Original Article

Progesterone for maintenance tocolytic therapy after threatened preterm labour: A randomised controlled trial

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Background: Women with preterm labour that is arrested with tocolytic therapy are at increased risk of recurrent preterm labour. The efficacy of maintenance tocolytic therapy after successful arrest of preterm labour remains controversial.

Aim: The purpose of this study was to determine whether supplementation of vaginal progesterone after inhibition of preterm labour is associated with an increased latency period and a decreased recurrent of preterm labour.

Methods: This trial was conducted in 70 women who presented with symptoms of threatened preterm labour, who after arrest of uterine activity were then randomised to progesterone therapy or no treatment. Treatment group received progesterone suppository (400 mg) daily until delivery and control group received no treatment.

Results: Longer mean latency until delivery (36/11 ± 17/9 vs 24/52 ± 27/2) (mean + standard deviation) days; respiratory distress syndrome 4 (10.8%) vs 12 (36.4%) \( P = 0.021 \); low birthweight 10 (27%) vs 17 (51.5%) \( P = 0.04 \); and birthweight (3101.54 ± 587.9 g vs r 2609.39 ± 662.9 g, \( P = 0.002 \)), were significantly different between the two groups.

No significant differences were found between recurrent preterm labour 13 (35.1%) vs 19 (57.6%), \( P = 0.092 \); admission to intensive care unit 9 (24.3%) vs 13 (39.4%), \( P = 0.205 \); and neonatal sepsis 2 (5.4%) vs 6 (18.2%) \( P = 0.136 \), for the progesterone and control groups, respectively.

Conclusion: The use of vaginal progesterone suppository after successful parenteral tocolysis associated with a longer latency preceding delivery but failed to reduce the incidence of readmission for preterm labour.

Key words: latency period, preterm labour, progesterone, recurrence of preterm labour.

Introduction

Approximately 65% of non-anomalous fetal and neonatal deaths are attributed to complications of prematurity¹ and those infants who survive a preterm birth have a higher incidence of both acute and long-term health sequel.¹,² Pharmacological therapy with a variety of drugs of different categories has been the primary method of treating acute preterm labour.³ Patients with arrested preterm labour are at increased risk for recurrence, but to this point, continued tocolytic treatment with any agent after arrest of acute preterm labour is of questionable value in extending gestation or improving outcome.³,⁴ The efficacy of maintenance tocolytic therapy after successful arrest of preterm labour remains controversial. This question is not limited to the use of a specific drug as the data are similar for terbutaline, magnesium sulphate, and calcium channel blockers.²,³ Accordingly, the results of this meta-analysis do not support the use of maintenance tocolytic therapy after successful treatment of preterm labour.⁴ In the last 40 years, progestins have been administered...
to pregnant women for several reasons, including threatening miscarriage, recurrent miscarriage, threatening abortion, prevention of preterm labour and luteal support during in vitro fertilisation treatment.\textsuperscript{5,6,7} Especially for progestins with an androgenic effect, there was fear for masculinisation of the female fetus. Research among exposed women and controls showed no difference with respect to the occurrence of abnormalities of the central nerve system, limbs and joints, urogenital tract and circulatory tract between treated and untreated pregnancies, even when 17OHP was administered in early pregnancy.\textsuperscript{8,9} The effectiveness of 17P in reducing preterm delivery (PTD) in at-risk pregnancies was first demonstrated in the 1970s.\textsuperscript{10,11} In 2003, two widely published double-blind trials, one of daily vaginal progesterone suppositories and the other of weekly intramuscular injections of 17alpha-hydroxyprogesterone, claimed that the treatments effectively reduce the incidence of preterm birth in women at risk of spontaneous preterm labour.\textsuperscript{12,13}

In study published in 2007, vaginal progesterone treatment reduced the rate of preterm birth among women who were at high risk for preterm birth because of a short cervix.\textsuperscript{14} Recently, Dwight et al. showed that treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with twin gestations.\textsuperscript{15}

