Progesterone for the prevention of preterm birth
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The effect of 17-alpha hydroxyprogesterone caproate on cervical length in multiple pregnancies

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Abstract

**Objectives** Previous studies in singleton pregnancies have indicated that progestogens may reduce the rate of cervical shortening during pregnancy. The aim of this study was to investigate whether 17-alpha hydroxyprogesterone caproate (17OHPC) treatment has an effect on cervical shortening in twin pregnancies.

**Methods** This was a secondary analysis on patients who had participated in a multicenter randomized clinical trial on the effectiveness of 17OHPC in preventing preterm birth in multiple pregnancies (the AMPHIA-trial). We included all trial participants with a twin gestation who had undergone repeated cervical length measurements during pregnancy. We performed a separate analysis for women with repeated measurements in centers where this was standard protocol for multiple pregnancies. The rate of cervical shortening for both the 17OHPC group and the placebo group was analyzed using a linear mixed model.

**Results** Of the 671 patients who participated in the trial, 282 (42%) carried a twin pregnancy and underwent two or more cervical length measurements. Of these women, 140 were monitored in centers where repeated measurements were standard protocol. We observed an overall reduction of cervical length from 41.6 mm at randomization to 26.9 mm at 32 weeks. In the 17OHPC group, cervical length decreased by 1.04 mm each gestational week, while this was 1.11 mm per week for the placebo group (p=0.6). For the overall group, each 10% decrease in cervical length lead to an increase in the risk for preterm birth (HR 1.14; 95% CI 1.08-1.21).

**Conclusions** In women with a twin pregnancy, there is progressive shortening of the cervix during pregnancy regardless of 17OHPC use.

Introduction

In the first decade of the new millennium numerous studies have been conducted on progestogens as a preventive treatment for preterm birth. Interest in the subject was sparked by two randomized controlled trials, both indicating a substantial decrease in recurrent spontaneous preterm birth after the use of progestogens.\(^1,2\) These findings led to trials being performed in several groups of pregnant women with a high risk of spontaneous preterm birth. Although trials have shown a benefit of progestogens in both women with a previous preterm birth and women with asymptomatic cervical shortening in the second trimester, the exact mechanism of action whereby progestogens prevent preterm birth remains unknown.\(^1-4\) Two secondary analyses of randomized trials in singleton pregnancies have indicated that progestogen treatment may reduce the rate of cervical shortening.\(^5,6\)
Progestogens have proven to be ineffective in preventing preterm birth in women with a multiple pregnancy.\textsuperscript{7-11} Whether this is due to an inadequate selection of patients who may benefit from this treatment or an altogether absence of treatment effect in multiple pregnancies is unclear.

Regardless of this uncertainty, the observation that progesterone reduced shortening of the cervix in singleton pregnancies raised the question whether this phenomenon is also present in women with a multiple pregnancy. To address this issue, we performed a secondary analysis of a multicenter, randomized placebo-controlled trial studying the effectiveness of 17-alpha hydroxyprogesterone caproate (17OHPc) in preventing preterm birth in multiple pregnancies.\textsuperscript{12} Our aim was to investigate whether 17OHPc treatment has an effect on cervical shortening in twin pregnancies.

Materials and Methods

From August 2006 until June 2009, 671 women with a multiple pregnancy (twin or higher order) were recruited in the AMPHIA-trial. Details on the methods in this trial have been described elsewhere.\textsuperscript{12} In short, consenting women were randomized to weekly injections of either 250 mg 17OHPc or placebo. Treatment started between 16 and 20 weeks of gestation and was continued until 36 weeks or delivery, whichever came first. The study was approved by the Institutional Review Board of the Academic Medical Centre in Amsterdam, and 52 centers participated in the trial. A transvaginal ultrasound at randomization to measure cervical length was part of the trial protocol. In nine participating centers, serial cervical length measurements during the course of pregnancy were part of standard management in multiple pregnancies.

In this secondary analysis, we included all women with a twin pregnancy who had participated in the AMPHIA trial and who had undergone more than one cervical length measurement during pregnancy. We performed a separate analysis for women with repeated measurements in the nine centers were this was standard practice for women with a multiple pregnancy. Data on cervical length measurements were extracted from clinical records and were entered into a web based case record form by trained research assistants. All caregivers, sonographers and research assistants were blinded to the trial allocation (17OHPc or placebo).

