

## ORIGINAL ARTICLE

# Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo B. Fonseca, M.D., Ebru Celik, M.D., Mauro Parra, M.D.,  
Mandeep Singh, M.D., and Kypros H. Nicolaides, M.D.,  
for the Fetal Medicine Foundation Second Trimester Screening Group\*

## ABSTRACT

**BACKGROUND**

Previous randomized trials have shown that progesterone administration in women who previously delivered prematurely reduces the risk of recurrent premature delivery. Asymptomatic women found at midgestation to have a short cervix are at greatly increased risk for spontaneous early preterm delivery, and it is unknown whether progesterone reduces this risk in such women.

**METHODS**

Cervical length was measured by transvaginal ultrasonography at a median of 22 weeks of gestation (range, 20 to 25) in 24,620 pregnant women seen for routine prenatal care. Cervical length was 15 mm or less in 413 of the women (1.7%), and 250 (60.5%) of these 413 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. The primary outcome was spontaneous delivery before 34 weeks.

**RESULTS**

Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (19.2% vs. 34.4%; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86). Progesterone was associated with a nonsignificant reduction in neonatal morbidity (8.1% vs. 13.8%; relative risk, 0.59; 95% CI, 0.26 to 1.25;  $P=0.17$ ). There were no serious adverse events associated with the use of progesterone.

**CONCLUSIONS**

In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery. (ClinicalTrials.gov number, NCT00422526.)

From the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London. Address reprint requests to Dr. Nicolaides at the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, United Kingdom, or at kypros@fetalmedicine.com.

\*The other members of the Fetal Medicine Foundation Second Trimester Screening Group are listed in the Appendix.

N Engl J Med 2007;357:462-9.  
Copyright © 2007 Massachusetts Medical Society.

**P**REMATURITY IS THE LEADING CAUSE OF neonatal death and handicap.<sup>1</sup> Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks.<sup>2,3</sup> Improvements in neonatal care have led to higher rates of survival among very premature infants, but a major effect on the associated mortality and morbidity will be achieved only by better identification of women at high risk for preterm delivery and by development of an effective intervention to prevent this complication.

The prophylactic administration of progesterone beginning in midgestation to women who previously had a preterm birth has been shown to halve the rate of recurrence.<sup>4-6</sup> However, a strategy in which therapeutic intervention is limited to women with a previous preterm delivery is likely to have a small effect on the overall rate of prematurity, because only about 10% of spontaneous early preterm births occur in women with this history.<sup>7</sup> A method that may better identify women at high risk with either singleton or twin pregnancies is ultrasonographic measurement of cervical length at 20 to 24 weeks of gestation.<sup>8-10</sup> Asymptomatic women found to have a cervical length of 15 mm or less are at greatly increased risk for spontaneous early preterm delivery. We designed a multicenter, randomized trial to evaluate the effect of vaginal progesterone on the incidence of spontaneous early preterm delivery in asymptomatic women found at routine mid-trimester screening to have a short cervix.

## METHODS

### STUDY PARTICIPANTS

The trial was conducted from September 2003 through May 2006 in five maternity hospitals in and around London (King's College Hospital, London; Queen Elizabeth Hospital, Woolwich; University Hospital of Lewisham, London; Southend University Hospital, Essex; and Darent Valley Hospital, Dartford); the Hospital Clínico Universidad de Chile, Santiago, Chile; the Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo; and the University Hospital, Larissa, Greece.

All women with singleton or twin pregnancies who were undergoing routine ultrasonography at 20 to 25 weeks of gestation for examination of fetal anatomy and growth were given the option

of transvaginal ultrasonographic measurement of cervical length as a predictor of spontaneous early preterm delivery.<sup>11</sup> The exclusion criteria were major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes, or a cervical cerclage. Gestational age was determined from the menstrual history and confirmed from the measurement of fetal crown-rump length at a first-trimester scan, which is carried out routinely in the participating hospitals.

