OBSTETRICS

Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial

Marie-Victoire Senat, MD, PhD; Raphael Porcher, MD, PhD; Norbert Winer, MD, PhD; Christophe Vayssière, MD, PhD; Philippe Deruelle, MD, PhD; Marianne Capelle, MD; Florence Bretelle, MD, PhD; Frank Perrotin, MD, PhD; Yves Laurent, MD; Laure Connan, MD; Bruno Langer, MD, PhD; Aymeric Mantel, MD; Shohreh Azimi; Patrick Rozenberg, MD; for the Groupe de Recherche en Obstétrique et Gynécologie

OBJECTIVE: The objective of the study was to evaluate the use of 17 alpha-hydroxyprogesterone caproate (17P) to reduce preterm delivery in women with a twin pregnancy and short cervix.

STUDY DESIGN: This open-label, multicenter, randomized controlled trial included women with a twin pregnancy between 24^{+0} and 31^{+6} weeks of gestation who were asymptomatic and had a cervical length of 25 mm or less measured by routine transvaginal ultrasound. Women were randomized to receive (or not) 500 mg of intramuscular 17P, repeated twice weekly until 36 weeks or preterm delivery. The primary outcome was time from randomization to delivery. Analysis was performed according to the intent-to-treat principle.

RESULTS: The 17P and control groups did not differ significantly for median [interquartile range] time to delivery: 45 (26–62) and 51 (36–66) days, respectively. However, treatment with 17P was associated with a significant increase in the rate of preterm delivery before 32 weeks.

CONCLUSION: Twice-weekly injections of 17P did not prolong pregnancy significantly in asymptomatic women with a twin pregnancy and short cervix.

Key words: 17 alpha-hydroxyprogesterone caproate, cervical length, preterm delivery, twins, ultrasonography

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From the Department of Obstetrics and Gynecology, Assistance Publique–Hôpitaux de Paris, Hopital Bicêtre, Hopital Antoine Béclère, Université Paris Sud, Faculté de Medecine, Paris, and Inserm, Center for Research in Epidemiology and Population Health, Villejuif (Dr Senat); Department of Biostatistics, Hôpital Saint-Louis, Paris Diderot University and Institut National de la Santé et de la Recherche Médicale, Paris (Dr Porcher); and the Departments of Obstetrics and Gynecology at the following institutions: Hôpital Mère-Enfant, Nantes (Dr Winer); Hôpital Paul de Viguier, Toulouse (Dr Vayssière); Hôpital Jeanne de Flandre, Lille (Dr Deruelle); Hôpital de La Conception, Marseille (Dr Capelle); Hôpital Nord, Marseille (Dr Bretelle); Hôpital Bretonneau, Tours (Dr Perrotin); Hôpital Morvan, Brest (Dr Laurent); Hôpital Paul de Viguier, Toulouse (Dr Connan); Hôpital Hautepierre, Strasbourg (Dr Langer); Hertford British Hospital, Levallois-Perret (Dr Mantel); and Hôpital Poissy-Saint Germain, Versailles-St Quentin University, Poissy (Dr Rozenberg); and the Department of Clinical Research Ile-de-France, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, Paris (Ms Azimi) France.

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Reprints: Marie Victoire Senat, MD, PhD, Hôpital Bicêtre. Service de Gynécologie et Obstétrique, 78 Avenue du Général Leclerc, 94 270 Kremlin Bicêtre, France. marie-victoire.senat@bct.aphp.fr.

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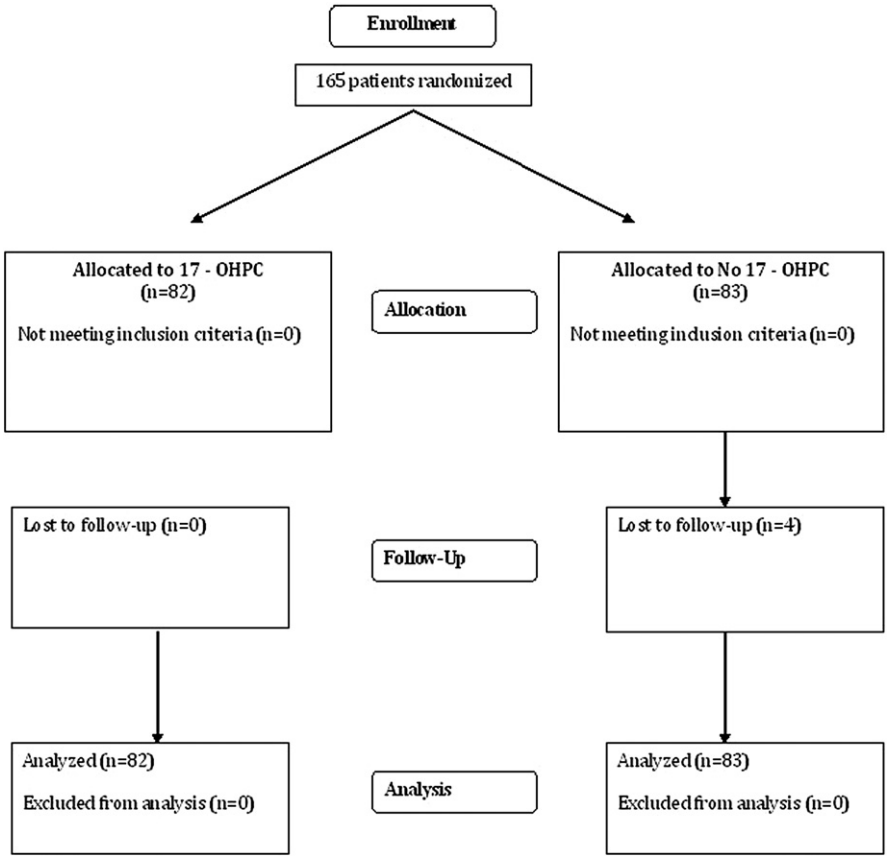
Despite relative stability in the twin birth rate in France between 2003 and 2010, the population of twins remains at high risk of preterm birth (PTB) and low birthweight. The latest French National Perinatal survey (2010), which studied a representative sample of births in France (including 14,761 live births), found twins accounted for 19% of premature babies and 23% of babies with low birthweight. Among live births, 41.7% of twins were preterm vs 5.3% of singletons: the risk of prematurity was almost 8 times higher in twins. Moreover, in 2003, 6.3% of twins were born before 32 weeks of gestation; in 2010, this rate reached 8.4%.[1] In the United States, the rate of PTB <at less than 32 weeks of gestation for twin pregnancies was 11.4%, 7.1 times the rate for singleton pregnancies (1.6%).[2]

