Liability Risk Low for Prescribers of Progesterone

Study results show progesterone can prevent preterm birth in asymptomatic women with previous history.

BY KATE JOHNSON
Montreal Bureau

With proper informed consent, the prescription of progesterone to prevent preterm birth in appropriate patients should not put physicians at increased risk of liability, according to several experts.

In fact, physicians may face a lawsuit if they fail to offer it when indicated, suggested Steve Caritis, M.D.

"You can envision a woman who has had two previous preterm births and her physician doesn't raise this option. If she has another preterm birth there could be liability for not informing her that the therapy exists," he said in an interview.

Dr. Caritis, professor and chief of maternal-fetal medicine at the University of Pittsburgh, was one of the investigators in the key study that led to the endorsement of progesterone therapy by the American College of Obstetricians and Gynecologists as a means of preventing preterm birth (ACOG Committee Opinion #291 [Obstet. Gynecol. 2003;102:1115-6]).

The randomized, placebo-controlled trial, conducted for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, found that weekly intramuscular injections of 250 mg of 17 α-hydroxyprogesterone caproate (17-OHPC) decreased the risk of preterm birth by 34% in women with at least one spontaneous preterm birth (N. Engl. J. Med. 2003;348:2379-85).

ACOG's endorsement of the therapy stresses the importance of restricting it to this very select group of high-risk patients. The opinion notes that the drug "has been studied only as a prophylactic measure in asymptomatic women, not as a tocolytic agent," and that further studies are needed to evaluate its use in women with multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. It also says that both the optimal route of drug delivery and its long-term safety remain unknown.

Given such issues, it is reasonable for physicians to have concerns about liability, but this should not deter them from prescribing the therapy where appropriate, said Larry Veltman, M.D., chair of ACOG's Committee on Professional Liability and chair of obstetrics and gynecology at Providence St. Vincent Medical Center in Portland, Ore.

"It is good medicine to have concerns about risks to the baby—this is a relatively new development and the risks and benefits still need to be thoroughly investigated. But to date, there have been no specific fetal or maternal risks identified," he told this newspaper. The main point of the committee opinion was not to caution physicians about risks, but rather to inform them about the treatment, explained Laura Riley, M.D., who, as past chair of ACOG's Committee on Obstetric Practice, was involved in preparing the opinion on progesterone therapy.

"It brought this treatment to the attention of people who don't necessarily read the [New England Journal of Medicine], so that people would know this is one option—the only preventive option for preterm birth," said Dr. Riley, medical director of labor and delivery at Massachusetts General Hospital in Boston.

Physicians at Northwest Perinatal Center, a subdivision of Women's Healthcare Associates in Portland, Ore., have been prescribing progesterone therapy for more than 2 years and until now have asked patients to sign a consent form stating that the treatment is not considered standard of care and that it does not ensure a term delivery, said Thomas Lee, M.D., a perinatologist who works at the center. "We are now questioning whether this is still necessary. The more experience we have with this therapy, the less concerned we are with liability issues," he said, adding that more than 80% of the 20 patients they have treated with it have delivered after 35 weeks.

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Dr. Sarah J. Kilpatrick backs the ACOG position.

At the University of Illinois at Chicago, Sarah J. Kilpatrick, M.D., said she feels very comfortable about offering the treatment without any specific informed consent. "Personally, I don't think there's a risk of liability," said the professor and head of obstetrics at the university.

"When you review the literature on risk of progesterone to the fetus you really can't come up with anything, but because there are no long-term data it is important to limit its use to only those women who can benefit from it. To me, the risk with progesterone is that people are going to use it inappropriately and therefore expose women to whom it may be not helpful," Dr. Kilpatrick said.

Dr. Caritis agreed that long-term safety issues are probably not high on the list of concerns for most physicians prescribing this therapy, but quality control and standardization issues may be. Currently, a commercial preparation of 17-OHPC is not available, and the drug can be obtained only through compounding pharmacies.