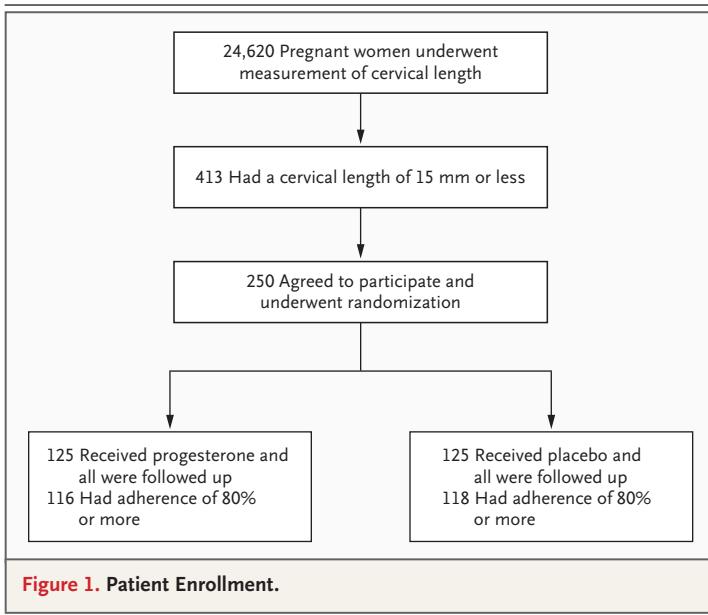
Women with a cervical length of 15 mm or less were invited to take part in a randomized, double-blind, placebo-controlled trial of progesterone. All women gave written informed consent, and the study was approved by the Multi-Centre Research Ethics Committee and the Medicine Control Agency in the United Kingdom, as well as the local ethics committees of the participating hospitals. The sponsor of the study, the Fetal Medicine Foundation, had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Quality control of screening, handling of data, and verification of adherence to protocols at the different centers were performed on a regular basis by the trial coordinators. The sonographers who performed the scans had received extensive training and passed a practical examination administered by an expert to demonstrate their competence in cervical assessment.

### RANDOMIZATION AND FOLLOW-UP

Each study participant was given a blister pack labeled "Progesterone Study," which contained either 200-mg capsules of micronized progesterone (Utrogestan, Besins International Belgium) or identical-appearing capsules of placebo containing safflower oil (Medicaps). The drug and placebo were purchased from the companies, which provided no financial support and had no involvement in study design, data collection, data handling, data analysis, study interpretation, the drafting of the manuscript, or the decision to publish.

The blisters were packaged by DHP Clinical Trial Supplies. Computer-generated random-number lists were created by the King's College Hospital pharmacy, and the appropriately numbered drug was dispensed by each hospital; central randomization was designed to ensure that there were exactly 125 women in each group. Each woman was instructed to avoid sexual inter-



course and to introduce one capsule into her vagina every night before going to sleep from 24 to 33 weeks 6 days of gestation.

The general practitioners of the women were informed in writing about the women's participation in the study, and their hospital notes were marked with a sticker labeled "Progesterone Study." Follow-up visits for ultrasound assessment of fetal growth and cervical length were carried out every 2 weeks until 34 weeks of gestation. At the time of randomization, the patients were informed that symptoms related to the administration of progesterone could include sleepiness, fatigue, headaches, and vaginal irritation, but that these symptoms are common in pregnancy. At each follow-up visit, we asked the patients whether they had noted an increase in severity or frequency of these symptoms and whether they had had any new symptoms since the beginning of treatment. Adherence was checked by counting the capsules at these visits. The investigators, participants, and clinicians were unaware of the treatment assignments. The general practitioners and obstetricians of the patients were also unaware of the results of cervical assessments on follow-up ultrasonography.

Information on the characteristics of the patients, including demographic data, measurements for calculation of body-mass index, and obstetrical and medical histories, was obtained from the patients at the first hospital visit and entered into a computer database. Data on pregnancy out-

comes were obtained from the hospital maternity records or the patients' general medical practitioners. The obstetrical records of all patients delivering before 34 weeks were examined to determine whether the delivery was medically indicated or spontaneous. Spontaneous deliveries included those with spontaneous onset of labor and those with rupture of membranes before labor.

