was set at 80%. Thirty-three patients per group were needed to detect a 12-day difference in time gained during pregnancy after discontinuation of intravenous magnesium tocolysis for the initial preterm labor episode.

The two groups were compared for demographic characteristics, the estimated gestation age at the time of admission and delivery, latency until delivery, birth weight, and respiratory distress syndrome. Categorical data were tested for significance with the Chi square and Fisher exact tests. Comparison Bishop Score and cervical dilatation were made With Cochran-Mantel-Haenszel test. Latency period were tested for significance with the Mann-Whitney U-test. Continuous data were evaluated for normal distribution and tested for significance with the student t test. Statistical significance was defined as $p< 0.05$. All patients were included in the analysis.

Results

A total of 70 patients with preterm labor were included in the study: 37 were randomly assigned to the Progesterone group and 33 were randomly assigned to the control group. The two study groups were not statistically different with respect to age, race, and parity, gestational age at admission, bishop score, and preterm delivery risk factors (Table 1).

Table 1: Maternal demographic and clinical characteristics at randomization

	Control group (%) N=33	Progesterone group (%) N=37	p-value
History of Infertility	7 (21.2)	6 (16.2)	NS
ART	1 (3)	3 (8)	NS
History of preterm labor	4 (12.1)	5 (13.5)	NS
Uterus anomalies	2 (6)	3 (8.1)	NS
Previous cervical surgery	0	0	NS
Polyhydramnios	1 (3)	0	NS
Parity(mean±SD)	2±. 1.39	2.38±2.19	NS
Age range(year)	25.5±0.9	26.1±0.9	NS
Modified Bishop score ≥3	21(63.6)	15(40.5)	NS
GA at admission (mean±SD) weeks	32.4± 2.1	31.1± 2.9	NS

Student t test for age and gestational age; Fisher exact test for previous preterm delivery, uterine or cervical surgery, and polyhydramnios; Cochran-Mantel-Haenszel test for modified Bishop score, $\chi 2$ test for frequency of modified Bishop score ≥3. Polyhydramnios defined as AFI>24cm.

Progesterone group demonstrated a longer mean latency until delivery (36.1± 17.9 vs. 24.5± 27.2) days .This observed difference was statistically significant ($p < 0.05$). There was significant difference between gestational age at delivery ($p < 0.05$) (Table 2). There were significant difference between the progesterone and control groups, respectively, in important neonatal variables. Twelve and four of the progesterone and control groups, respectively, had neonates with respiratory distress syndrome ($p < 0.05$). Low birth weight ($p < 0.05$), birth weight ($p < 0.005$) (Table 3).

Table 2: Delivery characteristics between groups with preterm labor

	progesterone group(N=37)	Control group(N=33)	p-value
Latency(mean±SD)days	36.1±17.9	24.5±27.2	0.037
Gestational age at delivery((mean±SD) weeks	36.7±1.5	34.5±1.2	0.041
Recurrence of preterm labor	13(35.1%)	19(57.6%)	NS

p-value were determined by the student t–test was used for comparison of continues variables, and by the chi square was used for comparison of categoric variables, Fisher's exact was used for comparison.

Table 3: Neonatal outcome between groups with preterm labor

	Control group (N=33)	Progesterone group (N=37)	p-value
Need to mechanical ventilator	6 (18.2%)	2 (5.4%)	NS
Neonatal intensive care unit (day)	3.8 ± 8.2	3.4 ± 7.6	NS
LBW	17 (51.5%)	10 (27%)	0.040
Admission in NICU	13 (39.4%)	9 (24.3%)	NS
Sepsis	6 (18.2%)	2 (5.4%)	NS
RDS	12 (36.4%)	4 (10.8%)	0.021
Birth weight (gr)	2609.39±662.9	3101.54±587.9	0.002

p-value determined by the student t–test was used for comparison of continues variables, and by the chi square was used for comparison categorical variables, Fisher's exact test was used for comparison.
LBW: birth weight < 2500gr.
RDS : respiratory distress syndrome.

No significant differences were found with recurrent preterm labor, time spent in the neonatal intensive care unit between the case and control groups, respectively. Neonatal sepsis occurred in eight patients in both groups with no significant difference. There were no cases of neonatal necrotizing enterocolitis, congenital malformations (genital organs), and intraventricular hemorrhage. There were no maternal complaints and adverse effects such as headache, anxiety, irritability, mood swings, and depression in groups believed to be related to the study medication.

Discussion

In this randomized clinical trial, we evaluated the efficacy of maintenance vaginal progesterone therapy in patients successfully treated with magnesium sulfate tocolysis for preterm labor. Maintenance tocolytic therapy with vaginal progesterone significantly prolonged pregnancy. Pregnancy prolongation after an episode of preterm labor is a clinically relevant measure of maintenance tocolytic efficacy. Our sample-size calculation was designed to detect a 12-day difference in pregnancy prolongation. This study was underpowered, but we were able to

observe a 22% difference in the incidence of recurrent preterm labor and in 12 days of latency.

