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Smoking, 17 Alpha-Hydroxyprogesterone Caproate, and Preterm Birth

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Abstract

Objective—The objective of this study was to determine if maternal smoking modifies the effectiveness of 17 α -hydroxyprogesterone caproate (17OHP-C).

Study Design—Secondary analysis of the Maternal-Fetal Medicine Units Network trial of 17OHP-C. The prevalence of preterm birth (PTB) by smoking status and treatment group was compared by chi-squared analysis and analysis of variance was used to compare gestational age (GA) at birth. Multivariable modeling was used to estimate the effect of smoking on 17OHP-C treatment.

Results—In this study, 459 women were included. Maternal smoking significantly modified the effectiveness of 17OHP-C treatment. In smokers, 17OHP-C significantly reduced the prevalence of multiple outcomes (PTB < 37 and < 35 weeks, spontaneous PTB < 37 and < 35 weeks), while in nonsmokers, only PTB < 37 weeks was reduced. Delivery GA was later in 17OHP-C versus placebo treated smokers (36.4 vs. 34.3 weeks, $p = 0.041$) but not nonsmokers (36.3 vs. 35.5 weeks, $p =$ nonsignificant). In multivariable modeling, 17OHP-C was more effective in smokers than nonsmokers as measured by multiple outcomes (PTB < 37 weeks [$p = 0.041$] and < 35 weeks [$p = 0.036$] and spontaneous PTB < 37 weeks [$p = 0.029$]).

Conclusion—In this cohort of women with a prior PTB, maternal smoking status significantly modified the effectiveness of 17OHP-C treatment.

Keywords

17 α -hydroxyprogesterone caproate; 17OHP-C; smoking; preterm birth; progesterone; tobacco

Identifying strategies to prevent preterm birth (PTB) remains the most pressing U.S. public health issue in obstetrics. Some progress has been made with the targeted use of progestogens, and administration of 17 α -hydroxyprogesterone caproate (17OHP-C) to women with a prior PTB is recommended by the Society for Maternal-Fetal Medicine and

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the American College of Obstetricians and Gynecologists (ACOG).^{1,2} This recommendation is based largely on the Maternal-Fetal Medicine Units (MFMU) trial published by Meis et al.³

Maternal tobacco smoking is an important risk factor for PTB with 4 to 13% of PTBs being attributable to smoking.^{4,5} In one study, approximately 23% of pregnant women smoked at the beginning of pregnancy and approximately 10% continued to smoke in the third trimester.⁶ Translated into raw numbers, this indicates that in the United States, there may be around 1 million births annually to women who smoke during pregnancy, far larger than the 180,000 births annually to women with a prior PTB.⁷ Accordingly, a PTB prevention strategy (beyond smoking cessation) that targeted pregnant smokers might have a large impact on PTB in the United States.

It is widely understood that PTB is the final common pathway of several pathological processes,⁸ so that women with a prior PTB form a heterogeneous group that may be unlikely to benefit equally from a single treatment approach. For example, we and others have demonstrated that maternal genotype,⁹ number of prior PTBs,^{10,11} prior PTB due to preterm premature rupture of membranes (PPROM),^{12,13} and maternal weight/obesity^{14,15} are significant modifiers of the effectiveness of fixed-dose 17OHP-C treatment. It is thus important to understand how other recognized PTB risk factors, such as smoking, might impact the effectiveness of 17OHP-C treatment.

That smoking might modify the effectiveness of 17OHP-C is plausible based on several precepts. Smoking has been reported to alter the metabolism of progestogens, possibly rendering pregnant smokers relatively progestogen deficient.¹⁶ 17OHP-C is postulated to achieve its benefits via anti-inflammatory mechanisms,^{17,18} and one pathway by which smoking is thought to increase PTB is via inflammation.⁸ Manuck et al have published pharmacogenomic data suggesting that 17OHP-C effectiveness may be linked to nitric oxide metabolism,⁹ which is adversely impacted by smoking.¹⁹ To gain further insight into these issues, we conducted a secondary analysis of the Meis et al MFMU 17OHP-C trial³ to investigate how smoking might modify the effectiveness of 17OHP-C.