Progesterone has long been considered important agents in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of PTD.\textsuperscript{12,16}

We therefore chose this pharmacological agent as the active drug for our study. We chose vaginal micronised natural progesterone, rather than intramuscular synthetic 17P. Vaginal route is preferable because of enhanced bioavailability and the absence of undesirable side-effects, such as sleepiness, fatigue and headaches.\textsuperscript{7} We used 400 mg of progesterone, in contrast to the 100- or 200-mg dose used in a randomised trial of women with a history of preterm birth or short cervix.\textsuperscript{12-14} We chose this high dose because we considered patients with a threaten preterm labour to be at particularly high risk for recurrent PTD.

This trial was designed to assess the use of progesterone therapy in women who presented with symptoms of threatened preterm labour.

\section*{Methods}

A randomised clinical trial was performed between March 2004 to December 2005 that included singleton pregnant women between 24 and 34 weeks of gestation who were admitted for threatened preterm labour. This study was performed in the obstetrics and gynaecology ward of vali-e-Asr teaching hospital in Tehran. The Ethics Committee of Tehran University of Medical Sciences approved this study.

Preterm labour was defined as the simultaneous presence of contractions (> six contractions in 30 min) and cervical changes, either shortening and/or softening or dilation, by manual examination. Recurrence of preterm labour was defined as recurrence of contractions within 48 h after discontinuation of intravenous treatment and arrest of contractions. Arrested preterm labour was defined as a 12-h contraction-free period after intravenous therapy had been discontinued.

Inclusion criteria were singleton pregnancy, intact membranes, no cerclage, cervical dilation of ≤ 2 cm, and the dating of pregnancy confirmed through first trimester ultrasound scanning.

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. At admission, all patients had an ultrasonographic examination, which included confirmation of the estimated gestational age. The women were initially hydrated with 500 mL of Ringer's lactate over a 30-min period. All patients were given intravenous magnesium sulphate, 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 intravenous (2-g dose every six hours) for 48 h. All patients received a single course of betamethasone, consisting of two 12 mg injections during the first 24 h after admission.

After arrested preterm labour was diagnosed, the patient was counselled about the study and offered an institutional review board-approved informed consent document. Patients included in the study were randomised within 48 h of arrest of labour.

The random list was prepared with a computer-generated number list. Odds (progesterone) and pairs (control) defined treatment allocation; the senior midwife managed the list. Patients who were enrolled as cases received vaginal progesterone suppository (400 mg) daily. The remaining patients were included as control subjects and received no drugs.

If the subjects were stable and undelivered after a total of 48 h, 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 based on data from a previous trial evaluating oral terbutaline for maintenance tocolysis. Significance level was set at 5% and power 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 labour episode.

The primary outcomes measure were the time until delivery (latency period) and recurrence of preterm labour within 48 h after discontinuation of intravenous treatment and arrest of contraction.

Secondary outcome measures were incidence of low birthweight, birthweight and perinatal morbidity (respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, proven sepsis) assessed at the admission to neonatal intensive care unit (NICU).

Categorical data were tested for significance with the $\chi^2$ 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’s $t$-test. Statistical significance was defined as $P < 0.05$. All patients were included in the analysis.

**Results**

In total, 137 pregnant women admitted to the department with symptoms and signs of preterm labour were eligible for the trial. Forty-two women delivered within 48 h. We excluded 15 women because they did not meet inclusion criteria. Ten of the remaining women refused to participate to the study. Seventy women were assigned randomly: 37 women received vaginal progesterone and 33 women did not. None of the patients was lost to follow up. Patients were compliant, and none of the women reported adverse events that were linked apparently to the treatment. (Fig. 1)

