

## ORIGINAL ARTICLE

# A Trial of 17 Alpha-Hydroxyprogesterone Caproate to Prevent Prematurity in Twins

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## ABSTRACT

**BACKGROUND**

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In singleton gestations, 17 alpha-hydroxyprogesterone caproate (17P) has been shown to reduce the rate of recurrent preterm birth. This study was undertaken to evaluate whether 17P would reduce the rate of preterm birth in twin gestations.

**METHODS**

We performed a randomized, double-blind, placebo-controlled trial in 14 centers. Healthy women with twin gestations were assigned to weekly intramuscular injections of 250 mg of 17P or matching placebo, starting at 16 to 20 weeks of gestation and ending at 35 weeks. The primary study outcome was delivery or fetal death before 35 weeks of gestation.

**RESULTS**

Six hundred sixty-one women were randomly assigned to treatment. Baseline demographic data were similar in the two study groups. Six women were lost to follow-up; data from 655 were analyzed (325 in the 17P group and 330 in the placebo group). Delivery or fetal death before 35 weeks occurred in 41.5% of pregnancies in the 17P group and 37.3% of those in the placebo group (relative risk, 1.1; 95% confidence interval [CI], 0.9 to 1.3). The rate of the prespecified composite outcome of serious adverse fetal or neonatal events was 20.2% in the 17P group and 18.0% in the placebo group (relative risk, 1.1; 95% CI, 0.9 to 1.5). Side effects of the injections were frequent in both groups, occurring in 65.9% and 64.4% of subjects, respectively ( $P=0.69$ ), but were generally mild and limited to the injection site.

**CONCLUSIONS**

Treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with twin gestations. (ClinicalTrials.gov number, NCT00099164.)

\*The other members of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are listed in the Appendix.

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**P**RETERM BIRTH IS RESPONSIBLE FOR A substantial portion of infant mortality and persistent disability. The problem of preterm birth has proved largely intractable. In 2004, 12.5% of all live-born infants in the United States were delivered preterm — that is, before 37 completed weeks of gestation.<sup>1</sup> In a study published in 2003, weekly injections of 17 alpha-hydroxyprogesterone caproate (17P) were shown to lower the risk of recurrent preterm birth by one third in women who had previously given birth to a preterm infant spontaneously.<sup>2</sup> Although this finding is encouraging, only a minority of women destined to deliver preterm would qualify for 17P on the basis of having had a previous spontaneous preterm delivery.<sup>3</sup>

It is unknown whether 17P can reduce the rate of preterm birth in women with other risk factors. One logical candidate risk factor is twin gestation. Twin gestations are increasingly common, and more than half result in premature births. Between 1980 and 2004, the rate of twin births rose dramatically in the United States (from 18.9 to 32.2 per 1000 live births), as did the absolute number (from 68,339 to 132,219).<sup>1</sup> Consequently, the morbidity and mortality burden of twins is increasingly disproportionate and substantial: almost one in four very-low-birth-weight infants (below 1500 g) born in the United States are twins, as are one in six infants who die in the first month of life.<sup>1,4</sup> Therefore, we evaluated the efficacy of 17P in preventing preterm birth in women with twin gestations.

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## METHODS

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### RECRUITMENT

Recruitment to this placebo-controlled, double-blind, randomized clinical trial of 17P for the prevention of preterm birth in twin gestations was undertaken at 14 sites from April 2004 through February 2006. Women carrying twins with a gestational age of at least 16 weeks and no more than 20 weeks 3 days were eligible. The exclusion criteria were serious fetal anomalies, spontaneous death of a fetus after 12 weeks, presumed monoamniotic placenta, suspected twin-to-twin transfusion syndrome, marked ultrasonographic growth discordance (a difference of at least 3 weeks of estimated gestational age between fetuses), planned nonstudy progesterone therapy after 16 weeks, in-place or planned cer-

clage, major uterine anomaly (e.g., bicornuate uterus), treatment with 10,000 or more units of unfractionated heparin per day, treatment with low-molecular-weight heparin at any dose, and major chronic medical diseases (e.g., insulin-requiring diabetes mellitus or pharmacologically treated hypertension). Twin gestations that were the result of intentional fetal reduction were also excluded.

