SPECIAL ARTICLE

A PREGNANCY-PREVENTION PROGRAM IN WOMEN OF CHILDBEARING AGE RECEIVING ISOTRETINOIN

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Abstract *Background.* Isotretinoin is effective in treating severe acne, but it is also teratogenic. To minimize pregnancies among exposed women, the manufacturer, together with the U.S. Food and Drug Administration, implemented a multicomponent Pregnancy Prevention Program in 1988. We report the results of an ongoing survey designed to assess compliance with this program.

Methods. Treated women enrolled in the survey through their physician, by filling out a form in the medication package, or by calling a toll-free telephone number. They were randomly assigned to be followed by telephone or by mail. Telephone interviews were conducted at the start of therapy, in the middle of it, and 6 months after it ended; mailed questionnaires were completed 6 months after therapy ended (median duration of therapy, 20 weeks).

Results. Between 1989 and 1993, 177,216 eligible women enrolled in the survey. Interviews with 24,503 women within one month of enrollment revealed that 99 percent had been told to avoid pregnancy. At that time, approximately 54 percent were not sexually active (of whom 37 percent used contraception) and 42 percent were sexually active (of whom 99 percent used contraception); 4 percent were infertile. Among 124,216 women with completed telephone or mail follow-up results, there were 402 pregnancies during therapy (3.4 per 1000 courses of isotretinoin); 72 percent of the pregnant women had elective abortions, 16 percent spontaneous abortions, 3 percent ectopic pregnancies, and 8 percent live births.

Conclusions. The pregnancy rate among women receiving isotretinoin therapy was substantially lower than that in the general population and was compatible with the characteristics and behavior of the enrolled women. (N Engl J Med 1995;333:101-6.)

IN 1982, the vitamin A analogue isotretinoin (Accutane) was introduced in the United States for the treatment of severe recalcitrant cystic acne. Because studies in animals had suggested that isotretinoin might be teratogenic in humans, the drug was contraindicated in women who were or might become pregnant during therapy or in the following month. The concern about human teratogenicity proved well founded, because it was soon demonstrated that approximately 25 to 30 percent of exposed fetuses had birth defects — the so-called Accutane embryopathy, consisting of craniofacial, heart, and central nervous system defects.[1] Despite prominent warnings to physicians in direct mailings, advertisements, and the package insert, reports of pregnancies in exposed women continued to accumulate, and by 1989 approximately 78 malformed infants had been reported.[2]

In the spring of 1988, this issue was reviewed by an advisory committee to the U.S. Food and Drug Administration. There was little debate about the teratogenicity of isotretinoin, but dermatologists and others asserted that its unique efficacy in the treatment of severe acne, together with its relatively short treatment course (15 to 20 weeks), warranted its continued availability.[3,4] As an alternative to removing the drug from the market or formally restricting its use, the manufacturer proposed an aggressive program designed to reduce the risk of pregnancy among women taking the drug. The committee recommended that the major components of this program be implemented, and the manufacturer's Pregnancy Prevention Program commenced in the fall of 1988.

The program was targeted at both prescribers and patients. In late 1988, materials were distributed to every dermatologist and to all nondermatologists identified as prescribers of isotretinoin in the United States. The materials included guidelines for physicians (instructing them, for example, to warn patients of risks, obtain negative pregnancy tests, and delay therapy until the second or third day of the next normal menstrual period). They also included a patient-qualification checklist, an information brochure for patients, contraceptive information, information about and the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling), and a consent form. In addition, in mid-1989 the manufacturer replaced traditional medication bottles with a 10-capsule blister pack that contained information directed specifically at women: the package included warnings about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon behind each capsule, and line drawings of malformations associated with isotretinoin. The program was reinforced by periodic communications directed at prescribers and pharmacists.

We designed and conducted a survey to assess the compliance of physicians and patients with the program and to identify the rate of pregnancy during

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Presented in part at meetings of the International Conference on Pharmacoepidemiology, Minneapolis, September 5–8, 1989; the Teratology Society, Victoria, B.C., Canada, June 8–12, 1990; the American Epidemiological Society, Pittsburgh, March 25–26, 1993; and the American Osteopathic College of Dermatology, Boston, October 10–14, 1993.

