

# Studies Back Progesterone to Prevent Preterm Birth

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

The American College of Obstetricians and Gynecologists in 2003 recommended 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 for-

mulation 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.

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 labor 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, who is professor and chief of maternal-fetal medicine at the University of Pittsburgh.

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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 progesterones, 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 PPRM," Dr. Caritis said. His institution offers only 17-OHPC to women with previous spontaneous preterm birth. For now, they do not give this treatment to women who have a short cervix, threatened preterm labor, or multifetal gestation.

Studies are underway in the maternal-fetal medicine units network evaluating 17-OHPC treatment for those indications. ■



Brief Summary (See Package Brochure for Full Prescribing Information)

#### Rx only

Plan B® is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

#### CONTRAINDICATIONS

Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the Plan B® regimen consisting of the emergency use of two progestin pills. POPs however, are not recommended for use in the following conditions:

- Known or suspected pregnancy
- Hypersensitivity to any component of the product
- Undiagnosed abnormal genital bleeding

#### WARNINGS

**Plan B® is not recommended for routine use as a contraceptive.**

**Plan B® is not effective in terminating an existing pregnancy.**

#### Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking Plan B®. At the time of expected menses, approximately 75% of women using Plan B® had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

#### Ectopic Pregnancy

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1,000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B®.

#### PRECAUTIONS

##### Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

##### STD/HIV

Plan B®, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

##### Physical Examination and Follow-up

A physical examination is not required prior to prescribing Plan B®. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking Plan B®.

##### Carbohydrate Metabolism

The effects of Plan B® on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking Plan B®.

Plan B® is a registered trademark of Women's Capital Corporation, a subsidiary of Duramed Pharmaceuticals, Inc.



Duramed Pharmaceuticals, Inc.  
Subsidiary of Barr Pharmaceuticals, Inc.  
Pomona, New York 10970

#### Drug Interactions

Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of Plan B® would be affected by these or any other medications.

#### Nursing Mothers

Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

#### Pediatric Use

Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of Plan B® emergency contraception before menarche is not indicated.

#### Fertility Following Discontinuation

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

#### ADVERSE REACTIONS

The most common adverse events in the clinical trial for women receiving Plan B® included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. The table below shows those adverse events that occurred in ≥5% of Plan B® users.

Table 3 Adverse Events in ≥5% of Women, by % Frequency

Most Common Adverse Events	Plan B® Levonorgestrel N=977 (%)
Nausea	23.1
Abdominal Pain	17.6
Fatigue	16.9
Headache	16.8
Heavier Menstrual Bleeding	13.8
Lighter Menstrual Bleeding	12.5
Dizziness	11.2
Breast Tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Plan B® demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

- Nausea: Occurred in 23% of women taking Plan B® (compared to 50% with Yuzpe)
- Vomiting: Occurred in 6% of women taking Plan B® (compared to 19% with Yuzpe)

#### DRUG ABUSE AND DEPENDENCE

There is no information about dependence associated with the use of Plan B®.

#### OVERDOSAGE

There are no data on overdosage of Plan B®, although the common adverse event of nausea and its associated vomiting may be anticipated.

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Revised FEBRUARY 2004

BR- 038 / 21000382503