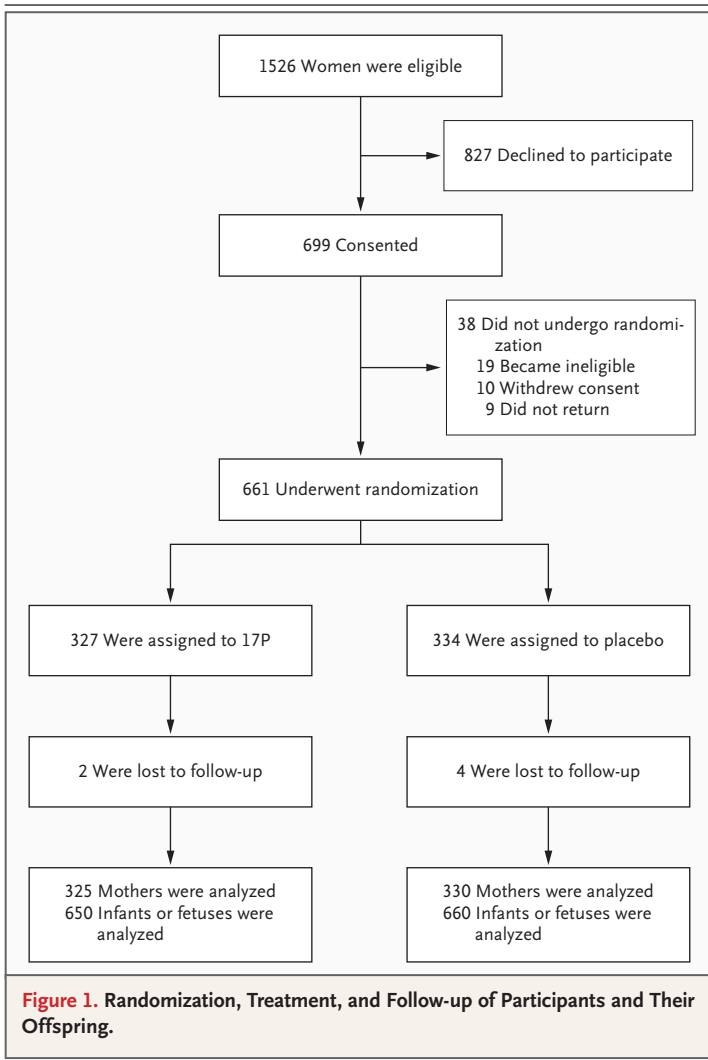
An ultrasonographic examination was required between 12 weeks and 20 weeks 6 days of gestation to confirm the duration of gestation and to screen for major fetal anomalies. For women who conceived spontaneously, the duration of gestation at the time of randomization was determined according to a previously described algorithm on the basis of the last menstrual period and the results of ultrasonography of the larger fetus.<sup>5</sup> For women who conceived by in vitro fertilization, the duration of gestation was calculated on the basis of the date of embryo transfer and the age of the embryos when transferred.

The study was approved by the institutional review boards at each clinical site and at the data-coordinating center. All women gave written informed consent before enrollment in the study.

### PROTOCOL

Eligible, consenting women were given a trial intramuscular injection of the placebo and were scheduled for a randomization visit not later than 20 weeks 6 days of gestation. At that visit, women who still met none of the exclusion criteria were assigned to receive identical-appearing injections of active agent (250 mg of 17P) or placebo (castor oil) prepared by a research pharmacy. The simple urn method of randomization<sup>6</sup> with stratification according to clinical center was used by the George Washington University Biostatistical Coordinating Center to create a randomization sequence for each center, and the boxes of 17P and placebo were packaged for each center according to the randomization sequences. The participating women, their caregivers, and the research personnel were unaware of the women's study-group assignments. After entering the study, the women returned for weekly injections through the end of the 34th week of gestation or until delivery, whichever occurred first. At each visit, they underwent systematic assessment for side effects. Otherwise, the women received usual clinical care.

