OBSTETRICS

Progesterone receptor polymorphisms and clinical response to 17-alpha-hydroxyprogesterone caproate

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OBJECTIVE: Seventeen-alpha-hydroxyprogesterone caproate (17-OHPC) reduces recurrent preterm birth (PTB). We hypothesized that single nucleotide polymorphisms in the human progesterone receptor (PGR) affect response to 17-OHPC in the prevention of recurrent PTB.

STUDY DESIGN: We conducted secondary analysis of a study of 17-OHPC vs placebo for recurrent PTB prevention. Twenty PGR gene single nucleotide polymorphisms were studied. Multivariable logistic regression assessed for an interaction between PGR genotype and treatment status in modulating the risk of recurrent PTB.

RESULTS: A total of 380 women were included; 253 (66.6%) received 17-OHPC and 127 (33.4%) received placebo. In all, 61.1% of women were African American. Multivariable logistic regression demonstrated significant treatment-genotype interactions (either a beneficial or harmful treatment response) for African Americans delivering <37 weeks' gestation for rs471767 and rs578029, and for Hispanics/Caucasians delivering <37 weeks' gestation for rs500760 and <32 weeks' gestation for rs578029, rs503362, and rs666553.

CONCLUSION: The clinical efficacy and safety of 17-OHPC for recurrent PTB prevention may be altered by PGR gene polymorphisms.

Key words: genetic polymorphisms, progesterone receptor, recurrent preterm birth, 17-alpha hydroxyprogesterone caproate

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More than 12% of infants born in the United States are born prematurely (<37 weeks' gestation), but these infants account for >70% of neonatal morbidity and mortality. Previous studies have suggested that susceptibility to spontaneous preterm birth (PTB) is inherited. Women who themselves are born preterm have a higher risk of delivering preterm; this risk is inversely correlated with maternal gestational age at birth.[1,2] Furthermore, the highest risk factor for PTB is a history of a prior PTB.[3] Multiple maternal genetic polymorphisms in a variety of genes have been associated with PTB.[2-4] African Americans have a higher rate of PTB even when controlling for social and other confounding factors, suggesting that the racial disparity to this complication may have a genetic component.[5-9]

Progesterone is a critical hormone involved with pregnancy maintenance; its absence or relative absence is associated with pregnancy failure, preterm labor, and other poor outcomes.[10,11] Progesterone has been the focus of several recent investigations of therapeutic modalities for PTB. In 2003, Meis et al[12] published results from a multicenter, prospective, double-blind, randomized controlled trial demonstrating that weekly treatment of 17-alpha-hydroxyprogesterone caproate (17-OHPC) reduces recurrent PTB by approximately one third. It appears that 17-OHPC is most efficacious in prolonging pregnancy in women with a previous early spontaneous PTB (<34 weeks' gestation).[13] Additional studies have examined other progesterone formulations in various high-risk cohorts

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TABLE 1
Single nucleotide polymorphisms studied

SNP	Public location	SNP type	Base change	Function or previously published association(s)
rs471767	chr. 11 100410507	UTR 3, transition substitution	A/G	Prematurity[28]
rs500760	chr. 11 100415201	Silent mutation, transition substitution	A/G	
rs1042839	chr. 11 100427412	Silent mutation, transition substitution	A/G	Recurrent miscarriage, ovarian cancer[38]
rs578029	chr. 11 100427614	Intron, transversion substitution	A/T	Prematurity (as part of haplotype block)[28]
rs1042838	chr. 11 100438622	Mis-sense mutation, transversion substitution	G/T	Increases PGR; ovarian cancer; uterine fibroids
rs666553	chr. 11 100443878	Intron, transition substitution	C/T	
rs653752	chr. 11 100453320	Intron, transversion substitution	C/G	
rs503362	chr. 11 100467037	Intron, transversion substitution	C/G	Prematurity[27]
rs493957	chr. 11 100494658	Intron, transition substitution	A/G	
rs582691	chr. 11 100500076	Intron, transition substitution	A/G	
rs3740753	chr. 11 100503981	Mis-sense mutation, transversion substitution	C/G	Recurrent miscarriage
rs10895068	chr. 11 100505424	UTR 5, transition substitution	+331 G/A	Increases PGR-B transcription relative to PGR-A, endometrial cancer,[19] epithelial ovarian cancer[34]
rs4754732	chr. 11 100513712	Intergenic/unknown, transition substitution	C/T	
rs568157	chr. 11 100529492	Intergenic/unknown, transition substitution	A/G	
rs471811	chr. 11 100549413	Intergenic/unknown, transition substitution	A/G	
rs474320	chr. 11 100549413	Intergenic/unknown, transversion substitution	A/T	
rs1942836	chr. 11 100554557	Intergenic/unknown, transition substitution	C/T	
rs954723	chr. 11 100568141	Intergenic/unknown, transition substitution	C/T	
rs10501973	chr. 11 100568786	Intergenic/unknown, transition substitution	A/G	
rs1893505	chr. 11 100572918	Intergenic/unknown, transition substitution	C/T	

