Vaginal progesterone as maintenance treatment after an episode of preterm labour (PROMISE) study: a multicentre, double-blind, randomised, placebo-controlled trial

M Palacio,¹ b T Cobo,¹ b E Antolín,¹ M Ramirez, d F Cabrera, e F Mozo de Rosales, f JL Bartha, g M Juan, h A Martí, i D Oros, j Á Rodríguez, k l E Scanzocchio, m JM Olivares, n S Varea, o J Rios, p q E Gratacos a b on behalf of the PROMISE Collaborative Group*

¹ BCNatal, Hospital Clinic of Barcelona and Hospital Sant Joan de Déu, Fetal i+D Fetal Medicine Research Centre, IDIBAPS, University of Barcelona, Barcelona, Spain ² Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain ³ Hospital General Universitario Gregorio Marañón, Madrid, Spain ⁴ Hospital Universitario Virgen Macarena, Sevilla, Spain ⁵ Complejo Hospitalario Universitario Insular Materno Infantil, Las Palmas de Gran Canaria, Spain ⁶ Hospital Universitario de Basurto, Bilbao, Spain ⁷ Hospital Puerta del Mar, Cádiz, Spain ⁸ Hospital de Son Llàtzer, Mallorca, Spain ⁹ Althaia Xarxa Assistencial Universitària de Manresa, Hospital de Sant Joan de Déu, Manresa, Spain ¹ Hospital Clínico Universitario Lozano Blesa, Instituto de Investigación Sanitaria de Aragón, Red SAMID, RETICS, Zaragoza, Spain ² Hospital of Barcelona Sabadell, Corporació Sanitària Parc Taulí, Sabadell, Spain ³ Institut Universitari Parc Taulí – UAB, Universitat Autònoma de Barcelona, Barcelona, Spain ⁴ Hospital Universitario Quirón-Dexeus, Barcelona, Spain ⁵ Consorci Sanitàri de Terrassa, Terrassa, Spain ⁶ Hospital Clinic of Barcelona, Clinical Trials Unit/Clinical Pharmacology Department, Hospital Clinic Barcelona, Barcelona, Spain ⁷ Biostatistics and Data Management Core Facility, IDIBAPS, Hospital Clinic Barcelona, Barcelona, Spain ⁸ Biostatistics Unit, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

Correspondence: Dr M Palacio, BCNatal, Barcelona Centre for Maternal–Fetal and Neonatal Medicine, Hospital Clinic, Sabino de Arana, 1, 08028 Barcelona, Spain. Email mpalacio@clinic.cat

Accepted 11 January 2016. Published Online 30 March 2016.

Objective To evaluate whether maintenance treatment with vaginal progesterone after an arrested preterm labour reduces the incidence of preterm delivery.

Design Multicentre, randomised, double-blind, placebo-controlled trial.

Setting Twelve tertiary care centres in Spain.

Population A total of 265 women with singleton pregnancy, preterm labour successfully arrested with tocolytic treatment, and cervical length of <25 mm.

Methods Randomisation was stratified by gestational age (from 24.0 to <31.0 weeks of gestation and from 31.0 to <34.0 weeks of gestation) and centre. Patients were randomly assigned, in a 1:1 ratio, to either daily vaginal capsules of 200 mg progesterone or placebo until delivery or 36.6 weeks of gestation, whichever occurred first.

Main outcome measures Primary outcome was delivery before 34.0 and 37.0 weeks of gestation. Secondary outcomes were discharge-to-delivery time, readmissions because of preterm labour, emergency service use, and neonatal morbidity and mortality.

Results From June 2008 through June 2012, 1419 women were screened: 472 met the inclusion criteria and 265 were randomised. The final analysis included 258 women: 126 in the progesterone group and 132 in the placebo group. There were no significant differences between the progesterone and placebo groups in terms of delivery at <34 weeks of gestation [9/126 (7.1%) versus 10/132 (7.6%), P = 0.91] or <37 weeks of gestation [36/126 (28.6%) versus 29/132 (22.0%), P = 0.22]. There were no differences observed between groups when considering the two strata of gestational age at inclusion.

Conclusions A maintenance treatment of 200 mg of daily vaginal progesterone capsules in women discharged home after an episode of arrested preterm labour did not significantly reduce the rate of preterm delivery.

Keywords Maintenance treatment, preterm labour, progesterone.

Tweetable abstract Maintenance progesterone in 258 women after arrested PTB showed no benefit.

Linked article This article is commented on by J Thornton, p. 2000 in this issue. To view this mini commentary visit http://dx.doi.org/10.1111/1471-0528.13976.


