Does Progesterone Treatment Influence Risk Factors for Recurrent Preterm Delivery?

*Paul J. Meis, MD, Mark Klebanoff, MD, Mitchell P. Dombrowski, MD, Baha M. Sibai, MD, Sharon Leindecker, MS, MBA, Atef H. Moawad, MD, Allison Northen, RN, Jay D. Iams, MD, Michael W. Varner, MD, Steve N. Caritis, MD, Mary J. O'Sullivan, MD, Menachem Miodovnik, MD, Kenneth J. Leveno, MD, Deborah Conway, MD, Ronald J. Wapner, MD, Marshall Carpenter, MD, Brian Mercer, MD, Susan M. Ramin, MD, John M. Thorp, MD, Alan M. Peaceman, MD, Steven Gabbe, MD, for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network**

Objective: To examine how demographic and pregnancy characteristics can affect the risk of recurrent preterm delivery and the how the effectiveness of progesterone treatment for prevention alters these relationships.

Methods: This was a secondary analysis of a randomized trial of 17α-hydroxyprogesterone caproate to prevent recurrent preterm delivery in women at risk. Associations of risk factors for preterm delivery (less than 37 completed weeks of gestation) were examined separately for the women in the 17α-hydroxyprogesterone caproate (n = 310) and placebo (n = 153) groups.

Results: Univariate analysis found that the number of previous preterm deliveries and whether the penultimate delivery was preterm were significant risk factors for preterm delivery in both the placebo and progesterone groups. High body mass index was protective of preterm birth in the placebo group. Multivariate analysis found progesterone treatment to cancel the risk of more than 1 previous preterm delivery, but not the risk associated with the penultimate pregnancy delivered preterm. Obesity was associated with lower risk for preterm delivery in the placebo group but not in the women treated with progesterone.

Conclusion: The use of 17α-hydroxyprogesterone caproate in women with a previous preterm delivery reduces the overall risk of preterm delivery and changes the epidemiology of risk factors for recurrent preterm delivery. In particular, these data suggest that 17α-hydroxyprogesterone caproate reduces the risk of a history of more than 1 preterm delivery.

(Obstet Gynecol 2005;106:557–561)

Level of Evidence: I

Approximately 10% of all pregnancies in the United States end in preterm birth, and this 10% accounts for approximately 70% of the perinatal deaths and one half of long-term neurologic morbidity.[1] Furthermore, the rates of preterm birth have been increasing in the United States in the past decades.[2] Preterm birth is thought to have many different causes. Attempts to elucidate these causes by examining the epidemiology of preterm birth have

**For a list of other members of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, see the Appendix.*

From the National Institute of Child Health and Human Development, Rockville, Maryland; Biostatistics Center, George Washington University, Rockville, Maryland; Division of Maternal-Fetal Medicine, University of Alabama, Birmingham, Alabama; and Departments of Obstetrics and Gynecology, Division of Maternal–Fetal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; Wayne State University, Detroit, Michigan; University of Tennessee, Memphis, Tennessee; University of Chicago, Chicago, Illinois; Ohio State University. Columbus, Ohio; University of Utah, Salt Lake City, Utah; University of Pittsburgh, Pittsburgh, Pennsylvania; University of Miami, Miami, Florida; University of Cincinnati, Cincinnati, Ohio; University of Texas Southwest, Dallas, Texas; University of Texas at San Antonio, San Antonio, Texas; Drexel University, Philadelphia, Pennsylvania; Brown University, Providence, Rhode Island; Case Western Reserve University, Cleveland, Ohio; University of Texas, Houston, Texas; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Northwestern University, Chicago, Illinois; and Vanderbilt University, Nashville, Tennessee.

Supported by grants from the National Institute of Child Health and Human Development (HD27860, HD36801, HD27917, HD21414, HD27861, HD27869, HD27905, HD34208, HD34116, HD21410, HD27915, HD34136, HD34210, HD34122, HD40500, HD40560, HD40512, HD34210, HD40544, MO1-RR-000080).