chr., chromosome; *PGR*, progesterone receptor; *SNP*, single nucleotide polymorphism; *UTR*, untranslated region.

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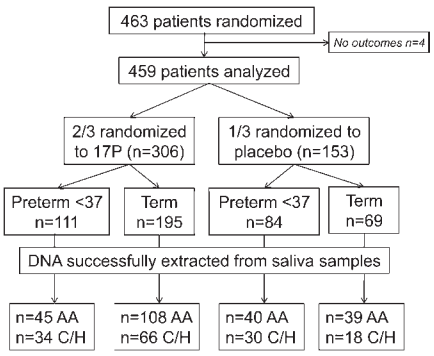
and have also shown therapeutic benefit with progesterone.[14-16]

The human progesterone receptor (PGR) is a member of the steroid and thyroid receptor superfamily. The gene encoding this receptor is located on chromosome 11q22-23 and consists of 8 exons.[17] Nuclear PGRs exist primarily as 2 distinct isoforms, PGR-A and PGR-B; both have been found in gestational tissues including the amnion and chorion.[18] Although both PGR-A and

FIGURE
Study enrollment



17P, 17-alpha-hydroxyprogesterone caproate; *AA*, African American; *C/H*, Caucasian or Hispanic.

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TABLE 2
Logistic regression results for African American patients with preterm birth <37.0 weeks' gestation

SNP	Additive	Codominant	Dominant	Recessive
rs471767	0.02[a]	0.06, 0.06	0.02[a]	0.17
rs500760	0.88	0.99, 0.86	0.92	0.85
rs1042839	0.99	0.99, NA	0.99	NA
rs578029	0.12	1, 0.04[a]	0.51	0.03[a]
rs1042838	0.99	0.99, NA	0.99	NA
rs666553	0.55	0.5, 0.78	0.49	0.92
rs653752	0.34	0.92, 0.32	0.74	0.21
rs503362	0.09	0.1, 0.22	0.07	0.44
rs493957	0.56	0.17, NA	0.32	NA
rs582691	0.1	0.06, 0.41	0.06	0.67
rs3740753	0.99	0.99, NA	0.99	NA
rs10895068	0.98	0.98, NA	0.98	NA
rs4754732	0.14	0.06, NA	0.1	NA
rs568157	0.45	0.28, 0.87	0.33	0.95
rs471811	0.07	0.38, 0.05	0.16	0.08
rs474320	0.99	0.99, NA	0.99	NA
rs1942836	0.11	0.16, 0.31	0.12	0.46
rs954723	0.34	0.88, 0.2	0.59	0.21
rs10501973	0.17	0.17, NA	0.17	NA
rs1893505	0.52	0.91, 0.44	0.86	0.35

P values are displayed for interaction between treatment (progesterone) and genotype for each of 4 inheritance models, and are adjusted for body mass index, smoking, and number of prior preterm births.
NA, not applicable; *SNP*, single nucleotide polymorphism.

[a] $P < .05$.

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PGR-B are encoded from a single gene, they are transcribed from 2 different promoters and are thought to have different biologic roles. PGR-A is smaller, lacks the 164 N-terminal amino acids that form an activation domain on the receptor, and is thought to inhibit the transcription of progesterone receptive genes. In contrast, PGR-B increases transcription of progesterone-responsive genes and has an overall quiescent effect on the myometrium.[19,20] Thus, the responsiveness of target tissues to progesterone may depend not only on circulating levels of progesterone but also on the ratio of PGR isoforms.[21,22] It has also been hypothesized that a relative increase in the ratio of PGR-A to PGR-B may contribute to a functional withdrawal of progesterone and lead to the initiation of labor.[23,24]

PGR polymorphisms have been implicated in several different obstetrical/gynecological disorders, including ovarian cancer, endometriosis, implantation failure, and recurrent miscarriage.[17,25-27] Few previous studies have assessed for a relationship between PGR single nucleotide polymorphisms (SNPs) and PTB.[17,28] While 17-OHPC clearly works for some women, more than one third of women fail treatment and have a recurrent PTB. The reasons for this variable responsiveness are unknown, but may be secondary to an inability to respond to both endogenous and exogenous progesterone.