*Members listed at the end of the article.

PROMISE collaborative group (see Appendix 1).
Introduction

Preterm birth before 37 completed weeks of gestation is responsible for most neonatal morbidity and mortality, and is also a leading cause of long-term disability in most industrialised countries, including Europe and the USA.1,2 The baseline risk of preterm birth is approximately 10%. Four groups of women have an increased risk of approximately 30% for preterm delivery: women with previous preterm delivery,3 women with a short cervical length at midgestation,4 women with a twin pregnancy,5 and women with an episode of preterm labour arrested with tocolytic medication.6 Progestagens have demonstrated a reduction in preterm birth in women with previous preterm delivery,6,7,8 or with asymptomatic short cervix,4,5,9 but not in women carrying twins.10–16 The use of vaginal progesterone as a maintenance treatment in women with arrested preterm labour is controversial.

Despite current tocolytic agents being superior to a placebo at delaying delivery at both 48 hours and 7 days,17 maintenance tocolytic therapy after successful treatment of an acute episode of preterm labour does not reduce the incidence of preterm delivery or improve perinatal outcome.18,19 Earlier clinical trials using 17-hydroxyprogesterone reported no apparent benefit on perinatal outcomes,20,21 whereas five small clinical trials using vaginal natural progesterone have reported prolongation of pregnancy.22–26 A recently published study failed to show the effectiveness of vaginal progesterone in preventing preterm birth after prolonged treatment in women with preterm labour, however.27

A recent meta-analysis has shown that vaginal progesterone, when used after arrested preterm labour, might be of some benefit;28 however, the authors are cautious with their conclusions because of the limited quality of the studies published (i.e. a limited sample size or lack of placebo or blinding), and call for well-designed trials to confirm these findings.

We therefore conducted a multicentre, double-blind, randomised, placebo-controlled clinical trial to evaluate the use of vaginal progesterone as a maintenance treatment in women discharged home after an arrested preterm labour, with the aim of reducing the incidence of preterm delivery.

Methods

Setting and participants

The PROMISE study (vaginal progesterone as maintenance treatment after an episode of preterm labour) was undertaken in 12 tertiary care hospitals in Spain. The study was planned to last 3 years and was extended for an extra year to obtain the required sample size, running from June 2008 to 2012. We received ethics approval for the trial in December 2007 from the institutional review board of the coordinating centre (ref. no. hcp.07.2600500).

Eligible patients were women with singleton pregnancies, aged 18–45 years, who had been admitted for preterm labour, and had been successfully treated with any tocolytic drug. In all these women, the decision to discharge had already been made by the managing doctor, and they each had a cervical length <25 mm and a gestational age between 24.0 and <34.0 weeks of gestation at the time of discharge.

Preterm labour was defined as a minimum of two regular painful contractions in 10 minutes, averaged over 30 minutes, accompanied by a change in cervical dilation, effacement, or both. Cervical length was measured according to the criteria of the Fetal Medicine Foundation (i.e. empty urinary bladder, internal and external os visualised, no pressure on the cervix, and the shortest of three measurements).29 Exclusion criteria were preterm rupture of membranes, cervical cerclage, receiving progesterone at ≥20 weeks of gestation, known or suspected infection, any coexisting maternal or fetal conditions that might need iatrogenic labour [pre-eclampsia or intrauterine growth restriction (IUGR)], present or previous liver disease (cholestasis gravidarum or abnormal hepatic blood tests), or grade-2 or upper renal laboratory abnormalities, history of diabetes mellitus, insulinised gestational diabetes, drug abuse, treatment with heparin for any reason, suspicion of inadequate treatment compliance, or peanut allergy.

Randomisation and intervention

After written informed consent was obtained from each woman, patients were randomly assigned to one of the two study arms in a 1 : 1 ratio. Randomisation was stratified by gestational age (24.0–30.6 and 31.0–33.6 weeks of gestation) and centre. The gestational ages of the two blocks were chosen because previous data from the coordinating centre (not shown) indicated that 31 weeks was the median gestational age of women admitted for preterm labour.

The randomisation sequence was computer-generated by the Clinical Trials Unit at Hospital Clinic of Barcelona, and implemented using a centralised controlled website randomisation service and eCRF. Recruiters or the trial coordinator did not have access to the randomisation sequence. The allocation code number was disclosed after the trial was completed.

On the day of discharge, women allocated to the study group received vaginal capsules of 200 mg natural micronised progesterone (Progeffik, Laboratorios Efik, Spain). Likewise, on the day of discharge the control group received identical capsules containing a placebo, to be
applied once daily until delivery or 36.6 weeks of gestation, whichever occurred first. The first capsule containing pla-

ceto or progesterone was to be self-administered by the

woman on her first night at home.