Materials and Methods

Population for Analysis

This is a secondary analysis of the Meis et al trial conducted by the MFMU that was designed to determine if 17OHP-C treatment reduces the risk of PTB in women with a prior PTB.³ Full details are available in the original publication. Briefly, the original study was performed at 19 participating centers between 1999 and 2002. Women presenting for prenatal care were screened between 15 and 20^{3/7} weeks' gestation for a history of prior spontaneous PTB that had occurred between 20 and 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 to 20^{6/7} weeks. There were 463 individual women in the original trial.

For this analysis, four patients with missing gestational age (GA) at delivery were excluded (Fig. 1), all of whom were nonsmokers. This secondary analysis was considered exempt by the Colorado Multiple Institutional Review Board.

Definitions

Reported maternal smoking status at any time during pregnancy before study enrollment was recorded at the time of enrollment. No additional information about the number of cigarettes smoked, and cessation efforts at each institution are available in the dataset. Other substance use was defined by an indication that “Patient had alcoholic drinks at any time during this pregnancy?” or “Patient used ‘street drugs’ at any time during this pregnancy?” for alcohol and street drugs, respectively. The presence of syphilis, gonorrhea, chlamydia, trichomonas vaginalis, bacterial vaginosis, herpes, urinary tract infection, or group B strep defined infection during pregnancy. Body mass index (BMI) was calculated from pre-pregnancy weight as reported by the patient.

PTB was defined as delivery before 37 weeks for the primary end point. PTB before 35 or 32 weeks were secondary outcomes. Three mutually exclusive and exhaustive PTB phenotypes were indicated PTB (iPTB) if PTB had been indicated for a fetal or maternal indication, spontaneous PTB (sPTB) due to preterm labor with intact membranes, or PTB related to PPROM (PPROM-PTB). GA was assigned based on a strict protocol including ultrasonography before 21 weeks’ gestation.³

Statistical Approach

Demographics and clinical characteristics were summarized by randomization to 17OHP-C versus placebo and by smoking categorization using mean and standard error for continuous and frequency with percentage for categorical measures. Differences were tested using two-sample *t*-tests for continuous and exact Pearson chi-square for categorical measures. Right-skewed continuous measures were analyzed on the log scale and were presented as geometric mean with 95% confidence interval (CI).

Rates of PTB outcomes were compared by treatment group and smoking status overall, as well as pairwise across select combinations of the four categories defined by the 2×2 matrix of treatment and smoking.

The odds of each PTB outcome were estimated overall by tobacco use, treatment randomization, and the interaction of tobacco use and treatment randomization; multivariable models were estimated using logistic regression and adjusted for > 1 previous PTB, maternal BMI (continuous), race/ethnicity, alcohol use, drug use, infection during pregnancy, and years of education. Odds ratios and 95% CIs are reported from modeling. Analyses conducted in SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

As reported in the original trial, in comparing the groups randomized to 17OHP-C versus placebo, the number of prior PTBs was higher in the placebo group (Table 1, left). Comparing smokers and nonsmokers, smokers were more likely to have had more than one

PTB, be White, to have fewer years of education, to have used alcohol and street drugs during pregnancy, and to have experienced an infection during pregnancy (Table 1, right). Smokers trended lower in BMI and prevalence of obesity but differences were not significant.

As also reported in the initial study, overall 17OHP-C was successful in achieving a significantly later GA at delivery, and lower prevalence of PTB < 37, < 35, and < 32 weeks than placebo (Table 2, left). Overall, differences in PTB outcomes between smokers and nonsmokers were not significant (Table 2, right), although smokers had an earlier GA at delivery and a higher prevalence of all PTB outcomes.