After delivery, study personnel reviewed deliv-



ery, newborn, and postpartum records and documented the date of delivery, the birth weight of the infants, and the neonatal course, as well as the occurrence of complications of pregnancy and obstetrical interventions. The infants were followed until discharge from the hospital of birth, or, if they were transferred, until discharge from the transfer hospital.

#### STUDY OUTCOMES

The primary study outcome was a composite of delivery or fetal death before 35 completed weeks of gestation (245 days). Fetal death includes miscarriage, termination of pregnancy, and stillbirth. Prespecified secondary outcomes included the time from randomization to fetal death or delivery, a composite of serious adverse fetal or neonatal outcomes, and selected individual maternal and

neonatal outcomes. In analyses that were not prespecified, we assessed the proportion of preterm births in each group at different gestational-age thresholds.

The data were analyzed according to the intention-to-treat principle. The unit of analysis was the pregnancy, and if the outcome occurred in either fetus or neonate, the pregnancy was considered to have met the outcome. For example, a pregnancy in which one fetus died at 22 weeks and the other was born alive at 37 weeks would be counted as meeting the primary outcome. However, for fetal or neonatal death, a proportional-odds model, which permits the distinction between the death of one fetus or neonate and the death of both, was also used to compare the two groups.

#### STATISTICAL ANALYSIS

The time to delivery or death of the first fetus was compared between the two groups by means of a proportional-hazards model with left truncation (i.e., with adjustment for gestational age at entry). Similarly, survival curves were plotted with the use of a modified product-limit estimator.<sup>7</sup> Continuous variables were compared with the Wilcoxon rank-sum test, and categorical variables with the chi-square test or Fisher's exact test, as appropriate.

On the basis of data from two studies performed by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, we estimated conservatively that in the placebo group, 35% of twins would be delivered before 35 completed weeks of gestation.<sup>8,9</sup> Thus, a total sample size of 600 was deemed sufficient to detect a 33% reduction in the rate of delivery or death before 35 weeks, under the assumptions of a type I error (two-sided) of 5% and a power of greater than 80%. This sample size also yielded 70% power if it was assumed that there would be no reduction in indicated preterm delivery and that the one-third reduction would apply only to spontaneous preterm deliveries (on the assumption of a 4:1 ratio of spontaneous to indicated deliveries at less than 35 weeks of gestation).

We estimated that a sample size of 600 would provide at least 70% power to detect a 33% reduction in the rate of the composite of the following serious adverse fetal or neonatal outcomes: fetal or neonatal death, respiratory distress syn-

drome, grade 3 or 4 intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, periventricular leukomalacia, bronchopulmonary dysplasia, severe retinopathy of prematurity, or early-onset, culture-proven sepsis. On the basis of our previous data, we expected that at least one component of this outcome would occur in one or both fetuses or neonates in 25% of pregnancies.<sup>9</sup>

An independent data and safety monitoring committee monitored the trial and reviewed the interim results. Before the study started, the group sequential method of Lan and DeMets with the modified O'Brien–Fleming spending function was chosen for adjustment of the significance level in interim analyses.<sup>10</sup> Two interim analyses were performed, and in the final analysis of the primary outcome, two-tailed P values of less than 0.048 were chosen to indicate statistical significance. However, since the adjustment is minimal, 95% confidence intervals are reported. For all other outcomes, a nominal P value of less than 0.05 was considered to indicate significance, and no adjustments were made for multiple comparisons.

RESULTS

We identified 1526 eligible women, of whom 699 (45.8%) gave consent and 661 (43.3%) were randomly assigned to treatment. Outcome data were available for 655 of these 661 women and for 1310 of 1322 fetuses or infants (Fig. 1). The baseline characteristics of the two study groups were similar (Table 1).

