Progesterone for the prevention of preterm birth
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17α-Hydroxyprogesterone Caproate for the Prevention of Adverse Neonatal Outcome in Multiple Pregnancies: A Randomized Controlled Trial

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Chapter 5

Abstract

Objective To estimate whether administration of 17α-hydroxyprogesterone caproate can prevent neonatal morbidity in multiple pregnancies by reducing the preterm birth rate.

Methods We conducted a multicenter, double-blind, placebo-controlled randomized trial in 55 obstetric clinics in the Netherlands. Women with a multiple pregnancy were randomized to weekly injections of either 250 mg 17α-hydroxyprogesterone caproate or placebo, starting between 16 and 20 weeks of gestation and continuing until 36 weeks of gestation. The main outcome measure was adverse neonatal outcome. Secondary outcome measures were gestational age at delivery and delivery before 28, 32, and 37 weeks of gestation.

Results We randomized 671 women. A composite measure of adverse neonatal outcome was present in 110 children (16%) born to mothers in the 17α-hydroxyprogesterone caproate group, and in 80 children (12%) of mothers in the placebo group (relative risk [RR] 1.34; 95% confidence interval [CI] 0.95–1.89). The mean gestational age at delivery was 35.4 weeks for the 17α-hydroxyprogesterone caproate group and 35.7 weeks for the placebo group (P < .02). Treatment with 17α-hydroxyprogesterone caproate did not reduce the delivery rate before 28 weeks (6% in the 17α-hydroxyprogesterone caproate group compared with 5% in the placebo group, RR 1.04; 95% CI 0.56–1.94), 32 weeks (14% compared with 10%, RR 1.37; 95% CI 0.91–2.05), or 37 weeks of gestation (55% compared with 50%, RR 1.11; 95% CI 0.97–1.28).

Conclusion 17α-hydroxyprogesterone caproate does not prevent neonatal morbidity or preterm birth in multiple pregnancies.

Introduction

Throughout the world, approximately 13 million neonates are born before 37 weeks of gestation each year, adding up to a global prevalence of preterm birth of almost 10%.1 Women with a multiple pregnancy are at strongly increased risk of delivering preterm. In the Netherlands, 48% of women with a multiple pregnancy deliver before 37 weeks, and 9% even before 32 weeks.2 Premature children not only require intensive medical care in the first period after birth but are also at high risk of handicaps and developmental problems later in life.3

In the past decade, it has been shown that prophylactic administration of progesterone to women with a singleton pregnancy and a history of spontaneous preterm birth can significantly reduce the incidence of preterm birth.4, 5 The exact mechanism of action by which progesterone suppletion can prevent preterm birth is not known. As progesterone appears to reduce the risk of preterm birth in case of asymptomatic cervical shortening,
its potency might be attributed to an effect on cervical ripening. One randomized trial demonstrated a reduction in preterm birth rate before 34 weeks after progesterone treatment in both singleton and twin pregnancies with second-trimester cervical shortening (RR 0.56, 95% CI 0.36–0.86). The proportion of twin pregnancies in that trial was small (24 twin compared with 226 singleton pregnancies) and for this subgroup the RR did not reach statistical significance. Randomized trials in unselected populations of women with a multiple pregnancy have failed to show a beneficial effect of prophylactic progesterone so far.\(^7\)\(^-\)\(^9\)

In the AMPHIA trial (17-alpha hydroxyprogesterone caproate in Multiple pregnancies to Prevent Handicapped InfAnts, ISRCTN 40512715), the hypothesis was tested that administration of 17\(^\alpha\)-hydroxyprogesterone caproate can prevent neonatal morbidity in multiple pregnancies by reducing the preterm birth rate. Furthermore, we tested whether women with a multiple pregnancy and asymptomatic cervical shortening in the second trimester were more likely to benefit from 17\(^\alpha\) hydroxyprogesterone caproate than others.