Our objective was to determine whether response to 17-OHPC is affected by an individual's PGR genotype. We hypothesize that genetic variation in the PGR contributes to the clinical response to 17-OHPC for the prevention of recurrent PTB.

Materials and Methods

This is a secondary analysis of women enrolled from September 1999 through February 2002 in a multicenter, prospective, double-blind, randomized controlled trial of 17-OHPC vs placebo, conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.[12] The trial enrolled 463 women with a singleton gestation who had a history of spontaneous PTB and randomized them to receive either weekly injections of 17-OHPC (n = 310) or placebo (n = 153), beginning at 16-$20^{3/7}$ weeks' gestation and continuing until $36^{6/7}$ weeks' gestation or delivery. The trial demonstrated a reduction in the rate of recurrent PTB from 54.9% in the placebo group to 36.3% in the treatment group ($P < .001$).

Institutional review board approval and subject consent for the original study, as well as future analyses such as this study, were obtained at each of the 19 participating network sites by trained research nurses.[12] This secondary analysis was reviewed by the University of Utah Institutional Review Board and determined to be exempt secondary to de-identification of data and study samples prior to this analysis. As a part of the original trial protocol, maternal saliva

TABLE 3
Logistic regression results for African American patients with preterm birth <32.0 weeks' gestation

SNP	Additive	Codominant	Dominant	Recessive
rs471767	0.74	0.4, 0.96	0.53	0.81
rs500760	0.6	0.16, 0.99	0.47	0.99
rs1042839	1	1, NA	1	NA
rs578029	0.38	0.07, 0.95	0.12	0.58
rs1042838	1	1, NA	1	NA
rs666553	0.79	0.14, 0.99	0.29	0.99
rs653752	0.91	0.51, 0.9	0.62	0.78
rs503362	0.78	0.59, 0.93	0.66	0.92
rs493957	0.8	0.99, NA	0.4	NA
rs582691	0.84	0.41, 0.76	0.56	0.59
rs3740753	1	1, NA	1	NA
rs10895068	1	1, NA	1	NA
rs4754732	0.53	0.53, NA	0.53	NA
rs568157	1	0.67, 0.63	0.83	0.7
rs471811	0.66	0.44, 0.72	0.86	0.39
rs474320	0.99	0.99, NA	0.99	NA
rs1942836	0.57	0.24, 0.8	0.33	0.59
rs954723	0.6	0.49, 1	0.46	1
rs10501973	0.8	0.8, NA	0.8	NA
rs1893505	0.63	0.34, 0.82	0.38	0.81

P values are displayed for interaction between treatment (progesterone) and genotype for each of 4 inheritance models, and are adjusted for body mass index, smoking, and number of prior preterm births.
NA, not applicable; *SNP*, single nucleotide polymorphism.
[a] $P < .05$.

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samples were collected for future analyses. Saliva samples were frozen at –20°C. DNA was extracted and amplified from saliva samples using established methods (Puregene; Qiagen Systems, Valencia, CA) per manufacturer's instructions in July and August 2008.

Individuals were genotyped with SNPs in the PGR gene using TaqMan chemistry (Applied Biosystems, Foster City, CA) with established primers according to kit protocols. Tagging SNPs were selected to encompass the large PGR haplotype block, and are listed, along with known function or previously published associations in Table 1.[29] SDS 2.3 software (Applied Biosystems) was used to automatically determine sample genotypes (autocaller) and generate cluster plots. Genotypes were subsequently manually verified, and SNPs were evaluated for deviation from Hardy-Weinberg equilibrium using the exact test, as previously described.[30] Samples were labeled only with a unique bar-coded study identification number, thus, researchers and laboratory personnel were blinded to all clinical data, including pregnancy outcome and treatment group assignment of the biologic samples. Only personnel at the statistical coordinating center had access to the key linking the study identification number with clinical data.

