Accutane®-Exposed Pregnancies—California, 1999

ACCUTANE® (ROCHE Laboratories, Nutley, New Jersey), known by the generic name "isotretinoin," is a prescription oral medication approved by the Food and Drug Administration (FDA) to treat severe, recalcitrant nodular acne.1 It is also a known human teratogen that can cause multiple major malformations. Embryopathy associated with the mother’s exposure to isotretinoin during the first trimester of pregnancy includes craniofacial, cardiac, thymic, and central nervous system malformations.2,3 In response to FDA recommendations,4 the manufacturer began a pregnancy-prevention program (PPP) in 1988 that included educational materials for physicians and patients and offered women reimbursement for contraceptive counseling by a physician. The PPP coordinators asked reproductive-aged women being treated with isotretinoin to enroll voluntarily in the Boston University Accutane Survey (BUAS).5 The total number of reproductive-aged women taking isotretinoin in the United States is unknown; however, 454,273 women enrolled in the BUAS from 1989 to October 1999. BUAS has estimated that 38%-40% of reproductive-aged women taking isotretinoin chose to enroll in the survey (BUAS, unpublished data, 1999). Although isotretinoin is contraindicated in pregnancy and has a package label warning users to avoid pregnancy while taking it, exposed pregnancies occur.5,7 Approximately 900 pregnancies occurred among BUAS enrollees during 1989-1998 (BUAS, unpublished data, 1999). Roche Laboratories began direct-to-consumer print advertisements in 1996, added television and radio advertisements to selected cities in 1997, and expanded the campaign to the entire United States in 1998.

During March 1999, CDC interviewed women who had had recent isotretinoin-exposed pregnancies. The objective of the study was to draw attention to the continued occurrence of isotretinoin-exposed pregnancies 11 years after the inception of the PPP and to learn more about why these exposed pregnancies happened. California was selected as the study site because of its large population and the availability of referrals from the California Teratogen Information Service and Clinical Research Center (CTIS). This report summarizes the results of the study, which suggest that some isotretinoin-exposed pregnancies can be prevented. The case reports describe the experiences of three study respondents.

Summary of Interviews

Eligible women resided in California, used isotretinoin while pregnant, had their last menstrual period after January 1, 1997, and reported their pregnancy to the BUAS or to the CTIS. Twenty-three women met these criteria; 14 consented to be interviewed. The nine eligible women who did not respond or declined to participate were enrolled in the BUAS. Two of the 14 respondents had pregnancies reported to both the BUAS and the CTIS. Nine respondents were interviewed in person and five by telephone. The interview included questions on indications for and use of isotretinoin, contraceptive history, pregnancy history, procedures used in the initial prescription of isotretinoin, and recall of advertisements for prescription acne medication.

The 14 respondents were aged 15-39 years at the time of the exposed pregnancy (median age: 25.5 years); 10 (71%) were aged 21-39 years. Eight (57%) reported having at least one instance of sexual intercourse without using contraception at the time of the exposed pregnancy; 13 (93%) did not use two forms of contraception as recommended in the PPP procedures. Ten had pregnancy tests before starting isotretinoin; however, three whose pregnancy test results were negative were pregnant when they began taking isotretinoin. Two respondents reported that their exposed pregnancies occurred while using leftover isotretinoin from earlier prescriptions, and one received and filled the isotretinoin prescription in Mexico.

Seven (50%) respondents reported viewing an advertisement for prescription acne treatment before taking isotretinoin. Four of the seven reported that the advertisement contributed to their decision to seek acne treatment and to ask their physician about isotretinoin. Four live-born infants with no major malformations resulted from these 14 pregnancies. One live-born infant had major malformations. The other pregnancy outcomes were four spontaneous abortions and five induced abortions. No information was available on the presence of malformations in the aborted fetuses.

Although all 14 respondents knew that isotretinoin should not be used during pregnancy, none reported seeing all components of the PPP, and four had not seen any component other than the information available on the isotretinoin packet. None of the women reported being referred for contraceptive counseling or being told that they would not have to pay for the counseling.

