OBSTETRICS

Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth

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OBJECTIVE: 17-alpha hydroxyprogesterone caproate 250 mg weekly reduces recurrent spontaneous preterm birth in women with a prior spontaneous preterm birth by 33%. The dose is not based on pharmacologic considerations. A therapeutic concentration has not been determined hampering any attempt to optimize treatment. This study evaluated the relationship between 17-alpha hydroxyprogesterone caproate plasma concentrations and the rate of spontaneous preterm birth in women with singleton gestation.

STUDY DESIGN: A single blood sample was obtained between 25 and 28 weeks' gestation from 315 women with a spontaneous preterm birth who participated in a placebo-controlled, prospective, randomized clinical trial evaluating the benefit of omega-3 supplementation in reducing preterm birth. All women in the parent study received 17-alpha hydroxyprogesterone caproate and 434 received omega-3 supplementation and 418 received a placebo. Plasma from 315 consenting women was analyzed for 17-alpha hydroxyprogesterone caproate concentration.

RESULTS: There were no differences between placebo and omega-3 supplemented groups in demographic variables, outcomes or in mean 17-alpha hydroxyprogesterone caproate concentration. Plasma concentrations of 17-alpha hydroxyprogesterone caproate ranged from 3.7-56 ng/mL. Women with plasma concentrations of 17-alpha hydroxyprogesterone caproate in the lowest quartile had a significantly higher risk of spontaneous preterm birth ($P = .03$) and delivered at significantly earlier gestational ages ($P = .002$) than did women in the second to fourth quartiles. The lowest preterm birth rates were seen when median 17-alpha hydroxyprogesterone caproate concentrations exceeded 6.4 ng/mL.

CONCLUSION: Low plasma 17-alpha hydroxyprogesterone caproate concentration is associated with an increased risk of spontaneous preterm birth. This finding validates efficacy of this treatment but suggests that additional studies are needed to determine the optimal dosage.

Key words: dose response, pharmacodynamics, 17-hydroxyprogesterone caproate concentration-response

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17-hydroxyprogesterone caproate (17-OHPC) reduces recurrent spontaneous preterm birth (SPTB) in women with a singleton gestation and a prior SPTB.[1] The American College of Obstetricians and Gynecologists endorses the use of 17-OHPC in women with a prior SPTB but notes that more research is required as to the optimal formulation and dosage.[2] Fundamental to any pharmaceutic intervention is the establishment of an appropriate dose that has been determined in dose ranging studies that compare efficacy and harms over a range of doses.[3,4] There are no data providing guidance on the optimal dose of 17-OHPC. The dose used in the Maternal-Fetal Medicine Network (MFMU) trial reported by Meis et al[1] was 250 mg weekly given as an intramuscular (IM) injection. This dose was chosen based on the dosage used in previous studies and a metaanalysis.[5-8] In the MFMU trial, a 33% reduction in recurrent SPTB rates was seen in women receiving weekly injections of 250 mg 17-OHPC compared with those receiving placebo. Whether a higher dose would have provided greater benefit or even harm is not known.

The outcome of interest for 17-OHPC against which various doses can be evaluated, is SPTB but dose ranging studies are difficult to complete given the large sample size that would be needed. An alternative approach is to relate plasma drug concentration to the frequency of preterm birth to assess if a concentration−outcome relationship exists.[9-12] The purpose of this study was to evaluate the relationship between 17-OHPC concentration and gestational length in women with singleton gestation.

Materials and Methods

This study used blood samples obtained from women who participated in the Omega-3 Maternal-Fetal Medicine Units Network (MFMU) trial that evaluated whether omega-3 supplementation reduced the rate of recurrent SPTB in women with a singleton gestation and a prior SPTB. All women received weekly intramuscular (IM) injections of 250 mg 17-OHPC starting between 16 0/7-21 6/7 weeks and continuing until delivery

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or 36 6/7 weeks. In addition, subjects were randomly assigned to receive a daily supplement containing 1200 mg of eicosapentaenoic acid (EPA, 20:5 n-3) and 800 mg of docosahexaenoic acid (DHA, 22:6 n-3), for a total of 2000 mg of omega-3 long-chain polyunsaturated fatty acids, divided into 4 capsules, or they received matching placebo capsules that contained only a minute amount of inert mineral oil. A blood sample was obtained between 25-28 weeks' gestation just before the next scheduled dose of 17-OHPC and analyzed for the plasma concentration of 17-OHPC using high performance liquid chromatography-mass spectrometry with a limit of detection of 1 ng/mL.[13]

Statistical analysis

The analysis was restricted to women who completed all their scheduled 17-OHPC injections. Demographic data were compared between the 2 treatment groups using χ^2 or the Wilcoxon test as appropriate. A logistic regression with an interaction term was conducted to determine whether there was an interaction between 17-OHPC concentration and treatment group with respect to the outcome of preterm birth. Survival curve analysis with indicated and term births censored was performed to compare length of gestation between women in the first and other 3 quartiles. A proportional hazards model was performed with adjustment for gestational age at study entrance, gestational age at blood sampling, race, ethnicity, and body mass index (BMI) to assess the relationship between 17-OHPC plasma concentrations and gestational age at delivery. A nominal P value $< .05$ was considered significant with no adjustments for multiple comparisons. All tests were 2-sided.

Results

Among the 852 women enrolled in the trial, 434 were randomized to receive omega-3 supplements and 418 were randomized to receive placebo. Blood samples were available on 512 subjects: 261 women in the omega-3 group and 251 in the placebo group. Among these women 162 in the omega-3 group and 153 in the placebo group received all of their scheduled 17-OHPC injections throughout the study and form the study population for this analysis. These women had received a median of 9 injections at the time of blood sampling that occurred at a mean gestational age of 27 weeks.

Table 1 summarizes the demographic and clinical characteristics of the study cohort stratified by omega-3 group assignment. There were no differences between the 2 groups in any of the parameters listed in the table. Mean plasma 17-OHPC concentrations were similar in the 2 treatment groups as were BMI and progesterone concentrations. A wide variation in plasma 17-OHPC concentrations was seen in both treatment groups with concentrations ranging from 3.7 ng/mL to 56 ng/mL in the entire cohort.

Because there were no differences in plasma 17-OHPC or progesterone concentrations and no interaction effect between 17-OHPC concentration and treatment group ($P = .52$), we combined the 2 treatment groups for further analyses. Because of the large variation in 17-OHPC concentrations, we stratified the concentration data by quartiles (Table 2). The SPTB rate was significantly ($P < .03$) greater among women in the first quartile compared with those in the other quartiles. Also, as demonstrated in the Kaplan-Meier curve of Figure 1, women in the first quartile of 17-OHPC concentration delivered significantly earlier than those in other quartiles ($P = .002$). In a proportional hazards model, after controlling for the gestational age when the subject started treatment with 17-OHPC, the gestational age at blood sampling, treatment group assignment, BMI, race, and ethnicity, those women in the combined second to fourth quartiles showed a 50% reduction in the hazard of delivering preterm (hazard ratio, 0.48; 95% confidence interval, 0.31−0.75; $P = .001$) compared with those women with plasma 17-OHPC concentrations in the first quartile.

To assess the relationship between concentration of 17-OHPC and SPTB rates,