Because of progesterone's role in maintaining pregnancy,[3-8] randomized trials have compared it with placebo in different

FIGURE 1
Enrollment, randomization, and follow-up of the study participants



Senat. 17P in twin pregnancy with a short cervix. Am J Obstet Gynecol 2013.

groups of singleton pregnancies at high risk of preterm delivery and found that prenatal progesterone administration significantly reduces the preterm delivery (PTD) rate.[9,10] In randomized trials of unselected twin pregnancies, however, prophylactic progesterone administration does not appear to reduce this rate.[11-18]

Cervical ultrasonography seems to improve the selection of twins at especially high risk of PTB. The good predictive value of transvaginal sonographic cervical length measurements in the diagnosis of very PTB in twin pregnancies has been shown in several studies,[19-26] including 2 separate systematic reviews with metaanalyses.[19,22] However, no well-designed, large, randomized trial has yet assessed the efficacy of progesterone in prolonging pregnancy in selected women with a twin pregnancy and short cervix, and uncertainty continues to surround the indications for its use, route of administration, and optimal dose in twin pregnancies.[9]

We therefore conducted a multicenter randomized trial to evaluate the use of 17 alpha-hydroxyprogesterone caproate (17P) to reduce the risk of PTD in women with a twin pregnancy and a cervical length of 25 mm or less.

MATERIALS AND METHODS

Subjects and screening

This open-label, multicenter, randomized controlled trial took place at 10 university hospitals across France. Women older than 18 years, carrying twins, asymptomatic, and with a cervical length of 25 mm or less measured in the sagittal plane by routine transvaginal ultrasound according to the standard technique[27] were eligible for inclusion. They were recruited by the attending physician or a research midwife at 24^{+0} through 31^{+6} weeks of gestation, immediately (the same day) after an ultrasound measurement of cervical length of 25 mm or less. Other inclusion criteria were agreement to regular follow-up and written informed consent.

Women with any of the following criteria were ineligible: cervical dilatation greater than 3 cm, premature rupture of the membranes, placenta previa, monochorial monoamniotic pregnancy, signs of twin-to-twin transfusion syndrome, severe intrauterine growth restriction of at least 1 fetus, known major structural or chromosomal fetal abnormality, death of 1 fetus, any maternal or fetal disease requiring PTD, progesterone therapy before inclusion, ongoing anticonvulsant treatment, or participation in any other treatment trial. Twin gestations resulting from intentional fetal reduction were also excluded.

A first-trimester ultrasound scan, routinely performed in France, determined gestational age and chorionicity for all patients. Monthly cervical length measurements after this scan until delivery were part of standard management for multiple pregnancies in all participating centers. Three separate measurements were taken each time, in the absence of contractions, and the shortest was kept for analysis.

Abdominal ultrasound was performed before inclusion to assess fetal well-being, quantity of amniotic fluid, placental site(s), and fetal weights.

The Ethics Committee of Poissy Saint-Germain Hospital (Comité de Protection des Personnes), Saint-Germain en Laye, France, approved the study protocol for all centers. The trial is registered at ClinicalTrials.gov (NCT00331695).

Randomization and follow-up

After verification of the inclusion and exclusion criteria, eligible consenting women were randomly assigned in a 1:1 ratio to receive 500 mg of intramuscular 17P, to be repeated twice weekly until 36 weeks or PTD, whichever occurred first, or to no treatment with 17P (control group). Additional management in both arms was determined by the attending physician, except that progesterone was not allowed in the control group. An independent, centralized, computer-generated