Does vaginal progesterone reduce preterm delivery among asymptomatic women who have a short cervix in the midtrimester?

Yes. When it was administered to women who had a sonographically determined short cervix (≤25 mm) during the midtrimester, vaginal progesterone reduced the risk of preterm birth at less than 33 weeks (relative risk [RR], 0.58; 95% confidence interval [CI], 0.42–0.80), less than 35 weeks (RR, 0.69; 95% CI, 0.55–0.88), and less than 28 weeks (RR, 0.50; 95% CI, 0.30–0.81), according to this meta-analysis of randomized, controlled trials. Vaginal progesterone also reduced the rate of neonatal morbidity and mortality (composite RR, 0.57; 95% CI, 0.40–0.81).

FAST TRACK

Despite the findings of this meta-analysis, there is no one-size-fits-all approach to a short cervix in the midtrimester

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 analysis of individual patient data. Am J Obstet Gynecol. 2012;206(2):124.e1–19.

EXPERT COMMENTARY

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This study by Romero and colleagues represents yet another attempt by obstetricians to successfully address the important issue of preterm delivery.

My main objection to this attempt?

It's a systematic review of already published data, with no original findings presented.

The investigators argue that the use of individual patient data strengthens their analysis. They observe that this approach "has been considered the gold standard for summarizing evidence across clinical studies since it offers several advantages, both statistically and clinically, over conventional meta-analyses, which are based on published aggregate data."

Their methodology included a literature search of multiple databases, including MEDLINE, EMBASE, CINAHL, LILACS, and the Cochrane Central Register of Controlled Trials. Two of the authors (Romero and Conde-Agudelo) made every effort to select only methodologically rigorous articles; about half of the articles identified initially were excluded.

The primary outcome of interest was preterm birth at less than 33 weeks of gestation. After exhaustive analysis, the investigators concluded that **universal cervical-length assessment, followed by administration of vaginal progesterone in cases involving a cervical length of 10 to 20 mm, is effective, economical, and without risk.**

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Women who have a history of a short cervix are at very high risk of preterm delivery. A patient who also has a history of prior preterm delivery as a complicating factor is at particularly high risk of recurrent preterm delivery. More puzzling is what to do with the asymptomatic short cervix in a nulliparous patient. For now, I would recommend that physicians discuss with these patients the options available, including the risks, benefits, and limitations of each. Depending on cervical length, these options may include vaginal progesterone, cerclage, or expectant management, with or without serial cervical-length measurement.

››JOHN T. REPKE, MD

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Although this conclusion sounds promising, it must be viewed with caution—for more than a few reasons.

Weaknesses of the analysis

Here are some of my reservations about this study:

- Meta-analyses should always be interpreted with caution, as should papers that rely on composite outcomes and secondary analyses to bolster their case, as this investigation does
- The true cost of the proposal for universal cervical-length screening is unclear. The figures the investigators present—that, "for every 100,000 women screened, 22 cases of neonatal death or long-term neurologic deficits could be prevented, and approximately $19 million could potentially be saved"—are not universally agreed on.
- Our ability to offer reliable cervical-length screening throughout the US health-care system to all obstetric patients is questionable, and I worry about the bottlenecks such screening would create in the provision of health care
- The US Food and Drug Administration (FDA) recently decided *against* approving vaginal progesterone.[1] Their reasons were numerous, but the most important reasons are summarized by the following FDA committee statements:
  - "From a statistical perspective, the evidence from this single study [Phase 3 study 300] does not support the efficacy of progesterone 8% gel for the prevention of preterm deliveries among women with a short cervical length"
  - "From a clinical perspective, it does not appear that the applicant has identified a population of US women who are likely to benefit from the use of progesterone gel to reduce their risk of preterm birth."

This latter point refers to the fact that preterm-birth reduction in this Phase-3 study was meaningful predominantly in centers outside the United States.

What are we to do?

For now, we lack sufficient data to support universal cervical-length screening and vaginal progesterone administration in cases involving a cervical length of 10 to 20 mm to prevent preterm delivery. That said, the FDA committee found this approach to lack statistically significant differences in the incidence of adverse events (maternal, fetal, and neonatal) and conceded, therefore, that a properly informed and counseled patient could be offered this treatment until more definitive data are available.

A completely unscientific approach would be to give vaginal progesterone to every pregnant woman in the United States and, at the end of 1 year, assess the change (or lack thereof) in the rate of prematurity, the cost of care, and neonatal morbidity and mortality. That would settle this issue once and for all—unlike clinical trials or repetitive analyses of already completed clinical trials, which seem unlikely to accomplish this end.

FAST TRACK

We lack sufficient data to support universal cervical-length screening and vaginal progesterone administration in cases involving a cervical length of 10 to 20 mm to prevent preterm delivery

Reference

1. Background document for the meeting of the Advisory Committee for Reproductive Health Drugs. January 20, 2012.