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Defining 17OHP-C responsiveness

Check for updates

TO THE EDITORS: We read with interest the Research Letter by Dr Caritis and associates that examined the interval of the gestational age difference at delivery (GADD) between the study pregnancy and prior births for women receiving 17-alpha hydroxyprogesterone caproate (17OHP-C) and placebo.[1] In this analysis, the GADD was analyzed as a surrogate for responsiveness to 17OHP-C by examining a "delta" (ie, difference) in length of gestation between births in a patient's history using data from the 2003 Meis et al report.[2] For example, a 37-week delivery compared to the same woman's prior 34-week delivery would result in a net +3 week GADD. To summarize, 17OHP-C was ineffective when using the GADD analysis to compare study drug—treated births to either an individual woman's earliest prior spontaneous preterm birth or last (ie, proximate) birth. Put another way, placebo and 17OHP-C GADD results were not significantly different for prolongation of pregnancies beyond 3 or 5 weeks when women served as their own controls.

GADDzooks! Are Caritis and colleagues suggesting that GADD failed as a yardstick? Or that 17OHP-C failed? The report by Caritis et al using GADD actually corrects for the known asymmetry in risk of recurrence for preterm birth in the Meis et al trial (41% of the control women in the Meis et al trial had ≥2 prior preterm births compared to 28% in the 17OHP-C-treated group, $P = .004$). By accounting for an individual woman's risk based on her prior preterm birth history, the effectiveness of 17OHP-C in the Meis et al trial appears to be eliminated.[1,2] It seems to us that 17OHP-C is ineffective for prevention of recurrent preterm birth at 35 weeks or less when an individual woman serves as her own control, even in the Meis et al dataset.[2,3] ■

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The authors report no conflicts of interest.

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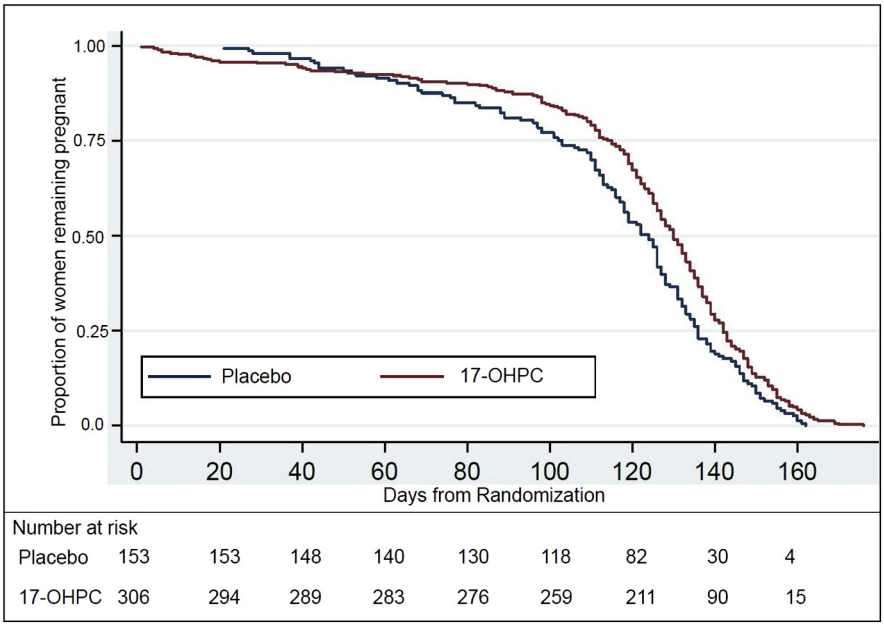
REPLY

Check for updates

We commend the authors for their clever use of our "GADD" acronym and we thank Nelson and colleagues for the opportunity to present additional data. In our research letter, we demonstrated that 17-alpha hydroxyprogesterone caproate (17-OHPC) responsiveness cannot be defined by the gestational age difference at delivery (GADD) from the earliest prior spontaneous preterm birth (sPTB) to the currently treated pregnancy.[1] The suggestion that GADD intervals could be used to define responsiveness to 17-OHPC stems from the possibility that women may gain a benefit from 17-OHPC even if they do not achieve the typical criterion of 37 weeks to define success.[2] In their letter, Nelson and colleagues ask whether GADD failed as a yardstick or whether 17-OHPC treatment failed. The focus of our analysis was to highlight that the GADD does not appear to be a good measure to define success of treatment with 17-OHPC, but we did not specifically address the efficacy of 17-OHPC.

A common statistical method used to judge success of an intervention is survival analysis, which has been used in many placebo-controlled randomized trials. Since risk at the start of a study should be balanced between subjects in the placebo and treatment group, differences in time to event between 17-OHPC and placebo reflect the efficacy of the intervention. The advantage of randomization is that risk antecedents such

FIGURE
Survival analysis comparing treatment with 17 alpha-hydroxyprogesterone caproate (17-OHPC) and placebo
***Log-rank test chi-square = 8.96 with a 2-sided *P* value = .0028**



Hauspurg. Letter to the Editor: Defining the clinical response to 17-alpha hydroxyprogesterone caproate. Am J Obstet Gynecol 2019.

as gestational age at earliest prior sPTB should be equally distributed in both study groups. Because of an imbalance between the 17-OHPC and placebo groups in terms of the number of prior preterm deliveries, the MFMU trial reported by Meis et al performed an adjusted analysis accounting for number of prior preterm births, which showed a reduction in risk of sPTB.[3] Similarly, we utilized Cox proportional hazards methods and compared models with and without adjustment for the number of previous preterm deliveries, which did not change the findings. We include here a survival curve generated from the original MFMU trial data that clearly demonstrates a prolongation of pregnancy with treatment with 17-OHPC compared to placebo, with a significant difference ($P = .003$) in the log-rank test for equality between the 2 curves (Figure). This demonstrates a clear distinction between groups, unlike the overlap of apparent benefit seen with application of various GADD intervals.[3] The survival analysis of the data reported by the MFMU demonstrates a time-related impact on "survival" that strongly favors 17-OHPC, supporting the efficacy of 17-OHPC in prevention of recurrent sPTB. ■

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