Statistical analysis

We performed a repeated measurements analysis in which we assessed the impact of increasing gestational age, treatment allocation as well as the interaction between the two. We used a linear mixed model to account for the fact that each subject had undergone a different number of measurements at varying gestational ages. The rate of cervical shortening in millimeters per gestational week was calculated for the 17OHPc group and the placebo group separately. We performed a separate analysis for women with
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repeated measurements in the nine centers where this was standard practice for multiple pregnancies. The mean cervical length at various gestational ages was compared using Student’s t-test.

Subsequently, we evaluated whether the amount of shortening of the cervix was associated with the risk of preterm delivery. To do so, we expressed cervical length at each measurement as the percentage of the cervical length that was measured at the first measurement. We then used Cox regression analysis to evaluate whether the amount of shortening of cervical length was related to time to delivery. P-values below .05 were considered to be statistically significant. All statistical analyses were conducted in R for Windows (version 2.10.0).

Results

A total of 671 patients participated in the trial. In 602 women the cervix was measured by means of transvaginal ultrasound at least once during pregnancy and 282 (42%) of these women carried a twin pregnancy and underwent two or more measurements. Of these 282 women, 150 women (53%) had been allocated to 17OHPc treatment and 132 women (47%) to placebo. Baseline characteristics are shown in Table 1.

In the 17OHPc group, the mean number of cervical length measurements was 4.1 per subject, while there were 4.0 measurements per subject in the placebo group (p=0.65) (Table 2). The rate of delivery before 37 weeks was similar in both groups (59% for 17OHPc vs. 52% for placebo, p=0.3), as was the percentage of women who received tocolysis for preterm labor (27% vs. 24%, p=0.7). The mean cervical length at 14 to 22 weeks of gestation calculated per subject was not statistically different between the 17OHPc group and the placebo group (44.9 vs. 43.6 mm at 14-18 weeks, p=0.5, 42.6 vs. 42.6 mm at 18-22 weeks, p=1.0). Overall, we observed a reduction of cervical length from a mean of 44.3 mm at 14-18 weeks to a mean of 30.0 mm at 30 weeks.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>17OHPc (n=150)</th>
<th>Placebo (n=132)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monochorionic</td>
<td>26 (17%)</td>
<td>21 (16%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Assisted reproductive techniques</td>
<td>56 (37%)</td>
<td>59 (45%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Caucasian</td>
<td>129 (86%)</td>
<td>106 (80%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>71 (47%)</td>
<td>79 (60%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>17 (11%)</td>
<td>9 (7%)</td>
<td>0.2</td>
</tr>
<tr>
<td>History of cervical surgery</td>
<td>2 (1%)</td>
<td>4 (3%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Maternal age (years)*</td>
<td>33.8 (±4.7)</td>
<td>33.7 (±4.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>Body Mass Index at booking*</td>
<td>24.2 (±4.5)</td>
<td>24.2 (±4.5)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

17OHPc = 17-alpha hydroxyprogesterone caproate; *Values are represented as mean (± standard deviation)
The effect of 17OHP on cervical length in multiple pregnancies

**Figure 1** Cervical length during pregnancy (all measurements)

**Figure 2** Cervical length during pregnancy (centers with standard repeated measurements)
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Table 2: Measurements in all patients included in the analysis

<table>
<thead>
<tr>
<th>Gestational age at measurement</th>
<th>17OHP (n=150)</th>
<th>Placebo (n=132)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>Measurements (n)</td>
<td>Cervical length (mm)*</td>
<td>Patients (n)</td>
</tr>
<tr>
<td>14.0-17.9 weeks</td>
<td>45</td>
<td>48</td>
<td>44.9 (±8.4)</td>
</tr>
<tr>
<td>18.0-21.9 weeks</td>
<td>96</td>
<td>127</td>
<td>42.6 (±10.2)</td>
</tr>
<tr>
<td>22.0-25.9 weeks</td>
<td>98</td>
<td>138</td>
<td>37.4 (±11.2)</td>
</tr>
<tr>
<td>26.0-29.9 weeks</td>
<td>94</td>
<td>151</td>
<td>34.9 (±11.7)</td>
</tr>
<tr>
<td>30.0-33.9 weeks</td>
<td>77</td>
<td>132</td>
<td>30.2 (±11.5)</td>
</tr>
<tr>
<td>≥34.0 weeks</td>
<td>12</td>
<td>16</td>
<td>26.3 (±10.4)</td>
</tr>
<tr>
<td>Number of measurements per patient*</td>
<td></td>
<td></td>
<td>4.1 (±2.6)</td>
</tr>
</tbody>
</table>

17OHP = 17-alpha hydroxyprogesterone caproate; *Values are represented as mean (± standard deviation)

to 34 weeks. When all measurements were analyzed using a mixed model, there was a statistically significant effect of gestational age on cervical length (p<0.001), but not of 17OHP treatment (p=0.6). In the 17OHP group, cervical length decreased by 1.04 mm each gestational week, while this was 1.11 mm per week for the placebo group (p=0.6) (Figure 1).