Because allele frequencies vary between races, women were stratified by self-reported race into 2 groups: African American and Caucasian/Hispanic. Women of other self-reported races were excluded. Allele and genotype frequencies were calculated for each SNP. Logistic regression was performed with PTB <37 weeks' gestation and very PTB <32 weeks' gestation as dependent variables. The interaction between PGR genotype and 17-OHPC therapy was evaluated by including an interaction term for these variables in the logistic regression model. Those SNPs identified to have significant treatment-genotype interactions were considered for a limited haplotype analysis. Haplotype phase was estimated using R-package haplo.stats version 1.4.4 (Mayo Clinic, Rochester, MN). Potential confounders (factors known to be associated with PTB), including prepregnancy body mass index (BMI), smoking status, and number of prior preterm deliveries, were controlled for in adjusted models.

Additive, codominant, dominant, and recessive inheritance models were considered. The additive model assumes that having 2 copies of minor allele has twice the effect of having 1 copy, the codominant model assumes that heterozygotes have an increased risk of disease over both homozygote groups, the dominant model assumes that having at least 1 copy of the minor allele is sufficient for disease, and the recessive model assumes that 2 copies of the minor allele are needed for disease. The treatment-genotype interaction was considered significant at $P < .05$. The inheritance model with the best *P* value was considered to be the best-fitting model for the respective SNP and was used to calculate odds ratios (ORs).

As this was an exploratory study, no adjustment to the alpha level was made for multiple comparisons, and all comparisons are reported. However, the false discovery rate (FDR) was calculated to evaluate the proportion of false positives among the identified positives.[31,32] We used the statistical framework proposed by Tusher et al[33] to calculate FDRs for these identified SNPs. SAS (SAS Institute, Cary, NC) and R (www.r-project.org) were used for the statistical analysis.

RESULTS

DNA was successfully extracted from the stored saliva samples of 388 of 459 women (84.5%) analyzed in the original

study (Figure). In all, 232 (59.8%) were self-identified African Americans, 94 (24.2%) were self-identified Caucasians, and 54 (13.9%) were self-identified Hispanics. Eight women of other self-identified races were excluded; our final study cohort consisted of 380 African American, Caucasian, or Hispanic women all with ≥1 documented spontaneous PTB. Maternal age, racial distribution, treatment assignment, number of prior spontaneous PTB, tobacco usage, and prepregnancy BMI were similar between the original cohort and our study population (data not shown). There was no center-to-center variation. Our study population had slightly lower rates of prematurity <37 weeks' gestation (39.2% vs 42.4%, $P = .002$) and <32 weeks' gestation (12.4% vs 14.4%, $P = .004$) during the original trial when compared with the entire original cohort.

On average, 96.9% (range, 93.0–99.0%) of samples were successfully genotyped for each SNP. All SNPs were in Hardy-Weinberg equilibrium (all P values $> .01$). Multivariable logistic regression revealed an interaction between genotype and treatment in the prediction of PTB <37 and <32 weeks' gestation for several SNPs and with varying inheritance models (Tables 2-5). This includes 2 SNPs identified in African Americans (rs471767 and rs578029); both were associated with PTB <37.0 weeks' gestation. The rs500760 was associated with PTB in Caucasian/Hispanic women <37.0 weeks' gestation. An additional 3 SNPs in Caucasian/Hispanics (rs503362, rs666553, and rs578029) were associated with PTB <32.0 weeks' gestation.

To further assess whether the risk of recurrent PTB was dependent on both 17-OHPC administration and PGR genotype, we calculated adjusted OR (aOR) of recurrent PTB. These OR were calculated based on treatment group and allele status for each SNP that reached statistical significance in regression models, using the "best" inheritance model. Women who received the placebo and had the predominant genotype comprised the reference group in each calculation (Table 6). As an example, among African American women homozygous for the dominant allele (A) in rs471767, there was a significantly lower odds of prematurity with 17-OHPC compared to placebo (aOR, 0.22; 95% confidence interval [CI], 0.09–0.51). In contrast, African American women with at least 1 copy of the minor allele (G) had similar rates of prematurity irrespective of treatment received (aOR of PTB with placebo, 0.51; 95% CI, 0.19–1.37 vs 0.47; 95% CI, 0.20–1.06 with 17-OHPC). This interaction between the rs471767 genotype and treatment was significant even when controlling for BMI, smoking history, and number of prior PTB ($P = .023$).

