Estimated Effect of 17 Alpha-Hydroxyprogesterone Caproate on Preterm Birth in the United States

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OBJECTIVE: A multicenter, randomized placebo-controlled trial among women with singleton pregnancies and a history of spontaneous preterm birth found that weekly injections of 17 alpha-hydroxyprogesterone caproate (17P), initiated between 16 and 20 weeks of gestation, reduced preterm birth by 33%. The current study estimated both preterm birth recurrence and the potential reduction in the national preterm birth rate.

METHODS: Using 2002 national birth certificate data, augmented by vital statistics from 2 states, we estimated the number of singleton births delivered to women eligible for 17P through both a history of spontaneous preterm birth and prenatal care onset within the first 4 months of pregnancy. The number and rate of recurrent spontaneous preterm births were estimated. To predict effect, the reported 33% reduction in spontaneous preterm birth attributed to 17P therapy was applied to these estimates.

RESULTS: In 2002, approximately 30,000 recurrent preterm births occurred to women eligible for 17P, having had a recurrent preterm birth rate of 22.5%. If 17P therapy were delivered to these women, nearly 10,000 spontaneous preterm births would have been prevented, thereby reducing the overall United States preterm birth rate by approximately 2%, from 12.1% to 11.8% ($P < .001$), with higher reductions in targeted groups of eligible pregnant women.

CONCLUSION: Use of 17P could reduce preterm birth among eligible women, but would likely have a modest effect on the national preterm birth rate. Additional research is urgently needed to identify other populations who might benefit from 17P, evaluate new methods for early detection of women at risk, and develop additional prevention strategies. (Obstet Gynecol 2005;105:267–72. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: III

Preterm birth (< 37 weeks of gestation) affects more than 480,000 or 12% of live births in the United States, and is a leading cause of infant mortality and long-term disability.[1] Between 1982 and 2002, the national preterm birth rate increased 27%,[1] and in the past decade almost all states have experienced increases in preterm birth (www.marchofdimes.com/peristats). A history of a spontaneous preterm birth is one of the strongest risk factors for preterm birth in a subsequent pregnancy.[2] Decades of research have not to date yielded broadly effective interventions to prevent preterm birth. A multicenter, randomized controlled trial conducted by the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network, demonstrated a significant 33% reduction in preterm birth with weekly injections of 17 alpha-hydroxyprogesterone caproate (17P) among women with a history of prior spontaneous preterm birth.[3] Reductions in preterm birth among women of diverse geographic and racial or ethnic backgrounds generate new optimism among all concerned with the tenacious problem of preterm birth (Iams JD. Supplemental progesterone to prevent preterm birth [editorial]. Am J Obstet Gynecol 2003;188:303). A separate, randomized clinical trial of high-risk women in Brazil given daily vaginal progesterone further support the Maternal-Fetal Medicine Units Network results.[4]

Responding to the Maternal-Fetal Medicine Units Network findings, the American College of Obstetricians and Gynecologists issued a Committee Opinion in November, 2003, "Use of Progesterone to Prevent Preterm Birth," in support of the use of 17P among women with a history of a prior spontaneous preterm birth.[5] How-

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ever, the full promise of progesterone in preventing recurrent preterm birth is not yet known. In particular, the Maternal-Fetal Medicine Units Network study was limited to high-risk eligible women who had a history of spontaneous preterm delivery, singleton gestation, and had initiated prenatal care by 16–20 weeks of gestation. To understand the potential national effect of 17P preventive therapy on preterm birth rates, we estimated the number of singleton preterm births delivered to women with a history of prior spontaneous preterm birth who accessed prenatal care within the first 4 months of gestation.

MATERIALS AND METHODS

This study defines "17P eligible" as singleton births to multiparous women with onset of prenatal care within the first 4 months of pregnancy, with a history of spontaneous preterm birth. Preterm birth is defined as less than 37 completed weeks of gestation and very preterm as less than 32 completed weeks. Spontaneous birth is defined as a noninduced vaginal delivery. To estimate the number of pregnant women in the United States who would be eligible for 17P preventive therapy, we analyzed the 2002 United States natality (birth certificate) file from the National Center for Health Statistics, Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/data/nvsr52/nvsr52_10.pdf). This database includes information on all live births in the nation. Studies have indicated, however, that reporting of a woman's history of a prior preterm birth on the birth certificate may not be complete and may underestimate the true occurrence of this event.[6] To address this potential limitation, we also analyzed data from longitudinal birth certificate files from New Jersey and Missouri and calculated rates of prior preterm birth and recurrence of spontaneous preterm birth. Longitudinal birth files link birth certificates for a range of years to an individual mother, thus serving as a valuable source of information on recurrent pregnancy outcomes such as preterm birth. These files are not available for all states or for the total United States. Nonetheless, New Jersey and Missouri data provided population-based estimates comparable to that of the general United States population. (See Appendix for details of state files and for state and United States profiles of preterm births). For all calculations used in this analysis, rates were similar for both states.

