Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data

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OBJECTIVE: To determine whether the use of vaginal progesterone in asymptomatic women with a sonographic short cervix (≤25 mm) in the midtrimester reduces the risk of preterm birth and improves neonatal morbidity and mortality.

STUDY DESIGN: Individual patient data metaanalysis of randomized controlled trials.

RESULTS: Five trials of high quality were included with a total of 775 women and 827 infants. Treatment with vaginal progesterone was associated with a significant reduction in the rate of preterm birth <33 weeks (relative risk [RR], 0.58; 95% confidence interval [CI], 0.42–0.80), <35 weeks (RR, 0.69; 95% CI, 0.55–0.88), and <28 weeks (RR, 0.50; 95% CI, 0.30–0.81); respiratory distress syndrome (RR, 0.48; 95% CI, 0.30–0.76); composite neonatal morbidity and mortality (RR, 0.57; 95% CI, 0.40–0.81); birthweight <1500 g (RR, 0.55; 95% CI, 0.38–0.80); admission to neonatal intensive care unit (RR, 0.75; 95% CI, 0.59–0.94); and requirement for mechanical ventilation (RR, 0.66; 95% CI, 0.44–0.98). There were no significant differences between the vaginal progesterone and placebo groups in the rate of adverse maternal events or congenital anomalies.

CONCLUSION: Vaginal progesterone administration to asymptomatic women with a sonographic short cervix reduces the risk of preterm birth and neonatal morbidity and mortality.

Key words: admission to neonatal intensive care unit, birthweight <1500 g, mechanical ventilation, prematurity, preterm birth, progestin, respiratory distress syndrome, transvaginal ultrasound, uterine cervix, 17α-hydroxyprogesterone caproate

Cite this article as: Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol 2012;206:124.e1-19.

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The majority of the authors report no conflict of interest except as stated in this paragraph. J.M.O'B. was involved in studies of progesterone gel treatment for preterm birth prevention sponsored by Columbia Laboratories Inc, the manufacturer of the preparation used in the PREGNANT Trial and a previous trial of vaginal progesterone in women at risk for preterm delivery. J.M.O'B. serves on advisory boards and is a consultant for Watson Pharmaceuticals, a company with a financial interest in marketing vaginal progesterone gel for the prevention of preterm birth. He and others are listed in the patent on the use of all progesterone compounds to prevent preterm birth (US Patent No. 7,884,093: Progesterone for the Treatment and Prevention of Spontaneous Preterm Birth). G.W.C. is an employee of Columbia Laboratories Inc.

This research was supported, in part, by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services.

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0002-9378/free • © 2012 Published by Mosby, Inc. • doi: 10.1016/j.ajog.2011.12.003

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Preterm birth is the leading cause of perinatal morbidity and mortality worldwide[1] and contributes to 70% of neonatal mortality and approximately half of long-term neurodevelopmental disabilities.[2] A recent systematic review has estimated that 12.9 million births, or 9.6% of all births worldwide, were preterm, of which approximately 11.9 million (92.3%) were in Africa, Asia, Latin America, and the Caribbean.[3] During the last 25 years, the preterm birth rate in the United States increased 36%, from 9.4% in 1981 to 12.8% in 2006.[4] This increase has been attributed to a higher frequency of "indicated" preterm births in singleton gestations and preterm delivery in multiple gestations resulting, in part, from the use of assisted reproductive technologies.[5-15]

Spontaneous preterm labor/delivery is considered to be one of the "great obstetrical syndromes",[16,17] a term that emphasizes that obstetrical disorders with a similar phenotype are caused by multiple pathologic processes,[18] have a long subclinical phase, and may result from complex gene-environment interactions.[19-22]

Progesterone is considered a key hormone for pregnancy maintenance, and a decline of progesterone action is implicated in the onset of parturition.[23-26] If such a decline occurs in the midtrimester, cervical shortening may occur, and this would predispose to preterm delivery. Therefore, an untimely decline in progesterone action has been proposed as a mechanism of disease in the "preterm parturition syndrome".[27]