Participants were given a calendar specifically designed for the study, in which follow-up visits, any adverse events, and forgotten capsules could be reported. Follow-up visits were arranged at weeks +1, +3, and +5 for clinical evaluation, ultrasound cervical length assessment, adherence to treatment, and reporting adverse events. From week +5 onwards, follow-up visits were left to doctors’ discretion. A final follow-up visit was arranged after delivery and the study calendars were collected.

Women who discontinued medication remained in the trial because of the intention-to-treat principle.

Outcomes

The two main outcomes were preterm birth before 34 and 37 weeks of gestation. Secondary outcomes were: dis-

charge-to-delivery time, readmissions because of preterm labour, emergency service use, and neonatal morbidity and mortality. Composite adverse neonatal outcome was con-

sidered if any of the following occurred: respiratory distress syndrome or need for respiratory support, necrotizing ente-

rochloalisis, intraventricular haemorrhage grade III or IV, or neonatal sepsis. We also evaluated potential maternal adverse events such as rate of chorioamnionitis, cholestasis, hyperemesis, urinary tract or vulvovaginal infection, endometritis, hyperglycaemia or gestational diabetes, som-

nolence, headache or dizziness, or postpartum haemorrhage or curettage.

Sample size

In our context, the rates of preterm delivery before 34 and 37 weeks of gestation were 25 and 40%, respectively. In various published references the rates were 45–83% for preterm delivery before 34 weeks of gestation,4–7,9 and 36–52% for preterm delivery before 37 weeks of gestation.7,8 The study target was to detect a 50% reduction in the incidence of birth at <34 weeks of gestation and a 40% reduction for delivery at <37 weeks of gestation. The sample size was driven by the most restrictive variable so that the analysis would cover both outcomes. Assuming a preterm delivery rate of ~25% at <34 weeks of gestation in the control group, a relative reduction of 50% effect (i.e. 12.5% in the experimental arm), 80% statistical power, and a 5% two-sided alpha level, the study required 336 valid patients (with 168 in each arm). It was decided to recruit 350 patients (175 in each arm) to mitigate the dropout rate. A hierarchical approach was predefined to handle the multiplicity arising from the use of two primary outcomes, as detailed in the data analyses section.

Data analyses

Statistical analysis was based on the modified intention-to-treat principle (mITT), including only women taking a first dose of the medication, regardless of any protocol deviation, as prespecified. The two main outcomes, rates of preterm birth before 34 and 37 weeks of gestation, assessed in a predefined hierarchical order to handle multiplicity, and the inferential analyses were based on a stratified Cochran–Mantel–Haenszel test. The stratum factor used for all the stratified and adjusted models was gestational age. We estimated between treatment rate differences for those variables based on a log-binomial model, fitting the link function to identity and adjusting by the stratification factor. Risk ratios were computed using the same model but fitting the link function to log. An interim analysis was planned when half of the sample size was recruited using the Haybittle–Peto approach (alpha-adjusted nominal level of 0.001 at the interim analysis and 0.05 at the final analy-

sis). The survival function and the median (95% confidence interval, 95% CI) for time to delivery were estimated by means of the Kaplan–Meier method; elective deliveries were censored. Group comparisons were performed using the stratified log-rank test and hazard ratios (HRs) and 95% CIs were taken from the Cox model. The remaining variables were analysed using Fisher’s exact test to compare categorical data, the Student’s t-test for continuous vari-

ables, and the Mann–Whitney U-test for ordinal and non-

normally distributed variables.

The analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA), and the level of significance was set at 5% (two-sided).

Results

The PROMISE study was undertaken from June 2008 to 2012. During the study period, 1419 women with single pregnancies, admitted because of preterm labour, and who were about to be discharged with a continuing pregnancy, were evaluated for inclusion criteria; Figure 1 shows the main reasons for exclusion. Other exclusion criteria were: maternal age <18 years (n = 22); maternal conditions (n = 22); diabetes mellitus (n = 10); cerclage (n = 11); already on progesterone (n = 11); gestational age <24 weeks (n = 8); fetal malformation (n = 6); iatrogenic preterm labour (n = 4); liver disease (n = 2); uterine mal-

formation (n = 3); receiving heparin (n = 3); and allergy to peanuts (n = 1). Therefore, 472 women remained eligi-

ble for the study. Of these, 265 women (56.1%) consented to participate in the study and were randomised to the progesterone group or to the placebo group. Of those, 258 received the first dose of medication at home and were included in the final analysis, as pre-specified (Figure 1).
An interim analysis was carried out by an independent data and safety monitoring board (DSMB), when 174 women were recruited using the Haybittle–Peto statistical approach. It concluded that the study should not be stopped, given that the statistical stopping rule was not achieved (i.e. $P < 0.001$). Therefore, the study proceeded to recruit the fixed final sample size as pre-planned in the protocol, and without any amendment. Finally, the study was stopped when 75.7% (265/350) of the total sample was included, because of funding limitations, mainly arising from the renewal of the insurance covering the study.