Corresponding author: Paul J. Meis, MD, Department of Obstetrics and Gynecology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; e-mail: pmeis@wfubmc.edu.

ISSN: 0029-7844/05

identified the association of many risk factors with preterm birth, including information about problems in previous pregnancies, demographic characteristics, and characteristics of the current pregnancy.[3,4,5]

Of these various risk factors, 1 of the most consistent and powerful is the history of a previous preterm delivery. The importance of this risk factor has been documented by many studies of various populations of pregnant women.[6–10] Recently, the results of 2 randomized trials of treatment using 17α-hydroxyprogesterone caproate injections or progesterone suppositories, respectively, have reported efficacy in reducing the rate of recurrent preterm delivery in women with this risk factor. These results have led to increased interest in women with this particular risk characteristic.[11,12] However, few studies have assessed whether risk factors in addition to a previous preterm delivery retain a significant association with preterm birth, and no studies have evaluated the potential of progesterone treatment to alter risk associations in pregnant women with a previous preterm delivery. To examine these questions, we performed this secondary analysis of data from a randomized trial of 17α-hydroxyprogesterone caproate to prevent recurrent preterm delivery.

PATIENTS AND METHODS

A total of 463 women with at least 1 previous spontaneous preterm delivery were enrolled into a randomized trial of 17α-hydroxyprogesterone caproate, using a 2 to 1 randomization, to prevent recurrent preterm birth. Of these, 310 women were treated with the active drug and 153 with placebo injections. The results of this trial showed a reduction in the rate of recurrent preterm delivery from 54.9% in the placebo group to 36.3% in the treatment group. The treatment was equally effective in both the African-American and non–African-American women enrolled.[11]

In this article, we evaluated demographic and pregnancy characteristics of the study women in the treatment and placebo groups of women separately for their association with preterm delivery in the index (study) pregnancy. The study was approved by the institutional review boards at Wake Forest University School of Medicine and at George Washington University, the site of our biostatistical center for the Maternal-Fetal Medicine Units Network. Variables examined for associations with preterm delivery in this cohort were age, race, parity, pregravid body mass index (BMI), education, tobacco and alcohol use, number of previous preterm deliveries, number of abortions or miscarriages, number of previous deliveries, time since preterm delivery, previous term delivery, and status (term or preterm) of the last delivery.

Within each group (17α-hydroxyprogesterone caproate and placebo) categorical variables were compared with the χ^2 test and continuous variables with the Wilcoxon rank-sum test. Next, we determined whether the association between each characteristic and preterm birth differed between women in the progesterone and placebo groups. We did this using a logistic regression model that included terms for the characteristic, treatment, and an interaction between the characteristic and treatment. A significant interaction term means that the association between the characteristic and preterm birth differed significantly between women assigned to progesterone or placebo, ie, that progesterone modified the epidemiology of preterm birth.

A significant interaction was found between progesterone treatment and 1 risk factor, pregravid BMI. As a result, multiple regression models were run for the progesterone and placebo groups of women. These separate regression models included variables associated with preterm delivery on univariate analysis at the $P = .15$ level of significance, including more than 1 previous preterm delivery, last delivery term or preterm, pregravid BMI, and tobacco use. Previous term delivery, time since last preterm delivery, and the outcome of the last delivery were correlated; therefore, only outcome of the last delivery term or preterm was included in the final model. Nominal 2-tailed P values are reported. SAS 8 software (SAS Institute, Inc., Cary, NC) was used for the analysis.

RESULTS

In this cohort of women, who were at high risk for preterm delivery because of a history of a previous spontaneous preterm birth, most historical and demographic risk factors did not have an association with preterm delivery in either the 17α-hydroxyprogesterone caproate or placebo groups (Tables 1 and 2). Among women who received progesterone, the only factors significantly associated with preterm delivery were having had more than 1 previous preterm delivery, shorter time since last preterm delivery, and the penultimate delivery having been preterm.