Supported by Hoffmann–La Roche.

treatment with isotretinoin and during the month after treatment.

Methods

The subjects were women of childbearing age (12 to 59 years of age) who were being treated with isotretinoin. To identify compliance with the program and the occurrence of pregnancy, the survey covered the treatment period and the subsequent six months, a period long enough to allow identification of pregnancies occurring as late as the first month after discontinuation of treatment. Thus, for example, women treated for a typical 5-month course would be followed for 11 months.

To maximize the proportion of treated women who participated, we provided multiple opportunities for enrollment. In addition to the materials described above, the program also included survey-enrollment consent forms; physicians were asked to encourage women to use these forms to enroll at the time isotretinoin was prescribed. A second opportunity was provided directly to the women through an enrollment-consent form that was included in each medication package. In 1990, a toll-free telephone number that women could call to enroll was added to the form. All forms indicated that participants would receive a $10 payment.

To minimize memory loss and biased recall, we collected information on the behavior of physicians and patients at the start of therapy as well as during treatment. However, inquiries at these times might have transformed the survey, which was intended to be observational, into a form of intervention. Therefore, we randomly assigned the women to be followed by one of two approaches. The first involved telephone contact during and after therapy, providing prospective information on physicians' and patients' behavior. Since the telephone calls might themselves enhance compliance with the program, we used a second approach with other participants: a questionnaire mailed after therapy that identified the occurrence of pregnancy and obtained retrospective information on contraceptive practices.

The enrollment forms were screened on receipt to exclude enrollments that were apparently fraudulent, men, and previously enrolled women. The eligible women were assigned, at random, to be followed by one of the two methods. Within two days, they were sent $10 and told when to expect contact. Each week, 100 women were randomly assigned to the group interviewed by telephone. They were contacted three times: at the start of therapy (within one month after enrollment), when we inquired about the patients' understanding of the hazards of isotretinoin and compliance with the program; in the middle of therapy (between two and four months after the start of isotretinoin), when we inquired about continued understanding of the hazards of isotretinoin and compliance with the program; and six months after the completion of therapy, when we asked about the occurrence of pregnancy during or after treatment. Women who could not be reached by telephone within specified intervals were transferred to the group followed up by mail.

Women not randomly assigned to the telephone group were sent a brief questionnaire six months after starting isotretinoin to determine the date on which they had completed or were expected to complete therapy. They were then mailed a questionnaire six months after that date, which included the same questions as the third telephone interview. Nonrespondents were contacted by air courier and, if this failed to elicit a response, by telephone.

Women who were pregnant at the time they began treatment, or who became pregnant during treatment or in the month after it ended, were interviewed by telephone regarding the pregnancy and its outcome; permission was sought to obtain relevant medical records and for our teratologist to examine all liveborn infants.

The protocol was approved by the Boston University Medical Center Institutional Review Board for Human Research. The survey began January 1, 1989, and is continuing at the present time.

Results

Enrollments

Between January 1, 1989, and December 31, 1993, 177,216 eligible women enrolled in the survey. The number increased from 21,267 in 1989 to 43,265 in 1993. Twenty percent enrolled through the form provided to physicians, 77 percent through the form included in the medication package, and 3 percent by telephone.

Follow-up

Telephone Interviews

Overall, 26,986 women were assigned to telephone follow-up. Because of start-up problems, we completed first telephone interviews of only 72 percent of the women assigned to the telephone group in the first year of the survey; this proportion subsequently increased to 96 percent. For the five-year study period, first telephone interviews were completed for 24,503 women. By June 30, 1994, the third telephone interview had been completed by 17,960 women (92 percent of the 19,621 eligible women — that is, those who had completed therapy at least six months before that date).

Mailed Questionnaires

Follow-up by mail involved 150,230 women assigned randomly to the mail group and 4420 women transferred from the telephone group. Of the 126,251 women eligible for the second mailed questionnaire by June 30, 1994, responses had been received from 84 percent by that date.