Table 1 shows the baseline characteristics of the participants. Two-thirds were white, and about 12% had a previous preterm birth; 6–7% had used progesterone before 20 weeks of gestation because of assisted-reproduction techniques, and atosiban was used in 65% of the women as a tocolytic agent. About one-third of women had a cervical length $<15$ mm at the time of randomisation.

The adherence rate (100% of capsules taken) was 82.6% ($n = 104$) in the progesterone group and 82.6% ($n = 109$) in the placebo group ($P = 0.56$), and in only two cases in each group were more than seven capsules not taken. Non-adherence occurred when the doctor or woman decided to stop the treatment.

There were no differences between groups regarding the primary outcome of preterm delivery before 34 and 37 weeks of gestation (Table 2). Stratum-adjusted between-treatment rate differences (95% CI) were 0.2% (−5.6 to 5.9%) and −7% (−17.7 to 3.5%) for preterm delivery before 34 and 37 weeks of gestation, respectively. No differences were observed between the two groups when the two strata of gestational age at randomisation were considered (24.0–30.6 and 31.0–33.6 weeks of gestation), or upon evaluating cervical length as $<15$ or $\geq 15$ mm at randomisation (Table 2). Kaplan–Meier survival curves showed no differences in the cumulative percentage of women who did not give birth before 37 weeks of gestation (Figure 2).

Table S1 shows the distribution of secondary and perinatal outcomes. There was no difference between the two groups in the discharge-to-delivery time [median (95% CI): 47.5 (40–52) versus 49 (43–53) days in progesterone and placebo groups, respectively], in the number of readmissions because of preterm labour, or in the number of women attending the emergency unit one or more times. Overall, there were 58 and 71 emergency consultations in the progesterone and the placebo groups, respectively ($P = 0.13$). Similarly, there were no differences observed in the proportion of neonates admitted to...
Palacio et al.

Table 1. Baseline characteristics of the study participants included in the analysis

<table>
<thead>
<tr>
<th></th>
<th>Progestrone group n = 126</th>
<th>Placebo group n = 132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>29.5 (5.4)</td>
<td>28.5 (5.7)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>67 (53.2%)</td>
<td>92 (69.7%)</td>
</tr>
<tr>
<td>Parous with ≥1 previous preterm</td>
<td>15 (11.9%)</td>
<td>16 (12.1%)</td>
</tr>
<tr>
<td>Late miscarriage</td>
<td>4 (3.2%)</td>
<td>6 (4.5%)</td>
</tr>
<tr>
<td>(15–22 weeks of gestation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92 (73%)</td>
<td>100 (75.8%)</td>
</tr>
<tr>
<td>Latin American</td>
<td>25 (19.8%)</td>
<td>19 (14.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (7.1%)</td>
<td>13 (0.8%)</td>
</tr>
<tr>
<td>Progestrone use &lt;20 weeks of gestation</td>
<td>10 (7.9%)</td>
<td>8 (6.1%)</td>
</tr>
<tr>
<td>Vaginitis or asymptomatic bacteriuria</td>
<td>31 (24.6%)</td>
<td>43 (32.6%)</td>
</tr>
<tr>
<td>Tocolytic use for preterm labour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atosiban</td>
<td>82 (65.1%)</td>
<td>87 (65.9%)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>15 (11.9%)</td>
<td>12 (9.1%)</td>
</tr>
<tr>
<td>More than one</td>
<td>24 (19.0%)</td>
<td>30 (22.7%)</td>
</tr>
<tr>
<td>Gestational age at randomisation (weeks)</td>
<td>31.7 (2.7)</td>
<td>31.9 (2.3)</td>
</tr>
<tr>
<td>24–30,31–36 weeks</td>
<td>57 (45.2%)</td>
<td>61 (46.2%)</td>
</tr>
<tr>
<td>31–36,37–40 weeks</td>
<td>69 (54.8%)</td>
<td>71 (53.8%)</td>
</tr>
<tr>
<td>Cervical length at randomisation (mm)</td>
<td>17.5 (6.5)</td>
<td>17.4 (6.3)</td>
</tr>
<tr>
<td>Cervical length of &lt;15 mm</td>
<td>36 (28.6%)</td>
<td>36 (27.3%)</td>
</tr>
<tr>
<td>Digital examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bishop score ≥3</td>
<td>75 (59.6%)</td>
<td>79 (59.8%)</td>
</tr>
<tr>
<td>Effacement &gt;50%</td>
<td>27 (22.9%)</td>
<td>22 (17.8%)</td>
</tr>
<tr>
<td>Dilatation ≥3 cm</td>
<td>3 (2.4%)</td>
<td>2 (1.6%)</td>
</tr>
</tbody>
</table>