Compliance with the intervention was determined by the proportion of protocol-specified injections (one injection every 7 days from randomization to delivery or to 34 weeks 6 days of gestation, whichever occurred first) that were received. The mean compliance rate was 94.5% in the 17P group and 95.0% in the placebo group (P=0.97).

The rate of the primary outcome did not differ significantly between groups. Fetal death or delivery before 35 weeks of gestation occurred in 41.5% of pregnancies in the 17P group (135 of 325) and 37.3% of pregnancies in the placebo group (123 of 330) (relative risk, 1.1; 95% confidence interval [CI], 0.9 to 1.3). Of those deliveries occurring before 35 weeks of gestation, 72.8% were spontaneous and 27.2% were medically indicated; the proportions of spontaneous and medically indicated deliveries were similar between the groups

Table 1. Baseline Characteristics of the Study Subjects.\*

Characteristic	17P Group (N=327)	Placebo Group (N=334)
Maternal age — yr	29.7±7.0	29.6±6.8
Gestational age at randomization — wk	19.2±1.5	19.2±1.4
Prepregnancy body-mass index†	26.7±6.5	27.1±7.1
Race — no. (%)‡		
Black	75 (22.9)	80 (24.0)
White	218 (66.7)	218 (65.3)
Asian	8 (2.4)	5 (1.5)
Other	26 (8.0)	31 (9.3)
Hispanic or Latino ethnic background — no. (%)‡	51 (15.6)	54 (16.2)
Marital status — no. (%)		
Married	248 (75.8)	243 (72.8)
Divorced, separated, or widowed	9 (2.8)	12 (3.6)
Never married	70 (21.4)	79 (23.7)
Educational level — yr	13.6±2.8	13.6±2.9
Nulliparous — no. (%)	151 (46.2)	145 (43.4)
Spontaneous conception — no. (%)	204 (62.4)	226 (67.7)
Previous preterm delivery — no. (%)	20 (6.1)	30 (9.0)
Dichorionic placenta — no. (%)	268 (82.0)	277 (82.9)
Smoking during pregnancy — no. (%)	38 (11.6)	31 (9.3)
Alcohol use during pregnancy — no. (%)	29 (8.9)	19 (5.7)
Illicit-substance use during pregnancy — no. (%)	5 (1.5)	8 (2.4)

\* Plus-minus values are means ±SD. P>0.05 for all between-group comparisons. Percentages may not sum to 100 because of rounding.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race and ethnic background were self-reported.

(Table 2). The mean gestational age at delivery did not differ significantly between groups, nor did the proportion of deliveries occurring before 37 weeks (the standard threshold for preterm birth), 32 weeks, or 28 weeks (Table 2). From the time of randomization, the estimated distributions of time to first miscarriage, fetal death, or delivery for the two groups were very similar (Fig. 2). The rates of selected obstetrical interventions were similar between the groups (Table 2).

In 21 pregnancies, a fetus died; these included 12 pregnancies (18 fetuses) in the 17P group and 9 pregnancies (12 fetuses) in the placebo group (relative risk, 1.4; 95% CI, 0.6 to 3.2). In 37 pregnancies, a fetus or neonate died; these included

