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

Tracy A. Manuck, M.D., Yinglei Lai, Ph.D., Paul J. Meis, M.D., Mitchell P. Dombrowski, M.D., Baha Sibai, M.D., Catherine Y. Spong, M.D., Dwight J. Rouse, M.D., Celeste P. Durnwald,

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Corresponding author & Reprints: Tracy A. Manuck, MD, 30 North 1900 East, Rm. 2B200, Salt Lake City, Utah 84132 (801) 581-7260 (office) / (801) 585-2594 (fax), tracy.manuck@hsc.utah.edu.

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Condensation: Clinical response to 17 alpha-hydroxyprogesterone caproate for prevention of recurrent prematurity may be altered by polymorphisms in the progesterone receptor gene.

In addition to the authors, other members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

University of Utah — M. Varner (University of Utah Health Sciences Center), E. Taggart (University of Utah Health Sciences Center), M. Belfort (Intermountain Healthcare)

University of Alabama at Birmingham — A. Northen, J. Hauth

Brown University — M. Carpenter, H. Silver, J. Tillinghast

Case Western Reserve University-MetroHealth Medical Center — P. Catalano, C. Milluzzi

University of Chicago — A.H. Moawad, P. Jones, M. Lindheimer

University of Cincinnati — M. Miodovnik, N. Elder, T. Siddiqi

Columbia University — M. D'Alton, V. Pemberton

University of Pittsburgh — M. Cotroneo, K. Lain

University of Miami — M.J. O'Sullivan, C. Alfonso, S. Beydoun

University of North Carolina, Chapel Hill — J.M. Thorp, K. Dorman, K. Moise

Northwestern University — A.M. Peaceman, G. Mallet, M. Socol

The Ohio State University — F. Johnson, M. Landon

University of Tennessee — R. Ramsey

University of Texas at San Antonio — D. Conway, O. Langer, S. Nicholson

The University of Texas Health Science Center at Houston — M. C. Day, L. Gilstrap

University of Texas Southwestern Medical Center — K.J. Leveno, J. Gold, G. Wendel

Drexel University — M. DiVito, J. Tolosa

Wake Forest University Health Sciences — E. Mueller-Heubach, M. Swain

Wayne State University — G. Norman, Y. Sorokin

The George Washington University Biostatistics Center — A. Das, E. Thom, L. Leuchtenburg

Eunice Kennedy Shriver National Institute of Child Health and Human Development — M. Klebanoff, D. McNellis, S. Tolivaisa

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M.D., Steve N. Caritis, M.D., Ronald J. Wapner, M.D., Brian M. Mercer, M.D., and Susan M. Ramin, M.D.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (Bethesda, MD). Authors are also affiliated with individual institutions as follows: The University of Utah, Salt Lake City, UT (T.A.M.); The George Washington University Biostatistics Center, Washington, DC (Y.L.); Wake Forest University Health Sciences, Winston-Salem, NC (P.J.M.); Wayne State University, Detroit, MI (M.P.D.); The University of Tennessee, Memphis, TN (B.S.); The National Institute of Child Health and Human Development, Bethesda, MD (C.Y.S.); The University of Alabama, Birmingham, AL (D.J.R.); The Ohio State University, Columbus, OH (C.P.D.); University of Pittsburgh, Pittsburgh, PA (S.N.C.); Thomas Jefferson University, Philadelphia, PA (R.J.W.); Case Western Reserve University, Cleveland, OH (B.M.M.); The University of Texas, Houston, TX (S.M.R)

Abstract

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

Study design—Secondary analysis of a study of 17-OHPC vs. placebo for recurrent PTB prevention. 20 PGR gene SNPs were studied. Multivariable logistic regression was used to assess for an interaction between PGR genotype and treatment status in modulating the risk of recurrent PTB.

Results—380 women were included; 253 (66.6%) received 17-OHPC and 127 (33.4%) received placebo. The majority (61.1%) of women were African-American. Multivariable logistic regression analysis demonstrated significant treatment-genotype interactions for African-Americans delivering <37 weeks' for rs471767 and rs578029, and for Hispanics/Caucasians delivering <37 weeks' for rs500760 and <32 weeks' for rs578029, rs503362, and rs666553.