Based on the 2002 United States natality data, the number of births to multiparous women (defined in the file as births to women having at least 1 previous live birth), with singleton gestation was 2,313,718 (Fig. 1). From this number, the estimated number of births to women who did not meet the 16–20 week prenatal care entry period (as per the Maternal-Fetal Medicine Units Network study protocol) was subtracted. Because entry to prenatal care is reported in the natality files report by month instead of week, the numbers of births with onset of prenatal care after both 4 and 5 months were calculated. Finding no substantial effect on resulting estimates, the more conservative 4-month cutoff was used. Thus excluded were those births to women with initiation of prenatal care after the fourth month (8.9%), those who did not receive prenatal care (1.1%), and those with missing data on timing of entry into prenatal care (1.9%). The resultant 2,037,292 births represent those women who initiated care early enough to have been candidates for 17P therapy. We next estimated the number of women with a history of preterm birth, probability of recurrent spontaneous preterm birth, and potential effect of 17P in reducing the national preterm birth rate. To estimate the number of preterm infants born to women whose prior infants were at highest risk for morbidity and mortality, analyses were also performed for the subset of preterm births to women with a history of very preterm birth (< 32 weeks).

Using the New Jersey and Missouri databases, rates of prior preterm birth and prior very preterm birth were calculated using the same inclusion criteria, as identified by the natality file: multiparous women with singleton pregnancies who received care within the first 4 months of pregnancy. The averaged rates from the 2 states were 8.7% for prior preterm birth and 1.3% for prior very preterm birth. These rates were applied to the 2,037,392 women. This resulted in 177,244 previous preterm births and 26,485 previous very preterm births (Fig. 1). However, exclusive use of vital records might underestimate the proportion of all spontaneous preterm births, because birth certificates do not indicate whether the delivery of a preterm infant born by cesarean section started as spontaneous preterm labor or premature rupture of the membranes, or whether an induction of labor was prompted by spontaneous membrane rupture without labor. Therefore, these numbers were adjusted based on historical data and standard assumptions that indicate that approximately 75% of all preterm births are spontaneous.[7,8] Applying this adjustment, 132,933 women would have had a prior spontaneous preterm birth, including 19,864 women with a prior very preterm birth. Theoretically, all of these women would have been eligible for 17P therapy (Fig. 1).

RESULTS

Results of the New Jersey and Missouri longitudinal file analysis indicated that for 17P-eligible women who had a preterm birth (< 37 weeks), the chance of preterm birth recurrence averaged 22.5%. Further, for those with a