In the women who did not receive the active drug, the factors that demonstrated an increase in risk for preterm delivery were more than 1 previous preterm delivery, shorter time since last preterm delivery, penultimate delivery preterm, and lower pregravid BMI.

Examination of interactions and treatment found a highly significant association with pregravid BMI and 17α-hydroxyprogesterone caproate treatment, $P < .001$. When variables associated with preterm birth on univariate analysis ($P < .15$) were examined using logistic regression analysis, the associations of

Table 1. Preterm Delivery in the Current Pregnancy Based on Historical Risk Factors, Examined Separately Among Women Receiving Progesterone or Placebo

	Progesterone Group (N = 310)		Placebo Group (N = 153)	
Risk Factors	**Preterm**	***P***	**Preterm**	***P***
No. of previous preterm deliveries				
1	31.8	.01	44.4	.002
> 1	47.7		69.8	
Previous abortions or miscarriages				
0	35.2	.272	52.3	.8
1	38.0		60.5	
2	26.7		60.0	
≥ 3	52.2		50.0	
Previous term delivery				
Yes	30.9	.053	49.3	.195
No	41.6		59.8	
Outcome of penultimate pregnancy				
Term	19.4	.003	30.4	.007
Preterm	40.5		61.5	
No. of previous term and preterm deliveries				
Preterm, index pregnancy	2.2 (1.2)	.684	2.4 (1.2)	.214
Term	2.3 (1.3)		2.3 (1.5)	
Time since last preterm delivery (y)				
Preterm, index pregnancy	4.0 (3.1)	.003	3.8 (3.2)	< .001
Term	5.0 (3.6)	.003	5.6 (3.7)	

Values are percentage or mean (standard deviation).

these risk factors with preterm birth were altered, as shown in the final models in Tables 3 and 4. The associations of pregravid BMI with preterm delivery differ strikingly between the 2 study groups. In the placebo group, high pregravid BMI had a highly significant negative (protective) association with preterm delivery, and low pregravid BMI was in the direction of a positive association of increased risk, (odds ratio 3.9, $P = .098$). In the 17α-hydroxyprogesterone caproate group, neither low nor high pregravid BMI was associated with an altered risk of preterm delivery.

We found an association between preterm delivery in the pregnancy immediately preceding the current gestation ("penultimate pregnancy") and preterm delivery in the current pregnancy. A preterm delivery in the penultimate pregnancy was significantly associated with preterm delivery in the 17α-hydroxyprogesterone caproate group ($P = .005$), and in the placebo group ($P = .043$). Tobacco use was not found to be associated with preterm delivery in either multivariate model. More than 1 preterm delivery retains a strong association in the placebo group, with odds ratio of 3.38 ($P = .009$), but no significant association in the 17α-hydroxyprogesterone caproate group ($P = .153$)

DISCUSSION

This analysis provides useful information to clinicians. Women recruited to the trial and randomly assigned to placebo were at high risk for preterm delivery due to their history of a previous spontaneous preterm delivery. This risk was modified by several maternal characteristics. It was greatly increased if they had had more than 1 preterm delivery, was increased if the last delivery was preterm, and was decreased if the woman's pregravid body mass index was high (obese).

Treatment with 17α-hydroxyprogesterone caproate not only decreased the overall risk of preterm delivery, but the increased risk of preterm birth related to a history of more than 1 previous preterm delivery was no longer apparent with progesterone treatment. A significantly increased risk for preterm delivery remained in this group of treated subjects if the penultimate pregnancy was delivered preterm.

Some of the results of this study should be interpreted with caution, because the analysis lacked the power to evaluate the significance of some of these associations. This is particularly true for the placebo group of patients. For example, low BMI had a high odds ratio for preterm delivery in the placebo group, but there were too few subjects (20) with this characteristic to reach statistical significance. Likewise, evaluation of characteristics such as race and age may have been limited by the sample size.