Data are numbers (%) or means (SDs).

intermediate or intensive care units, or in neonatal death or the composite adverse outcomes rate: 7/126 (5.6%) versus 9/132 (6.8%) in the progesterone and the placebo groups, respectively (P = 0.80).

Regarding potential adverse maternal events, in 13 (10.2%) and 15 (11.4%) women of the progesterone and the placebo groups, respectively, one or more related or serious adverse events were reported (P = 0.84; Table S2).

Discussion

Main findings
This is the first multicentre, double-blind, randomised, placebo-controlled trial reporting the use of progesterone as a maintenance treatment after arrested preterm labour and hospital discharge.

Our trial found that the rate of preterm birth at <34 and <37 weeks of gestation was not reduced by maintenance treatment with natural micronised vaginal progesterone at 200 mg/day in women discharged after an episode of arrested preterm labour and with a cervical length of <25 mm.

Strengths and limitations
The results of our study are strengthened by the robust design and by the use of a placebo. The clinical question about the potential benefit of progesterone as a maintenance treatment, once the decision of discharge has been taken, is clearly addressed. The extended use of progesterone beyond the proven indications may make replication of a study with the same characteristics as the PROMISE trial difficult.

A limitation of the study was that the estimated sample size was not achieved, as a result of the discontinuance of insurance funding. In addition, the sample size assumed a larger effect and a higher percentage of preterm delivery, as described in another high-risk population, because there were no previous studies reporting these figures in a population similar to ours. Considering the results after 75.7% of the sample had been recruited, however, and the stratum-adjusted rate differences between the two groups, no clinically relevant changes in the main results should be expected. Recruitment was lower than expected and this was mainly a result of the low consent rate (50–60%), which is in line with other recent trials involving pregnant women even without the use of drugs.4,30 This leads to the prolongation of the study over time, which increases fatigue in the investigator team, limits funding, and hinders achieving the expected goal in a reasonable time. Despite the subgroups (gestational age and cervical length) being predefined, the absence of statistical significance for the interaction test with the treatment (except for gestational age with birth at <37 weeks of gestation) recommends a lot of caution in the interpretation of the subgroups.

Interpretation
Our results are in conflict with most of the studies using progestogens for this indication [either natural progesterone or 17-alpha-hydroxy-progesterone caproate (17P)]; however, most of the randomised controlled trials (RCTs) published were exploratory, with a limited sample size, including fewer than 100 women,21–25,31 or not using a placebo,20,24,25,31 and one was retrospective.26 Most of these studies suggested that natural progesterone may have a beneficial effect in prolonging pregnancy. The only well-designed RCT with an adequate sample size, but without a placebo, using 500 mg 17P per week,20 and a small trial also using 17P,21 showed that this strategy did not prolong pregnancy. This was a similar conclusion to that of a recently-published RCT using progesterone in women with preterm labour still on tocolysis.27 Regardless of these
result, information about any potential benefit of vaginal progesterone after the preterm labour episode has been arrested and tocolysis is complete is lacking.

Even though the preterm birth rate at <34 and <37 weeks of gestation in our study population was much higher than in the general population, it was lower than expected considering a population of women admitted because of preterm labour: 19/258 (7.4%) and 65/258 (25.2%), respectively, whereas most published studies have reported a preterm birth rate of 10–17% at <34 weeks of gestation and 35–60% at <37 weeks of gestation.

