OBSTETRICS

Does 17-alpha hydroxyprogesterone caproate prevent recurrent preterm birth in obese women?

Kent D. Heyborne, MD; Amanda A. Allshouse, MS; J. Christopher Carey, MD

OBJECTIVE: We sought to determine if maternal weight or body mass index (BMI) modifies the effectiveness of 17-alpha hydroxyprogesterone caproate (17OHP-C).

STUDY DESIGN: We performed a secondary analysis of the Maternal-Fetal Medicine Units Network Trial for the Prevention of Recurrent Preterm Delivery by 17-Alpha Hydroxyprogesterone Caproate. Binomial regression models were estimated to determine the relative risk (RR) of preterm birth (PTB) in women randomized to 17OHP-C vs placebo according to BMI category and maternal weight. Adjusted models considered inclusion of potential confounders.

RESULTS: In all, 443 women with complete data were included. 17OHP-C is effective in preventing PTB <37 weeks only in women with prepregnancy BMI <30 kg/m^2 (RR, 0.54; 95% confidence interval, 0.43—0.68). Above this BMI threshold there is a nonsignificant trend toward an increased risk of PTB (RR, 1.55; 95% confidence interval, 0.83—2.89) with 17OHP-C treatment. When analyzing by maternal weight, a similar threshold is observed at 165 lb, above which 17OHP-C is no longer effective.

CONCLUSION: The effectiveness of 17OHP-C is modified by maternal weight and BMI, and treatment does not appear to reduce the rate of PTB in women who are obese or have a weight >165 lb. This finding may be due to subtherapeutic serum levels in women with increased BMI or weight. Studies of adjusted-dose 17OHP-C in women who are obese or who weigh >165 lb are warranted, and current recommendations regarding the uniform use of 17OHP-C regardless of maternal BMI and weight may deserve reassessment.

Key words: 17-alpha hydroxyprogesterone caproate, body mass index, obesity, prematurity, preterm birth, progesterone

Cite this article as: Heyborne KD, Allshouse AA, Carey JC. Does 17-alpha hydroxyprogesterone caproate prevent recurrent preterm birth in obese women? Am J Obstet Gynecol 2015;213:844.e1-6.

The sequelae of preterm birth (PTB), including neonatal, childhood, and adult morbidity and mortality, remain the most critical pregnancy-related public health issues in the developed world.[1-4] A history of PTB is the strongest risk factor known, with reported recurrence rates as high as 55%.[5]

Weekly administration of intramuscular 17-alpha hydroxyprogesterone caproate (17OHP-C) is the most effective modality currently available to prevent recurrent PTB.[5] The 250-mg dosage of 17OHP-C used in the initial Maternal-Fetal Medicine Units (MFMU) Network Progesterone Trial was extrapolated from previous trials, and dose-finding studies have not been done. A recent study demonstrated that women with serum 17OHP-C levels below a threshold concentration experience higher levels of recurrent PTB than women with levels above the threshold.[6] Pharmacokinetic simulations by the same group of investigators showed that serum 17OHP-C levels are inversely related to maternal body mass index (BMI).[7] These observations raise the question of whether 17OHP-C is less effective at higher maternal weight or BMI. To address this question we performed a secondary analysis of the original Prevention of Recurrent Preterm Delivery by 17-Alpha Hydroxyprogesterone Caproate by Meis et al.[5] Our hypothesis is that the effectiveness of 17OHP-C for prevention of recurrent PTB is modified by increased maternal weight and/or BMI.

Materials and Methods

Patient sample

This is a secondary analysis of the MFMU Trial for the Prevention of Recurrent Preterm Delivery by 17-Alpha Hydroxyprogesterone Caproate.[5] Full details are available in the original publication. Briefly, the original study was performed at 19 participating

From the Department of Obstetrics and Gynecology, Denver Health and Hospital Authority, Denver (Drs Heyborne and Carey); Department of Obstetrics and Gynecology, University of Colorado Denver, Denver (Drs Heyborne and Carey); and University of Colorado School of Public Health, Aurora (Ms Allshouse), CO.

Received April 2, 2015; revised June 12, 2015; accepted Aug. 5, 2015.

