First 'No-Period Pill' Receives FDA Approval

BY SHERRY BOSCHERT
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The first oral contraceptive that does not include regularly scheduled intervals for menstrual bleeding has been approved by the Food and Drug Administration.

The new contraceptive, Lybrel, is being called the "no-period pill" in news accounts, but it induced amenorrhea in only a minority of the more than 2,400 women enrolled in two 1-year clinical studies that led to the pill's approval, FDA officials said in a press briefing.

Unscheduled breakthrough bleeding or spotting lasting a median of 4-5 days per month was reported in the last month of the studies by 41% of women who took Lybrel the entire year, with higher rates in earlier months. Thus, the amenorrhea rate for study completers was 59%. About half of women dropped out of the studies before then, however, so the amenorrhea rate among all enrollees was probably about 30%-35%, said Dr. Daniel Shames of the FDA.

The studies did not assess the pill's effects on symptoms of menstruation, such as bloating, headaches, or cramping. Wyeth Pharmaceuticals, the maker of Lybrel, will not be able to make claims about the product's effects on menstrual symptoms, he said.

Lybrel contains a low-dose combination of common contraceptive medications—90 mcg of the progestin levonorgestrel and 20 mcg of the estrogen ethinyl estradiol. It comes in a 28-pill pack and generally will be more expensive than other oral contraceptives, many of which are generic medications.

Safety and efficacy did not differ significantly from those of other oral contraceptives, according to the FDA. In general, about 1% of oral contraceptive users have unintended pregnancies each year.

Without regular periods, women on Lybrel may have more difficulty recognizing if they become pregnant, Dr. Shames cautioned. "Women should take a pregnancy test if they believe they may be pregnant."

The high proportion of dropouts in the studies may be because women were not expecting breakthrough bleeding and spotting, he speculated. In the study definitions, bleeding required sanitary protection; spotting was bleeding that was not heavy enough to require sanitary protection.

Women who choose Lybrel for contraception after discussing it with their physician or other health care provider can be prepared for breakthrough bleeding and spotting, and may be more likely to continue taking the pill. "Many will decide they don't want this experience, but others will who know what to expect," Dr. Shames said.

Like other oral contraceptives, Lybrel increases the risk of blood clots, heart attacks, and strokes. The FDA has asked Wyeth to conduct a postmarketing study of serious adverse events (primarily thromboembolic events) to determine if long-term effects are any different than with other contraceptives.

The elimination of regular periods is not expected to increase risk. Contraceptive regimens that employ progestin alone stop menstruation for time spans longer than a year and have not increased the rates of adverse events, Dr. Shames said.

Three other oral contraceptives that aim to reduce menstrual bleeding times have been approved in the past 2 years. The Seasonale regimen induces a week of menstruation four times per year instead of monthly. Monthly bleeding on the Loestrin 24 and Yaz regimens can last 3 days or fewer instead of the usual 7 days. Older regimens use placebo pills to allow bleeding for 7 days.

The decrease in breakthrough bleeding and spotting on Lybrel over time may occur because "the endometrium stabilizes, we believe," Dr. Shames said. "However, at the end of a year, a fair proportion of women still has bleeding and spotting." ■

Risk of Lymphoma Doubled in Offspring of Radiologic Technicians

LOS ANGELES — Radiologic technicians who work during pregnancy have twice the risk of having a child who develops lymphoma than those who do not work during pregnancy, Kimberly J. Johnson reported at the annual meeting of the American Association for Cancer Research.

Such work did not increase the risk of leukemia or solid tumors among the offspring, Ms. Johnson of the department of pediatrics, division of epidemiology/clinical research, at the University of Minnesota, Minneapolis, and her colleagues wrote in a poster presentation.

The study used 63 years' worth of self-reported data involving 81,354 offspring of 38,239 female members of the U.S. Radiologic Technologists cohort. During that time, 230 of their offspring developed leukemia, lymphoma, or solid tumors before the age of 19. A radiologic technician was considered to have worked during pregnancy if she reported having worked during the child's birth year and the prior year.

