



# Does vaginal progesterone reduce the risk of preterm birth in a high-risk woman?

**No** Prophylactic treatment with vaginal progesterone did not reduce the incidence of preterm birth (i.e., birth at 32 weeks' gestation or earlier) in women who had a history of spontaneous preterm birth, according to the results of a randomized, double-blind, placebo-controlled multinational trial.

*O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30:687-696.*

## ► EXPERT COMMENTARY

**Alan M. Peaceman, MD**, Professor of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, Ill.

Two studies published in 2003 rekindled interest in the use of progestational agents for the prevention of recurrent preterm birth. Da Fonseca and colleagues randomized patients who had risk factors for premature birth to daily vaginal administration of a natural progesterone suppository or placebo and demonstrated a significant reduction in birth before 34 weeks.<sup>1</sup> In a larger, multicenter trial in the United States, Meis and associates randomized patients who had a prior preterm birth to weekly administration of intramuscular 17 $\alpha$ -progesterone caproate or placebo.<sup>2</sup> Compared with the control group, the treatment group had a one-third reduction in births before 37 weeks, and a near 50% reduction in deliveries before 32 weeks' gestation.

Since these studies were published, there has been much enthusiasm about the use of progesterone to reduce the incidence of preterm birth, but obstacles remain to widespread implementation of recommendations. First, 17 $\alpha$ -progesterone caproate is

not approved by the Food and Drug Administration for any indication in this country, and is not available from any major drug manufacturer. Physicians who have adopted its use for patients who have a history of preterm birth have to obtain it from a compounding pharmacy.

Use of a vaginally administered preparation would likely overcome these obstacles and meet with greater patient acceptance, but widespread use awaits further research confirming its efficacy.

## In outcomes, few differences between treatment and placebo groups

O'Brien and colleagues recruited women between 18 and 23 weeks' gestation who had previously delivered prematurely and assigned them to daily vaginal administration of 90 mg of progesterone (in gel) or placebo. Treatment was administered until 37 weeks'

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

The negative results of this well-designed study should persuade you not to adopt the vaginal route of progesterone administration as a means of preventing recurrent preterm birth. Although data have been published that vaginal progesterone reduces the rate of preterm birth in patients with a very short cervical length ( $\leq 15$  mm), this is a small fraction of the patients at risk.

The final word isn't in yet, but studies under way may shed light on the optimal dosing and route of administration for different subpopulations of patients—so that further benefit can be achieved.

» ALAN M. PEACEMAN, MD

## FAST TRACK

Widespread use of vaginal progesterone to reduce the risk of preterm birth awaits further research to confirm its efficacy

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gestation, delivery, or premature rupture of membranes. Outcomes were similar in the two groups, with no statistical differences in delivery before 32 or 37 weeks' gestation, or in mean birth weight.

Nor did the groups differ in the incidence of admission for preterm labor, use of tocolytic therapy, neonatal morbidity, or NICU admission.

The authors concluded that vaginally administered progesterone does not reduce

the frequency of recurrent preterm birth in women who have a history of spontaneous preterm birth.

#### References

1. Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk. *Am J Obstet Gynecol.* 2003;188:419-424.
2. Meis PJ, Klebanoff M, Thom E, et al, for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17-alpha-hydroxyprogesterone caproate. *N Engl J Med.* 2003;348:2379-2385.

## Does menopausal estrogen therapy increase the risk of benign proliferative breast disease?

**Yes** Use of unopposed estrogen (as 0.625 mg of conjugated equine estrogen daily) more than doubled the risk of benign proliferative breast disease, according to the findings of this randomized controlled trial. It's unclear whether this finding ultimately translates to a greater risk of breast cancer.

*Rohan TE, Negassa A, Chlebowski RT, et al. Conjugated equine estrogen and risk of benign proliferative breast disease: a randomized controlled trial. J Natl Cancer Inst. 2008;100:563-571.*

#### ► EXPERT COMMENTARY

**Andrew M. Kaunitz, MD**, Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Jacksonville, Fla. Dr. Kaunitz serves on the OBG MANAGEMENT Board of Editors.

**B**enign proliferative breast disease (BPBD) is a relatively common condition that is diagnosed by biopsy. It is important because of the economic and psychological burdens of biopsy and because BPBD may be a precursor to breast cancer. Some experts believe that the earliest phase of a continuum leading to invasive cancer

is BPBD without atypia, followed by BPBD with atypia, in situ cancer, and then invasive disease.

#### Population was derived from WHI study

In this report, the risk of incident BPBD was compared among hysterectomized women 50 to 79 years old who participated in the Women's Health Initiative (WHI). These women were randomized to conjugated equine estrogen (CEE) or placebo and monitored for, on average, 6.9 years of follow-up. They underwent baseline and annual clinical breast examination and mammography.

Overall, 232 new cases of BPBD were diagnosed among 10,739 women—approximately two thirds of them in the group randomized to CEE. Compared with women randomized to placebo, women taking CEE had twice the risk of being diagnosed with BPBD without atypia (hazard ratio [HR], 2.34; 95% confidence interval [CI], 1.71-3.20). For the subgroup of women with BPBD in whom histopathology was moderately extensive or florid (but lacking atypia), risk was similarly elevated (HR, 2.22).

#### **FAST TRACK**

The study showed that unopposed conjugated equine estrogen more than doubled the risk of benign proliferative breast disease in menopausal women

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## Examining the EVIDENCE



Use of CEE was not associated with a substantially increased risk of atypical hyperplasia.

### Limitations of the study

This trial tested only one estrogen regimen and dosage. It also was terminated earlier than expected, which may have rendered the risk estimates less precise. In addition, a significant number of participants stopped taking CEE during the trial.

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study found a significantly heightened risk of BPBD with use of unopposed estrogen, raising concerns about the potential for subsequent breast cancer. However, the same WHI estrogen-only trial from which this study<sup>1</sup> derives, as well as the Nurses Health Study,<sup>2</sup> found no increased risk of invasive breast cancer with estrogen therapy.

The authors of this WHI report suggest that longer follow-up of participants may help resolve this contradiction. In the meantime, some clinicians may choose to advise women who are beginning unopposed estrogen therapy that they face an elevated risk of breast biopsy for benign breast disease.

>> ANDREW M. KAUNITZ, MD

### References

1. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA*. 2004;291:1701-1712.
2. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med*. 2006;166:1027-1032.