Vaginal Progesterone Reduces Preterm Birth, Neonatal Morbidity and Mortality in Women at Risk

Significant Findings Published in the American Journal of Obstetrics & Gynecology

Philadelphia, PA, December 14, 2011 – Women with a short cervix should be treated with vaginal progesterone to prevent preterm birth, according to a landmark study by leading obstetricians around the world. Vaginal progesterone decreased the rate of preterm birth by 42%, and significantly reduced the rate of respiratory distress syndrome and the need for mechanical ventilation, as well as a composite of several complications of premature newborns (e.g. infection, necrotizing enterocolitis, intracranial hemorrhage, etc.). An early online version of the study was published today in the American Journal of Obstetrics and Gynecology (AJOG), and is available on the AJOG website free of charge.

“Our analysis provides compelling evidence that vaginal progesterone prevents preterm birth and reduces neonatal morbidity/mortality in women with a short cervix,” said lead investigator Dr. Roberto Romero, Chief of the Perinatology Research Branch and Head of the Program in Perinatal Research and Obstetrics of the Division of Intramural Research for the NICHD/NIH/DHHS, Bethesda, MD and Detroit, MI. “Importantly, progesterone reduced early preterm birth (those occurring before 33 or 28 weeks of gestation). These immature babies are at the greatest risk for complications, death, and long-term disability (e.g. cerebral palsy). Progesterone also decreased a fraction of ‘late preterm births,’ which are the most common preterm deliveries. The profile of adverse events was no different from placebo. Follow-up studies of babies exposed to progesterone in utero to the age of 18 or 24 months showed no evidence of any behavioral or physical problems. The authors of this study recommend that transvaginal sonographic measurement of the cervix be performed in all pregnant women between 19 to 24 weeks of gestation to assess the risk of preterm delivery. This strategy also allows the identification of women at risk for preterm delivery during their first pregnancy. Other strategies, which are based on treating women with a previous preterm birth, do not address the challenge of prevention in women with their first pregnancy.”
Preterm birth is the leading cause of perinatal morbidity and mortality worldwide. Moreover, preterm birth is also the main cause of infant mortality (death to the age of one year). Approximately 12.9 million births worldwide are preterm, of which 92.3% occur in Africa, Asia, Latin America, and the Caribbean. In the United States and Europe, there are 1,000,000 preterm births per year.

Progesterone is a natural hormone produced by the ovary during the menstrual cycle and in early pregnancy, and subsequently, in the placenta. A decline in progesterone action is considered to be important for the onset of labor. If such a decline occurs in the mid-trimester, cervical shortening may lead to the onset of preterm labor. The administration of progesterone is postulated to work by maintaining a high concentration of the hormone in the uterine cervix.

Several studies had evaluated the administration of vaginal progesterone versus placebo to prevent preterm birth when a short cervix was found by ultrasound in the mid-trimester of pregnancy. What is unique about the study published today is that investigators worldwide pooled the data from the different studies and performed a meta-analysis of individual patient data (IPD). This is the "gold standard" for summarizing evidence across clinical trials. It has the advantage of increasing the power to detect differences in efficacy and adverse events, and also allows subgroup analyses that may not have been possible in each individual study.

The IPD meta-analysis included five high-quality trials of vaginal progesterone versus placebo, was conducted at multiple centers in both developed and developing countries, and included a total of 775 women and 927 infants. The primary endpoints were: 1) preterm birth at <33 weeks; and 2) a composite index of perinatal morbidity and mortality. The authors also studied other secondary endpoints and explored the effect of cervical length, a history of previous preterm birth, maternal age, race/ethnicity, and body mass index on progesterone action.

The results were remarkably consistent and significant across trials performed in different parts of the world. Administering vaginal progesterone to asymptomatic women with a short cervix revealed by sonogram in the mid-trimester was associated with a 42% reduction in the rate of preterm birth before 33 weeks of gestation. There was also a significant reduction in the risk of preterm birth before 35, 34, and 28 weeks.

The study also found a 43% decrease in neonatal morbidity and mortality. Vaginal progesterone significantly reduced the risk of respiratory distress syndrome by 52%, and there was significantly lower admission to NICUs (placebo, 20.7% vs. progesterone, 29.1%).

Results of previous trials about the effects of vaginal progesterone or injectable progestins (synthetic compounds with progesterone action) in women with a twin gestation had been negative. However, a subset of patients in the study published today focused on women with a twin gestation and a short cervix. In this particular group, vaginal progesterone reduced the rate of preterm birth at <33 weeks by 30% and significantly reduced the composite neonatal morbidity/mortality of twins. Dr. Romero indicated that a study of vaginal progesterone in twin pregnancies with a short cervix is urgently needed to confirm these findings because the reduction in preterm birth did not reach significance (most likely due to the small number of twins available to study).

A major finding of this study is that progesterone benefits not only women who have a short cervix, but also those who have a prior preterm birth and a short cervix. This has practical
implications, because vaginal progesterone is a less expensive and less invasive alternative than the placement of a cervical suture (cerclage) in patients who had a previous preterm birth and have a short cervix.

“The results of this analysis of five large randomized trials have the potential to result in a sea change in obstetrical practice in the U.S. and Europe and eventually in the rest of the world,” commented AJOG Co-Editor-in-Chief, Thomas J. Garite, MD. “Prematurity is the leading cause of death and damage for newly born babies and despite enormous efforts, no impact has been made in the rate of preterm birth, which is actually rising in recent years.”

As advocated in an accompanying editorial by C. Andrew Combs, MD, PhD, Obstetrix Medical Group, San Jose, CA, in the print version of the Journal, the potential for reducing prematurity lies in implementing routine vaginal ultrasound for all pregnant women in the middle months of pregnancy to measure the length of the cervix and if a short cervix is found, treat these patients with progesterone. The majority of premature births occur in women with no risk factors, so this approach has real potential to make an impact in the overall premature birth rate. Two recently published cost analysis studies, suggest that this approach can not only save lives and prevent the devastating damages often caused by prematurity, but can also result in a annual savings of nearly 1/2 billion dollars in health care costs in the U.S. alone.


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NOTES FOR EDITORS
Full text of the article is available to credentialed journalists upon request. Contact Francesca Costanzo at 215-239-3249 or ajogmedia@elsevier.com to obtain a copy. Journalists wishing to schedule interviews with the author should contact Roberto Romero, MD, at 313-993-2700 or prbchiefstaff@med.wayne.edu.

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