Vaginal progesterone reduces preterm birth, neonatal morbidity and mortality in women at risk

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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*).

"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