In Table 3, we have tabulated the PTB prevalence in four (smoking status $\times$ treatment group) subgroups, and report overall 2×4 chi-square p -values, as well as select pairwise p -values from subgroup analyses. Overall chi-square results indicate differences in PTB rates across the four subgroups for multiple PTB outcomes (PTB < 37 weeks, sPTB < 37 weeks, PPROM-PTB < 37 weeks, PTB < 35 weeks, and sPTB < 35 weeks).

In pairwise comparisons between subgroups, PTB prevalence was highest (70%) and GA at delivery earliest among smokers treated with placebo. Among smokers, PTB outcomes among women randomized to 17OHP-C were significantly more improved than for women randomized to placebo for GA at delivery, PTB < 37 weeks, sPTB < 37 weeks, PTB < 35 weeks, sPTB < 35 weeks, and iPTB < 35 weeks. In contrast and despite a larger sample size per group, differences in PTB for 17OHP-C versus placebo among nonsmokers were only significant for PTB < 37 weeks. When comparing GA at delivery, delivery is significantly later in 17OHP-C treated smokers (36.4 vs. 34.3 weeks, $p = 0.041$) but not nonsmokers (36.3 vs. 35.5 weeks, $p = 0.160$). In other words, 17OHP-C has a significantly larger effect in smokers than in nonsmokers.

Among the group randomized to placebo, PTB was, as noted, most prevalent among smokers, with differences nearing significance compared with nonsmokers for PTB < 37 weeks and sPTB < 37 weeks, and differences reaching statistical significance for PTB < 35 weeks and sPTB < 35 weeks. In contrast, among women randomized to 17OHP-C, PTB outcomes were not significantly different in smokers versus nonsmokers. In other words, smoking was observed to significantly increase PTB outcomes in placebo-randomized but not 17OHP-C-randomized patients.

The interaction of treatment randomization and smoking status is presented graphically in Fig. 2 from two different perspectives for each outcome. Fig. 2 (left) depicts adjusted odds ratios for PTB in smokers versus nonsmokers according to treatment group (17OHP-C vs. placebo), again showing that smoking increases PTB outcomes in placebo-treated but not 17OHP-C-treated women. Fig. 2 (right) depicts adjusted odds ratios for PTB in 17OHP-C versus placebo-randomized women according to smoking status, again showing that 17OHP-C has a much larger effect in smokers than in nonsmokers. Among the six multivariable-adjusted models depicted, the joint effect of smoking and 17OHP-C on PTB is statistically significant for PTB < 37 weeks ($p = 0.041$) and < 35 weeks ($p = 0.036$) and sPTB < 37

weeks ($p = 0.029$); borderline significant for sPTB < 35 weeks ($p = 0.066$) and otherwise not significant.

Comment

We demonstrate here that maternal smoking status may significantly modify the effectiveness of 17OHP-C treatment for the prevention of PTB, with 17OHP-C being significantly more effective in smokers than in nonsmokers. Although in this study, the incidence of PTB < 37 weeks did remain significantly reduced in nonsmokers treated with 17OHP-C, the mean GA at delivery was not significantly prolonged, and there was no reduction in the more important outcome of PTB < 35 weeks. In comparison, 17OHP-C retained its effect on multiple PTB outcomes in the smoking population. Although further dividing the study population into smaller subgroups creates a possibility of incorrectly interpreting null results as evidence of “no relationship” (i.e., type II error), here we observe significant differences among the smaller smoking groups, while the 17OHP-C nonsmoking group is the largest subgroup, making this a less likely explanation. Given the high cost and difficult logistics of weekly 17OHP-C intramuscular injections, it may be important to focus this intervention on selected subgroups with the largest benefit, and the reduced benefits in nonsmokers may not be cost effective if the findings of this study are confirmed.