#### OUTCOME MEASURES

The primary outcome measure was spontaneous delivery before 34 completed weeks (238 days) of gestation. The secondary outcome measures were birth weight, fetal or neonatal death, major adverse outcomes before discharge from the hospital (intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity, or necrotizing enterocolitis), and need for neonatal special care (admission to a neonatal intensive care unit, ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion). All outcomes were determined before the randomization code of the trial was broken.

#### STATISTICAL ANALYSIS

The sample-size calculation was based on a reduction in the incidence of spontaneous delivery before 34 weeks from 28% in the placebo group to 14% in the progesterone group, with a power of 80%. To detect this difference at a significance level of 5%, we needed to recruit 250 patients with cervical length of 15 mm or less.

The analysis was performed according to the intention-to-treat principle. Baseline data for the progesterone and placebo groups were summarized by the median and the interquartile range. Comparisons between groups were performed with the use of the Mann-Whitney U test. Univariate comparisons of dichotomous data were performed with the use of Fisher's exact test. The P values for all hypothesis tests were two-sided, and P values of 0.05 or less were considered to indicate statistical significance. The risk of spontaneous preterm birth before 34 weeks was quantified by the relative risk and 95% confidence interval. Effect modification was assessed with the use of the Mantel-Haenszel test for homogeneity.<sup>12</sup> Multivariable analysis was performed by logistic regression.<sup>13</sup> The risk of spontaneous preterm birth from randomization until 34 weeks was assessed using Kaplan-Meier analysis,<sup>14</sup> where

gestational age was the time scale, spontaneous delivery was the event, and elective deliveries were treated as censored. For the purposes of this analysis, all pregnancies were considered to be no longer at risk for the event at the start of the 34th week. Hazard ratios were estimated with the use of the Cox proportional-hazards model, with a formal test of the proportional-hazards assumption.<sup>14,15</sup> Logistic regression was used to assess the risk of adverse events in the offspring. The analyses of infant outcomes used robust standard errors and were clustered on a maternal identifier to account for the nonindependence of twin pairs. Odds ratios were converted to relative

risks with the use of the method of Zhang and Yu.<sup>16</sup> All statistical analyses were performed with the Stata software package, version 8.2.

RESULTS

A total of 24,620 (82.3%) of the 29,918 pregnant women fulfilling the entry criteria for screening agreed to undergo transvaginal ultrasonographic measurement of cervical length at 20 to 25 weeks (median, 22 weeks) (Fig. 1). There were 24,189 singleton and 431 twin pregnancies. The median cervical length was 34 mm (range, 0 to 67 mm), and the length was 15 mm or less in 413 of the

**Table 1. Characteristics of the Study Participants.**

Characteristic	Progesterone Group (N=125)	Placebo Group (N=125)	P Value
Age — yr			0.91
Median	29	29	
Interquartile range	24–34	24–34	
Obstetrical history — no. (%)			0.33
Nulliparous	71 (56.8)	69 (55.2)	
Parous with no previous preterm births	39 (31.2)	33 (26.4)	
Parous with ≥1 previous preterm birth	15 (12.0)	23 (18.4)	
Race — no. (%) <sup>*</sup>			0.61
White	46 (36.8)	49 (39.2)	
Black	68 (54.4)	69 (55.2)	
Other	11 (8.8)	7 (5.6)	
Body-mass index <sup>†</sup>			0.11
Median	23.8	25.4	
Interquartile range	21.6–27.7	22.3–28.4	
Cigarette smoking during pregnancy — no. (%)	6 (4.8)	10 (8.0)	0.44
Single vs. multiple gestations — no. (%)			0.89
Singleton	114 (91.2)	112 (89.6)	
Twin (dichorionic)	8 (6.4)	9 (7.2)	
Twin (monochorionic, diamniotic)	3 (2.4)	4 (3.2)	
Days of gestation at randomization			0.78
Median	165	164	
Interquartile range	159–168	160–169	
Cervical length at randomization — mm			0.74
Median	11.0	12.0	
Interquartile range	9–14	9–14	
Adherence rate <80% — no. (%)	9 (7.2)	7 (5.6)	0.80

<sup>\*</sup> Race was self-reported.