Progesterone actions are mediated by genomic and nongenomic effects which have been studied in the uterine cervix, myometrium, sperm, etc.[28-101] A blockade of progesterone action can lead to the clinical, biochemical, and morphologic changes associated with cervical ripening.[28-101] A short cervix detected with transvaginal ultrasound is a powerful predictor of preterm birth in women with singleton and twin gestations.[27,102-109] The shorter the sonographic cervical length, the higher the risk of spontaneous preterm birth.[102-105,110-123] Moreover, a short cervix is associated with intraamniotic infection and inflammation, and this may modify the response to interventions.

★ EDITORS' CHOICE ★

An interest in the role of progestogens (natural and synthetic) for the prevention of preterm birth has existed for decades.[124-130] Recently, the administration of vaginal progesterone was proposed for the prevention of preterm birth in women with a sonographic short cervix in the midtrimester based on its biologic effects on the cervix, myometrium, and chorioamniotic membranes. In 2007, Fonseca et al,[131] on behalf of the Fetal Medicine Foundation of the United Kingdom, reported that the administration of vaginal progesterone in women with a cervical length ≤15 mm was associated with a significant 44% reduction in the rate of spontaneous preterm birth <34 weeks of gestation. Similar findings were reported by DeFranco et al[132] in a secondary analysis of a randomized clinical trial of vaginal progesterone in women with a history of preterm birth in which the cervix was measured. Hassan et al[133] reported the largest randomized clinical trial to date, indicating that vaginal progesterone, when administered to women with a cervical length of 10-20 mm, reduces the rate of preterm birth at <33, <28, and <35 weeks, and this was associated with a significant 61% reduction in the rate of respiratory distress syndrome (RDS).[133] Since the publication of the trial of Hassan et al,[133] several trials evaluating vaginal progesterone in women at high risk of spontaneous preterm birth,[134-136] including a subset of women with a short cervix, have been published.

An individual patient data (IPD) metaanalysis is a specific type of systematic review in which the original research data for each participant in a study are sought directly from the investigators responsible for that trial.[137] Such an approach has been considered the gold standard for summarizing evidence across clinical studies since it offers several advantages, both statistically and clinically, over conventional metaanalyses, which are based on published aggregate data.[138] These advantages include standardizing and updating of data sets, the ability to verify the quality of the data and the appropriateness of the analyses, the improvement of consistency across trials (eg, definition of outcomes), the performance of subgroup analyses that could effectively identify groups of patients who might benefit from an intervention, the investigation of interaction between patient-level covariates and treatment effects, and the performance of time-to-event analyses.[139-141]

Using IPD from randomized controlled trials, we performed a metaanalysis to evaluate the efficacy and safety of vaginal progesterone for the prevention of preterm birth and neonatal morbidity and mortality in asymptomatic women with a sonographic short cervix in the midtrimester. We also sought to determine whether there were clinical benefits associated with the administration of vaginal progesterone in singleton and twin pregnancies.

MATERIALS AND METHODS

The study was conducted based on a prospectively prepared protocol, and is reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for metaanalyses of randomized controlled trials[142] and suggested guidelines for IPD metaanalyses.[141]

Literature search

We searched MEDLINE, EMBASE, CINAHL, and LILACS (all from inception through December 31, 2011); the Cochrane Central Register of Controlled Trials (www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) (1960 through December 31, 2011); ISI Web of Science (www.isiknowledge.com) (1960 through December 31, 2011); Research Registers of ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.anzctr.org.au, www.nihr.ac.uk, and www.umin.ac.jp/ctr); and Google Scholar using a combination of key words and text words related to *progesterone* ("progesterone," "progestins," "progestogen," "progestagen," "progestational agent") and *preterm birth* ("preterm," "premature"). Proceedings of the Society for Maternal-Fetal Medicine and international meetings on preterm birth, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. Experts in the field were contacted to identify further studies. No language restriction was used.