Implanon's Efficacy in Obese Still Not Known

BY DAMIAN McNAMARA
Miami Bureau

Miami Beach — Nearly a year after the approval of a contraceptive implant, its advantages and disadvantages are becoming better known, but there are still no data on its efficacy in overweight or obese women, according to a presentation at an ob.gyn. conference sponsored by the University of Miami.

The Food and Drug Administration cleared Implanon (Organon International) for marketing in July 2006. It is the first single-rod, 68-mg etonogestrel, subdermal implant. The core is 40% ethylene vinyl acetate, which provides a slow, steady release of progestin for up to 3 years, according to clinical trials.

However, women who weighed more than 130% of their ideal body weight were excluded from the preapproval studies, said Dr. Paul M. Norris, adding that for physicians, such an exclusion would be "very impractical" in the United States.

Implanon replaces the six-rod Norplant device, which was removed from the market following reports of product migration and side effects, he said. "The data on Norplant suggested it was still efficacious, although less so, in overweight patients. But I am not sure you can apply this finding to Implanon."

Implanon is inserted in the subepidermal groove of a woman's arm between her biceps and triceps, about 6-8 inches up from the crux of elbow. Physicians can order Implanon only if they have completed a training program on insertion and removal sponsored by the manufacturer.

"The device to insert the implant looks like the Depo Provera syringe," said Dr. Norris, who is on the obstetrics and gynecology faculty at the University of Miami. He is also on the speakers' bureau for Organon. "The blue placebo injector for practice has a pregnancy rate of about 85% so make sure you are using the white injector with the active ingredient!"

Insertion time is faster than the Norplant, about a mean of 1 minute, compared with 4 minutes for the Norplant, The 4 cm-long, 2 mm-diameter Implanon rod is not radio-opaque. "If you lose an implant, you cannot palpate it 3 years later. It is easy to pick up on ultrasound, but you need at least a 10-MHz wand, which is not common in most [primary care physician] offices," he said.

Implanon's contraceptive effects are reversible—a woman's fertility quickly returns after removal, according to the manufacturer.

The mean removal time for Implanon is 3 minutes, compared with 11 minutes for Norplant, Dr. Norris said. "This is the mean, and some cases can take almost an hour." In clinical trials, 1% of 923 participants experienced complications at implant insertion and 1.7% had complications at implant removal.

Contraindications include a known or suspected pregnancy. "It likely won't hurt the pregnancy, but it will not prevent a pregnancy if it is already there," Dr. Norris said. History of or current thrombotic disease, history of breast cancer, hepatic tumors, active liver disease, and undiagnosed abnormal genital bleeding are other contraindications. "Make sure there is nothing serious going on before you place the Implanon."

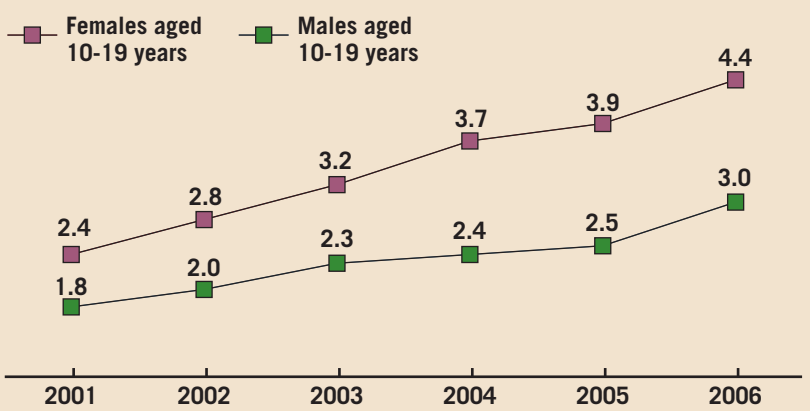
Bleeding changes were the most common reason women chose to stop Implanon treatment in clinical trials (cited by 11% of participants). Irregular bleeding and spotting is a common side effect, Dr. Norris said. In the studies, patients using Implanon reported an average of 18 days of bleeding or spotting every 90 days

Prolonged bleeding occurs in almost 20% of patients, so you will have some patients who are unhappy, Dr. Norris said. "The bottom line is you counsel patients about the unpredictable pattern and frequency of bleeding."

In terms of contraceptive efficacy, six pregnancies were reported in 20,648 cycles in the clinical trials. These patients were likely to have been already pregnant when they had the implant inserted, Dr. Norris said. ■

DATA WATCH

Rate of Sleep Aid Use Higher in Young Females Than in Young Males
(per 1,000)



Source: Medco Health Solutions Inc.