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

women (1.7%). Two hundred fifty women with a short cervix (60.5%), including 226 with singleton and 24 with twin pregnancies, agreed to participate in the trial.

There were no significant differences in baseline characteristics between the placebo and the progesterone groups (Table 1). The rate of the primary outcome — spontaneous birth before 34 weeks of gestation — was 19.2% in the progesterone group and 34.4% in the placebo group (relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86) (Table 2). Four women (two in each group) had medically indicated preterm delivery. The proportional reduction over time in the incidence of all deliveries before 34 weeks was similar in the progesterone and the control groups. The risk of spontaneous preterm birth in the two groups was assessed using Kaplan–Meier analysis

(Fig. 2). The cumulative percentage of patients who did not give birth spontaneously before 34 weeks was significantly higher in the progesterone group than in the placebo group (hazard ratio, 0.57; 95% CI, 0.35 to 0.92;  $P=0.02$ ). Multivariable analysis demonstrated that adjustment for maternal characteristics at the time of randomization did not attenuate the apparent protective effect of progesterone (Table 2).

The relative risk of spontaneous preterm birth before 34 weeks of gestation did not vary significantly according to maternal age, body-mass index, race, obstetrical history, whether the pregnancy was singleton or twin, or cervical length at the time of randomization (Fig. 3). Among women without a history of delivery before 34 weeks, the incidence of spontaneous preterm birth was significantly higher in the placebo group than in

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

Outcome	Progesterone Group† no. (%)	Placebo Group‡ no. (%)	Relative Risk (95% CI)	P Value	Adjusted Relative Risk (95% CI)	P Value
<b>Maternal</b>						
Spontaneous delivery at <34 wk	24 (19.2)	43 (34.4)	0.56 (0.36–0.86)	0.007	0.56 (0.32–0.91)	0.02
Any delivery at <34 wk	26 (20.8)	45 (36.0)	0.58 (0.38–0.87)	0.008	0.60 (0.35–0.94)	0.02
<b>Perinatal</b>						
Fetal death	1 (0.7)	1 (0.7)		0.98		
Neonatal death	2 (1.5)	7 (5.1)	0.29 (0.06–1.42)	0.13	0.34 (0.06–1.81)	0.22
Birth weight <2500 g	56 (41.2)	59 (42.8)	0.96 (0.69–1.26)	0.81	0.97 (0.68–1.29)	0.85
Birth weight <1500 g	18 (13.2)	27 (19.6)	0.68 (0.36–1.21)	0.20	0.74 (0.36–1.37)	0.35
Composite adverse outcomes	11 (8.1)	19 (13.8)	0.59 (0.26–1.25)	0.17	0.57 (0.23–1.31)	0.19
Intraventricular hemorrhage§	1 (0.7)	2 (1.4)	0.51 (0.05–5.30)	0.58	0.33 (0.01–8.84)	0.52
Respiratory distress syndrome	11 (8.1)	19 (13.8)	0.59 (0.26–1.25)	0.17	0.57 (0.23–1.31)	0.19
Retinopathy of prematurity	2 (1.5)	0				
Necrotizing enterocolitis	0	1 (0.7)				
Composite therapy	34 (25.0)	45 (32.6)	0.77 (0.48–1.15)	0.21	0.75 (0.44–1.16)	0.20
Neonatal intensive care	33 (24.3)	42 (30.4)	0.80 (0.49–1.21)	0.30	0.80 (0.47–1.24)	0.34
Ventilation	16 (11.8)	25 (18.1)	0.65 (0.33–1.21)	0.18	0.64 (0.30–1.25)	0.20
Phototherapy	16 (11.8)	14 (10.1)	1.16 (0.56–2.25)	0.68	1.09 (0.50–2.19)	0.82
Treatment for sepsis	3 (2.2)	11 (8.0)	0.28 (0.07–1.01)	0.05	0.29 (0.07–1.10)	0.07
Blood transfusion	4 (2.9)	5 (3.6)	0.81 (0.22–2.86)	0.75	0.79 (0.19–3.10)	0.74