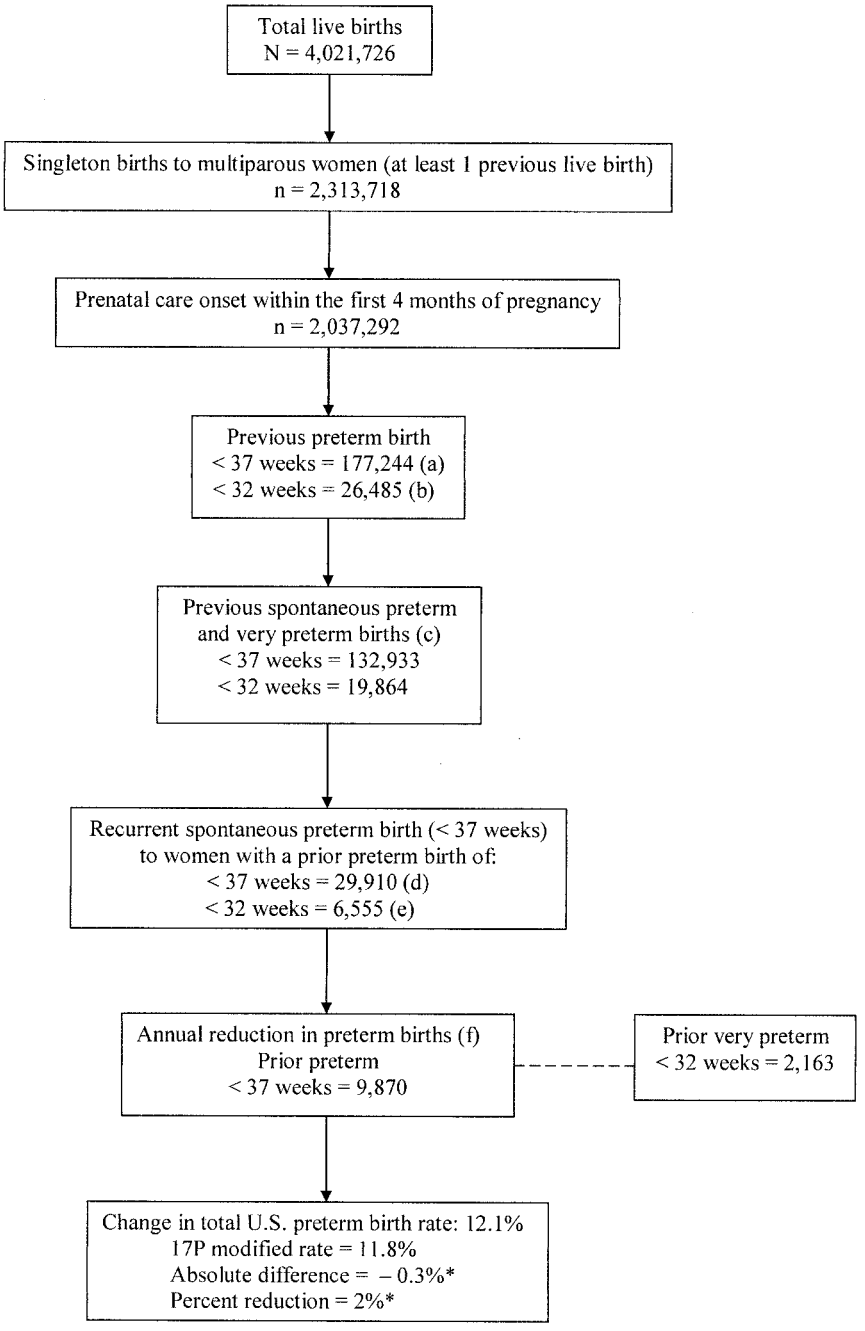

Fig. 1. Estimated preterm birth recurrence and potential effect of 17 alpha-hydroxyprogesterone caproate (17P) among singleton births to multiparous women with prenatal care onset within 4 months of gestation, United States 2002. Numbers were calculated from the following estimates: (a) 8.7%—estimated, averaged singleton preterm birth rate among multiparous women who received prenatal care within 4 months of gestation; (b) 1.3%—estimated, averaged singleton very preterm birth rate among multiparous women who received prenatal care within 4 months of gestation; (c) 75% of preterm births are spontaneous; (d) 22.5%—estimated, averaged rate of preterm birth among 17P-eligible women with a previous preterm birth; (e) 33%—estimated, average rate of preterm birth among 17P-eligible women with a previous very preterm birth; (f) 33%—reported reduction by Meis et al.[3] * $P < .001$.

history of very preterm (< 32 weeks) birth, the probability of having a preterm birth in the subsequent pregnancy averaged 33%. These estimates are consistent with those previously reported by the multicenter NICHD Maternal-Fetal Medicine Units Network Preterm Prediction Study.[2] Therefore, in the absence of 17P, we estimated that the 132,933 women eligible to receive 17P would have had 29,910 recurrent preterm births in 2002. The corresponding estimate of recurrent preterm births to women with a history of a spontaneous very preterm birth in the absence of 17P was 6,555 births.

Meis et al[3] concluded that 33% of preterm birth (relative risk 0.66, 95% confidence interval 0.54–0.81) could be prevented if progesterone were universally administered to and accepted by all women with a singleton pregnancy and with a history of prior spontaneous preterm birth. Therefore, 33% of the above noted 29,910 recurrent preterm births in 2002, or 9,870 preterm births, might have been

prevented if eligible women received 17P preventive therapy. If 17P use were restricted to women with a history of a previous spontaneous very preterm birth, 2,163 preterm births might have been prevented.