Randomized clinical trials with large sample sizes are needed to determine whether vaginal progesterone reduces recurrent preterm labor. This study is unique among the published trials evaluating vaginal progesterone because we specifically investigated the maintenance tocolytic efficacy.

We have yet to find an effective agent for maintenance tocolytic therapy. This is not surprising because the pathophysiologic mechanisms involved in preterm labor are complex, probably differ among patients, and may not involve uterine contractions as the primary event leading to preterm labor. Consequently a tocolytic agent such as progesterone may not be effective for all patients because the cause of preterm labor is multifactorial. The rates of several complications of prematurity such as LBW, RDS were decreased among the infants of women assigned to this therapy. In this study, although the reduction in neonatal morbidity in the progesterone group was significant, but since our mean gestational age at recruitment was relatively late (32 weeks), then a more robust and clinically relevant study would have been to limit it to 24-30 weeks gestation.

There were no maternal complaints, adverse effects, or complications in either group believed to be related to the study medications.

Neither recent trials nor meta-analyses show a benefit of maintenance tocolytic therapy (2, 3). Despite a lack of evidence supporting efficacy, however, many clinicians continue to use these agents. Progesterone significantly prolonged pregnancy; it may decrease maternal anxiety and the symptoms of uterine contractions. Progesterone appears to be better tolerated than betasympatho-mimetic agents, with lessened hemo-dynamic and metabolic side effects (4).

Researchers have recently been testing progesterone injections for preventing pregnancy loss or preterm birth, with promising results. Among high-risk women (who had spontaneously delivered before 37 weeks), progesterone treatment reduced the number of uterine contractions and significantly reduced preterm delivery rates. This means that, while some women still delivered prematurely, progesterone treatment helped more high-risk women carry their pregnancies longer than a placebo treatment did (5,6). Vaginal progesterone suppositories have been shown to decrease the rate of preterm birth in patients at increased risk. Adverse effects of progesterone suppositories were not mentioned (6). The mechanisms of action of progesterone in prolonging gestation are not entirely known. The actions of progesterone on the pregnant myometrium include relaxation of myometrial smooth muscle, blocking of the action of oxytocin, and inhibition of the formation of gap junctions (8,9). Adequate progesterone concentrations in myometrium are able to counteract prostaglandin stimulatory activity as well as oxytocin properties that enhance the activity of ß-agonists.17 Progesterone decreases the concentration of myometrial oxytocin receptors, which counteract the effect of estrogens. The same is true with respect to the number and properties of gap junctions. Progesterone also inhibits prostaglandin production by amnion–chorion–decidua and has been shown to increase the binding of progesterone in the fetal membranes at term, which may explain the predominant effect of estrogen in promoting prostaglandin reduction and triggering labor (11, 10). In conclusion, progesterone may be used either for maintenance tocolysis to increase gestational age at delivery, and improve perinatal outcome, or as a preventive

agent in a high-risk population of women at risk of preterm birth.
Randomized clinical trials with large sample size are needed to determine whether maintenance tocolysis with vaginal progesterone reduces the incidence of recurrent preterm labor and improves perinatal outcomes.

References

1- Berkowitz GS, Papiernik E. Epidemiology of preterm births. Epidemiol Rev 1993; 15(2): 414-443.
2- Rust OA, Bofill JA, Arriola RM, Andrew ME, Morrison JC. The clinical efficacy of oral tocolytic therapy. Am J Obstet Gynecol 1996; 175(4 Pt 1): 838-842.
3- Sanchez-Ramos L, Kaunitz AM, Gaudier FL, Delke I. The efficacy of maintenance therapy after acute tocolysis: meta- analysis. Am J Obstet Gynecol 1999; 181(2): 484-490.
4- Thornton JG. Maintenance tocolysis. BJOG 2005 ; 112(Suppl 1): 118-121.
5- Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al.Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. New England Journal of Medicine 2003; 348(24): 2379-2385.
6- da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. American Journal of Obstetrics & Gynecology 2003; 188(2): 419-424.
7- How HY, Hughes SA, Vogel RL, Gall SA, Spinnato JA. Oral terbutaline in the outpatient management of preterm labor. Am J Obstet Gynecol 1995; 173: 1518-1522.
8- Siiteri PK, Serón-Ferré M. Some new thoughts on the feto-placental unit and parturition in primates. In: Novy MJ, Resko JA, eds. Fetal endocrinology. New York: Academic Press, 1981: 1-34.
9- Garfield RE, Kannan MS, Daniel EE. Gap junction formation in myometrium: control by estrogens, progesterone, and prostaglandins. Am J Physiol 1980; 238: 81-89.
10- Challis JRG. Sharp increases in free circulating oestrogens immediately before parturition in sheep. Nature 1971; 229: 208-208.
11- Mitchell B, Cruickshank B, McLean D, Challis J. Local modulation of progesterone production in human fetal membranes. J Clin Endocrinol Metab 1982; 55: 1237-1239.