Results from the limited haplotype analysis as described in the methods section are shown in Table 7. As an example, when the rs471767 rs578029 haplotype block was examined among African American women, it is notable that while all women had a decreased odds of PTB <37 weeks' gestation with 17-OHPC, those women with the GA haplotype also had a lower odds of PTB when they received placebo (Table 7). The odds of PTB among those with the GA haplotype was seemingly unaffected by treatment (placebo aOR, 0.58; 95% CI, 0.26–1.29, 17-OHPC aOR, 0.50; 95% CI, 0.22–1.12).

The estimated FDR for the reported SNPs based on the African American group was >99.9% and 65.1% for SNPs based on the Caucasian/Hispanic group. The FDR applies to all of the reported significant findings, not to individual SNPs.[31,32]

TABLE 4
Logistic regression results for Caucasian/Hispanic patients with preterm birth <37.0 weeks' gestation

SNP	Additive	Codominant	Dominant	Recessive
rs471767	0.85	0.85, 0.66	0.94	0.6
rs500760	0.15	0.03,[a] 0.84	0.04[a]	0.74
rs1042839	0.19	0.14, NA	0.16	NA
rs578029	0.73	0.9, 0.99	0.96	0.99
rs1042838	0.08	0.05, NA	0.06	NA
rs666553	0.82	0.74, 0.99	0.77	0.99
rs653752	0.77	0.22, 0.59	0.41	0.18
rs503362	0.63	0.5, 0.99	0.53	0.92
rs493957	0.13	0.1, 0.99	0.1	0.99
rs582691	0.25	0.39, NA	0.3	NA
rs3740753	0.13	0.08, NA	0.1	NA
rs10895068	0.67	0.87, 1	0.73	1
rs4754732	0.32	0.28, NA	0.29	NA
rs568157	0.74	0.73, 0.83	0.71	0.96
rs471811	0.69	0.66, 0.94	0.64	0.98
rs474320	0.37	0.32, NA	0.34	NA
rs1942836	0.6	0.93, 0.99	0.87	0.99
rs954723	0.6	0.49, 0.83	0.52	0.96
rs10501973	0.62	0.52, 0.99	0.56	0.99
rs1893505	0.72	0.48, 0.72	0.51	0.89

P values are displayed for interaction between treatment (progesterone) and genotype for each of 4 inheritance models, and are adjusted for body mass index, smoking, and number of prior preterm births.
NA, not applicable; *SNP*, single nucleotide polymorphism.
[a] $P < .05$.
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TABLE 5
Logistic regression results for Caucasian/Hispanic patients with preterm birth <32.0 weeks' gestation

SNP	Additive	Codominant	Dominant	Recessive
rs471767	0.1	0.1, 1	0.07	1
rs500760	0.09	0.09, 0.99	0.08	0.99
rs1042839	0.99	0.99, NA	0.99	NA
rs578029	0.02[a]	0.1, 0.99	0.05	0.99
rs1042838	0.99	0.99, NA	0.99	NA
rs666553	0.04[a]	0.11, 0.99	0.05	0.99
rs653752	0.98	0.2, 0.99	0.34	0.99
rs503362	0.05	0.03,[a] 1	0.03[a]	1
rs493957	0.38	0.3, 0.75	0.28	0.96
rs582691	0.99	0.99, NA	0.99	NA
rs3740753	0.99	0.99, NA	0.99	NA
rs10895068	0.68	0.99, 1	0.95	0.99
rs4754732	0.67	0.46, NA	0.54	NA
rs568157	0.53	0.26, 0.61	0.29	0.95
rs471811	0.17	0.60, 0.99	0.33	0.99
rs474320	0.99	0.99, NA	0.99	NA
rs1942836	0.80	0.20, 0.99	0.32	0.99
rs954723	0.12	0.77, 0.12	0.50	0.08
rs10501973	0.53	0.75, 0.99	0.61	0.99
rs1893505	0.2	0.44, 0.28	0.97	0.11

P values are displayed for interaction between treatment (progesterone) and genotype for each of 4 inheritance models, and are adjusted for body mass index, smoking, and number of prior preterm births.
NA, not applicable; *SNP,* single nucleotide polymorphism.

[a] $P < .05$.

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COMMENT

We have demonstrated evidence of a relationship between clinical response to 17-OHPC and PGR polymorphisms. Notably, we found several SNPs in both African American and Caucasian/Hispanic women that appear to alter responsiveness to 17-OHPC. The SNPs studied were selected for comprehensive screening of the large (approximately 200-kilobase long) PGR HapMap haplotype block.