After adjusting for maternal age and birth year, the investigators found no significant changes in the hazard ratio for leukemia or for solid tumors, but the hazard ratio for lymphoma was 1.99. A significant increase in the risk of lymphoma was seen among children born between 1960 and 1984 but not among those born between 1921 and 1959.

—Robert Finn

DRUGS, PREGNANCY, AND LACTATION

Assessment of Prenatal SSRI Use

Studies released over the last year have raised a spectrum of concerns regarding the use of antidepressants during pregnancy, while others have brought into focus the risk for new onset or relapse of depression during pregnancy and the impact of maternal depression during pregnancy on obstetrical outcome and neonatal well-being. These findings received a considerable amount of attention in the literature and in the media.

Among the concerns raised was the extent to which fetal exposure to one selective serotonin reuptake inhibitor (SSRI)—paroxetine—has been associated with an increased risk for cardiovascular malformations. In other studies, SSRI use during pregnancy was associated with compromised neonatal adaptation with symptoms of jitteriness, tachypnea, and tremulousness, the so-called "neonatal abstinence syndrome."

BY LEE COHEN, M.D.

This finding of transient neonatal jitteriness and tremulousness has been highly consistent across studies that date back to the mid-1970s, when similar concerns were raised regarding prenatal exposure to the older tricyclics. About 25% of children born to mothers treated with SSRIs, particularly late in pregnancy, appear to have these symptoms.

It is noteworthy, however, that the clinical relevance of the syndrome seems small. Even in the most rigorous study to date, which described a subgroup of children exposed in utero to SSRIs, those who had these symptoms required no particular treatment interventions during the acute neonatal period. The precise underlying mechanism for this finding has never been well understood.

Also reported last year was our collaborative study with investigators at the University of California, Los Angeles, and Emory University, Atlanta, demonstrating that the rate of depressive relapse associated with antidepressant discontinuation during pregnancy is high—about 70%—compared with 25% among pregnant women who maintained treatment with these medicines across pregnancy.

These new data on teratogenicity, treatment-emergent neonatal syndromes, and relapse risk have provided more well-delineated information on the risks and benefits of antidepressant use during pregnancy. The information is extremely important in this setting, because antidepressant use during pregnancy in the United States may be as high as 4%-6%, based on estimates by some of our recent work.

A study published last summer by investigators from the University of Michigan, Ann Arbor, illustrates the fact that while depression is relatively common during pregnancy, most women at risk for illness don't receive any treatment, and, when treatment is prescribed, it is often suboptimal.

In the study, 1,837 pregnant women from five hospital-affiliated obstetrics clinics were screened for depression, 276 of whom were identified as being at risk. Only 20% of the at-risk women were receiving some form of antidepressant treatment. Of the group getting treatment, 48% received a combination of medication and counseling with psychotherapy, 21% received antidepressants only, and 31% received psychotherapy only. Still, in many cases, the treatment was inadequate. Only 43% of those who were taking antidepressants for 6-8 weeks were given the recommended daily dose.

Among the women who met the criteria for major depressive disorder, only 33% received any type of treatment; only 11% received what was reported to be adequate antidepressant therapy (Gen. Hosp. Psychiatry 2006;28:289-95). The low rate of treatment of depression during pregnancy may reflect concerns regarding the effects of antidepressants on the fetus. However, even women in the study who received psychotherapy alone did not receive an adequate intensity of treatment.

One has to wonder whether these findings reflect concerns over the past year about fetal exposure to antidepressants. It is notable that, even when a clinical decision is made to use antidepressant therapy, treatment is incomplete.

Incomplete treatment of depression during pregnancy represents a failure in clinical risk-benefit decision, because the woman and child are exposed to both medication and the adverse effects of the disorder. And clinical depression untreated during pregnancy is the strongest predictor of postpartum depression—which can have enduring effects for the patient, her newborn, and her family.

The Michigan study underscores the need for effective strategies to detect and treat women at risk for depression during pregnancy. Sustaining euthymia and maintaining emotional well-being during this period should be our major clinical goals.

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