OBSTETRICS

# 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial

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**OBJECTIVE:** The objective of the study was to evaluate the efficacy of 17 alpha-hydroxyprogesterone caproate (17OHP-C) in prolonging gestation in patients with a short cervix and other risk factors for preterm delivery, such as previous preterm birth, cervical surgery, uterine anomalies, or prenatal diethylstilbestrol (DES) exposure.

**STUDY DESIGN:** This open-label, multicenter, randomized controlled trial included asymptomatic singleton pregnancies from $20^{+0}$ through $31^{+6}$ weeks of gestation with a cervical length less than 25 mm and a history of preterm delivery or cervical surgery or uterine malformation or prenatal DES exposure. Randomization assigned them to receive (or not) 500 mg of intramuscular 17OHP-C weekly until 36 weeks. The primary outcome was time from randomization to delivery.

**RESULTS:** After enrolling 105 patients, an interim analysis demonstrated the lack of efficacy of 17OHP-C in prolonging pregnancy. The study was discontinued because of futility. The groups were similar for maternal age, body mass index, parity, gestational age at inclusion, history of uterine anomalies, DES syndrome, previous preterm delivery or midtrimester abortion, and cervical length at randomization. The enrollment-to-delivery interval did not differ between patients allocated to 17OHP-C (n = 51) and those allocated to the control group (n = 54) (median [interquartile range] time to delivery: 77 [54—103] and 74 [52—99] days, respectively). The rate of preterm delivery less than 37 (45% vs 44%, $P > .99$), less than 34 (24% vs 30%, $P = .51$), or less than 32 (14% vs 20%, $P = .44$) weeks was similar in patients allocated to 17OHP-C and those in the control group.

**CONCLUSION:** 17OHP-C did not prolong pregnancy in women with singleton gestations, a sonographic short cervix, and other risk factors of preterm delivery (prior history, uterine malformations, cervical surgery, or prenatal DES exposure).

**Key words:** 17 alpha-hydroxyprogesterone caproate, cervical length, prematurity, preterm birth, preterm labor, progesterone

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Preterm birth (PTB) occurs in about 12% of US pregnancies and 7% of those in France.[1,2] Worldwide, prematurity is now the second leading cause of death in children aged younger than 5 years and the leading cause of death in the first month of life.[3] It also increases the risks of neurological and learning disabilities.[4]

Substantial progress has nonetheless occurred in this field over the past decade. A second-trimester measurement of cervical length (CL) by transvaginal ultrasound (TVU) can predict the likelihood of PTB.[5-9] Furthermore, recent studies and metaanalyses have provided sound evidence about the benefits of prophylactic progestogen for stopping progression to PTB.[10-14]

In 2003, Meis et al[15] published the results of their double-blind, placebo-controlled trial of pregnant women with a documented history of spontaneous PTB: weekly injections of 17 alpha-hydroxyprogesterone caproate (17OHP-C) substantially reduced the rate of recurrent PTB and therefore the risk of several specific neonatal complications. However, 2 other randomized controlled trials evaluated vaginal progesterone in this high-risk group and reported conflicting results.[16,17] Accordingly, some clinical practice guidelines recommend that women with a history of preterm birth be offered treatment with 17OHP-C 250 mg intramuscularly weekly from 16-20 through 36 weeks' gestation.[18,19]

Surprisingly, these results about the use of progestogens in women with a history of spontaneous PTB and unknown CL appear to conflict with other data. Two randomized clinical trials[20,21] and an individual patient meta-analysis[12] showed that vaginal progesterone (the equivalent of the natural hormone), when given to women with a short cervix, reduced the rate of preterm birth less than 33 weeks and neonatal morbidity/mortality, whereas a recent randomized clinical trial with 17OHP-C in nulliparous women with a CL less than 30 mm showed no evidence of reduction in the preterm birth rate.[22]

Finally, no randomized controlled trials have evaluated the effectiveness of progestogens in women with a short CL and any of a history of PTB, cervical surgery, uterine malformation, or prenatal exposure to diethylstilbestrol (DES), although this population is at especially high risk for preterm delivery.[23] We therefore conducted a multicenter randomized trial to evaluate the use of 17OHP-C for prolonging pregnancy in this population.

## Material and Methods

### Subjects and screening

This open-label, multicenter, randomized controlled trial was performed in 11 university hospitals across France. Women were potentially eligible for inclusion if they presented an asymptomatic singleton pregnancy considered at high risk for PTB because of a history of spontaneous PTB or of cervical surgery, a uterine malformation, or prenatal exposure to DES. In this asymptomatic high-risk group, the follow-up included serial CL measurements by TVU at 2 week intervals, starting at $16^{+0}$ weeks of gestation.

Enrollment in the trial was offered to women between $20^{+0}$ and $31^{+6}$ weeks of gestation who had a TVU CL measurement (in the sagittal plane according to the standard technique[6]) less than 25 mm. No further CL measurements were taken once one was found to be less than 25 mm. Women also had to be at least 18 years old, agree to regular follow-up, and provide written informed consent.

Women with any of the following characteristics were ineligible: cervical dilatation greater than 3 cm, chorioamnionitis, premature rupture of the membranes, placenta previa, twin pregnancy, severe intrauterine growth restriction, any known major structural or chromosomal fetal abnormality, any maternal or fetal disease requiring induced PTB, progestogen therapy before inclusion, ongoing anticonvulsant treatment, or participation in any other treatment trial.

A first-trimester ultrasound scan, routinely performed in France, was used to determine gestational age. The placement of a cerclage was left to the physician's discretion when the CL was less than 25 mm before 23 weeks. Abdominal ultrasound was performed before inclusion to assess both fetal well-being and the quantity of amniotic fluid, and vaginal sonography to confirm the CL (<25 mm). The Ethics Committee of Poissy Saint-Germain Hospital (Comité de Protection des Personnes), Saint-Germain en Laye, France, approved the study protocol for all centers. The trial is registered at ClinicalTrials.gov (no. NCT00331695).

The 17OHP-C used in our trial was Progestérone Retard Pharlon (Bayer Pharma AG, Berlin, Germany), the only 17OHP-C commercially available in France. It is licensed by the Agence Nationale de Sécurité du Médicament and has been marketed in France since 1958. It is currently manufactured by Bayer Pharma AG, which produces it in Germany in accordance with the detailed guidelines for starting materials established in part II of the European Union Good Manufacturing Practices. The manufacturer of the active substance is included in Bayer's audit program.

### Randomization and follow-up

After verification of the inclusion and exclusion criteria, eligible consenting women were randomly assigned in a 1:1 ratio to receive 500 mg of intramuscular 17OHP-C weekly until 36 weeks or PTB, whichever occurred first, or to no treatment with 17OHP-C (control group). Additional management in both arms was determined by the attending physician, except that progestogens were not allowed in the control group. An independent, centralized, computer-generated randomization sequence (CleanWeb; Télémedecine Technologies, Boulogne, France) was used for this allocation, based on a randomization list established by the study statistician, according to a permuted block method, balanced, and stratified by center.

If an episode of preterm labor occurred before 34 weeks, the woman was admitted and received tocolysis and a course of betamethasone 12 mg, given intramuscularly and repeated after 24 hours. The attending physician determined the type, duration, and regimen of tocolysis and decided about any maintenance tocolysis. Patients in the 17OHP-C arm continued treatment




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