**Table 2. Outcomes According to Treatment Group.\***

Outcome	17P Group (N=325)	Placebo Group (N=330)	Relative Risk (95% CI)
Delivery or fetal death at <35 wk — no./total no. (%)	135/325 (41.5)	123/330 (37.3)	1.1 (0.9–1.3)
2 Live births	125/325 (38.5)	115/330 (34.8)	1.1 (0.9–1.4)
≥1 Fetal death	10/325 (3.1)	8/330 (2.4)	1.3 (0.5–3.2)
Spontaneous	101/324 (31.2)	86/330 (26.1)	1.2 (0.9–1.5)
Medically indicated	33/324 (10.2)	37/330 (11.2)	0.9 (0.6–1.4)
Gestational age at delivery — wk	34.6±3.9	34.9±3.6	
Gestational age at delivery or fetal death — no. (%)			
<37 Wk	226 (69.5)	232 (70.3)	1.0 (0.9–1.1)
<32 Wk	55 (16.9)	48 (14.5)	1.2 (0.8–1.7)
<28 Wk	26 (8.0)	20 (6.1)	1.3 (0.8–2.3)
Tocolytic therapy — no./total no. (%)	71/324 (21.9)	97/330 (29.4)	0.7 (0.6–1.0)
Corticosteroid treatment for fetal maturation — no./total no. (%)	80/324 (24.7)	90/330 (27.3)	0.9 (0.7–1.2)
Cerclage placement — no./total no. (%)	6/324 (1.9)	4/330 (1.2)	1.5 (0.4–7.2)
Hypertensive disorder — no. (%)	66 (20.3)	55 (16.7)	1.2 (0.9–1.7)
Chorioamnionitis — no./total no. (%)	6/324 (1.9)	6/330 (1.8)	1.0 (0.3–3.1)
Cesarean delivery — no./total no. (%)	200/324 (61.7)	204/328 (62.2)	1.0 (0.9–1.1)
Side effects — no./total no. (%)			
Any	211/320 (65.9)	210/326 (64.4)	1.0 (0.9–1.1)
Injection site	197/320 (61.6)	203/326 (62.3)	1.0 (0.9–1.1)
Urticaria	11/320 (3.4)	4/326 (1.2)	2.8 (0.9–8.7)
Nausea	5/320 (1.6)	10/326 (3.1)	0.5 (0.2–1.5)
Other†	24/320 (7.5)	23/326 (7.1)	1.1 (0.6–1.8)
Leading to discontinuation of study drug	2/320 (0.6)	1/326 (0.3)	2.0 (0.3–27.5)

\* Plus-minus values are means ±SD. Data on complications are based on clinical diagnoses in the medical records.  
 † The most common other side effects were fatigue, dizziness, and headache.

22 pregnancies (34 fetuses or neonates) in the 17P group and 15 pregnancies (22 fetuses or neonates) in the placebo group (relative risk, 1.5; 95% CI, 0.8 to 2.8). Using a proportional-odds model to account for both fetuses or neonates dying versus one dying versus neither dying yielded similar results. The rates of other selected neonatal outcomes, including major congenital malformations, were similar between the groups (Table 3).

The rate of the composite outcome of serious adverse events (fetal or neonatal death, respiratory distress syndrome, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, stage 2 or 3 necrotizing enterocolitis, bronchopulmonary dysplasia, severe retinopathy of prematurity, or early-onset, culture-proven sepsis) was 20.2%

in the 17P group and 18.0% in the placebo group (relative risk, 1.1; 95% CI, 0.9 to 1.5).

Side effects of the injections were frequent in both the 17P and the placebo groups, occurring in 65.9% and 64.4% of subjects, respectively (P=0.69), but were generally mild and most often limited to the injection site (Table 2). Three women (two in the 17P group and one in the placebo group) discontinued injections because of side effects; the two women receiving 17P had intense injection-site reactions. In addition, one woman in the 17P group had subjective heart palpitations and presyncope immediately after the first injection. She did not return for any study follow-up and did not provide any outcome information.