The novel finding we report here has a second potentially important implication, namely, the adverse effect of smoking on recurrent PTB was diminished by 17OHP-C administration in this trial. Among the documented, adverse health effect of smoking is a well-known increased risk of PTB⁸ and recurrent PTB,²⁰ impacting 1 million births annually and resulting in as many as 60,000 PTBs per year in the United States.^{4,6} Although the original study by Meis et al³ was not powered to detect an increase in PTB due to smoking, we did find trends that echo this known association among women randomized to placebo for the majority of PTB outcomes with the trend reaching significance in the case of PTB < 35 weeks and sPTB < 35 weeks. The negative effect of smoking on PTB appeared to be reduced in 17OHP-C-treated patients, and from adjusted analyses, this effect modification was significant for PTB < 37 weeks and < 35 weeks and sPTB < 37 weeks. As this study only included women with at least one prior PTB, any effect of 17OHP-C on a first PTB would be speculative. Given the large number of pregnant smokers, the high incidence of PTB among pregnant smokers, and the relatively poor success of cessation programs, if the finding of this study are confirmed in currently ongoing trials, the use of 17OHP-C in women who are unable or unwilling to stop smoking may be worthy of further investigation. The authors recognize the numerous adverse health effects of smoking and these findings should not be interpreted as permissive toward smoking during pregnancy, but a last resort to reduce one risk of smoking in a vulnerable population.

Both the mechanisms by which 17OHP-C prevents PTB and by which smoking increases PTB are poorly understood. Accordingly, mechanisms by which smoking might modify 17OHP-C's effects are speculative. Smoking is known to impact the metabolism of multiple sex steroids. In a study by Toriola et al,¹⁶ for example, smoking was noted to reduce levels of progesterone while actually increasing levels of 17 α -hydroxyprogesterone. It is possible that smokers treated with 17OHP-C may thus be both relatively progesterone deficient and

have relatively augmented levels of 17OHP-C. Smoking is known to produce an inflammatory state,²¹ and inflammatory pathways are central to PTB.⁸ 17OHP-C may exert its PTB prevention via anti-inflammatory mechanisms, possibly making smokers ideal candidates.^{17,18} Pharmacogenomic studies suggest that 17OHP-C effectiveness may be linked to nitric oxide metabolism,⁹ which is adversely impacted by smoking.¹⁹

The strengths of this study are the prospective data collection that occurred at the time of the original trial by trained research nurses. The cohort is large and diverse, and includes many of the population groups at increased risk of PTB. PTB was the primary outcome of the original trial and allowed us to make rigorous comparisons between women who did and did not deliver early during the original trial.

Weaknesses of this study are that smoking status was only recorded at study intake and was obtained by maternal history. Serum cotinine levels or other objective measures of smoking status were not obtained as part of the primary study. Maternal report would, if anything, represent actual smoking status.²² If there were in fact many smokers in the “nonsmoker” group, this would bias results toward the null and thus only serve to strengthen our findings. The number of cigarettes smoked in this study was recorded at study entry, but this variable was not made available to us in this public dataset we used for our secondary analysis. A dose–response analysis would be germane. Smoking cessation efforts at each institution and their effectiveness are not reported in the dataset.

Klebanoff²³ has recently opined on the perils of subgroup analysis on the topic of 17OHP-C treatment. Our subgrouping meets the suggested criteria from that article.

Smoking status was identified before randomization, and we properly compared the treatment effect between the two groups and found it to be significantly different. We have offered plausible reasons why the effect of 17OHP-C might be different in smoker versus nonsmokers, but acknowledge that this was not a planned subgroup analysis. Accordingly, our findings are best viewed as hypothesis generating at present, and analysis of ongoing or future trials will shed further light on this issue.

In summary, we report data indicating that smoking significantly modifies the effectiveness of 17OHP-C for the prevention of PTB. We would not recommend any changes in practice based on these findings at present. However, if these findings are confirmed by currently ongoing trials, we believe that a trial of 17OHP-C to prevent PTB in women who are unwilling or unable to quit smoking may be warranted, and that the recommendation for the continued administration of 17OHP-C for the prevention of recurrent PTB in nonsmokers may warrant reconsideration.