The ages and geographic distributions were similar among women assigned to telephone follow-up and those assigned to mail follow-up and among women with incomplete and those with complete follow-up (data not shown).

Characteristics of Women and Behavior of Physicians at Start of Therapy

Among the 24,503 women who completed first telephone interviews, the median age was 26 years (the 10th and 90th percentiles were 17 and 39, respectively), the median number of years of education was 14 (i.e., 2 years beyond high school), and the median duration of acne was 8 years. Dermatologists were the prescribing physicians for 92 percent of the patients. Past treatments for acne (data unavailable for 1989) included oral antibiotics (96 percent of the patients), tretinoin (Retin-A) (82 percent), benzoyl peroxide (74 percent), and orally administered vitamin A (11 percent).

Selected information related to the behavior of physicians is shown in Table 1. Virtually all the women were told of the importance of avoiding pregnancy; 85 percent were told of the importance of using effective contraception for one month before starting isotretinoin. In 1989–1990, 78 percent were told to wait for pregnancy-test results and 63 percent to wait until the next menstrual period before starting isotretinoin. Forty-six percent of the women reported having serum pregnancy tests before starting treatment; 60 percent had had some type of pregnancy test. These findings prompted the manufacturer, in late 1990, to introduce a new medication package with certain points high-

Table 1. Selected Information Obtained from Telephone Interviews with Women of Childbearing Age Conducted at the Start of Therapy with Isotretinoin.*

Survey Question	Survey Year					
	1989 (N = 4308)	1990 (N = 5016)	1991 (N = 4685)	1992 (N = 4717)	1993 (N = 5014)	all (N = 23,740)
	percentage of women answering yes					
Did your doctor tell you the importance of						
Avoiding pregnancy?	99	98	98	99	99	99
Using effective contraception for 1 month before starting isotretinoin?	85	85	88	84	84	85
Waiting for pregnancy-test result before starting isotretinoin?	79	77	83	85	87	82
Waiting until next menstrual period before starting isotretinoin?	64	63	74	75	77	70
Did you have a pregnancy test before starting isotretinoin?						
Serum test	48	45	54	54	56	51
Any test	62	58	67	66	69	64

*The table excludes data on 763 women who reported having undergone hysterectomy or being postmenopausal.

lighted in large, bold print. These included warnings about the need to have a negative blood pregnancy test before starting therapy; to wait until the next menstrual period before starting therapy; and to use effective birth control one month before starting therapy, during therapy, and one month after completing it. During the next three years, compliance with the first two behavioral recommendations increased (by approximately 10 to 25 percent, as gauged by responses to questions 3, 4, and 5 in Table 1).

Overall, 96 percent of the women interviewed indicated that they were not sexually active or that they were using birth control. Early in 1992, the questionnaire was modified to allow more complete information to be obtained regarding sexual activity and birth control; among 9593 women interviewed since then, 3.7 percent were infertile (3.3 percent because of hysterectomies and 0.4 percent for other reasons) and in 0.3 percent the risk of pregnancy was unknown. The largest proportion, 54 percent, were not sexually active (20 percent used birth control and 34 percent did not), whereas 42 percent were sexually active (41 percent used birth control and 0.6 percent did not). (For sexually active women who did not use birth control, the survey staff intervened by reading to them a warning about the risk of birth defects and by requesting permission to inform the prescribing physician.)

Information about the women's contraceptive status at the start of therapy is shown in Table 2 according to age. Methods are classified according to the schema used in the 1988 National Survey of Family Growth, a periodic survey that identifies reproductive factors in a nationally representative sample of U.S. women.[5]

Outcomes

As of June 30, 1994, 124,216 women had completed final telephone interviews or mailed questionnaires. Of these, 122,582 (99 percent) reported taking isotretinoin for less than 365 days; except where otherwise noted, analyses are restricted to the latter group.