A few factors may explain this low preterm birth rate: in our study, only women for whom the decision to be discharged was already made were included, thereby probably excluding women at the highest risk who were not discharged before delivery. Nonetheless, in the study of

Table 2. Primary outcomes in the progesterone and the placebo groups

<table>
<thead>
<tr>
<th></th>
<th>Progesterone* n = 126</th>
<th>Placebo* n = 132</th>
<th>Treatment effect**</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery &lt;34 weeks of gestation</td>
<td>9 (7.1%)</td>
<td>10 (7.6%)</td>
<td>RD: -0.2% (–5.9% to +5.6%)</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 0.95 (0.40–2.24)</td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;37 weeks of gestation</td>
<td>36 (28.6%)</td>
<td>29 (22.0%)</td>
<td>RD: +7.1% (–3.5% to +17.7%)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.29 (0.85–1.98)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous delivery &lt;34 weeks of gestation</td>
<td>8 (6.3%)</td>
<td>9 (6.8%)</td>
<td>RD: -0.3% (–5.5% to +4.9%)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.06 (0.39–2.93)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous delivery &lt;37 weeks of gestation</td>
<td>31 (24.6%)</td>
<td>24 (18.2%)</td>
<td>RD: +8.4% (–1.2% to +18.0%)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.61 (0.95–2.71)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>38.0 (37.4–38.3)</td>
<td>38.2 (37.6–38.6)</td>
<td>HR: 1.21 (0.95–1.56)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Considering gestational age at randomisation***

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Women randomized 24*–30** weeks of gestation</td>
<td>n = 57</td>
<td>n = 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;34 weeks of gestation</td>
<td>38.1 (37.4–38.9)</td>
<td>38.0 (37.3–38.9)</td>
<td>HR: 1.13 (0.78–1.63)</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 0.92 (0.33–2.57)</td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;37 weeks of gestation</td>
<td>6 (10.5%)</td>
<td>7 (11.5%)</td>
<td>RD: -0.9% (–12.2% to +10.3%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.16 (–17.6% to +14.5%)</td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;32 weeks of gestation****</td>
<td>5/57 (8.8%)</td>
<td>2/61 (3.3%)</td>
<td>RD: +3.9% (–5.3% to +13.0%)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.78 (0.45–7.13)</td>
<td></td>
</tr>
<tr>
<td>Women randomized 31**–36*** weeks of gestation</td>
<td>n = 69</td>
<td>n = 71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;34 weeks of gestation</td>
<td>37.9 (37.3–38.3)</td>
<td>38.4 (37.4–38.7)</td>
<td>HR: 1.32 (0.94–1.84)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 0.01 (–6.6% to +6.8%)</td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;37 weeks of gestation</td>
<td>3 (4.3%)</td>
<td>3 (4.2%)</td>
<td>RD: +3.9% (–5.3% to +13.0%)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.78 (0.45–7.13)</td>
<td></td>
</tr>
</tbody>
</table>

**Considering cervical length at randomisation*****

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical length of &lt;15 mm</td>
<td>n = 36</td>
<td>n = 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;34 weeks of gestation</td>
<td>4 (11.1%)</td>
<td>4 (11.1%)</td>
<td>RD: -0.0% (–14.5% to +14.5%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 1.00 (0.27–3.69)</td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;37 weeks of gestation</td>
<td>17 (47.2%)</td>
<td>8 (22.2%)</td>
<td>RD: +25.0% (+3.8% to +46.2%)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 2.12 (1.05–4.29)</td>
<td></td>
</tr>
<tr>
<td>Cervical length at ≥15 mm</td>
<td>n = 90</td>
<td>n = 96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;34 weeks of gestation</td>
<td>5 (5.6%)</td>
<td>6 (6.3%)</td>
<td>RD: -0.7% (–7.5% to +6.1%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 0.89 (0.28–2.81)</td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;37 weeks of gestation</td>
<td>19 (21.1%)</td>
<td>21 (21.9%)</td>
<td>RD: -0.8% (–12.6% to +11.1%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR: 0.97 (0.56–1.67)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are numbers (%) or medians (95% CI) (weeks).

**Treatment effect adjusted by the randomisation stratum: HR, hazard ratio (95% CI); RD, rate difference (95% CI); RR, relative risk (95% CI).

Negative values favour progesterone and positive values favour placebo for RD. Values < 1 favour progesterone and values >1 favour placebo for RR and HR.

***Treatment by gestational age interaction tests were P = 0.87 and P = 0.16 at 34 and 37 weeks of gestation, respectively.