Conclusion—The clinical efficacy of 17-OHPC for prevention of recurrent PTB may be altered by PGR gene polymorphisms.

Keywords/phrases

17-alpha hydroxyprogesterone caproate; genetic polymorphisms; progesterone receptor; recurrent preterm birth

Introduction

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. 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.¹² 17-OHPC appears to be 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 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 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}

Progesterone receptor 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 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 preterm birth. 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 progesterone receptor 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 to 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 (NICHD) Maternal-Fetal Medicine Units (MFMU) 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<0.001).

Institutional Review Board (IRB) 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 determined to be exempt from IRB approval procedures secondary to de-identification of data and study samples prior to this analysis. As a part of the original trial protocol, maternal saliva 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, Foster City, CA) was used to automatically determine sample genotypes (“auto-caller”) 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 ID 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 ID 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 progesterone 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. Potential confounders (factors known to be associated with PTB), including pre-pregnancy body mass index (BMI), smoking status, and number of prior preterm deliveries, were controlled for in adjusted models.

Additive, co-dominant, dominant, and recessive inheritance models were considered. The additive model assumes that having two copies of minor allele has twice the effect of having one copy, the co-dominant model assumes that heterozygotes have an increased risk of disease over both homozygote groups, the dominant model assumes that having at least one copy of the minor allele is sufficient for disease, and the recessive model assumes that two copies of the minor allele are needed for disease. The treatment-genotype interaction was considered significant at $p < 0.05$. 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.

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. to calculate FDRs for these identified SNPs.³³ 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 1). Two-hundred-thirty-two (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 one or more documented spontaneous PTB. Maternal age, racial distribution, treatment assignment, number of prior spontaneous PTB, tobacco usage, and pre-pregnancy 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' (39.2% vs. 42.4%, $p=0.002$) and <32 weeks' gestation (12.4% vs. 14.4%, $p=0.004$) 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 >0.01). 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 2a-2d). This includes 2 SNPs identified in African-Americans (rs471767 and rs578029); both were associated with PTB < 37.0 weeks' gestation. 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 odds ratios of recurrent PTB. These odds ratios 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 3). 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% CI 0.09-0.51). In contrast, African-American women with at least one 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 17OHPC). This interaction between the rs471767 genotype and treatment was significant even when controlling for body mass index, smoking history, and number of prior PTB ($p=0.023$).

Results from the limited haplotype analysis as described in the methods section are shown in Table 4. 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 4). The odds of PTB among those with the 'GA' haplotype was seemingly unaffected by treatment [placebo aOR 0.56 (0.25-1.24), 17-OHPC aOR 0.43 (0.19-0.95)].

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 false discovery rate applies to all of the reported significant findings, not to individual SNPs.^{31, 32}

Comment

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

The rs471767 SNP is located just upstream (5') of the progesterone receptor 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 preterm birth in a group of Hispanic and Caucasian patients in Utah, although information regarding supplemental progesterone use

was not available for those women, and an interaction between progesterone 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 17OHPC (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 4). These patterns follow those noted for the individual SNP analysis.

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 one 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 between progesterone administration, PGR genotype, and PTB. Diaz-Cueto, et al. studied 4 PGR polymorphisms in 64 preterm patients and 54 controls and concluded that polymorphisms in the PGR gene are unlikely to be associated with PTB in a Hispanic population.³⁵ Gouyang and colleagues 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 body mass index <18.5 kg/m².¹⁷ However, in 2007, Ehn, et al. 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=0.008).²⁷ Similarly, our results support a relationship between SNP rs503362, response to 17-OHPC, and early prematurity (<32 weeks') among non-African-American women. Ehn, et al. also reported a relationship between 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 progesterone receptor 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 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 SPTB. Furthermore, current practice

recommendations would not support withholding progesterone therapy in women with a history of one or more prior spontaneous PTB.³⁷ Thus, this prospectively collected dataset is unique in that we are able to compare genotypes of women at high risk for spontaneous PTB who have received 17-OHPC vs. those who have received placebo.