The median duration of therapy for women followed by telephone was 141 days, and for those followed by mail, it was 140 days. There were 45,773 person-years of isotretinoin exposure. Pregnancies during therapy were reported by 402 women (0.3 percent); 46 were pregnant when therapy began, and 356 became pregnant during therapy. The pregnancy rate for the survey population (Table 3) was 3.4 per 1000 20-week courses of isotretinoin (the annualized rate was 8.8 per 1000 person-years) (Fig. 1). (Among 1382 women who took isotretinoin for one to two years, there were 1727 person-years of exposure and 19 pregnancies, for a rate of 11.0 per 1000 person-years.) The pregnancy rates were 3.1 and 3.4 per 1000 20-week courses for the women in the telephone and mail groups, respectively. Among the 138 women in the telephone group who were warned not to continue isotretinoin therapy without taking steps to avoid pregnancy (69 of whom reported nonsurgical infertility), 2 subsequently became pregnant (1 of whom had reported being infertile); exclusion of this group did not appreciably affect the pregnancy rate among women followed by telephone. Data for 1989 to 1993 suggest a decrease in the pregnancy rate over time, though continuing follow-up for the most recent cohorts may produce slight changes in these rates.

Overall, 46,249 women reported not using birth control (on the basis of telephone data, approximately 99

Table 2. Contraceptive Status of the Women, as Ascertained by Telephone Interviews at the Start of Therapy, According to Age.*

Contraceptive Status	Age (yr)			
	<25 (N = 11,220)	25–34 (N = 8287)	35–44 (N = 4299)	≥45 (N = 697)
	percentage			
Not practicing contraception	56	19	12	13
Not sexually active	55	19	12	11
Sexually active	1	<1	<1	3
Practicing contraception†	44	80	85	78
Tubal ligation or hysterectomy	<1	12	35	49
Vasectomy	<1	10	20	16
Birth-control pill	35	39	12	2
Intrauterine device	<1	1	2	2
Diaphragm	1	5	4	2
Condom	4	8	6	3
Rhythm method	<1	<1	<1	<1
Other	3	4	4	3
Nonsurgically sterile	<1	<1	2	5
Unknown	<1	<1	<1	3

*Totals may not equal 100 percent, because of rounding.

†The primary method was determined with the use of the schema of the National Survey of Family Growth.[5]

percent were not sexually active at the beginning of therapy or during it). Eighty-eight became pregnant during treatment (1.9 per 1000 20-week courses). In comparison, among the 76,149 women who practiced contraception, 268 became pregnant (3.6 per 1000 20-week courses) ($P<0.001$).[6] On the basis of the primary contraceptive method being used at the start of treatment (reported in the third telephone interview or the second mailed questionnaire), we estimated method-specific pregnancy rates during therapy. Among women using nonsurgical means of contraception, rates for the most commonly used methods were 3.2 pregnancies per 1000 20-week courses for birth-control pills (39,053 women), 10.3 for condoms (7686 women), and 8.1 for diaphragms (3023 women). The rates among women who had had tubal ligations or whose male partners had had vasectomies were 0.4 (4 of 10,949 women) and 0.3 (2 of 7394 women), respectively.

There were 136 pregnancies that were conceived during the month after discontinuation of therapy, for a rate of 13.4 per 1000 person-years (Fig. 1). Pregnancy rates were also calculated for the next three months, when pregnancy was no longer discouraged by the program; these were 29.0, 37.1, and 43.2 per 1000 person-years, respectively.

Of the 402 women with pregnancies conceived during treatment with isotretinoin, 290 (72 percent) had elective terminations, 63 (16 percent) had spontaneous abortions, 13 (3 percent) had ectopic pregnancies, none had stillbirths, 32 (8 percent) had live births, and in 4 (1 percent) the outcome could not be determined. Among the 136 pregnancies occurring during the month after therapy, a smaller proportion (55 percent) were electively terminated and a larger proportion (28 percent) were carried to term or were continuing at the time of analysis. For pregnancies occurring in the subsequent three months, 23 percent were terminated and 61 percent were carried to term or were continuing.