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Fig. 1.
Selection of patients for this study from initial patient cohort.

Fig. 2.

ORs and 95% CIs for preterm birth. Adjusted ORs from six models including an interaction between smoking and 17OHP-C. ORs for smoking by treatment group are presented in the left portion of the figure, and ORs for treatment by smoking status are presented in the right portion of the figure. *p*-Values from some interactions are included; the remaining interactions are NS. CI, confidence interval; NS, nonsignificant; OR, odds ratio.

Table 1

Demographics and clinical characteristics

Characteristic	Randomization		Smoking during pregnancy		p-Value
	17OHP-C N = 306	Placebo N = 153	Smokers N = 100	Nonsmokers N = 356	
# Previous preterm deliveries ^a	1.41 (0.04)	1.59 (0.07)	1.61 (0.09)	1.43 (0.04)	0.071
> 1 previous preterm delivery	28.1 (86)	41.2 (63)	42.0 (42)	29.8 (107)	0.022
No previous term deliveries	50.3 (154)	53.6 (82)	46.0 (46)	52.9 (190)	0.258
GA at randomization (wk) ^a	18.9 (0.08)	18.8 (0.12)	18.9 (0.14)	18.8 (0.08)	0.518
Maternal age ^b	25.5 (25.0, 26.1)	26.1 (25.3, 27.0)	25.1 (24.1, 26.2)	25.9 (25.4, 26.5)	0.186
Race or ethnic group					
African American	59.2 (181)	58.8 (90)	59.0 (59)	59.1 (212)	< 0.001
White/other	27.5 (84)	24.2 (37)	39.0 (39)	22.8 (82)	
Hispanic	13.4 (41)	17.0 (26)	2.0 (2)	18.1 (65)	
Marital status					
Together	51.0 (156)	46.4 (71)	41.0 (41)	51.8 (186)	0.102
Otherwise	10.1 (31)	11.8 (18)	10.0 (10)	10.9 (39)	
Never married	38.9 (119)	41.8 (64)	49.0 (49)	37.3 (134)	
Maternal pre-pregnancy BMI ^a	26.5 (0.41)	25.5 (0.51)	25.0 (0.65)	26.5 (0.37)	0.051
Obese	31.6 (93)	24.8 (37)	23.2 (22)	31.0 (108)	0.162
Maternal height ^a	63.9 (0.18)	63.6 (0.25)	64.1 (0.30)	63.7 (0.16)	0.225
Maternal weight ^a	154 (2.49)	148 (3.21)	148 (4.16)	153 (2.24)	0.306
Years of school ^a	11.7 (0.13)	11.9 (0.19)	11.4 (0.15)	11.9 (0.13)	0.027
Smoked	22.9 (70)	19.6 (30)	100.0 (100)	–	Omitted
Drank alcohol	8.8 (27)	6.5 (10)	17.0 (17)	5.6 (20)	< 0.001
Used street drugs	3.6 (11)	2.6 (4)	12.0 (12)	0.8 (3)	< 0.001
Infections	32.0 (98)	35.9 (55)	42.0 (42)	30.9 (111)	0.042

Abbreviations: BMI, body mass index; GA, gestational age; 17OHP-C, 17 α -hydroxyprogesterone caproate.

Notes: Values presented are percentage (frequency) unless otherwise noted. Tails of BMI were censored in publicly released data. Censored values are included in categorical but not in continuous summary statistics.

^aMean (standard error).

^bGeometric mean (95% CI).