Case Reports

Case 1. After taking isotretinoin for 1 month, a 25-year-old woman was notified by her dermatologist that her pregnancy test was positive, de-
spite negative results on a pregnancy test before beginning isotretinoin. She had been using two forms of contraception but did not wait for menstruation before starting isotretinoin therapy as recommended by the PPP. Her infant was born with multiple anomalies including complex congenital heart disease consisting of double outlet right ventricle with dextrocardia and aortic atresia, hydrocephalus, and facial dysmorphism. After extensive medical treatment and cardiac surgery, the infant died at age 9 weeks.

Case 2. A 35-year-old woman who had been taking isotretinoin for approximately 6 months tested positive on a home pregnancy test. She was 12 weeks pregnant when she discontinued isotretinoin use. Since 1989, she had had three isotretinoin-exposed pregnancies; only the third pregnancy resulted in a live birth. The first course of isotretinoin was prescribed by a dermatologist; she obtained the other prescriptions from a friend who was a health-care worker. The outcome of the third exposed pregnancy was a full-term infant with no apparent malformations.

Case 3. A 35-year-old woman who was using an intrauterine device tested positive on a home pregnancy test. She had been taking isotretinoin for approximately 3 years before this pregnancy and had taken two doses of isotretinoin since her last menstrual period. She did not have acne. She took isotretinoin for approximately 1 week each month before menstruation to prevent oily skin. She was a health-care provider and received the prescription from a colleague who did not ask about or recommend contraception. She elected to terminate the pregnancy because of the exposure.

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CDC Editorial Note: These cases identified challenges to preventing isotretinoin-exposed pregnancies; 13 of the 14 respondents did not use two forms of effective contraception, and eight had used no contraception when the exposed pregnancy occurred. The study also illustrated problems with acquiring a prescription outside a clinical setting, using leftover medication, purchasing the medication outside the United States, failing to perform pregnancy testing before therapy, and failing to wait 3 days after menstruation before beginning treatment.5,7

Although the 14 respondents did not represent all women taking isotretinoin or all women with isotretinoin-exposed pregnancies, they were similar to others enrolled in the BUAS (e.g., the average age of the respondents was similar to the women enrolled in the BUAS [median: 26 years]); however, respondents included more women aged >30 years than in previous studies of isotretinoin-exposed pregnancies.6,7 Seventy-one percent had some type of pregnancy test before starting isotretinoin, which is similar to the 60% reported for all women enrolled in the BUAS.5 The highest percentage of pregnancies in the BUAS occurred among women using oral contraceptives; nevertheless, more than half the 14 respondents reported at least one instance of sexual intercourse when contraception was not used, indicating that failure to use contraception may be as important as contraceptive failure.

The warning label on isotretinoin packaging states that it should not be used by women of childbearing potential unless the patient meets such conditions as having “severe, disfiguring nodular acne that is recalcitrant to standard therapies”.1 At least half of the 14 respondents did not take the criteria on the package insert. When isotretinoin treatment is necessary, physicians should provide precautions, contraindications, and all PPP elements; care should be taken by women and their physicians to ensure that contraceptive recommendations are understood and followed. In addition, women of childbearing potential should not use isotretinoin unless they are under the care of a physician familiar with isotretinoin use.

REFERENCES


The findings in this study are subject to at least two limitations. First, these cases were a convenience sample of 14 women from California, and they may not represent all isotretinoin-exposed pregnancies. Second, the findings cannot be generalized to evaluate the overall effectiveness of the PPP or other prevention programs. Despite the increased demand that may be generated by Accutane advertising, physicians should limit use of the drug in women of childbearing potential to those who meet the criteria on the package insert. When isotretinoin treatment is necessary, physicians should provide precautions, contraindications, and all PPP elements; care should be taken by women and their physicians to ensure that contraceptive recommendations are understood and followed. In addition, women of childbearing potential should not use isotretinoin unless they are under the care of a physician familiar with isotretinoin use.