OBSTETRICS

17-hydroxyprogesterone caproate for preterm rupture of the membranes: a multicenter, randomized, double-blind, placebo-controlled trial

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OBJECTIVE: Preterm rupture of membranes (PROM) is associated with an increased risk of preterm birth and neonatal morbidity. Prophylactic 17-hydroxyprogesterone caproate (17OHP-C) reduces the risk of preterm birth in some women who are at risk for preterm birth. We sought to test whether 17OHP-C would prolong pregnancy or improve perinatal outcome when given to mothers with preterm rupture of the membranes.

STUDY DESIGN: This is a multicenter, double-blind, placebo-controlled, randomized clinical trial. The study included singleton pregnancies with gestational ages from $23^{0/7}$ to $30^{6/7}$ weeks at enrollment, documented PROM, and no contraindication to expectant management. Consenting women were assigned randomly to receive weekly intramuscular injections of 17OHP-C (250 mg) or placebo. The primary outcome was continuation of pregnancy until a favorable gestational age, which was defined as either $34^{0/7}$ weeks of gestation or documentation of fetal lung maturity at $32^{0/7}$ to $33^{6/7}$ weeks of gestation. The 2 prespecified secondary outcomes were interval from randomization to delivery and composite adverse perinatal outcome. The planned sample size was 222 total women.

RESULTS: From October 2011 to April 2014, 152 women were enrolled; 74 women were allocated randomly to 17OHP-C, and 78 were allocated randomly to placebo. The trial was stopped when results of a planned interim analysis suggested that continuation was futile. The primary outcome was achieved in 3% of the 17OHP-C group and 8% of the placebo group ($P = .18$). There was no significant between-group difference in the prespecified secondary outcomes, randomization-to-delivery interval (17.1 ± 16.1 vs 17.0 ± 15.8 days, respectively; $P = .76$) or composite adverse perinatal outcome (63% vs 61%, respectively; $P = .93$). No significant differences were found in other outcomes, which included rates of chorioamnionitis, postpartum endometritis, cesarean delivery, individual components of the composite outcome, or prolonged neonatal length of stay.

CONCLUSION: Compared with placebo, weekly 17OHP-C injections did not prolong pregnancy or reduce perinatal morbidity in patients with PROM in this trial.

Key words: 17-hydroxyprogesterone caproate, preterm rupture of membranes, prevention of preterm birth

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Preterm rupture of the fetal membranes (PROM) complicates 2-4% of pregnancies[1,2] and is responsible for approximately 10-30% of preterm births and perinatal deaths in the United States.[1-3] When PROM occurs very early in gestation, the result is often early preterm birth accompanied by substantial neonatal morbidity and/or death. To minimize these risks, a strategy of expectant management is often adopted, with a goal of prolonging the pregnancy until a more favorable gestational age is reached.[1,2,4] However, even with conservative treatment, 50-60% of women with PROM deliver within 1 week.[1,5]

Some adjunctive medications may improve the outcome of expectant management of PROM according to recent metaanalyses.[6-8] Antenatal corticosteroids reduce the rates of several neonatal complications, which includes respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death.[6] Antibiotics also reduce neonatal morbidity, in part by prolonging the latency period from PROM to delivery.[7] Tocolytic agents may prolong the latency period slightly, but any benefit of this may be negated by an increased rate of chorioamnionitis.[8] No other treatments have proved useful.

Progestogens might be especially beneficial after PROM because their properties include suppression of myometrial activation, reduced expression of myometrial gap junctions and contraction-related proteins, reduced production of inflammatory cytokines, inhibition of cervical ripening, and reduced cell death in the chorion and decidua.[9-11] Vaginal progesterone and 17-hydroxyprogesterone caproate (17OHP-C) reduce the rate of preterm birth in women with a short cervix[12] or with a history of spontaneous preterm birth.[13] These agents are recommended in these settings if the membranes are intact.[14] However, a previous trial found no benefit of 17OHP-C for women with PROM, although the trial had limited statistical power because of small sample size.[15]

The goal of the present study was to determine whether the administration of 17OHP-C to women with PROM would prolong pregnancy or reduce perinatal morbidity and death. We selected intramuscular 17OHP-C rather than vaginal micronized progesterone because of the possibility that insertion of intravaginal medication might increase the risk of chorioamnionitis or that the drug might be partly or completely washed out by amniotic fluid leakage after PROM.

Methods

This was a multicenter, randomized, placebo-controlled, double-blind clinical trial performed at 14 hospitals across the United States. The study sites were acute care hospitals with neonatal intensive care units. Before enrollment of any subject, the protocol was registered at clinicaltrials.gov (NCT #01119963), and the study was approved by the institutional review board of each hospital. No protocol amendments were made after the trial commenced. The trial is reported according to the guidelines of the CONSORT 2010 Statement.[16]

A previous version of the trial under a different protocol was terminated prematurely because of problems with drug supply.[17] Our current report does not include any of the subjects from the previous version.

Inclusion/exclusion criteria

Inclusion criteria were singleton pregnancy at $23^{0/7}$–$30^{6/7}$ weeks of gestation, mother at least 18 years old, and spontaneous PROM. *PROM* was defined by (1) a positive placental alpha-1 microglobulin test (AmniSure; QIAGEN, Germantown, MD) from a vaginal swab,[18,19] (2) vaginal leakage of indigo carmine dye that had been instilled by amniocentesis, or (3) $\geq$2 of the following findings: a positive nitrazine test of a vaginal swab; ferning observed on a microscope slide of vaginal fluid; gross pooling of clear fluid in posterior vaginal fornix on speculum examination; and/or ultrasound examination that showed oligohydramnios.

Exclusion criteria included any of the following conditions: contraindications to expectant management (such as suspected intraamniotic infection or inflammation, active preterm labor, nonreassuring fetal heart rate tracing, intrauterine fetal death, preeclampsia, active uterine bleeding, documented fetal lung maturity (FLM), or other condition that required immediate delivery); fetal conditions likely to cause serious neonatal morbidity (such as malformations that involved vital organs or likely to require surgical repair, fetal viral infection, hydrops); cervical cerclage present at the time of PROM; medical conditions that had been treated with systemic steroids; and contraindications to 17OHP-C (such as allergy to drug or vehicle, current or past thromboembolic disorder, current or past hormone-sensitive cancer, undiagnosed vaginal bleeding, cholestatic jaundice of pregnancy, or other active liver disease, uncontrolled hypertension).

Patients with PROM who were excluded initially because they were having contractions or bleeding could become eligible later if their contractions or bleeding subsided. We did not discriminate whether PROM had occurred before the onset of contractions (prelabor PROM, premature PROM) or after. This was based partly on the belief that the distinction between spontaneous PROM after preterm labor vs prelabor PROM is somewhat arbitrary, because the 2 may merely be different manifestations of a common "spontaneous parturition syndrome," sharing common risk factors, antecedents, and covariates.[20-22] It also was based partly on the belief that most of the adverse obstetrics events that occur in a quiescent patient after PROM are attributable directly to the consequences of PROM, such as oligohydramnios (which leads to cord compression or abruption) or loss of barrier function (which leads to ascending infection or cord prolapse), or attributable to the underlying factors that cause PROM in the first place (such as infection or inflammation that leads to labor or chorioamnionitis or cervical insufficiency that leads to silent dilation and early preterm birth), regardless of whether PROM occurred before or after the onset of contractions. Finally, it was based partly on the observation that the clinical treatment of patients with threatened preterm parturition typically is guided more by whether the