Preterm birth 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 progesterone receptor genotype, the first step towards identifying the subset of women who are the optimal candidates for 17-OHPC therapy. 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 progesterone, or who should be the focus of other types of preterm birth interventions. This work can be used to conduct further studies, including investigating other potential candidate genes which 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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Figure 1. Study enrollment

17P = 17-alpha hydroxyprogesterone caproate

AA = African-American

C/H = Caucasian or Hispanic

Table 1

Single nucleotide polymorphisms (SNPs) 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	

Abbreviations: SNP = single nucleotide polymorphism, UTR = untranslated region; PGR=progesterone receptor

Table 2a-2d

Logistic regression results. P-values are displayed for the interaction between treatment (progesterone) and genotype for each of the 4 inheritance models, and are adjusted for body mass index, smoking, and number of prior preterm births.

2a. Results for African-American patients with preterm birth <37.0 weeks' gestation.				
SNP	Additive	Co-dominant	Dominant	Recessive
rs471767	0.02 *	0.06, 0.06	0.02 *	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 *	0.51	0.03 *
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

2b. Results for African-American patients with preterm birth <32.0 weeks' gestation.				
SNP	Additive	Co-dominant	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

2b. Results for African-American patients with preterm birth <32.0 weeks' gestation.				
SNP	Additive	Co-dominant	Dominant	Recessive
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

2c. Results for Caucasian/Hispanic patients with preterm birth <37.0 weeks' gestation.				
SNP	Additive	Co-dominant	Dominant	Recessive
rs471767	0.85	0.85, 0.66	0.94	0.6
rs500760	0.15	0.03 [*] , 0.84	0.04 [*]	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

2d. Results for Caucasian/Hispanic patients with preterm birth <32.0 weeks' gestation.				
SNP	Additive	Co-dominant	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 [*]	0.1, 0.99	0.05	0.99
rs1042838	0.99	0.99, NA	0.99	NA

2d. Results for Caucasian/Hispanic patients with preterm birth <32.0 weeks' gestation.				
SNP	Additive	Co-dominant	Dominant	Recessive
rs666553	0.04 *	0.11, 0.99	0.05	0.99
rs653752	0.98	0.2, 0.99	0.34	0.99
rs503362	0.05	0.03 *, 1	0.03 *	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<0.05*
p<0.05*
p<0.05*
p<0.05

Table 3

Adjusted odds ratios (aOR) and 95% confidence intervals for preterm birth as a function of progesterone receptor genotype and progesterone treatment. Results of logistic regression controlling for smoking status, number of prior spontaneous PTB, number of preterm births, and pre-pregnancy BMI are shown. For each group and marker, the aOR for the “best” inheritance model is displayed. Individuals receiving placebo and with the predominant (wild type) genotype are the reference group (Ref).

Group	SNP	Model	Genotype	aOR – placebo	aOR – 17OHPC
African-Americans <37 weeks' 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 weeks' gestation	Rs500760	Co-dominant	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)
	Rs503362	Dominant	GG	1.0 (ref)	2.89 (0.54-15.6)
Caucasian/Hispanics <32 weeks' gestation	Rs666553	Additive	CG or CC	2.42 (0.35-16.7)	0.28 (0.02-3.51)
			CC	1.0 (ref)	2.79 (0.54-14.29)
			CT	5.76 (0.98-34.0)	0.96 (0.83-11.06)
	Rs578029	Additive	TT	33.2 (0.95-1154)	0.33 (0.005-22.4)
			TT	1.0 (ref)	3.80 (0.64-22.71)
			AT	2.57 (0.49-13.3)	0.64 (0.79-5.21)
			AA	6.58 (0.24-177)	0.11 (0.004-3.11)

Table 4

Adjusted odds ratios (95% confidence intervals) of preterm birth based on haplotypes, adjusting for body mass index, smoking, and number of prior preterm births.

Group	Haplotype Block	Haplotype	aOR – placebo	aOR – 17-OHPC
African-Americans <37 weeks' 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 weeks' gestation	Rs503362 rs666553	GC	1.0 (ref)	13.98 (1.27-153.32)
		GT/CC/CT	4.37 (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	5.35 (0.95-30.04)	2.67 (0.19-38.15)

* Insufficient observations for rs503362/rs578029 in the analysis of Caucasian/Hispanics <32 weeks' gestation.