**Materials and Methods**

We conducted a multicenter, double-blind, placebo-controlled, randomized trial. The study was approved by the research ethics committee of the Academic Medical Center in Amsterdam (Ref MEC 05/102) and written informed consent was provided by the participant. A total of 55 obstetric clinics in the Netherlands participated in this study, which was positioned within a nationwide consortium for women’s health research (www.studies-obsyn.nl). Women with a multiple pregnancy and a gestational age between 15 and 19 weeks were eligible for participation in the AMPHIA trial. Before inclusion, chorionicity had to be accurately determined by means of ultrasonography. Women with a previous spontaneous preterm birth before 34 weeks, serious congenital defects or death of one or more fetuses, early signs of twin-to-twin transfusion syndrome, or primary cerclage were excluded from participation. Patients were counseled by their own gynecologist or by a research assistant from our nationwide network. After written informed consent was obtained, patients were randomized in a 1:1 ratio to either weekly intramuscular injections of 250 mg 17\(^\alpha\)-hydroxyprogesterone caproate or placebo injections.

An independent data manager rendered a computer-generated list that was stratified by chorionicity (monochorionic compared with multichorionic), parity (nulliparous compared with multiparous), and number of multiples (twin compared with higher order), using random blocks of maximum block size 6. Randomization was accessible through a website. Monochorionicity was defined as at least two fetuses sharing one chorion. A nonstandardized transvaginal ultrasound examination for cervical length measurement was performed at randomization or at the next visit. Baseline demographics, obstetric
histories, and medical histories were recorded into online accessible case record forms by trained research nurses.

Each randomization prompted an e-mail notification to ACE Pharmaceuticals, Zeewolde, The Netherlands, to have a study pack containing 20 ampoules with either 1 mL 17α-hydroxyprogesterone caproate (250 mg/mL in castor oil) or placebo (castor oil) delivered to the clinic. Study medication and placebo were identical in packaging, color, and consistency. Allocation code was known only to ACE Pharmaceuticals. Study medication was prepared by Bayer HealthCare (formerly Schering AG), Berlin, Germany. Patients received their first injection between 16 and 20 weeks of gestation, after which they received weekly injections until 36 weeks of gestation or until delivery, whichever came first. Injections were administered at the clinic, by a general practitioner or, in case the patient or a family member had a background in medical practice, at the patient’s home. Forms containing injection dates and possible side effects were kept in the patient’s file as well as by the patient herself. All details of delivery, maternal assessments, and admissions during pregnancy were recorded in a web-based case record form. In case of admission of one or more children to the neonatal intensive care unit (NICU), details of this admission were also recorded. Participants, caregivers, and data collectors were all blinded to allocation.

The primary outcome measure was composite adverse neonatal outcome. This composite outcome contained severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage grade II B or worse, necrotizing enterocolitis, proven sepsis, and death before discharge from the hospital. Presence of any of the components of neonatal morbidity was defined by the neonatologist’s diagnosis at discharge. Secondary outcome measures were side effects (soreness, itching, and swelling), gestational age at delivery, preterm birth before 28, 32, and 37 weeks, length of admission at the NICU, maternal morbidity, hospitalization of the mother due to (threatened) preterm labor, and costs.

Assuming a decrease of the incidence of adverse neonatal outcome from 7.2% without to 3.8% with progesterone, using a two-sided test with an α of 0.05 and a β of 0.2, a sample size of 660 women (330 per arm) was needed for this study.

All analyses were based on the intention-to-treat principle and prespecified in the trial protocol. For the primary outcome, the effectiveness of progesterone compared with placebo was assessed by calculating a risk ratio (RR) with 95% confidence intervals (95% CIs). The RR was determined using binomial generalized estimating equations with a log link function. The generalized estimating equations were used to account for dependency of children from the same pregnancy by using the mother as a cluster variable. The use of generalized estimating equations is necessary because regression models that ignore the dependency are likely to incorrectly estimate the precision of covariate effects (i.e., variances of regression parameters). Furthermore, to account for the stratified randomization, the analysis was adjusted for chorionicity, number
of multiples, and previous vaginal birth by including these stratification variables as covariates in the regression models. Consequently, equal percentages in both treatment groups do not necessarily result in a risk ratio of 1, but can be different from 1 as a result of different distributions of the stratification variables within both treatment groups.