Among the 32 liveborn infants, 13 had been examined by the survey teratologist by January 1995. Six had no defects, one had major anomalies (ear, eye, craniofacial, and brain), and six had minor anomalies (ear in two, ear and craniofacial in two, and hypoplastic scrotum and confluent eyebrows in one each). The examiner, who knew the exposure status of the mothers, did not consider the latter two defects to be associated with isotretinoin; thus, five infants (38 percent) were judged to have defects compatible with the isotretinoin embryopathy. Birth records available for four additional infants revealed no defects. Parental reports, available for 13 of the remaining 15, identified 1 infant as having cerebral palsy and developmental delay and 1 who died from defects involving the ear, eye, heart, kidney, and liver.

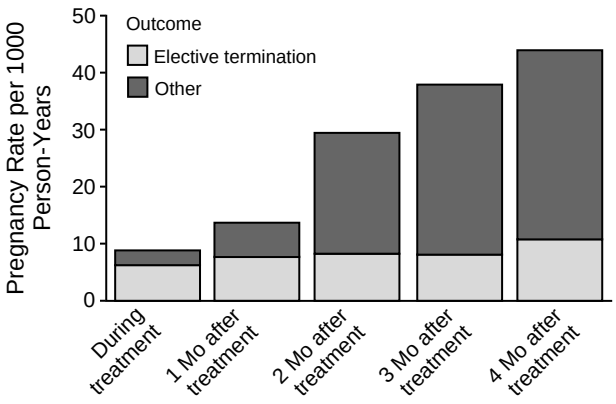

Figure 1. Pregnancy Rates and Outcomes during and after Therapy with Isotretinoin in 122,582 Women, 1989 to 1993.

Discussion

Among women enrolled in this survey, understanding of the teratogenic risks of isotretinoin and of the need to avoid pregnancy was virtually universal. Compliance with other aspects of the program was less complete, although in no case did compliance for any measure decline during the study period. Apart from ensuring that the women understood the risks, perhaps the most important aspect of the program was the recommendations that women ensure that pregnancy tests were negative, that they wait until menses had begun before initiating isotretinoin therapy, and that they use effective birth control preceding, during, and immediately after treatment. Information from the first months of the survey revealed incomplete compliance with these guidelines. As a result, the manufacturer reinforced physician education about these three recommendations and changed the medication package to highlight their importance. Within months after distribution of the new package, compliance with these recommendations, though still incomplete, improved.

Whatever attention is directed to the education and compliance of patients and physicians, the most relevant measure of the effectiveness of efforts to prevent pregnancies is the pregnancy rate. Among U.S. women 15 to 44 years of age, the pregnancy rate is approximately 109 per 1000 person-years.[7] For women in the same age group in the survey population, the rate during isotretinoin

Table 3. Pregnancy Rates during Isotretinoin Treatment, Based on Completed Follow-up by Telephone and Mail.*

Variable	1989	1990	1991	1992	1993	All
No. of women	18,075	28,757	29,639	30,048	16,063	122,582
Pregnancies reported†	73	102	91	90	46	402
Person-years of isotretinoin exposure	7,045	10,759	11,093	11,190	5,686	45,773
Rate per 1000 20-wk courses of isotretinoin	4.0	3.6	3.1	3.1	3.1	3.4

*The table excludes data on 1634 women who reported taking isotretinoin for one year or more and includes 78 reports of pregnancies awaiting confirmation.

†Values include 46 women who were pregnant at the time they began taking isotretinoin.

exposure was 8.8 per 1000 person-years, or approximately 8 percent of that of the general population.

The program sought to exclude from isotretinoin treatment women who were at high risk of becoming pregnant. The prevalence of sexually active women not using contraception was low (0.6 percent), and among those practicing contraception the use of oral contraceptives (one of the most effective methods) was high (49 percent) as compared with the respective proportions (7 and 28 percent) in the National Survey of Family Growth.[5] Irrespective of method, major factors associated with successful contraception include duration of use, education, and motivation.[8] We have only recently collected information on duration of use, but we know that the enrolled population was relatively well educated and that motivation was likely to have been quite high, given knowledge of the risks. Furthermore, pregnancy had to be avoided for only six months, on average. Thus, the observed low rates are compatible with the demographic and other characteristics of these women. Though a causal link between implementation of the program and low rates of pregnancy cannot be proved by observational study, such an effect is likely, given the frequency of reported compliance with components of the program.