This study confirms that the presence of several factors add significant increased risk for recurrent preterm delivery in women with a history of a previous preterm delivery. Previous investigators have

Table 2. Preterm Delivery in the Current Pregnancy Based on Demographic Characteristics, Examined Separately Among Women Receiving Progesterone or Placebo

	Progesterone Group (N = 310)		Placebo Group (N = 153)	
Risk Factors	Preterm	*P*	Preterm	*P*
Maternal age (y)				
< 18	33.3	.967	62.5	.917
19–36	36.4		54.7	
>36	37.5		50.0	
Parity				
≥ 2	34.8	.449	59.1	.128
1	39.2		45.8	
Maternal race				
African American	35.4	.689	52.2	.426
Non–African American	37.6		58.7	
Pregravid body mass index				
< 20	37.5	.883	80.0	< .001
20–29	34.8		62.0	
> 29	37.6		24.3	
Maternal education (y)				
≤ 12	35.9	.811	53.4	.592
> 12	37.4		58.0	
Tobacco use				
Yes	32.9	.498	70.0	.064
No	37.3		51.2	
Alcohol use				
Yes	33.3	.739	50.0	.755
No	36.6		55.2	

Values are percentages.

Table 3. Logistic Regression Analysis of Risk Factors for Preterm Birth in Women Treated With 17α-Hydroxyprogesterone Caproate

Risk Factors	Odds Ratio	95% Confidence Interval	*P*
> 1 previous preterm	1.54	0.85–2.79	.153
Last delivery preterm	2.81	1.36–5.82	.005
Body mass index < 20	1.29	0.58–2.88	.535
Body mass index > 29	1.75	0.94–3.24	.077
Tobacco use	0.72	0.35–1.45	.354

reported a high rate of recurrent preterm delivery, with rates of preterm delivery from 15% to 62%, depending on the population studied and on the number of prior preterm deliveries. In the population of women entered into this trial, the rate of preterm delivery at less than 35 weeks of gestation was very similar to the report of Owen et al[13] of a group of

Table 4. Logistic Regression Analysis of Risk Factors for Preterm Birth in Women Treated With Placebo

Risk Factors	Odds Ratio	95% Confidence Interval	*P*
> 1 previous preterm	3.38	1.36–8.40	.009
Last delivery preterm	3.07	1.03–9.13	.043
Body mass index < 20	3.92	0.78–19.79	.098
Body mass index > 29	0.14	0.05–0.38	< .001
Tobacco use	1.48	0.49–4.54	.49

women with a prior preterm delivery in the Maternal-Fetal Medicine Units Network.

Previous investigators have identified several risk factors for recurrent preterm delivery. Adams found that African-American women had higher rates of recurrent preterm birth than white women, and that additional significant risk factors were young age and short interpregnancy interval.[7] Other investigators have not found that race modifies the risk for recurrent preterm delivery. Race may not have indicated a significant risk for recurrent preterm delivery for several reasons. The majority of our subjects were African American, the sample size was relatively small, and a previous preterm delivery may have produced a greater increase in risk for recurrent preterm delivery for white women.

Several investigators have examined risk factors for recurrent preterm birth in the Maternal-Fetal Medicine Units Network Preterm Prediction Study. Mercer et al[3] identified low BMI, high Bishop score, and history of vaginal bleeding as significant risk factors, whereas Iams et al[8] found that both a short cervix, measured by transvaginal ultrasound, and a positive fetal fibronectin test significantly predicted recurrent preterm delivery. Information from these last tests was not available in the current study.

The modification of the associations between body mass index and preterm delivery by progesterone treatment is striking. Women with a high BMI had a lower risk of recurrent preterm delivery; however, this protective effect of obesity was not found in the 17α-hydroxyprogesterone caproate–treated women. These results may represent a dilutional effect of the dose used in larger women. A recent report by Holt et al[14] found that oral contraceptives were less effective in preventing pregnancy in obese women. The results may also be attributed to impaired absorption of drugs administered by injection to obese individuals.

