

Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH, for the Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med.* 2007;357:462–469.

### Q. Does progesterone reduce the risk of preterm birth among women with a short cervix?

**A.** Yes. In this randomized, placebo-controlled study of 250 gravidas with a cervical length of 15 mm or less, those who were randomized to a daily dose of 200 mg of intravaginal micronized progesterone starting at 24 weeks' gestation had a lower rate of spontaneous delivery before 34 weeks (19.2%) than did women in the control group (34.4%) (relative risk, 0.56; 95% confidence interval, 0.36 to 0.65). However, progesterone did not reduce the rate of perinatal mortality or neonatal morbidity.

The trial included both singleton and twin gestations.

prematurity debate. The first is that history is probably not any more useful in screening for risk of prematurity than it is for screening for gestational diabetes. This is not to say that history is unimportant, but rather to emphasize that history alone may be insufficient to identify populations that may be at risk for preterm delivery and therefore might possibly benefit from intervention.

The second is the suggestion, based on earlier work by Iams and associates,<sup>3</sup> that decreased cervical length may distinguish a group of women at high risk for preterm delivery.

#### EXPERT COMMENTARY

**John T. Repke, MD**, Professor and Chair, Department of Obstetrics and Gynecology, Penn State College of Medicine—Milton S. Hershey Medical Center, Hershey, Pa. Dr. Repke serves on the OBG MANAGEMENT Board of Editors.

The study by Fonseca and colleagues is an important contribution to the ever-expanding body of literature on ways to reduce preterm birth. It immediately follows a paper in the same issue of the *New England Journal of Medicine* declaring the failure of intramuscular 17 $\alpha$ -hydroxyprogesterone caproate (17P) to prevent preterm birth in twin gestations.<sup>1</sup> In contrast, an earlier study from 2003 found 17P to be more effective than no treatment in preventing spontaneous preterm delivery in singleton pregnancies of women with a history of premature delivery.<sup>2</sup>

The trial by Fonseca and colleagues capitalizes on two unique aspects of the

#### What to make of equivocal findings?

Is an intervention worthwhile if it has no effect on key outcomes such as morbidity and mortality? And what are we to make of the fact that intramuscular 17P is effective in singleton but not twin gestations?

The current trial was insufficiently powered to affirm the null hypothesis with respect to perinatal mortality and neonatal morbidity—ie, there were not enough patients in the study to determine whether the lack of difference in these variables was real or due to insufficient sample size. However, intravaginal progesterone seems more attractive than intramuscular injection—at least intuitively. It may be that a local anti-inflammatory response is what reduced spontaneous preterm delivery—and that may be why intramuscular injection of synthetic progestin at a remote site was less effective, depending on whether the pregnancy was a singleton or twin gestation.

#### FAST TRACK

**Progesterone was associated with a lower rate of preterm birth, but did not reduce perinatal mortality and neonatal morbidity**

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## Preventing preterm birth: Lessons from the real world

In my own practice, I estimate that fewer than 20% of patients who might be eligible for progesterone accept the treatment after I review all the data with them. Two illustrative cases highlight the conundrum a clinician faces with respect to “measurable outcome differences.”

**Patient #1** is a healthy 30-year-old gravida 3 para 1102 whose obstetric history includes:

- a full-term delivery in 2002 that was complicated by premature onset of contractions but never required tocolytic therapy
- a delivery at 29 weeks in 2005 that was complicated by preterm premature rupture of membranes and chorioamnionitis.

Her current pregnancy is managed with cervical-length assessment (all measurements exceed 35 mm) and

17 $\alpha$ -hydroxyprogesterone caproate. She delivers a healthy 3,500-g infant at term without complication.

**Patient #2** is a healthy 31-year-old gravida 3 para 0202 who delivered at 33 weeks in 2002 and at 35 weeks in 2003. Both deliveries were secondary to idiopathic preterm labor. Her current pregnancy is followed routinely, with no cervical-length assessment. After counseling, she decides against progesterone therapy and goes on to deliver a 3,300-g healthy infant at 39 weeks' gestation.

### The dilemma

These two cases are medically similar; both were eligible for progesterone treatment. One patient chose it and one did not—yet their obstetric outcomes were identical.

—John T. Repke, MD

### FAST TRACK

## Make certain that cervical length is measured during ultrasonographic screening

We must also be concerned about the yet-unexplained observation of higher—though statistically insignificant—rates of miscarriage and intrauterine fetal death among women receiving intramuscular 17P, compared with placebo.<sup>2</sup>

### Too early to elevate either regimen to “standard of care”

In my opinion, it is still too early to elevate either intravaginal or intramuscular progesterone to the level of “standard of care.” What may be reasonable in this age of increasing use of first- and mid-trimester ultrasonographic screening is to make certain that information on cervical length is provided. Also important is a candid discussion with the patient about the range of options for management of a short cervix in pregnancy. In the meantime, more than a dozen trials on the prevention of pre-

maturity are in progress. The hope is that more definitive answers to the prematurity riddle are “just around the corner”—which, I suspect, was also the hope in 1975.<sup>4</sup>

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Greco T, Graham CA, Bancroft J, Tanner A, Doll HA. The effects of oral contraceptives on androgen levels and their relevance to premenstrual mood and sexual interest: a comparison of two triphasic formulations containing norgestimate and either 35 or 25 µg of ethinyl estradiol. *Contraception*. 2007;76:8–17.