The rs471767 SNP is located just upstream (5') of the PGR promoter region. It is plausible that genetic variation in the upstream region of the PGR in the area of rs471767 may alter expression of the PGR gene product, possibly through alterations in the ratio of the PGR-A to B isoform ratio. Carriage of the minor allele for SNP rs471767 has been previously associated with spontaneous PTB in a group of Hispanic and Caucasian patients in Utah, although information regarding supplemental progestin use was not available for those women, and an interaction between progestin use and carriage of the minor allele could not be assessed.[28]

Some results seem to indicate an *increased* odds of PTB with 17-OHPC treatment. For example, Caucasian/Hispanic women who received 17-OHPC and had the GG genotype for rs503362 had a relatively increased odds of (aOR, 2.89; 95% CI, 0.54–15.6). This is in contrast to those patients with the GC or CC genotypes, whose odds of PTB was higher with placebo (aOR, 2.42; 95% CI, 0.35–16.7), but significantly less with 17-OHPC (aOR, 0.28; 95% CI, 0.02–3.51). When the rs503362 rs666553 haplotype block was examined, Caucasian/Hispanic women with the GC haplotype had a 10-fold higher risk of PTB <32 weeks' gestation (Table 7). These patterns follow those noted for the individual SNP analysis. These results indicating increased odds of PTB with 17-OHPC treatment highlight the importance of future study and refinement of a response (or harm) genotype profile to ensure patient safety.

The functional PGR +331 A/G mutation (rs10895068) has been previously shown to alter transcription rates of PGR-B relative to PGR-A, and has been associated with an increased risk of ovarian cancer.[34] We did not observe an interaction between rs10895068 and 17-OHPC prophylaxis. There are several possible reasons for this lack of observation. The +331 A/G mutation may have a different effect on gestational tissues. Alternatively, this mutation may be involved with the PTB phenotype, but not be affected by treatment with 17-OHPC. As inclusion in this study required women to have at least 1 prior spontaneous PTB, our study is not able to detect genetic differences between women with and without a history of PTB.

Previous studies of PGR variation among women with PTB have been limited, and in contrast to this work, have not examined for an interaction among progestin administration, PGR genotype, and PTB. Diaz-Cueto et al[35] studied 4 PGR polymorphisms in 64 preterm patients and 54 control subjects and concluded that polymorphisms in the PGR gene are unlikely to be associated with PTB in a Hispanic population. Guoyang et al[17] genotyped 78 primarily Hispanic women with PTB for 3 PGR SNP and found an association between PGR genotype and PTB in 2 of these SNP but only for women with a BMI <18.5 kg/m^2. However, in 2007, Ehn et al[27] conducted a study of the PGR gene with several notable results. These authors examined 18 SNPs in 415 maternal-fetal infant pairs, and found a relationship between prematurity and SNP rs503362 ($P = .008$). Similarly, our results support a relationship among SNP rs503362,

TABLE 6
Preterm birth, progesterone treatment, and progesterone receptor genotype

Group	SNP	Model	Genotype	aOR (95% CI) placebo	aOR (95% CI) 17-OHPC
African Americans <37 wk' gestation	Rs471767	Dominant	AA	1.0 (ref)	0.22 (0.09–0.51)
			AG or GG	0.51 (0.19–1.37)	0.47 (0.20–1.06)
	Rs578029	Recessive	TT or TA	1.0 (ref)	0.33 (0.17–0.62)
			AA	0.28 (0.05–1.53)	0.91 (0.27–3.06)
Caucasian/Hispanics <37 wk' gestation	Rs500760	Codominant	TT	1.0 (ref)	0.13 (0.04–0.39)
			CT	0.30 (0.07–1.20)	0.25 (0.08–0.85)
			CC	0.64 (0.05–8.76)	0.11 (0.02–0.75)
Caucasian/Hispanics <32 wk' gestation	Rs503362	Dominant	GG	1.0 (ref)	2.89 (0.54–15.6)
			CG or CC	2.02.42 (0.35–16.7)	0.28 (0.02–3.51)
	Rs666553	Additive	CC	1.0 (ref)	2.79 (0.54–14.29)
			CT	2.05.76 (0.98–34.0)	0.96 (0.08–11.06)
			TT	3.033.2 (0.95–1154)	0.33 (0.005–22.4)
	Rs578029	Additive	TT	1.0 (ref)	3.80 (0.64–22.71)
			AT	2.02.57 (0.49–13.3)	0.64 (0.08–5.21)
			AA	3.06.58 (0.24–177)	0.11 (0.004–3.11)