For continuous outcome variables on the child level, linear generalized estimating equations were used to estimate the mean difference with 95% CIs. Secondary outcomes on the mother level were compared between treatment groups using a log-binomial model, again estimating risk ratios. Differences in continuous variables such as gestational age and birth weight were analyzed by means of linear regression analysis. Furthermore, the time to delivery or death of the first fetus was compared between the treatment groups by Cox proportional hazards model, and were graphically presented in a Kaplan-Meier curve.

We also planned a predefined subgroup analysis in women with a cervical length less than 25 mm in the second trimester to assess whether treatment effects were related to cervical length.

All statistical analyses were conducted in R for Windows 2.10.0. Pooled meta-analysis of the current and previous studies was performed using Review Manager 5.1.

Results

Between August 1, 2006, and July 1, 2009, a total of 1,865 women who met the inclusion criteria were counseled for the trial, of which 671 (36%) agreed to participate. There were 653 women (97%) with a twin pregnancy, 17 (3%) with a triplet, and one with a quadruplet (Fig. 1). Baseline characteristics are described in Table 1. Randomization took place at a mean gestational age of 16.7 weeks.

A total of 1,322 children were liveborn in this trial. The primary outcome was available for 681 children (100%) in the 17α-hydroxyprogesterone caproate group and 674 children (99%) in the placebo group (Fig. 1). Study outcomes are presented in Table 2. After birth, 269 children were admitted to a NICU. A composite measure of adverse neonatal outcome was present in 110 children (16%) born to mothers in the 17α-hydroxyprogesterone caproate group and in 80 children (12%) of mothers in the placebo group (RR 1.34; 95% CI 0.95–1.89). Congenital anomalies were present in 4% of all children. The most commonly reported congenital anomalies were hypospadias and epispadias,5 ventricular septal defect,4 and preauricular tag.4 The occurrence of congenital anomalies did not differ between the 17α-hydroxyprogesterone caproate and placebo group (5% compared with 4%, RR 1.28; 95% CI 0.75–2.18). Twenty-three pregnancies (3.4%) resulted in intrauterine fetal death or delivery before 24 weeks of at least one of the fetuses. These numbers did not differ between the 17α,
hydroxyprogesterone caproate and placebo groups (3% compared with 4%, RR 0.75; 95% CI 0.33–1.68).

The average gestational age at delivery was 35.4 weeks in the 17α-hydroxyprogesterone caproate group and 35.7 weeks in the placebo group (P32). Treatment with 17α-hydroxyprogesterone caproate did not reduce delivery before 28 weeks (6% in the 17α-hydroxyprogesterone caproate group compared with 5% in the placebo group, RR 1.04; 95% CI 0.56–1.94), 32 weeks (14% compared with 10%, RR 1.37; 95% CI 0.91–2.05), or 37 weeks (55% compared with 50%, RR 1.11; 95% CI 0.97–1.28). There was a statistically significant difference in gestational age at preterm premature rupture of membranes between the 17α-hydroxyprogesterone caproate and the placebo group (31.1 compared with 33.9 weeks; P04). However, due to the large number of variables that were tested, this is likely to be a chance finding. Time to delivery in both groups was assessed using Kaplan-Meier analysis (Fig. 2). Log-rank test resulted in a P value of .123.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>17OHP N=336</th>
<th>Placebo N=335</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at randomisation (years)</td>
<td>32.7 ± 4.4</td>
<td>32.8 ± 4.7</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>24.9 ± 5.1</td>
<td>24.3 ± 4.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>287 (85%)</td>
<td>288 (86%)</td>
</tr>
<tr>
<td>African</td>
<td>9 (3%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>6 (2%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (4%)</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Higher professional education</td>
<td>109 (32%)</td>
<td>133 (40%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>176 (52%)</td>
<td>180 (54%)</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>33 (10%)</td>
<td>30 (9%)</td>
</tr>
</tbody>
</table>

Pregnancy characteristics

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>17OHP N=336</th>
<th>Placebo N=335</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at randomisation (weeks)</td>
<td>16.7 ± 1.5</td>
<td>16.8 ± 1.6</td>
</tr>
<tr>
<td>Pregnant after fertility treatment*</td>
<td>140 (42%)</td>
<td>120 (36%)</td>
</tr>
<tr>
<td>Higher order multiple</td>
<td>9 (3%)</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Monochorionic</td>
<td>57 (17%)</td>
<td>57 (17%)</td>
</tr>
</tbody>
</table>