Table 2

Overall effect of smoking and randomization on PTB outcomes

	Randomization			Smoking during pregnancy		
	17OHP-C N = 306	Placebo N = 153	p-Value	Smokers N = 100	Nonsmokers N = 356	p-Value
GA at delivery (wk) ^a	36.3 (0.28)	35.3 (0.38)	0.033	35.7 (0.47)	36.0 (0.26)	0.610
Delivery before 37 wk ^a gestation	36.3 (111)	54.9 (84)	< 0.001	44.0 (44)	42.1 (151)	0.733
Spontaneous	22.2 (68)	34.6 (53)	0.005	28.0 (28)	25.9 (93)	0.701
Indicated because of complications	6.9 (21)	9.8 (15)	0.357	7.0 (7)	8.1 (29)	0.836
Premature rupture of membranes	7.2 (22)	10.5 (16)	0.281	9.0 (9)	8.1 (29)	0.837
Delivery before 35 wk ^a gestation	20.6 (63)	30.7 (47)	0.020	28.0 (28)	22.8 (82)	0.291
Spontaneous	12.7 (39)	19.0 (29)	0.094	18.0 (18)	13.9 (50)	0.340
Indicated because of complications	2.0 (6)	3.9 (6)	0.352	3.0 (3)	2.5 (9)	> 0.99
Premature rupture of membranes	5.9 (18)	7.8 (12)	0.549	7.0 (7)	6.4 (23)	> 0.99
Delivery before 32 wk ^a gestation	11.4 (35)	19.6 (30)	0.023	16.0 (16)	13.6 (49)	0.626

Abbreviations: GA, gestational age; PTB, preterm birth; 17OHP-C, 17 α -hydroxyprogesterone caproate.

Note: Values in cell represent column percentage (frequency).

^aMean and standard error.

Table 3

Overall and pairwise differences in PTB of subgroups defined by smoking and randomization

Outcome	Estimates within each subgroup				<i>p</i> -Values			
	17OHP-C (N = 306)		Placebo (N = 153)		17OHP-C vs. placebo		Smoker vs. nonsmoker	
	Smokers N = 70	Nonsmokers N = 236	Smokers N = 30	Nonsmokers N = 123	Subset: smokers	Subset: nons	Subset: placebo	Subset: 17OHP-C
GA at delivery (wk) ^a	36.4 (0.57)	36.3 (0.32)	34.3 (0.80)	35.5 (0.43)	0.110	0.160	0.188	0.898
Delivery before 37 wk' gestation	32.9 (23)	37.3 (88)	70.0 (21)	51.2 (63)	< 0.001	0.013	0.069	0.572
Spontaneous	18.6 (13)	23.3 (55)	50.0 (15)	30.9 (38)	0.004	0.129	0.056	0.421
Indicated because of complications	5.7 (4)	7.2 (17)	10.0 (3)	9.8 (12)	0.730	0.419	> 0.99	0.793
Premature rupture of membranes	8.6 (6)	6.8 (16)	10.0 (3)	10.6 (13)	0.643	0.225	> 0.99	0.793
Delivery before 35 wk' gestation	18.6 (13)	21.2 (50)	50.0 (15)	26.0 (32)	0.004	0.002	0.015	0.737
Spontaneous	11.4 (8)	13.1 (31)	33.3 (10)	15.4 (19)	0.024	0.013	0.036	0.839
Indicated because of complications	0.0 (0)	2.5 (6)	10.0 (3)	2.4 (3)	0.038	> 0.99	0.09	0.343
Premature rupture of membranes	7.1 (5)	5.5 (13)	6.7 (2)	8.1 (10)	0.817	0.367	> 0.99	0.773
Delivery before 32 wk' gestation	11.4 (8)	11.4 (27)	26.7 (8)	17.9 (22)	0.067	0.106	0.308	> 0.99

Abbreviations: GA, gestational age; PTB, preterm birth; 17OHP-C, 17 α -hydroxyprogesterone caproate.

Note: Values in cell represent column percentage (frequency). *p* values < 0.05 are shown in bold.

^aMean and standard error.