When the numbers of potentially preventable preterm births are applied to the 4,021,726 total United States live births in 2002, there is a 2% decrease in the United States preterm birth rate, from 12.1% to 11.8%, or an absolute difference of 0.3%; $P < .001$ (Fig. 1). Among the smaller cohort of 2,037,292 spontaneous singleton births to multiparous women with onset of prenatal care during the first 4 months of pregnancy, regardless of history of preterm birth (Fig. 1), universal use of 17P would have reduced the preterm birth rate in this cohort from 9.4% to 8.5%, reflecting an estimated 11% reduction, or an absolute difference of 0.9%, $P < .001$.

DISCUSSION

Two key findings are reported from this study. First, we estimated that in 2002, approximately 30,000 preterm singleton infants were born to women with a history of prior preterm birth, based on a preterm birth recurrence rate of about 22.5%. Second, we estimated that universal intervention with17P therapy for eligible women would likely have a real but modest effect on the overall national preterm birth rate, reducing it by 2%, from 12.1% to 11.8% in 2002, which would have prevented about 10,000 preterm births. In addition, 17P preventive therapy is likely to afford a more substantial reduction of expected preterm births among the targeted cohort of women with a history of prior spontaneous preterm birth. Subsequent analyses are also needed to estimate the effect in currently eligible, yet targeted groups of pregnant women (eg, by maternal age, ethnicity, gestational age of previous preterm, and whether the delivery was spontaneous or indicated). If eligible populations expand as clinical trials investigate efficacy of 17P in other risk populations, the effect on prevention of preterm birth may be even more substantial. Importantly, 17P provides promise for future research aimed at reducing preterm birth, in an area of clinical research that has produced very few successes.

We estimated that nearly 133,000 women may be eligible for 17P therapy in a given year. This estimate conservatively excludes women who initially received prenatal care after the fourth month of pregnancy, because eligibility in the Maternal-Fetal Medicine Units Network trial was between 16–20 weeks. Thus, if more women received prenatal care in the first trimester, the potential pool of women eligible for 17P would likely increase.

There were several limitations of our analysis, primarily reflecting the criteria and assumptions that were used. For example, we used the 33% estimate of 17P efficacy of the Maternal-Fetal Medicine Units Network clinical trial,[3] which may not be fully generalizable to the United States population. Greene (Greene MF. Progesterone and preterm delivery–déjà vu all over again [editorial]. N Engl J Med 2003;348:2453–4) suggests that the findings of the Maternal-Fetal Medicine Units Network study are representative of a population that is very high risk and using a treatment that was very highly managed, as evidenced by the very high rate of preterm birth in the placebo group (54.9%). History of prior preterm birth is likely to have been underreported on birth certificates, and longitudinal birth files from New Jersey and Missouri may not be representative of all United States live births. In addition, we were unable to ascertain the actual proportion of preterm births that were truly spontaneous. Another possible confounder, which could not be addressed due to an absence of published estimates, is the proportion of eligible pregnant women in 2002 already receiving some form of progesterone. Finally, the necessary use of live births instead of pregnancies as the unit of analysis may have underestimated the potential effect of 17P.

Although the potential benefit of 17P on overall preterm birth rates is likely to be limited, there are a number of barriers that could be addressed to maximize public health benefit for eligible women. First, 17P is currently primarily accessed only through compounding pharmacies. Commercial production of the product that is licensed for use during pregnancy, and reimbursed by public and private payers, would likely substantially increase access to patients and providers. Knowledge and attitudes of providers and patients about 17P is currently unknown. Additional education and safety monitoring may be needed to expand provider usage. In the Maternal-Fetal Medicine Units Network trial, all potential study participants were required to receive a placebo injection and return for follow-up to be eligible for enrollment, possibly preselecting a more motivated or adherent group of women. It is unknown whether women in the general population, particularly those at high risk for preterm birth, will be able to overcome the financial and logistic obstacles of attending weekly clinic visits and accept the discomfort of weekly injections. Finally, some of the eligible women in our study could not have received 17P because they did not initiate prenatal care in the first 4 months of gestation. This emphasizes that improving access to prenatal care early in pregnancy remains a fundamental element for moving research to clinical practice and improving birth outcomes. Further studies, requiring data not currently available, are needed to estimate how removing these barriers may further enhance the effect of 17P on preterm birth rates.