Figure 2. Gestational age at delivery. Log-rank test resulted in a P value of .123.
Table 2. Outcomes according to study group

<table>
<thead>
<tr>
<th>Neonatal outcome</th>
<th>17OHP</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite adverse neonatal outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal outcome</td>
<td>N=681</td>
<td>N=680</td>
<td></td>
</tr>
<tr>
<td>Infant respiratory distress syndrome</td>
<td>110 (16%)</td>
<td>80 (12%)</td>
<td>1.3 (1.0-1.9)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>82 (12%)</td>
<td>51 (8%)</td>
<td>1.5 (1.0-2.4)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>8 (1%)</td>
<td>5 (1%)</td>
<td>1.6 (0.5-5.1)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>4 (1%)</td>
<td>2 (0%)</td>
<td>2.0 (0.4-10.7)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16 (2%)</td>
<td>9 (1%)</td>
<td>1.7 (0.6-4.4)</td>
</tr>
<tr>
<td>Death before discharge</td>
<td>23 (3%)</td>
<td>11 (2%)</td>
<td>2.1 (0.9-4.7)</td>
</tr>
<tr>
<td>Mean Birth weight (grams)</td>
<td>2318 ± 684</td>
<td>2374 ± 666</td>
<td>P = 0.29</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 grams</td>
<td>363 (53%)</td>
<td>354 (53%)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>&lt; 1500 grams</td>
<td>90 (13%)</td>
<td>63 (10%)</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>32 (5%)</td>
<td>25 (4%)</td>
<td>1.3 (0.8-2.2)</td>
</tr>
<tr>
<td>5 minute Apgar Score &lt;7</td>
<td>53 (8%)</td>
<td>52 (8%)</td>
<td>1.0 (0.6-1.6)</td>
</tr>
<tr>
<td>NICU admittance</td>
<td>153 (22%)</td>
<td>116 (16%)</td>
<td>1.3 (1.0-1.7)</td>
</tr>
</tbody>
</table>

**Delivery**

- **Gestational age at delivery (weeks)**
  - <37 weeks (all) | 35.4 ± 3.6 | 35.7 ± 3.8 | P = 0.32
  - >32 weeks | 186 (55%)  | 165 (49%)  | 1.1 (1.0-1.3)
  - <28 weeks | 48 (14%)   | 34 (10%)   | 1.4 (0.9-2.1)
  - Labour induction | 134 (40%)  | 151 (45%)  | 0.9 (0.7-1.0)
- **Fetal indication** | 23 (7%)  | 29 (19%)  | 0.9 (0.6-1.5)
- **Maternal indication** | 44 (33%)  | 57 (38%)  | 0.9 (0.6-1.2)
- **Combined** | 6 (4%)    | 6 (4%)    | 1.1 (0.4-3.3)
- **Elective** | 61 (46%)  | 59 (39%)  | 1.1 (0.9-1.5)

- **Mode of delivery**
  - Spontaneous | 143 (43%)  | 160 (48%)  | 0.9 (0.7-1.0)
  - Planned caesarean section | 75 (22%)  | 60 (18%)  | 1.2 (0.9-1.7)
  - Emergency caesarean section | 71 (21%)  | 76 (23%)  | 0.9 (0.7-1.2)
  - Forceps or ventouse | 45 (13%)  | 34 (10%)  | 1.3 (0.9-2.0)
- **2 live births** | 325 (97%)  | 324 (97%)  | 1.0 (1.0-1.0)
- **≥1 child died during delivery** | 5 (1%)  | 7 (2%)  | 0.7 (0.2-2.2)