### FAST TRACK

## A low-dose OC was associated with improvement in premenstrual mood

## Q. Does the dosage of estradiol in OCs affect mood and sexual interest?

**A.** It may affect premenstrual mood. In this comparison of two oral contraceptives (OCs) containing the same progestin but different dosages of ethinyl estradiol, women using the 25-µg formulation were significantly more likely to report improvement in premenstrual mood than were those using the 35-µg pill, although this effect was not reflected in measures of free testosterone (FT) or dehydroepiandrosterone sulfate (DHEA-S). Sexual interest was not affected significantly with either formulation.

The progestin used in this study was a triphasic regimen of norgestimate in dosages of 0.18, 0.215, and 0.25 mg.

### EXPERT COMMENTARY

**Andrea J. Rapkin, MD**, Professor of Obstetrics and Gynecology, David Geffen School of Medicine, UCLA, Los Angeles, Calif.

OCs are the most widely used method of reversible contraception in the world.<sup>1</sup> Since the 1970s, at least 50% of users have reported emotional lability, depression, magnification of premenstrual symptoms, and decreased libido<sup>2–4</sup>—and almost 30% have cited these effects as a reason for discontinuing the pill.<sup>5</sup> As Greco and colleagues point out, complaints of depression and decreased libido have diminished somewhat since lower-dose (<35 µg) ethinyl estradiol formulations were developed. The psychopharmacology underlying these symptoms, and whether the decreased libido and mood changes share a common etiology, have yet to be clarified.

There are many potential reasons for the emotional lability, increased premenstrual symptoms, and decreased libido associated with OCs, including:

- abrupt withdrawal of hormones in regimens containing 21 active pills followed by a 7-day pill-free interval

- suppression of endogenous hormones, including biologically available testosterone, dehydroepiandrosterone, and other neuroactive steroid metabolites of progesterone
- direct adverse effects of the estrogen or progestin
- genetic and environmentally determined “vulnerability factors.”

### Strengths of the study

By comparing two triphasic OCs with identical progestin dosages but different quantities of ethinyl estradiol, the authors isolated the variable of estrogen dose. They also assessed concentrations of FT and DHEA-S, and measured depression and sexual interest using reliable tools.

Another strength is that women were prospectively randomized to the two regimens and studied during the first 3 months of OC use—before discontinuation due to side effects, although there were some study dropouts.

### Effects on hormones, mood

As expected, the lower-dose OC reduced FT to a lesser degree than did the 35-µg pill. Overall, scores on the Beck Depression Inventory during the premenstrual week showed a slight improvement in mood in both groups after 3 months on the OC. However, a greater percentage of women using the 25-µg formulation showed improvement in mood, although the authors were careful to point out that a causal relationship between this improvement and the dosage of estradiol cannot be confirmed.

The authors also noted that improvement in premenstrual mood with OC use has previously been reported, but wrongly claimed that placebo-controlled studies have not shown a significant difference between OC and placebo for this variable. On the contrary, I would point

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to two recent randomized trials that demonstrated efficacy of an OC containing 20 µg of ethinyl estradiol and 3 mg of the progestin drospirenone in a 24/4-day regimen for the severe form of premenstrual syndrome called premenstrual dysphoric disorder (PMDD).<sup>6,7</sup> This formulation received Food and Drug Administration approval for treatment of PMDD in women who desire hormonal contraception.

The mildly anti-androgenic drospirenone, a spironolactone analogue equivalent to approximately 25 mg of spironolactone, has not been studied in isolation (ie, apart from a combination OC) with respect to premenstrual mood and sexual functioning. However, its anti-androgenic effect was not deleterious in the PMDD studies<sup>6,7</sup> and may have played a role in treatment outcome—although a similar study of the same dose of drospirenone combined with 30 µg of ethinyl estradiol in a 21/7-day regimen was not more effective than placebo for severe premenstrual symptoms.<sup>8</sup> One reason may be that the 24/4-day regimen provides more complete suppression of the hypothalamic–pituitary–ovarian axis.

DHEA-S and other neuroactive steroid metabolites of progesterone are suppressed in women taking OCs. One study found no deterioration in mood despite suppression of these steroids in women given a 20-µg OC.<sup>9</sup> Paoletti and associates<sup>10</sup> have even suggested that the suppression of DHEA-S may be responsible for mood improvement with the OC containing 30 µg of ethinyl estradiol and 3 mg of drospirenone, compared with untreated women.

**Symptoms were assessed only during premenstrual week.** Because the women in the study by Greco and colleagues did not complete daily mood ratings, it is impossible to know whether the OC with the lower dose of ethinyl estradiol was better for moodiness unrelated to the premenstrum. Other symptoms of premenstrual syndrome, such as anxiety, irritability, and mood swings, were not assessed prospectively.

**Bottom line: Lower dose of estradiol is probably better**

The study by Greco and colleagues adds to evidence that an OC containing a lower dose of ethinyl estradiol is better for premenstrual mood, although this effect is unlikely to be related to its effect on androgens. It remains unclear how a lower estrogen dose affects mood in women who have a history of premenstrual syndrome and whether mood improvement with a lower estrogen dose is related to a lower degree of androgen suppression.

When there is concern about a patient's mood or depression, prescribe a low-dose OC, such as one containing 20 µg of ethinyl estradiol and 3 mg of drospirenone in a 24/4-day regimen (Yaz). Most women experience no adverse effects of OCs on mood. Those with a history of depression should be aware that there may be a deterioration of mood on the OC. ■

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**FAST TRACK**  
**When there is concern about a patient's mood, prescribe a low-dose OC containing 20 µg of estradiol and 3 mg of drospirenone**