"Compounding pharmacies do not have anybody regulating them, and what regulations they do have are kind of loose. Therefore, I think there's a concern from physicians about the quality of the compound that comes from these pharmacies. You don't know how they're making the product and whether they're doing the proper testing," said Dr. Caritis.

He said a good compounding pharmacy should provide quality control information outlining its protocol for pyrogen, bacteriologic, and virologic testing, among other things.

The Maternal-Fetal Medicine Units Network is trying to interest a pharmaceutical company in marketing a commercial progesterone formulation for the prevention of preterm birth, said Dr. Caritis. However, there are other barriers that will have to be addressed, according to Dr. Kilpatrick. Less than half of the 30 patients who have been offered this treatment at her center have accepted it, she said. Cost is one of the issues. Although it is an inexpensive therapy (between $60 and $120 for a 10-week supply), Medicaid and most insurance companies will not pay for it, she said. ■

Studies Back Progesterone Injections to Prevent Preterm Birth

BY SHERRY BOSCHERT
San Francisco Bureau

San Francisco — Recent studies provide some guidance in applying recommendations from the American College of Obstetricians and Gynecologists on the use of progesterone to prevent preterm birth, Steve Caritis, M.D., said at a meeting on antepartum and intrapartum management, sponsored by the University of California, San Francisco.

Only intramuscular injections of 17 α-hydroxyprogesterone caproate (17-OHPC) have been shown convincingly to prevent recurrent preterm birth, he said.

The American College of Obstetricians and Gynecologists recommended in 2003 that progesterone may be used to help prevent preterm birth but should be restricted to pregnant women with a documented history of spontaneous preterm birth before 37 weeks' gestation. The statement noted that "the ideal progesterone formulation remains unknown until further research is done."

A 1990 metaanalysis of studies using 17-OHPC found that this agent dramatically lowered the risks for preterm labor and preterm birth.

Metaanalysis of studies using 17-OHPC showed the overall odds of preterm birth were reduced by 43%.

DR. CARITIS

Although some individual studies had shown a benefit, most were too small to detect significant changes in benefit. When combined in the metaanalysis, they provided the power to show a dramatic impact of 17-OHPC, which reduced the overall odds of preterm birth by 43%, and the odds of preterm birth in women at high risk for preterm birth by 50%, he said.

A separate study conducted for the National Institutes of Child Health and Human Development Maternal-Fetal Medicine Units Network randomized 459 pregnant women who had at least one previous preterm birth to receive weekly injections of 17-OHPC or placebo starting between gestational weeks 16 and 20. The study was stopped early when it became evident that 17-OHPC decreased the risk for preterm birth before 37 weeks by 34%.

Critics of that study noted that the control group had a very high rate of preterm birth and that castor oil (in which 17-OHPC is dissolved) is a uterine stimulant, said Dr. Caritis, professor and chief of maternal-fetal medicine at the University of Pittsburgh. Both the treatment and control groups received castor oil, so it is hard to argue that this created a methodologic problem, he added. The preterm birth rate among controls was similar, however, to rates seen in two other studies, and was not unexpected, he said.

Critics also noted a higher rate of spontaneous abortions at less than 20 weeks in the 17-OHPC group. The five spontaneous abortions in that group were counted as preterm births, so there would have been a more significant benefit in the 17-OHPC group, compared with placebo, if these losses had been excluded, he countered. "I think this is still the best study we have" on preventing preterm birth with progesterone, Dr. Caritis said.

A third study randomized 142 women with singleton gestations and a history of preterm birth to vaginal suppositories of 100 mg of progesterone or placebo starting at 24-34 weeks' gestation, later than the 16-20 weeks' initiation in the 17-OHPC trial. Results showed a 50% reduction in preterm birth before 37 weeks of gestation with the progesterone suppositories and an 85% reduction in preterm births before 34 weeks' gestation. The latter result "makes me a little suspicious," he said.

The vaginal suppository trial excluded patients with preterm premature rupture of the membranes (PPROM). "We don't think that's appropriate. It's hard to differentiate preterm labor with or without PPROM," Dr. Caritis said.

There is no evidence that oral progesterone affects preterm birth risk, he added. ■