**Pregnancy**

- **Tocolytic therapy** | 73 (22%)  | 64 (19%)  | 1.1 (0.8-1.5)
- **Corticosteroids** | 100 (30%)  | 84 (25%)  | 1.2 (0.9-1.5)
- **Cerclage placement** | 4 (1%)  | 5 (1%)  | 0.8 (0.2-3.0)
- **PPROM** | 34 (10%)  | 28 (8%)  | 1.2 (0.8-2.0)
- **Gestational age at PPROM (weeks)** | 31.1 ± 6.1 | 33.9 ± 4.0 | P = 0.04
- **Hypertensive disorder** | 54 (16%)  | 57 (17%)  | 0.9 (0.7-1.3)
- **Intravenous medication** | 20 (37%)  | 18 (32%)  | 1.2 (0.7-2.0)
- **Gestational diabetes** | 7 (2%)  | 7 (2%)  | 1.0 (0.4-2.8)
- **Chorioamnionitis** | 20 (6%)  | 15 (5%)  | 1.3 (0.7-2.5)
- **Intra-uterine fetal death before onset of labour** | 0 (0%)  | 2 (1%)  | n/a

**Side effects (self-reported)**

- **Any side effects** | 57 (17%)  | 76 (23%)  | 0.7 (0.5-1.0)
- **Swelling** | 11 (3%)  | 16 (5%)  | 0.7 (0.3-1.5)
- **Soreness** | 30 (9%)  | 40 (12%)  | 0.7 (0.5-1.2)
- **Itching** | 16 (5%)  | 22 (7%)  | 0.7 (0.4-1.3)
- **Bruising** | 6 (2%)  | 9 (3%)  | 0.7 (0.2-1.6)
- **Systemic reaction** | 2 (1%)  | 1 (0%)  | 2.0 (0.2-21.7)
- **Other** | 12 (4%)  | 13 (4%)  | 0.9 (0.4-2.0)
- **Leading to discontinuation of study drug** | 10 (2%)  | 12 (3%)  | 0.8 (0.4-1.9)

*Pre-eclampsia and/or hypertension with need for antihypertensive medication. **As determined through pathology assessment of placenta
Of the 671 randomized women, 30 (9%) women in the 17α-hydroxyprogesterone caproate group and 35 (10%) in the placebo group stopped treatment early. A mean number of 12.7 injections were administered per patient, with a mean interval of 7.5 days between injections. Reasons for stopping treatment early were side effects (2.4%), “too stressful” (2.2%), related to pregnancy (1.9%), other (1.5%), or unknown (1.2%). Five patients were lost to follow-up.

Side effects of treatment were reported by 57 women (17%) in the 17α-hydroxyprogesterone caproate group and 76 women (23%) in the placebo group (RR 0.74; 95% CI 0.54–1.00). Most frequently reported side effects were soreness, itching, and swelling. On account of side effects 22 women (3.3%) discontinued injections before the end point (36 weeks or delivery before 36 weeks of gestation) was reached.

At baseline (less than 24 weeks of gestation) a cervical length measurement was performed in 542 women (81%). Thirteen women (2.4%) had a cervical length less than 25 mm, whereas in 61 women (11.3%) the cervix was shorter than 35 mm. Subgroup analysis for women with a cervix shorter than 25 mm at baseline showed no effect of 17α-hydroxyprogesterone caproate on preterm birth (Table 3). In view of the low number of women with a cervix below 25 mm, we also performed a post hoc subgroup analysis for women with a cervix shorter than 35 mm. Within this group there were fewer preterm births in the 17α-hydroxyprogesterone caproate group, although this difference was not statistically significant (Table 3).

### Discussion

This randomized controlled trial among women with a multiple pregnancy shows no reduction of preterm birth or neonatal morbidity after treatment with 17α- hydroxyprogesterone caproate. The lack of effectiveness is consistent with previous trials and suggests that this treatment should not be used for the prevention of preterm birth in women with a multiple pregnancy.
Meta-analysis of the effect of progestogens in the prevention of preterm delivery before 34 weeks of gestation. *Reported outcome is delivery before 35 weeks of gestation.

A total of 55 Dutch obstetric clinics participated in this trial. Although this large number of hospitals provides a reliable representation of obstetric care in the Netherlands, overseeing inclusion of patients into trials can be difficult. This may be the reason why, during the recruitment period of nearly 3 years, only 1,865 patients were counseled, whereas registration numbers show that at least twice as many eligible patients would have presented themselves at these hospitals. Even so, baseline characteristics of patients included in the study reflect national statistics on women with a multiple pregnancy, which suggests that inclusion bias did not play a role in this trial.