Baseline characteristics of the patients are given in the (Table 1). The two groups were similar with respect to maternal age, race, parity, gestational age at admission, Bishop score, and PTD risk factors (Table 1). Progesterone group demonstrated a longer mean latency until delivery ($36.1 \pm 17.9$ vs $24.5 \pm 27.2$) days. This observed difference was statistically significant = 0.03. There was significant difference between gestational age at delivery at delivery $P=0.041$ (Table 2). There were significant differences between the progesterone and the control groups’ gestational age at delivery. Four (10.8%) and 12 (36.4%) women in the progesterone and control groups, respectively, had neonates with respiratory distress syndrome, $P=0.021$. Low birthweight 10 (27%) vs 17 (51.5%), $P=0.04$, and birthweight $3101.54 \pm 587.9$ g vs $3609.39 \pm 662.9$ g, $P=0.002$ were significantly different between the two groups (Table 2). No significant differences were found between recurrent preterm labour 13 (35.1%) vs 19 (57.6%), $P=0.092$; admission to intensive care unit 9 (24.3%) vs 13 (39.4%), $P=0.205$; and neonatal sepsis 2 (5.4%) vs 6 (18.2%) $P=0.136$, for the progesterone and control groups, respectively.

There were no cases of neonatal necrotizing enterocolitis, congenital malformations (genital organs) and intraventricular haemorrhage. There were no

![Figure 1](image-url) Flow diagram of the study.
Progesterone as a tocolytic therapy

maternal complaints, adverse effects such as headache, anxiety, irritability, mood swings and depression in either group believed to be related to the study medication.

Conclusion

In this randomised clinical trial, we evaluated the efficacy of maintenance vaginal progesterone therapy in patients successfully treated with magnesium sulphate tocolysis for preterm labour. Maintenance tocolytic therapy with vaginal progesterone significantly prolonged pregnancy. Our sample-size calculation was designed to detect a 12-day difference in pregnancy prolongation. It may be that vaginal progesterone maintenance the quiescence of uterine after successful treatment of acute preterm labour. This study was underpowered, but they were able to observe a 22%

Table 1 Maternal demographic and clinical characteristics at randomization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control</th>
<th>Progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 33</td>
<td>n = 37</td>
</tr>
<tr>
<td>History of infertility</td>
<td>7 (21.2%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>ART</td>
<td>1 (3%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>History of preterm birth</td>
<td>4 (12.1%)</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Uterus anomalies</td>
<td>2 (86%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Previous cervical surgery</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Polyhydramnins</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Primiparous</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Multiparous</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Age(years (mean ± SD))</td>
<td>25.5 ± 0.9</td>
<td>26.1 ± 0.9</td>
</tr>
<tr>
<td>Modified Bishop score of ≥3</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>GA at admission (mean ± SD, weeks)</td>
<td>32.4 ± 2.1</td>
<td>31.1 ± 2.9</td>
</tr>
</tbody>
</table>

Student’s 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, χ² test for frequency of modified Bishop score of ≥3; polyhydramnios; AFI > 24 cm.
ART, assisted reproductive technology; GA, gestational age; SD, standard deviation.

Table 2 Primary and secondary outcome measures in women with preterm labour treated with progesterone maintenance therapy and their controls

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Progesterone</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 33</td>
<td>n = 37</td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (day, mean ± SD)</td>
<td>(24.5 ± 27.2)</td>
<td>(36.1 ± 17.9)</td>
<td>0.037</td>
</tr>
<tr>
<td>Gestational age at delivery (mean ± SD, weeks)</td>
<td>34.5 ± 1.2</td>
<td>36.7 ± 1.5</td>
<td>0.041</td>
</tr>
<tr>
<td>Recurrence of preterm labour</td>
<td>19 (57.6%)</td>
<td>13 (35.1%)</td>
<td>0.092</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need to mechanical ventilator</td>
<td>6 (18.2%)</td>
<td>2 (5.4%)</td>
<td>0.136</td>
</tr>
<tr>
<td>Neonatal intensive care unit (day)</td>
<td>3.8 ± 8.2</td>
<td>3.4 ± 7.6</td>
<td>0.83</td>
</tr>
<tr>
<td>LBW</td>
<td>17 (51.5%)</td>
<td>10 (27%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Admission in NICU</td>
<td>13 (39.4%)</td>
<td>9 (24.3%)</td>
<td>0.205</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6 (18.2%)</td>
<td>2 (5.4%)</td>
<td>0.136</td>
</tr>
<tr>
<td>RDS</td>
<td>12 (36.4%)</td>
<td>4 (10.8%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2609.39 ± 662.9</td>
<td>3101.54 ± 587.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