In a survey based on self-reports, one must ask whether the information is valid. Follow-up rates were high in both the telephone and mail groups, and responses regarding knowledge, behavior, and compliance were similar whether elicited at the start of treatment (in the first telephone interview) or six months after its completion (in the second mailed questionnaire) (data not shown). The low pregnancy rates during isotretinoin treatment and the increase in pregnancies in the four months afterward are consistent with intentional avoidance of pregnancy during the period of teratogenic risk. The high proportion of women having therapeutic abortions during treatment and the low proportion having them during the subsequent four months further support the validity of these data. Although some underreporting of pregnancies and therapeutic abortions is likely, we believe that the survey design and study population minimize this problem.

Evaluation of the representativeness of a survey based on voluntary enrollment requires information on both the total number of women of childbearing age who are treated with isotretinoin and the differences between enrolled and unenrolled women. Unfortunately, the number of treated women is not known. Available estimates, based on complex and unvalidated assumptions, suggest that the numbers of women of childbearing age for whom isotretinoin was prescribed were approximately 76,094 in 1991, 83,887 in 1992, and 90,390 in 1993 (Bylancik A, Hoffmann–La Roche: personal communication). If these estimates are correct, we can assume on the basis of their 95 percent confidence intervals that the 117,652 women who enrolled in the survey represented 44 to 52 percent of the women treated with isotretinoin. Whether participants differed in pregnancy risk from women who did not enroll is not known. We assumed, a priori, that the women who did not enroll were more likely to be noncompliant and at high risk for pregnancy; on the other hand, women may not enroll specifically because they are infertile or in other ways not at risk for pregnancy.

Despite its limitations, we believe that our design was as successful as could be expected in a setting of voluntary participation. Alternative designs cannot ensure representativeness, and because of the need for patient consent, the potential for selection bias is inescapable.

Before the introduction of isotretinoin, the unique issues related to teratogenic drugs were not adequately considered — such drugs were either removed from use or left on the market with no pregnancy-prevention program. The isotretinoin program offers a novel approach that seeks to keep the drug available while minimizing the teratogenic hazard.[4] The results suggest that the program encourages communication between physicians and patients regarding the drug's teratogenic risk and the need to prevent pregnancy, promotes the selection of patients at low risk for pregnancy, and is associated with low pregnancy rates. These benefits occurred in a particular context: physicians and patients were highly committed to using the drug, pregnancy had to be avoided for only a limited time, and the physicians belonged largely to a single specialty (dermatology), enhancing the feasibility of the educational campaign.

Whether similar benefits could be achieved with drugs used for other purposes remains unclear, but this question may soon require resolution. Thalidomide appears to be an effective treatment for various medical conditions,[9-11] as does methotrexate,[12,13] prompting interest in making these teratogenic drugs more widely available.[10,13-15] The experience gained with isotretinoin can serve as a basis for considering how such drugs should be used and monitored, with a view to ensuring that pregnancies and malformations are reduced to an absolute minimum.

We are indebted to the following members of the Slone Epidemiology Unit Accutane Advisory Committee, who provided independent and critical advice in the design, analysis, and interpretation of this survey: P. Stolley, M.D. (chair), E. Decker, Pharm.D., K. McKoy, M.D., J. Melski, M.D., P. Pochi, M.D., R. Stern, M.D., C. Catz, M.D. (National Institute of Child Health and Human Development liaison), J. Cordero, M.D. (Centers for Disease Control and Prevention liaison), W. Dai, M.D., Dr.P.H., and J. LaBraico, M.D. (Hoffmann–La Roche liaison); to D. Gute, M.P.H., Ph.D., for his assistance in the initial survey design; to E. Lammer, M.D., for conducting the infant examinations; to J. Trussell, Ph.D., for guidance in assessing contraceptive efficacy; to the American Academy of Dermatology for its support; to the Slone Survey staff; to S. Shapiro, M.B., for his support and advice; and to the many physicians and patients who participated in the survey.

References

1. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. N Engl J Med 1985;313:837-41.

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