In contrast with previous studies on this subject that used preterm delivery as the primary outcome measure, we used a composite measure of neonatal morbidity and mortality. This outcome is in our opinion more relevant from a clinical and societal perspective compared with duration of pregnancy. Because we found no effect on either outcome, the discussion is rather academic. However, studies reporting on the effectiveness of progestogens in women with a short cervix showed a significant effect on duration of pregnancy, yet not on neonatal outcome.6

In accordance with the results of previous trials, there were more preterm births in the 17α-hydroxyprogesterone caproate group than in the placebo group in this study, although the difference was not statistically significant. The trial by Rouse et al that was published in 2007 showed a RR of 1.1 (95% CI 0.9–1.3) for delivery or fetal death before 35 weeks after treatment with 17α-hydroxyprogesterone caproate in twin pregnancies.9 Norman et al carried out a trial in twin pregnancies using vaginal progesterone, with an OR for delivery or fetal death before 34 weeks of 1.36 (95% CI 0.89–2.09).8 When we add our study data, the results of a randomized trial in triplets by Caritis et al7 and data
from a recently published trial by Combs et al\textsuperscript{12} to their meta-analysis, we find a pooled OR of 1.1 (95% CI 0.9 –1.4) for delivery before 34 weeks of gestation (Fig. 3).

The possibility that progesterone has a harmful effect on multiple pregnancies should not be ruled out based on lack of statistical significance. Although there is no clear explanation as to how progesterone can induce preterm birth, these findings should raise caution in researchers planning future studies on this intervention in multiple pregnancies.

The percentage of women with a cervical length shorter than 25 mm at 15–20 weeks (3%) was lower in our study population than has been described in the literature for multiple pregnancies in the second trimester (9–13%).\textsuperscript{13-15} This may be a result of the relatively early gestational age at which the cervix was measured in our study. We decided to perform an additional unplanned subgroup analysis on 71 women with a cervix shorter than 35 mm. Within this group, there was a nonsignificant trend toward less neonatal morbidity and less preterm birth in patients treated with 17\(\alpha\)-hydroxyprogesterone caproate. As this was a post hoc analysis and relative risks did not reach statistical significance, we cannot draw any conclusions from this finding. However, there is an indication that second-trimester cervical length measurement may be able to select patients with a multiple pregnancy who can benefit from 17\(\alpha\)-hydroxyprogesterone caproate treatment. Further studies are needed to test this hypothesis.

Although the exact mechanism of action by which progesterone prevents preterm delivery remains unknown, in vitro studies have shown that progesterone has an inhibitory effect on prostaglandins and oxytocin, and that it can decrease the number of oxytocin receptors and gap junctions in the myometrium.\textsuperscript{16, 17} The available studies on the effectiveness of progesterone to prevent preterm birth show that progesterone is effective in women with a previous preterm birth and can be effective in women with a short cervix in the second trimester. Our study confirms that such a beneficial effect is not present in unselected women with a multiple pregnancy. One might hypothesize that in women with a singleton pregnancy who deliver preterm, some have a disorder that disenables them to carry a pregnancy to term. In women with a multiple pregnancy, on the other hand, there is a high risk of preterm birth because carrying multiple fetuses presents an increased burden to a woman’s body. Progesterone might be effective in the first category, but not in the second.

However, we should be aware that a fraction of women with a multiple pregnancy also have an intrinsic decreased capacity to carry a pregnancy to term. Thus, the search for subgroups of women with a singleton pregnancy who are at increased risk for preterm birth and benefit from progesterone should also continue for women with a multiple pregnancy. Such subgroup analysis should in our opinion also be performed, if possible, in the previous studies assessing progesterone in multiple pregnancies.

In conclusion, our study confirms that 17-alpha hydroxyprogesterone caproate does not prevent neonatal morbidity or preterm birth in multiple pregnancies. In fact, there were slightly more preterm births in the 17\(\alpha\)-hydroxyprogesterone caproate group
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as a whole. This study was underpowered to determine a beneficial effect of 17α-hydroxyprogesterone caproate in women with a multiple pregnancy and a short cervical length in the second trimester.

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