****Only n = 118 women, from 24.0 to <31.0 weeks of gestation, were considered.

*****Treatment by gestational age interaction tests were P = 0.93 and P = 0.034 at 34 and 37 weeks of gestation, respectively.
Martinez de Tejada et al., randomisation was performed within 48 hours of tocolysis, and although a higher rate of preterm birth was observed, no differences between the groups were found. Our study therefore complements that of Martinez de Tejada et al., as the results of both studies give information about the potential benefit of progesterone for this indication, regardless of the point at which the maintenance treatment is started. Also, ethnicity may explain the low rate of preterm birth. Most of the women in our study were white, which is known to be a population at low risk of preterm birth compared with women of other ethnicities. Although in most studies ethnicity is not reported, country and centre of publication (i.e. India, Iran, and Turkey) could suggest that the basal risk of their population may be higher than ours. This, together with the fact that in most studies intervention was started shortly after labour was arrested, and not excluding women with recurrence of preterm labour and eventually preterm birth in the same admission episode, may explain the higher prevalence of preterm birth.

Factors that may influence the potential benefit of progesterone, including the previous preterm birth rate, the gestational age at inclusion, and the uterine cervical conditions at randomisation, were comparable with those of other studies. The percentages of nulliparous women were imbalanced; however, together with the percentage of parous women with previous term pregnancy, which is a low-risk population for preterm delivery, it is unlikely that this fact might have affected the findings. On the other hand the most relevant parameter, the previous preterm birth rate, was comparable between the two groups of study, and was similar to that found in other studies, at approximately 10%. Our gestational age at inclusion was around 31–32 weeks of gestation, in line with some studies, but later than that of other studies. Of the latter, one was retrospective and the other three reached the same conclusions as our study. Finally, cervical conditions (i.e. Bishop score) were similar, or less advanced, although the cervical length was similar or shorter than in the studies reporting these data.

Figure 2. Kaplan–Meier plot for delivery among women receiving vaginal progesterone compared with placebo. Placebo 38.2 [37.6–38.7]; Progesterone 38.2 [37.4–38.3]; HR 1.22 [0.95–1.56]; P = 0.10. Note: Kaplan–Meier Estimates Median [95% CI] and stratified log-rank P-value.

The cut-off point chosen to select women at risk is another variable to be taken into account. There is still not a clear cut-off point to be used as a risk factor for preterm birth in this particular population. Our inclusion criteria included a cut-off point of <25 mm, which selected 25% of women for whom the decision to discharge was made. In addition, we show the results in women with earlier gestational age at admission or with very short cervical length at discharge. Although the sample size was limited in these subgroups, we could not see differences in the stratum including women with a lower gestational age (n = 118) or in the group with a cervical length of <15 mm (n = 72). On the other hand, progesterone has not been shown to have an impact in women with long cervical length and prior preterm birth. Therefore, it is plausible that its use would not be beneficial in the population admitted because of preterm labour and cervical length ≥25 mm.

Another factor that may influence the potential benefit of progesterone is the dose and kind of progesterone used. Our study used 200 mg/day of vaginal natural progesterone, a dose that was described to be useful for women at risk at the time the study was designed. One may think that women of our particular population of risk may need a higher dose; however, in other populations such as twins, higher doses have been proven to be of no benefit and, on the other hand, the only RCT adequately sized using 17P used high doses without demonstrating any prolongation of pregnancy. Therefore, until the mechanisms of action of progestogens are more fully understood, the dose and kind of progesterone may not provide the unique answer.

The mechanism by which progesterone may benefit women at risk because of prior preterm birth or short cervical length is still unknown. Progesterone has been shown to enhance tocolysis in vitro, and Facchinetti et al. demonstrated a reduced shortening of the cervix in women with preterm labour treated with 17P. These findings do not necessarily lead to clinically relevant outcomes, however, and both the American Congress of Obstetricians and Gynaecologists and the Society of Obstetricians and Gynaecologists of Canada have called for additional information to determine the population of women for whom progesterone could be of benefit. Although no short-term maternal or neonatal adverse outcomes were associated with the use of vaginal progesterone in this study, caution must be taken until safety issues are examined in the absence of benefit.
Conclusion

In conclusion, the PROMISE study shows that maintenance treatment with vaginal progesterone (200 mg/day) in women discharged home after arrested preterm labour, and with a cervical length of <25 mm, does not seem to reduce the rate of preterm birth at <34 and <37 weeks of gestation. More data are needed before it is used for this indication.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

MP was responsible for the original idea, design, implementation of the study, and wrote the first draft. MP, TC, EA, MR, FC, FM, JLB, MJ, AM, DO, AR, ES, and JMO were the principal investigators at their centres, and were responsible for recruitment, implementation, and surveillance of the trial in their sites. SV, JR, and EG also participated in the original discussions regarding the design, development, and methodological issues of the study, and JR was the statistician of the study. MP, TC, SV, JR, and EG also participated in the analysis and interpretation of the results. All authors reviewed and approved the final version of the report. All the other authors cited in the collaborative group were responsible for the direct recruitment and acquisition of data at their sites or for the analysis of data and critical review of the article, and approved the final version of the article.