P-values were determined using Student’s t-test for comparison of continues variable, and χ² for comparison of categorical variables, P-value < 0.05 was considered significant.
LBW, low birthweight (< 2500 g); NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SD, standard deviation.
difference in the incidence of recurrent preterm labour and in 12 days of latency. The rates of several complications of prematurity such as low birthweight and respiratory distress syndrome were correspondingly 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, however, the trial was not designed with sufficient power to address these end-points.

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 before), 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. 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.\(^{11-14}\)

The comparison this study with previous data is difficult because of the different study design (drug used for treatment, way of administration and time of interventions). The main difference is related to the fact that previous studies were all performed to stop preterm labour (mainly contractions) with the use of progestin derivatives as prophylactic agent. Those studies showed that the prophylactic administration of progesterone beginning in midgestation to women who previously had a preterm birth has been shown to halve the rate of recurrence.\(^{11-14}\) However, we included patients after tocolysis was obtained. The strength of the actual study is that the clinical effects of 17P and progesterone suppository have been described so far only in patients who were at risk for PTD because of their poor obstetric history, having given birth to twin, and short cervix, whereas our findings were obtained in patients who were at risk because of a preterm labour episode.

In recent trial, Facchinetti et al. showed that patients who were treated successfully for a preterm labour episode underwent a progressive shortening of the cervix that was attenuated by 17P treatment. Such an effect is associated with a reduction in the rate of PTD.\(^{17}\) They also showed that latency period was significantly longer in 17P group (35.3 ± 19.1 days) than in the observation group (25.5 ± 15.1 days; \(P = 0.003\)).\(^{17}\) A similar study by Facchinetti et al. has been performed also after inhibition of preterm labour and showed that latency until delivery was significantly longer in vaginal progesterone group (36.1 ± 17.9 vs 24.5 ± 27.2) days.

Our first trial had several possible limitations. First, it was not double blind. Sample size and power to detect clinically important outcomes were small. Our mean gestational age at recruitment was relatively late (32 weeks), and then a more robust and clinically relevant study would have to limit it to 24–30 weeks gestation. The trial was not designed with sufficient power to address important infant's outcomes.

The mechanisms of action of progesterone in prolonging gestation are not entirely known. Progesterone significantly prolonged pregnancy; it may decrease maternal anxiety and the symptoms of uterine contractions, secondary to tocolytic therapy. Progesterone may have an effect at the level of the myometrium resulting in potentiation of muscle relaxation. 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.\(^{18-21}\)

Adequate progesterone concentrations in myometrium are able to counteract prostaglandin stimulatory activity as well as oxytocin properties that enhance the activity of \(\beta\)-agonists. 17 Progesterone decreases the concentration of myometrial oxytocin receptors, which counteract the effect of oestrogens. 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 oestrogen in promoting prostaglandin reduction and triggering labour.\(^{20,21}\) We have yet to find an effective agent for maintenance tocolytic therapy. This is not surprising because the pathophysiological mechanisms involved in preterm labour are complex, probably differ among patients, and may not involve uterine contractions as the primary event leading to preterm labour. Consequently, a tocolytic agent such as progesterone may not be effective for all patients because the cause of preterm labour is multifactorial.

Double-blind randomised clinical trials with large sample size are needed to determine whether vaginal progesterone has any clinical advantage.

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