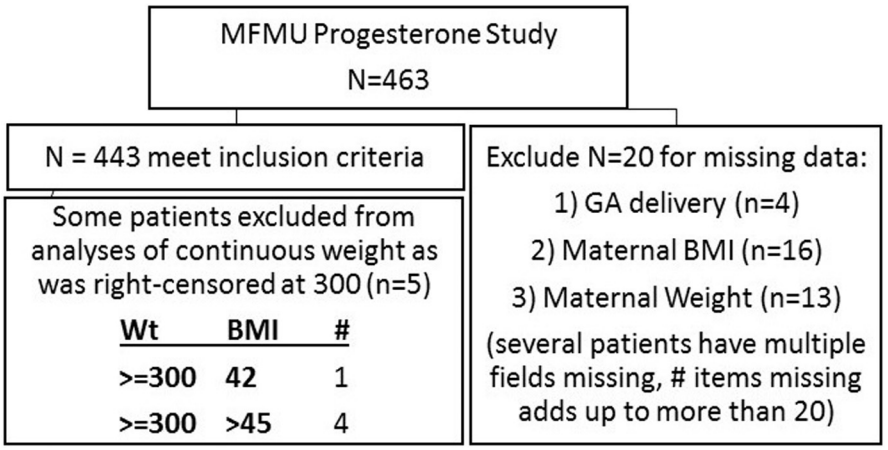
The contents of this report represent the views of the authors, not those of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network or the National Institutes of Health, which made the database from the Prevention of Recurrent Preterm Delivery by 17-Alpha Hydroxyprogesterone Caproate Trial available for secondary analysis.

The authors report no conflict of interest.

Corresponding author: Kent D. Heyborne, MD. kent.heyborne@dhha.org

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2015.08.014

FIGURE 1
Patient selection from original cohort



Selection of patients for this study from initial patient cohort.

BMI, body mass index; *GA*, gestational age; *MFMU*, Maternal-Fetal Medicine Units; *Wt*, weight.

Heyborne. 17-Alpha hydroxyprogesterone caproate in obese women. Am J Obstet Gynecol 2015.

centers from 1999 through 2002. Women presenting for prenatal care were screened between 15-20 3/7 weeks' gestation for a history of spontaneous PTB that occurred between 20-36 6/7 weeks. Eligible patients were randomized in a 2:1 fashion to weekly intramuscular injections of 250 mg of 17OHP-C or placebo, respectively, beginning at 16-20 6/7 weeks. There were 463 individual women in the original trial. For this analysis, patients with missing gestational age at delivery, maternal BMI, and/or maternal weight were excluded, leaving 443 patients for this analysis (Figure 1). Reported maternal prepregnancy height and weight were obtained at the time of study enrollment and BMI was calculated. Actual weight at enrollment, total weight gain, and weight at delivery were not recorded. The MFMU study was approved by institutional review boards at each of the study sites with each subject providing written informed consent. This secondary analysis was considered exempt by the Colorado Multiple Institutional Review Board.

Definitions and outcomes

For this analysis, we used the same primary outcome variable as the original study, namely preterm delivery <37 weeks. To investigate the interaction of maternal weight and BMI on 17OHP-C effectiveness, we used 2 standard

TABLE 1
Clinical and demographic characteristics of women randomized to 17-alpha hydroxyprogesterone caproate or placebo

Description	Value	17OHP-C N = 294 (%)	Placebo N = 149 (%)	*P* value
No. of previous preterm deliveries	Mean (SE)	1.40 (0.04)	1.61 (0.07)	.016
>1 Previous preterm delivery	>1	83 (28.23)	63 (42.28)	.004
≥1 Previous term deliveries	≥1	145 (49.32)	69 (46.31)	.615
Gestational age at randomization, wk	Mean (SE)	18.9 (0.09)	18.8 (0.12)	.581
Maternal age, y	Mean (SE)	26.1 (0.31)	26.6 (0.43)	.382
Race	Black	177 (60.20)	89 (59.73)	.862
	Caucasian	74 (25.17)	34 (22.82)	
	Hispanic	38 (12.93)	23 (15.44)	
	Other/unknown	5 (1.70)	3 (2.01)	
Marital status	Married/living with partner	149 (50.68)	69 (46.31)	.629
	Divorced/widowed/separated	29 (9.86)	18 (12.08)	
	Never married	116 (39.46)	62 (41.61)	
Years of school completed	Mean (SE)	11.8 (0.13)	12.0 (0.19)	.379
Smoked during pregnancy	Yes	65 (22.11)	30 (20.13)	.713
Drank alcohol during pregnancy	Yes	26 (8.84)	10 (6.71)	.469

17OHP-C, 17-alpha hydroxyprogesterone caproate.

Heyborne. 17-Alpha hydroxyprogesterone caproate in obese women. Am J Obstet Gynecol 2015.