A computer search was performed of PubMed using the terms "preterm birth" and "progesterone," yielding 150 published papers from 1965 to the

present. This study is the first to examine how treatment with progesterone influences the effect of other risk factors for recurrent preterm delivery. The modification of risk factors by progesterone treatment may provide insight into the mechanisms of action of progesterone to prevent preterm birth. It is likely that preterm birth has multiple possible causes. Perhaps recurrent preterm deliveries are related to a problem for which progesterone treatment is particularly efficacious. This analysis also provides reassuring information for women with more than 1 previous preterm delivery. Our findings suggest that progesterone treatment remains effective in the prevention of preterm delivery in this population at very high risk for recurrent preterm delivery.

REFERENCES

1. McCormick MC. The contribution of low birth weight to infant mortality and childhood mortality. N Engl J Med 1985;312:82–90.
2. Mattison DR, Damus K, Fiore E, Petrini J, Alter C. Preterm delivery: a public health perspective. Paediatr Perinat Epidemiol 2001;15 suppl 2:7–16
3. Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ. The preterm prediction study: A clinical risk assessment system. Am J Obstet Gynecol 1996;174:1885–95.
4. Michielutte R, Ernest JM, Moore ML, Meis PJ, Sharp PC, Wells HB, et al. A comparison of risk assessment models for term and preterm low birthweight. Prev Med 1992;21:98–109.
5. Meis PJ, Michielutte R, Peters TJ, Wells HB, Sands RE, Coles EC, et al. Factors associated with preterm birth in Cardiff, Wales. I. Univariable and multivariable analysis. Am J Obstet Gynecol 1995;173:590–6.
6. Bakewell JM, Stockbauer JW, and Schramm WF. Factors associated with repetition of low birthweight: Missouri longitudinal study. Paediatr Perinat Epidemiol 1997;11:suppl 1:119–29
7. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283:1591–6.
8. Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, et al. The preterm prediction study: Recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1998;178:1035–40.
9. Carr-Hill RA, Hall MA. The repetition of spontaneous preterm labour. Br J Obstet Gynecol 1985;92:921–8.
10. Keirse MJ, Rush RW, Anderson AB, Turnbull AC. Risk of pre-term delivery in patients with previous pre-term delivery and/or abortion. Br J Obstet Gynecol 1978;85:81–5.
11. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17alpha-hydroxyprogesterone caproate [published erratum appears in N Engl J Med 2003;349:1299]. N Engl J Med 2003;348:2379–85.
12. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419–24.
13. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA 3rd, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA 2001;286:1340–48.
14. Holt VL, Scholes D, Wickland KG, Cushing-Haugen KL, Daling JR. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol 2005;105:46–52.

APPENDIX

Other members of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows: University of Alabama-Birmingham: J. Hauth, D. Rouse; Brown University: H. Silver, J. Tillinghast; Case Western Reserve University: P. Catalano, C. Milluzzi; University of Chicago: P. Jones, M. Lindheimer; University of Cincinnati; N. Elder, T. Siddiqi; Columbia University: M. D'Alton, V. Pemberton; George Washington University Biostatistics Center: E. Thom A. Das; University of Pittsburgh: M. Cotroneo, K. Lain; University of Miami: C. Alfonso, S. Beydoun; National Institute of Child Health and Human Development: C. Spong, D. McNellis, S. Pagliaro; University of North Carolina at Chapel Hill: K. Dorman, K. Moise; Northwestern University: G. Mallet, M. Socol; Ohio State University: F. Johnson, M. Landon; University of Tennessee: R. Ramsey; University of Texas at San Antonio: O. Langer, S. Nicholson; University of Texas at Houston: M. C. Day, L. Gilstrap; University of Texas Southwestern Medical Center: J. McCampbell, G. Wendel; Drexel University: M. DiVito, J. Tolosa; University of Utah: M. Belfort, E. Taggart; Wake Forest University: E. Mueller-Heubach, M. Swain; Wayne State University: G. Norman, Y. Sorokin.