\* For perinatal outcomes, the relative risks, 95% confidence intervals, and P values were estimated by logistic regression clustered on maternal identifiers to account for nonindependence between twin pairs. Relative risks were adjusted for maternal age, body-mass index, smoking status, race, history of preterm birth, and cervical length at the time of randomization.

† There were 125 pregnancies and 136 infants in the progesterone group.

‡ There were 125 pregnancies and 138 infants in the placebo group.

§ Intraventricular hemorrhage was grade 2 in all infants.

the progesterone group (34 of 109 [31.2%] vs. 20 of 112 [17.9%]; relative risk, 0.57; 95% CI, 0.35 to 0.93;  $P=0.03$ ). Among women with singleton pregnancies, the incidence of spontaneous preterm birth was significantly higher in the placebo group than in the progesterone group (36 of 112 [32.1%] vs. 20 of 114 [17.5%]; relative risk, 0.54; 95% CI, 0.34 to 0.88;  $P=0.02$ ).

There were no significant differences between the two groups in the secondary outcomes (Table 2). There were no important adverse events or side effects in either group. None of the women reported any increase in the frequency or severity of general or local side effects, such as sleepiness, fatigue, headaches, or genital irritation, or any new symptoms after the onset of treatment.

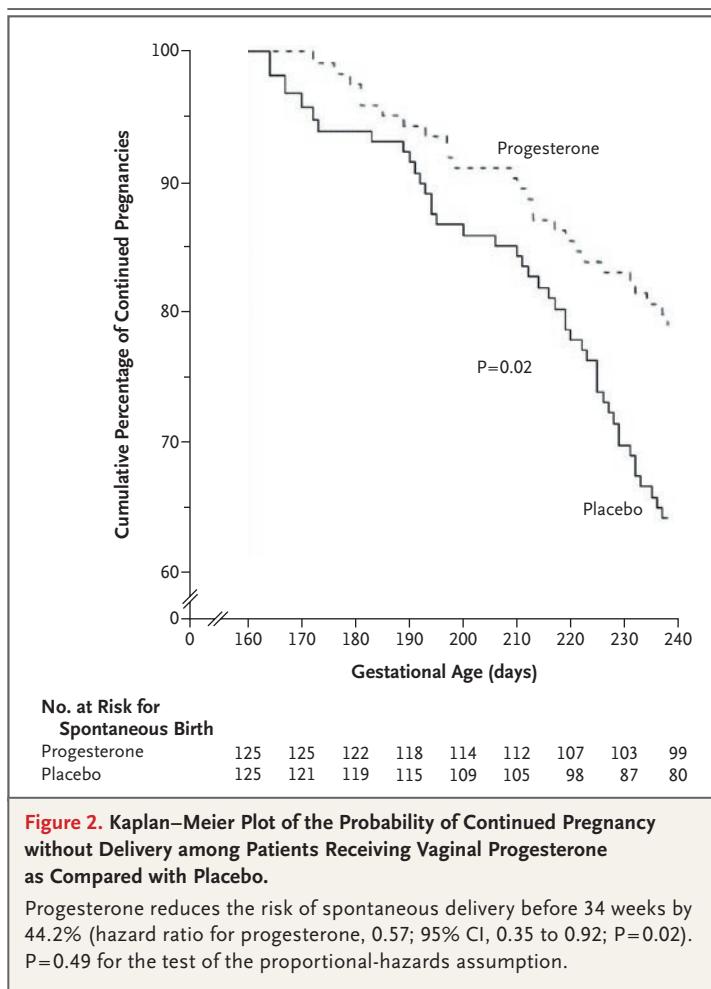
Data on pregnancy outcome were also obtained from 23,795 (96.6%) of the 24,620 women in whom cervical length was originally measured; spontaneous delivery before 34 weeks occurred in 489 (2.1%). The cervical length was 15 mm or less in 408 women (1.7%), of whom 126 (30.9%) delivered preterm, accounting for 25.8% of the early deliveries. The cervical length was 16 to 25 mm in 1975 women (8.3%), of whom 100 (5.1%) delivered preterm, accounting for 20.4% of the early deliveries.