In the nine centers where repeated cervical length measurement was part of the standard protocol for multiple pregnancies, 140 women were included, with 79 women (56%) allocated to 17OHP and 61 women (44%) to placebo. The mean number of measurements per patient in this group was 5.0 (±2.9). When we restricted the analysis to these patients, the linear mixed model showed a decrease in cervical length of 1.07 mm per gestational week for the 17OHP group and a decrease of 1.24 mm per week for the placebo group (p=0.6) (Figure 2).

The mean percentage of cervical shortening, defined as the cervical length at the last measurement relative to the first measurement, was 28.3% with an interquartile range from 9.0% to 47.5%. Cox regression showed that, overall, each 10% decrease of the cervical length lead to an increase in the risk for preterm birth (hazard ratio [HR] 1.14; 95% confidence interval [CI] 1.08-1.21). In the 65 (23%) women that had a cervical shortening of more than 50% as compared to 217 (77%) women with a shortening less than 50%, the risk for preterm birth was increased even further (HR 1.97; 95% CI 1.39-2.77).

Discussion

In this secondary analysis of a large, randomized controlled trial evaluating the effectiveness of 17OHP in women with a multiple pregnancy, we did not find an effect of 17OHP treatment on the process of cervical shortening in twin pregnancies. However, both cervical length at randomization and the percentage of shortening between 16 and 26 weeks were strongly predictive for preterm delivery.
For our analysis, we included patients who underwent multiple measurements of the cervix. In centers where repeated measurements are not part of the standard treatment protocol, it is to be expected that a large proportion of the women who undergo repeated measurements do so because of symptoms of preterm delivery. To estimate the effect of 17OHPc on cervical shortening in asymptomatic women, we performed a separate analysis in women who underwent repeated measurements as part of a standard protocol, regardless of symptoms of preterm labor. As we did not find a difference between the results of the two analyses, we think our findings are robust.

A limitation of this study was that the trial protocol did not predefine measurement techniques, nor was there a trial-based certification of sonographers. However, as measurement techniques are often standardized within individual centers, we expect the rate of cervical shortening measured in individual patients to be independent of measurement technique.

Our data show a marked decrease in cervical length during the course of pregnancy in all patients, regardless of treatment with 17OHPc. Previous studies have indicated that progestogens may reduce the rate of cervical shortening in singleton pregnancies. Facchinetti et al. performed a randomized, non-blinded trial in patients who had undergone a successful episode of 48 hours of tocolysis for preterm labour.5 Women were randomly assigned to 341 mg of 17OHPc every 4 days or no treatment. Transvaginal cervical length measurements at randomization, 7 days later and 21 days later showed a decreased rate of cervical shortening in the 17OHPc group (p=0.002). In a randomized trial by O’Brien et al. women with a history of preterm birth and/or asymptomatic cervical shortening in the second trimester were randomized to either a daily dose of 90 mg vaginal progesterone or placebo.6 Cervical length was measured at randomization and at 28 weeks of gestation. Between these two measurements, patients treated with progesterone had significantly less cervical shortening than patients in the placebo group (p=0.02).
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The observation that progestogen treatment reduces the rate of cervical shortening in singleton pregnancies could not be reproduced in twin pregnancies. Apparently, cervical length is a consequence of the process of preterm birth that occurs relatively late in the chain of events, and is a sign of the process of preterm delivery that has been started, rather than a causative factor. If this were to be true, progestogens are able to stop the process that is occurring in women with a short cervix in a singleton pregnancy, but not in women with a short cervix in a multiple pregnancy.

This finding may also explain the inefficacy of progestogens in this population. Theoretically, cervical shortening in multiple pregnancies is mainly caused by mechanical factors, whereas in singleton pregnancies other factors, such as inflammation and production of prostaglandins and oxytocin, may play a larger role. The latter factors are more likely to be mediated by exogenous administration of progestogens.

In the main trial 17OHP did not reduce preterm birth or neonatal morbidity in multiple pregnancies. The study was underpowered to detect a reduction of preterm birth or neonatal morbidity after 17OHP treatment in women with a cervical length below 25 mm before 24 weeks. Although this hypothesis needs further research, our finding that cervical shortening in twin pregnancies is not influenced by 17OHP treatment, renders a beneficial effect of 17OHP on women with a multiple pregnancy and asymptomatic cervical shortening less probable.

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References