Details of ethics approval

Favourable ethical opinion for this study was granted in December 2007 by the institutional review board of the coordinating centre: Comité Ético d’Investigació Clínica (ref. no. hcp.07.2600500). This trial was registered first under its Spanish name (as we were applying to the Spanish government). The submission to www.clinicaltrials.gov was under the English name, however, and this is how the trial has been referred to since then in all international settings (number NCT00646802).

Funding

This project was supported by Instituto de Salud Carlos III (EC07/90023) and Ministerio de Sanidad y Política Social (TRA-096). The funding sources had no role in the study design, data gathering, data analysis, data interpretation, or writing of the article. The investigators had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgements

We thank all the women participating in the PROMISE trial and all the physicians recruiting for the trial; Antoni Trilla, Inaki Carralo and Felix Méndez for their enthusiastic support; the members of our DSMB for their guidance; and all the personnel at the different centers for their dedication and hard work. We also thank the CTU personnel for their monitoring assistance and Donna Pringle and Helen Robson for their help with the English version of the manuscript. We also thank the Society for Maternal Fetal-Medicine, which awarded the presentation of this trial with the Award of Research Excellence (33rd Annual Meeting, February 11–16, 2013 at San Francisco). This work was also presented at the 12th World Congress in Fetal Medicine, June 23–27, 2013 at Marbella, Spain. The PROMISE study was supported by the Instituto de Salud Carlos III (EC07/90023) and Ministerio de Sanidad y Política Social (TRA-096). Progesterone and placebo were purchased from Laboratorios EiM (Madrid, Spain).

Steering committee: Montse Palacio, Teresa Cobo, Joan Albert Arnaiz, and Sara Varea.

Data monitoring committee: Nuria Ramos, Andrea Pejeante, and David García.

Data safety monitoring board: Xavier Carné, Kellie E. Murphy, Caroline Crowther, Arne Ohlsson, and Ferran Torres.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Secondary outcomes in the progesterone and the placebo groups.

Table S2. Related and severe adverse events reported in the progesterone and the placebo groups.

References

7 da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the


Appendix 1.

PROMISE Collaborative Group

Francisco Cabrera Morales, Andrés Arencibia Molina, Elena Cortés Cros, Begoña Vega Guedes, Beatriz Sánchez Lerma, Leonor Valle Morales (Complejo Hospitalario Universitario Insular Materno Infantil, Las Palmas de Gran Canaria); Águeda Rodríguez, Maria Grimau, Silvia Pina, Jordi Costa, Belén Cochs, Laia Martí (Corporació Sanitària Parc Taulí, Sabadell); Francisco Mozo de Rosales, Amelia Valladolid, Tamara Dehesa, Maria Victoria Sanromán, Maria José Fernández Mellado (Hospital Universitario de Basurto, Bilbao); Montse Palacio, Teresa Cobo, Mónica Martínez, Marta López, Joan Albert Arnaiz, Vicenç Cararach, Eduard Gratacos (Hospital Clinic de Barcelona, Barcelona); Daniel Oros, Manuel Ángel Romero, Ernesto Fabre Daniel Oros-Espinosa (Hospital Clínico Universitario “Lozano Blesa”, Zaragoza); José Luis Bartha, Fernando Bugatto, Victoria Melero, Sol Caballero, María Antonia Fajardo (Hospital Puerta del Mar, Cádiz); Anna Martí Canamares, María Carmen Bergós Sorolla, Patricia Zabala Franco (Althaia Xarxa Assistencial Universitària de Manresa. Hospital de Sant Joan de Déu de Manresa, Manresa); Miquel Juan, Ana Martínez Barrabés, Javier Grau, Beatriz Soriano (Hospital Son Llàtzer, Palma de Mallorca); José María Oliveras Hidalgo, Ángels Vives, Alejandra Rodríguez Veret, Mª del Pilar Míllán, Esperanza García Cancela (Hospital de Terrassa. Consorci Sanitari de Terrassa, Terrassa); Elena Schazzocchio, Carme Comas, Sonia Rombaut, Alberto Rodríguez, Bernat Serra (Hospital Universitario Quirón-Dexeus, Barcelona); Eugenia Antolín, Ángel Aguaron, Fátima Yllana, Maria del Carmen Vinuela, Nieves Crespo, (Hospital Universitario Gregorio Marañón, Madrid); María Ramírez, Almudena Perea, Carlos Bedoya (Hospital Universitario Virgen Macarena, Sevilla).