DISCUSSION

The results of this randomized trial demonstrate that in women with a short cervix, the daily vaginal administration of 200 mg of progesterone from 24 to 34 weeks of gestation significantly reduces the rate of spontaneous preterm delivery. There was no significant reduction in perinatal mortality or neonatal morbidity. However, the trial was not designed with sufficient power to address these end points.

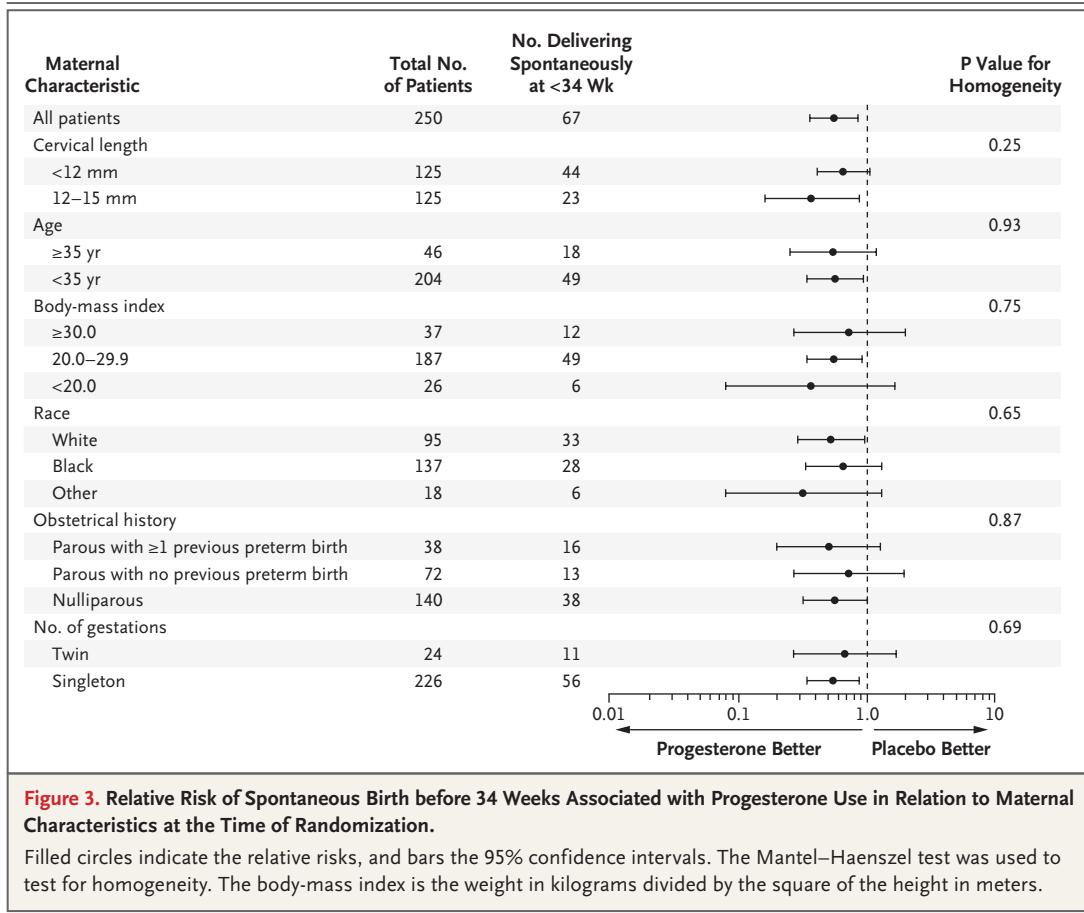
Our multicenter screening study, involving close to 25,000 pregnancies, confirms that transvaginal ultrasonographic measurement of cervical length at 22 weeks of gestation identifies a subgroup of about 1.5% of the female population at particularly high risk for early preterm delivery. In the control group of women with cervical lengths of 15 mm or less, the incidence of spontaneous early preterm delivery was 34%. This is much higher than the overall female population rate of about 2% in the United Kingdom.<sup>17</sup>