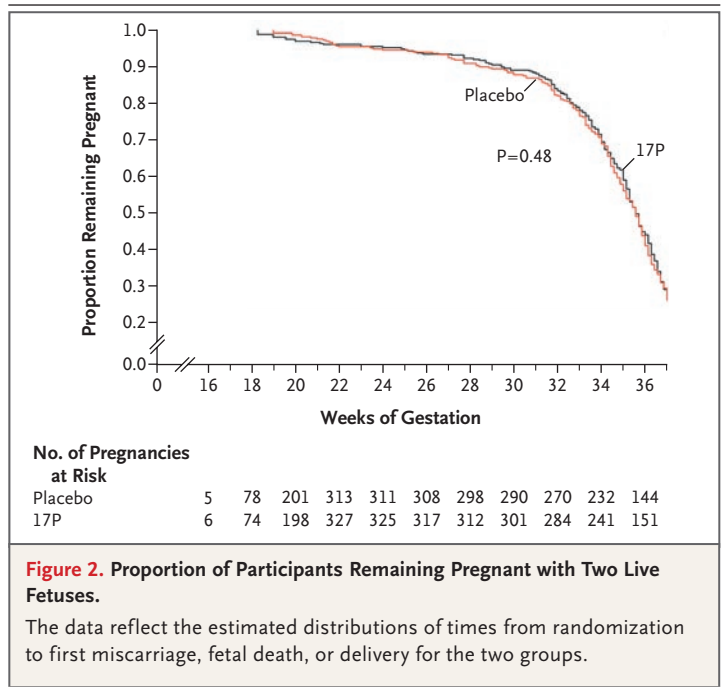
DISCUSSION

In this randomized trial conducted among women carrying twins, weekly 250-mg injections of 17P failed to lower the rate of preterm birth, to prolong gestation, or to improve fetal or neonatal outcome.

Our results are generalizable to most women in the United States who are pregnant with twins. The study subjects were drawn from a broad geographic area and were racially and ethnically diverse. Roughly half were nulliparous, and two thirds conceived spontaneously. Although most of the subjects were recruited from academic medical centers, they were not at unusually high risk for preterm birth. On average, the women in this trial delivered at 34.8 weeks, as compared with a national average of 35.2 weeks for women carrying twins.<sup>1</sup> Our results may not be applicable to women carrying twins as a result of intentional fetal reduction from a higher-order multiple gestation, since these women were excluded from the trial.

In previous trials demonstrating a benefit of 17P, the study participants were carrying singletons, and most were at risk for spontaneous preterm birth because of preterm birth in a previous pregnancy.<sup>11</sup> One previous trial conducted in women with twin gestations failed to find a benefit of 17P; however, this trial was statistically underpowered, with only 77 participants, and 17P was initiated much later in gestation than in our study, at a mean of 29 weeks.<sup>12</sup> In a trial reported elsewhere in this issue of the *Journal*,<sup>13</sup> progesterone treatment reduced the rate of preterm birth among women who were at high risk for preterm birth because of a short cervix. In that trial, which involved mostly women with singleton gestations, both the formulation (micronized progesterone) and the route of administration (vaginal) were different from those in our trial. Concurrently with our twins trial, we enrolled triplets in a companion trial, the results of which are currently being analyzed.

Potential limitations of our study should be noted. Because less than 10% of women in our trial had previously given birth prematurely, it is uncertain whether 17P might be of benefit in twin gestations in which the mother has a history of spontaneous preterm birth. Our choice of using the same dose of 17P (250 mg per week) that was used in our previous trial<sup>2</sup> of 17P in



**Figure 2. Proportion of Participants Remaining Pregnant with Two Live Fetuses.**

The data reflect the estimated distributions of times from randomization to first miscarriage, fetal death, or delivery for the two groups.

women with singleton gestations might be questioned, because plasma volume is known to be approximately 20% greater in twin than in singleton gestations.<sup>14</sup> Thus, it is possible that a larger dose of 17P might have been efficacious. However, unless there is a threshold effect for 17P, which has not previously been suggested, a lower-than-optimal dosage would have been expected to have an attenuated effect on preterm birth, rather than no effect.

We based our primary outcome on delivery or fetal death before 35 completed weeks of gestation, rather than on rates of adverse fetal or neonatal outcomes. Short- and long-term complications of preterm birth are a direct function of gestational age, and delivery before 35 weeks is a more stringent cutoff point for preterm birth than is the standard definition of delivery before 37 weeks. Moreover, in well-dated pregnancies (as in this trial), the assessment of gestational age at delivery is highly reliable and objective.