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Drugs, Pregnancy, and Lactation

Hypnotic Sleep Aids

BY GERALD G. BRIGGS, B.PHARM, FCCP

The physical discomforts of pregnancy induced by the surge of progesterone and the expanding uterus can result in sleep deprivation in pregnancy. An increased need to urinate, nausea and vomiting, heartburn, difficulty in finding a comfortable sleeping position, and, as the pregnancy progresses, the kicking and movement of the fetus, all conspire against a good night's sleep.

Prescribing sleeping medications in pregnancy may not be the best solution because long-term use can lead to habituation in the woman and her fetus. But patients often seek drug therapy to help them sleep, so it is essential to know what is relatively safe and what is not. Hypnotics fall into five subclasses:

► **Oral barbiturates.** Included in this group are aprobarbital (pregnancy risk factor C) (Alurate); pentobarbital (D) (Nembutal); and secobarbital (D) (Seconal). Developmental toxicity has not been proven, but more studies are needed regarding the potential for behavioral toxicity after long-term in utero exposure. Their long elimination half-lives (24, 22-50, and 28 hours, respectively) can cause prolonged sedation, or hangover. They are controlled substances with potential for abuse, which makes them more difficult to prescribe. Although they are excreted into milk in low amounts, they can be classified as compatible with breast-feeding.

► **Benzodiazepines.** Estazolam (ProSom), flurazepam (Dalmane), quazepam (Doral), and temazepam (Restoril) are in this category. Data on using these agents in pregnancy are limited. Although there has been no proven association between any of these agents and birth defects, they probably have effects on the embryo or fetus similar to diazepam (Valium), including neonatal motor depression (floppy infant syndrome) and/or withdrawal if used in the third trimester. Moreover, all four agents are categorized as contraindicated (risk factor X) by their manufacturers, so they should not be prescribed. Small amounts of quazepam and temazepam are excreted into milk, and the other two agents are most likely in milk as well. Occasional dosing during breast-feeding is probably safe, but the long-term effects on a nursing infant are unknown.

► **Nonbenzodiazepines.** There are five drugs in this category: chloral hydrate (for example, Somnote), ramelteon (Rozerem), zaleplon (Sonata), and low-dose (25-75 mg) trazodone (Desyrel), all risk factor C, and zolpidem (Ambien), risk factor B. The use for sleep of the antidepressant trazodone is off label, but the drug is sometimes combined with other antidepressants for this purpose. As with the benzodiazepines, the human pregnancy data are limited or nonexistent. There are no animal data for chloral hydrate, an old product that is now rarely used, but animal data on the other nonbenzodiazepines suggest low risk in pregnancy. But, as with most drugs, the best course is to avoid them in the first trimester. Occasional use in the second and third trimesters probably is low risk, but long-term use (more than 4 weeks) should be avoided. Small amounts of these drugs are excreted into milk, but occasional, short-term use probably is compatible with breast-feeding.

► **OTC antihistamines.** There are two in this category, diphenhydramine (such as Benadryl), and doxylamine (Unisom Nighttime Sleep Aid). Diphenhydramine (risk factor B) is safe throughout gestation, as is doxylamine (risk factor A). A major advantage of these antihistamines is that both have antiemetic properties that can reduce pregnancy-induced nausea and vomiting. If pyridoxine (vitamin B_6) is taken with doxylamine, the combination is the antiemetic most frequently studied in pregnancy. There is little or no experience with these agents during lactation. Although some manufacturers consider them contraindicated during breast-feeding, the lack of toxicity reports suggests these antihistamines probably are low risk for full-term nursing infants.

► **Natural products.** About 50 natural products are or have been advocated for sleep, but few have enough data to recommend their use in pregnancy or lactation. Moreover, the content and purity of natural products are often unregulated.

Natural agents that seem to be low risk are ginseng (not Siberian), honey, nutmeg, oats, and St. John's wort. But note that ginseng can cause hypertension and hypoglycemia. Agents to be avoided include American hellebore, butterbur or other petasites, kava, marijuana, melatonin (available only as an orphan drug in the United States), mugwort, passion flower, quassia, rauwolfia, Siberian ginseng, taumelloolch, tulip tree, and valerian.

A nonpharmacologic approach is the best and safest course for pregnant patients with insomnia. If medications are required, occasional, short-term use is recommended; one of the OTC antihistamines is probably best. A nonbenzodiazepine agent, such as zolpidem would be my second choice. For more information, visit www.babycenter.com, a Web site frequently visited by women to obtain information about their pregnancies, including tips on sleeping well.

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