In the small number of twin pregnancies included in our study, a nonsignificant reduction



in preterm delivery was associated with progesterone treatment. In a larger study published elsewhere in this issue of the *Journal* that examined twin pregnancies specifically,<sup>18</sup> the intramuscular administration of 17 alpha-hydroxyprogesterone caproate (17P) did not reduce the incidence of preterm birth.

We used 200 mg of progesterone, in contrast to the 100-mg dose used in a randomized trial of women with a history of preterm birth.<sup>5</sup> We chose this high dose because we considered patients with a very short cervix to be at particularly high risk for preterm delivery,<sup>8–10</sup> although it is unknown whether there is a dose–response relationship between progesterone and the reduction in risk of preterm delivery. We chose vaginal micronized natural progesterone, rather than intramuscular synthetic 17P. Micronized progesterone can be administered either orally or vaginally, but the latter route is preferable because of enhanced



bioavailability and the absence of undesirable side effects, such as sleepiness, fatigue, and headaches.<sup>19,20</sup>

The American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommends that women who have had a previous preterm delivery should be considered for treatment with progesterone in a subsequent pregnancy but notes that the ideal formulation, optimal route of delivery, and long-term safety of progesterone remain unknown.<sup>21</sup> Epidemiologic and animal studies have found no significant relationship between clinically administered progesterone and congenital malformations.<sup>22</sup> However, in one study, embryonic deaths occurred in pregnant rhesus monkeys treated with intramuscular injections of 17P.<sup>23</sup> In one randomized trial of women with previous preterm births, the intramuscular administration of 17P was associated with a nonsignificant increase in miscarriage or fetal death (3.6%, vs. 1.3% in controls).<sup>4</sup>

Although progesterone proved effective in re-

ducing spontaneous preterm birth in women with cervical lengths less than 15 mm, it should be noted that less than one third of the women in our overall study group who had spontaneous preterm delivery met this criterion. Future randomized trials should investigate the effectiveness of progesterone in other high-risk populations.

Measuring cervical length is a readily learned skill for obstetrical sonographers. Furthermore, ultrasound screening is available routinely in maternity units in developed countries, and studies have shown that transvaginal ultrasonography is acceptable to pregnant women and does not cause discomfort in the vast majority.<sup>24,25</sup> The findings of our study provide support for a strategy of routine screening of pregnant women by ultrasonographic measurement of cervical length and the prophylactic administration of progesterone to those with a short cervix.

Supported by a grant (Charity No. 1037116) from the Fetal Medicine Foundation, London.

No potential conflict of interest relevant to this article was reported.

## APPENDIX

In addition to the authors, the following institutions and investigators participated in the Fetal Medicine Foundation Second Trimester Screening Group: **Scientific advisory committee:** S. Thornton, University of Warwick, Coventry; Z. Alfirevic, University of Liverpool, Liverpool; and G. Smith, Cambridge University, Cambridge — all in the United Kingdom; **Cervical assessment:** King's College Hospital, London — P. Radhakrishnan, O. Khoury, L. Divianathan, A. Kaul, A. Rao, R. Kuppusamy; Queen Elizabeth Hospital, Woolwich, United Kingdom — F. Molina, S. Turan, K. Gajewska, V. Palanappian; University Hospital of Lewisham, London — G. Paramasivam, A. Atzei, S. Poggi, H. Vafaie; Southend University Hospital, Essex, United Kingdom — P. Hagan, H. Coward, Z. Milovanovic; Darent Valley Hospital, Dartford, United Kingdom — D. Nikolopoulou, F. Tsolakidis; Hospital Clinico Universidad de Chile, Santiago, Chile — G. Rencoret, D. Pedraza, E. Valdes; Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo — S. Valadares, R. Damiao; University Hospital, Larissa, Greece — H. Skentou.