In summary, the results of our trial do not support the use of 17P to reduce the risk of preterm birth in twin gestations. Why 17P has been effective in women with singleton gestations and a history of spontaneous preterm birth<sup>2</sup> but was not effective in the present trial in women carrying twins is a question that will be answered only when the mechanisms underlying preterm

**Table 3. Selected Neonatal Outcomes among Live-Born Infants According to Treatment Group.\***

Outcome	17P Group (N=632)	Placebo Group (N=648)	Relative Risk (95% CI)†
	no. (%)		
Birth weight‡			
<2500 g	377 (60.0)	415 (64.0)	0.9 (0.8–1.0)
<1500 g	81 (12.9)	64 (9.9)	2.0 (1.0–3.9)
Major malformation	3 (0.5)	4 (0.6)	0.5 (0.1–2.4)
5-Minute Apgar score <7	27 (4.3)	33 (5.1)	0.9 (0.5–1.6)
Patent ductus arteriosus	18 (2.8)	31 (4.8)	0.7 (0.4–1.3)
Pneumonia	8 (1.3)	10 (1.5)	1.0 (0.4–2.7)
Mechanical ventilation	70 (11.1)	77 (11.9)	1.0 (0.7–1.5)
Seizures	5 (0.8)	5 (0.8)	1.3 (0.4–5.0)
Components of the composite outcome of serious adverse events§			
Severe retinopathy of prematurity	0	0	—
Respiratory distress syndrome	96 (15.2)	87 (13.4)	1.2 (0.8–1.6)
Early-onset, culture-proven sepsis	24 (3.8)	26 (4.0)	1.0 (0.6–1.9)
Stage 2 or 3 necrotizing enterocolitis	3 (0.5)	4 (0.6)	0.8 (0.1–3.0)
Bronchopulmonary dysplasia	19 (3.0)	17 (2.6)	1.2 (0.6–2.7)
Grade 3 or 4 intraventricular hemorrhage	7 (1.1)	6 (0.9)	1.0 (0.3–3.1)
Periventricular leukomalacia	5 (0.8)	6 (0.9)	0.9 (0.3–2.8)

\* Data on complications are based on clinical diagnoses in the medical records.

† Relative risks were calculated according to the pregnancy, not the neonate (i.e., if either neonate had the outcome, the pregnancy was credited with the outcome).

‡ In the 17P group, birth weight was recorded for 628 infants.

§ The composite outcome of serious adverse events includes fetal or neonatal deaths as well as the listed individual components.

birth and the actions of 17P are better understood. Further investigation is warranted to assess whether 17P is effective in other conditions in which the risk of preterm birth is increased.

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#### APPENDIX

In addition to the authors, the members of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are as follows: *University of Alabama at Birmingham* — W.W. Andrews, A. Northen, J. Sheppard; *Brown University* — J. Tillinaghast, D. Allard; *Case Western Reserve University* — C. Milluzzi, C. Heggie, H. Ehrenberg, B. Stetzer, A. Merlino; *Columbia University* — R. Berkowitz, S. Bousleiman, S. South, L. Paley, V. Carmona, R. Wapner; *Drexel University* — M. Hoffman, M. Talucci, S. Wilson, C. Tocci, M. Lake; *University of North Carolina* — K. Boggess, K. Dorman, S. Timlin; *Northwestern University* — W. Grobman, G. Mallett, M. Dinsmoor, P. Simon, M. Huntley, M. Ramos; *Ohio State University* — F. Johnson, M. Landon, C. Latimer; *University of Pittsburgh* — H. Simhan, M. Cotroneo, E. Daugherty; *University of Texas at Houston* — D. Soebbing-Cross, J. Martinez, B. Glenn-Cole, L. Gilstrap; *University of Texas Southwestern Medical Center* — K. Leveno, L. Moseley; *University of Utah* — K. Anderson, F. Porter, C. Jolley, S. Quinn, A. Guzman; *Wake Forest University* — P. Meis, M. Swain, K. Johnson, K. Lanier, C. Leftwich; *Wayne State University* — G. Norman, C. Sudz, S. Blackwell; *George Washington University Biostatistics Center* — V. Momirova, A. Braga, E. Cardenas, L. Leuchtenburg; *National Institute of Child Health and Human Development* — S. Pagliaro.

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