Although the results of the NICHD Maternal-Fetal Medicine Units Network study provide encouraging news about the potential for using 17P for women with recurrent preterm birth, 2 main concerns persist (Einstein FH, Bracero LA. Progesterone and preterm birth [letter]. Am J Obstet Gynecol 2004;190:1798. Tita ATN, O'Day MP. Prophylactic progesterone to prevent preterm birth [letter]. Am J Obstet Gynecol 2004;190:1799. O'Shaughnessy RW. Supplemental progesterone to prevent preterm birth [letter]. Am J Obstet Gynecol 2004;190:1800–1. Riskin-Mashiah S. Progesterone and preterm birth [letter]. Am J Obstet Gynecol 2004;190:1802–3. Iams JD. Supplemental progesterone to prevent preterm birth [editorial]. Am J Obstet Gynecol 2003;188:303). First, any expansion of 17P eligibility criteria beyond those provided by the American College of Obstetricians and Gynecologists Committee Opinion[5] should be evidence-based, dependent upon appropriate controlled clinical trials to minimize unnecessary use of 17P and potential adverse effects on pregnant women and infants. Second, long-term follow-up of mothers and infants exposed in utero to 17P is needed to assure the safety of this treatment. Also, despite the apparently broad effect of 17P in the Maternal-Fetal Medicine Units Network trial, further investigation is needed to assess whether clinical efficacy will vary by population subgroups, including by race or ethnicity, maternal age, parity, and prenatal care use, geographic region, and biologic parameters. The methodology presented here may therefore need to be modified to account for differences in yet unknown clinical, chemical, and genetic heterogeneities that might influence the response to 17P. These differences in susceptibility to preterm birth represent an important active area of research.

In conclusion, it is likely that 17P preventive therapy will play an important role in reducing the risk of recurrent preterm birth. At the present time, the effect of this drug on the total occurrence of preterm birth in the United States is likely to be real, but modest. The limited overall effect of 17P underscores that preterm birth is a complex disorder for which no single intervention will likely achieve a substantial reduction in the overall preterm birth rate. Preterm birth is a leading cause of death and disability among infants. There is a critical need for research to better understand the causes of preterm birth, develop methods to identify women at risk early in pregnancy, and evaluate innovative strategies for prevention.

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APPENDIX

Missouri Longitudinal Data File

For this analysis, the Missouri file linked first and second births and includes data for the years 1989–1997.

(Herman AA, McCarthy BJ, Bakewell JM, Ward RH, Mueller BA, Maconochie NE, et al. Data linkage methods used in maternally-linked birth and infant death surveillance data sets from the United States [Georgia, Missouri, Utah and Washington State], Israel, Norway, Scotland and Western Australia. Pediatr Perinat Epidemiol 1997;11 suppl:5–22.)

New Jersey Longitudinal Data File

The New Jersey file links up to 6 births and spans the years 1996–2001.

(Denk CE, Kruse LK. The dynamics of prenatal care use across pregnancies [abstract]. Ninth Annual Maternal and Child Health Epidemiology Conference, Tempe, Arizona, December 2003. Denk CE, Kruse LK, Rotondo FM. Breastfeeding initiation in successive births [abstract]. American Public Health Association Annual Meeting, San Francisco, California, November 15–19, 2003. Denk CE, Kruse LK. Validating medical risk factors on the New Jersey electronic birth certificate [abstract]. American Public Health Association Annual Meeting, Philadelphia, Pennsylvania, November 9–13, 2002.)

Table 1. Preterm and Very Preterm Birth Rates, 2000–2002 Average Percentage of All Live Births

	Preterm			Very Preterm		
	Missouri	New Jersey	United States	Missouri	New Jersey	United States
Total	12.5	11.8	11.9	2	2.1	1.9
By race or ethnicity						
White	11.2	10.3	10.7	1.6	1.5	1.5
Black	19.6	17.7	17.6	4.2	4.5	4.1
Native American	14.3	11.8	12.9	1.8	1.7	2
Asian	12.3	9.3	10.2	1.6	1.3	1.4
Hispanic	11.7	12.3	11.4	1.7	2.2	1.7
By maternal age (y)						
< 20	14.8	15.5	14	2.8	3.4	2.7
20–29	11.9	11.2	11.3	1.8	2	1.8
30–39	12.5	11.6	11.8	1.8	2	1.8
40+	15.9	15.5	15.6	2.3	2.7	2.6

All race categories exclude Hispanic births. Source: National Center for Health Statistics.