## REFERENCES

- Mathews TJ, Curtin SC, MacDorman MF. Infant mortality statistics from the 1998 period linked with birth/infant death data set. *Natl Vital Stat Rep* 2000; 48(12):1-25.
- Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005;352:9-19.
- Veen S, Ens-Dokkum MH, Schreuder AM, Verloove-Vanhorick SP, Brand R, Ruys JH. Impairments, disabilities, and handicaps of very preterm and very-low-birthweight infants at five years of age: the Collaborative Project on Preterm and Small for Gestational Age Infants (POPS) in the Netherlands. *Lancet* 1991;338:33-6.
- Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348:2379-85. [Erratum, *N Engl J Med* 2003;349:1299.]
- 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.
- Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth. *Cochrane Database Syst Rev* 2006;1:CD004947.
- Mercer BM, Goldenberg RL, Moawad AH, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. *Am J Obstet Gynecol* 1999;181:1216-21.
- Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. *N Engl J Med* 1996;334:567-72.
- To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. *Am J Obstet Gynecol* 2006;194:1360-5.
- To MS, Skentou CA, Royston P, Yu CK, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. *Ultrasound Obstet Gynecol* 2006;27:362-7.
- To MS, Skentou C, Chan C, Zagaliki A, Nicolaides KH. Cervical assessment at the routine 23-week scan: standardizing techniques. *Ultrasound Obstet Gynecol* 2001;17:217-9.
- Introduction to stratified analysis. In: Greenland S, Rothman KJ. *Modern epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998:253-80.
- Hosmer DW Jr, Lemeshow S. *Applied logistic regression*. 2nd ed. New York: John Wiley, 2000.
- Hosmer DWLS. *Applied survival analysis: regression modeling of time to event data*. New York: John Wiley, 1999.
- Grambsch PMT. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515-26.
- Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690-1.
- Data from Office of Population Census and Surveys: NHS maternity statistics, England: 2002-2003. London: Department of Health Statistical Office, 2004.
- Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007;357:454-61.
- Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmouh L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. *Fertil Steril* 1994;62:485-90.
- Friedler S, Raziell A, Schachter M, Strassburger D, Bukovsky I, Ron-El R. Luteal support with micronized progesterone following in-vitro fertilization using a down-regulation protocol with gonadotrophin-releasing hormone agonist: a comparative study between vaginal and oral administration. *Hum Reprod* 1999;14:1944-8.
- ACOG committee opinion: use of progesterone to reduce preterm birth. *Obstet Gynecol* 2003;102:1115-6.
- Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. *Birth Defects Res A Clin Mol Teratol* 2005;73:906-18.
- Hendrickx AG, Korte R, Leuschner F, et al. Embryotoxicity of sex steroidal hormones in nonhuman primates. II. Hydroxyprogesterone caproate, estradiol valerate. *Teratology* 1987;35:129-36.
- Heath VC, Southall TR, Souka AP, Novakov A, Nicolaides KH. Cervical length at 23 weeks of gestation: relation to demographic characteristics and previous obstetric history. *Ultrasound Obstet Gynecol* 1998;12:304-11.
- Clement S, Candy B, Heath V, To M, Nicolaides KH. Transvaginal ultrasound in pregnancy: its acceptability to women and maternal psychological morbidity. *Ultrasound Obstet Gynecol* 2003;22:508-14.

Copyright © 2007 Massachusetts Medical Society.

## ELECTRONIC ACCESS TO THE JOURNAL'S CUMULATIVE INDEX

At the *Journal's* site on the World Wide Web ([www.nejm.org](http://www.nejm.org)), you can search an index of all articles published since January 1975 (abstracts 1975-1992, full text 1993-present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the full text of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet ([www.nejm.org](http://www.nejm.org)).