Results of logistic regression controlling for smoking status, number of prior spontaneous preterm births, number of preterm births, and prepregnancy body mass index are shown. For each group and marker, aOR for "best" inheritance model is displayed. Individuals receiving placebo and with predominant (wild type) genotype are ref.
aOR, adjusted odds ratios; *CI,* confidence interval; *ref,* reference group; *SNP,* single nucleotide polymorphism; *17-OHPC,* 17-alpha-hydroxyprogesterone caproate.

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response to 17-OHPC, and early prematurity (<32 weeks') among non-African American women. Ehn et al[27] also reported a relationship among SNPs rs653752 and rs4754732 and prematurity; we did not find an association between these polymorphisms and 17-OHPC response.

These study results should be interpreted with certain limitations in mind. This is a secondary analysis and the original study was not designed to detect differences in rates of PGR polymorphisms. We investigated only maternal genotypes; fetal DNA was not available. We did not correct for multiple comparisons, as this study was exploratory. Due to a smaller number of non-African Americans, we grouped Caucasian and Hispanic women for analysis, which may have biased our results. However, prior studies have shown a negligible risk of confounding due to admixture of Caucasian and Hispanic populations.[36] Our sample size was limited, particularly when studying recurrent PTB <32 weeks' gestation. Furthermore, we cannot infer the mechanism of variable responsiveness to 17-OHPC; plasma levels of progesterone or the metabolism of 17-OHPC may be altered by these polymorphisms in the PGR. Given the complexity of the PTB phenotype, it is likely that other genes also contribute to 17-OHPC responsiveness for the prevention of recurrent PTB.

There are several strengths to our study. Our study cohort consisted of a relatively large number of women with at least one prior spontaneous PTB. Furthermore, current practice recommendations would not support withholding 17-OHPC therapy in women with a history of ≥1 prior spontaneous PTB.[37] Thus, this prospectively collected data set is unique in that we are able to compare genotypes of women at high risk for spontaneous PTB who have received

TABLE 7
Preterm birth and progesterone receptor haplotypes

Group	Haplotype block	Haplotype	aOR (95% CI) placebo	aOR (95% CI) 17-OHPC
African Americans <37 wk' gestation	rs471767 rs578029	AT/GT	1.0 (ref)	0.30 (0.12–0.71)
		AA	1.18 (0.40–3.51)	0.24 (0.08–0.75)
		GA	0.58 (0.26–1.29)	0.50 (0.22–1.12)
Caucasian/Hispanics <32 wk' gestation	rs503362 rs666553	GC	1.0 (ref)	13.98 (1.27–153.32)
		GT/CC/CT	2.04.37 (0.94–20.36)	1.53 (0.11–21.67)
	rs578029 rs666553	TC	1.0 (ref)	16.19 (1.27–206.77)
		AC/AT/TT	2.05.35 (0.95–30.04)	2.67 (0.19–38.15)

OR adjusted for body mass index, smoking, and number of prior preterm births.
aOR, adjusted odds ratios; *ref,* reference group; *17-OHPC,* 17-alpha-hydroxyprogesterone caproate.
Insufficient observations for rs503362/rs578029 in the analysis of Caucasian/Hispanics <32 wk' gestation.

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17-OHPC vs those who have received placebo.

PTB is a complex phenotype with few proven interventions. Intramuscular treatment with 17-OHPC is one therapy proven to decrease rates of recurrent PTB. This study provides important initial information regarding probability of success with 17-OHPC treatment. We have demonstrated that an individual's response to 17-OHPC may be altered by their PGR genotype, the first step toward identifying the subset of women who are the optimal candidates for 17-OHPC therapy, or those who should not receive this treatment due to safety concerns. If response to 17-OHPC therapy can be correlated with PGR genotype, this may provide a means to identify patients who should receive different doses or formulations of progestin, or who should be the focus of other types of PTB interventions. This work can be used to conduct further studies, including investigating other potential candidate genes that may lead to the creation of a 17-OHPC response panel, enabling clinicians to direct 17-OHPC therapy at those women most likely to benefit. ■

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