# Pregnancy prevention among women taking isotretinoin

## *Failure to comply with the recommendations*

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**ABSTRACT**

**OBJECTIVE** To assess whether prescribing physicians advised female patients taking isotretinoin according to pregnancy prevention recommendations, whether women understood those recommendations, and whether women complied with recommendations to prevent pregnancy.

**DESIGN** Cross-sectional study designed to collect patients' self-reported information. Women were interviewed by telephone with a standardized questionnaire.

**SETTING** Quebec.

**PARTICIPANTS** Participants were recruited through pharmacies, medical clinics, and newspapers in Quebec. All subjects (45 women 14 years and older) were treated with isotretinoin at the time of the interview or in the preceding 6 months.

**MAIN OUTCOME MEASURES** Women's self-report of their physician's behaviour regarding prevention of pregnancy, women's comprehension of the information, and their level of compliance with recommendations.

**RESULTS** Prescribing physicians discussed the risks of teratogenesis with 93% of the women but gave written information to only 36% of them. Seventy-eight percent of the women admitted not using 2 contraceptive methods all the time during the treatment, and 3 women reported having had sexual intercourse without any contraception. Physicians prescribed a pregnancy test before treatment for 44% of the women. Only 18% of the women waited for their next menstrual period to begin isotretinoin treatment, and this advice was given by 20% of physicians. A statistically significant relationship between counseling and recommendations given by physicians and women's use of double contraception was highlighted.

**CONCLUSION** Female patients reported physicians did not always advise them according to recommendations concerning pregnancy prevention. Women understood the information received but did not fully comply. The extent of pregnancy prevention measures taken by physicians was linked to women's compliance. Further study exploring underlying reasons for women's noncompliance could provide information on changing such behaviour.

**EDITOR'S KEY POINTS**

- Women from Quebec were surveyed to determine whether they received appropriate counseling on pregnancy prevention when using isotretinoin, and whether or not they complied with those recommendations.
- Although most women recalled being given information about pregnancy prevention, there were substantial gaps in the information recalled. Many women did not have a pregnancy test first, did not wait for the next period to begin treatment, or used only 1 or no method of birth control.
- Use of double contraception improved when physicians so counseled patients, and pharmacists gave verbal and written advice to most women. The authors recommend strengthening the Pregnancy Prevention Program now in place and having pharmacists verify administration of pregnancy tests and monitor birth control methods before dispensing the medication.

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Isotretinoin (Accutane) has been available in Canada since April 1983.[1] The teratogenic risks[1-8] and the fact that 50% of pregnancies are unplanned[9] make preventing conception during treatment crucial.

Consequently, the Pregnancy Prevention Program (PPP) was implemented in 1988.[10,11] Isotretinoin's product monograph states that the PPP must be used by physicians prescribing isotretinoin to female patients of childbearing age.[12] The PPP includes a checklist of criteria that must be met before prescribing to fertile women, birth control information, printed materials to give to patients, and a detailed consent form. This program is free and accessible to any physician from the manufacturer (800 470-2263). All the information concerning the means of pregnancy prevention is clearly stated in the black box of the product monograph. In spite of these prevention measures, exposure during pregnancy continues to occur in Canada.[13,14] Twenty-six women contacted a Canadian teratogen information service (Motherisk Program) about exposure to isotretinoin during pregnancy between 1988 and 1991[11] and 11 other women contacted the service for this reason in 2002-2003.[15] The pregnancy rate among isotretinoin users is estimated to be 2.7/1000 in the United States[16] and 0.6/1000 in France.[17] Canadian data are unavailable.

To our knowledge, the behaviour of Canadian isotretinoin users who are not pregnant and the way they perceive their physicians' efforts to prevent pregnancy during the use of this medication have not been studied. Studies in other countries report that both prescribing physicians and female users do not comply with the monograph or recommendations regarding pregnancy prevention.[16,18,19]

Thus, the present study was designed to assess whether prescribing physicians advised female patients taking isotretinoin according to pregnancy prevention recommendations, whether women understood those recommendations, and whether women complied with recommendations to prevent pregnancy.

## METHOD

A cross-sectional descriptive study was designed to collect patients' self-reported information. Women were recruited between November 2003 and July 2004. Women included in the study were of childbearing age (14 years and older), were fertile as far as they knew, and were treated with isotretinoin at the time of the interview or in the 6 preceding months. There were no other exclusion criteria. Material to recruit participants was sent to more than 200 pharmacies. Fifty-two pharmacies (11 in rural regions) participated. Advertisements were posted in eight family practice clinics and in one dermatology clinic. Advertisements were also published in three newspapers covering various areas of the province of Quebec (176 000 copies). All eligible women who contacted us were included in the study, making up a convenience sample of 47 women.

A standardized questionnaire was administered by telephone interview. The questionnaire, designed by the authors, was mainly based on the Accutane survey[16] questions. Scientific validation ensured that all the important points of the monograph concerning pregnancy prevention were assessed. The questionnaire was pilot-tested before our study. The women's point of view was used to evaluate both the physicians' and the women's behaviour. As we intended to evaluate the information received by the women and their understanding, their point of view was the best way to assess these issues. Many studies, including the Accutane survey, used women's self-reports to assess physicians' behaviour when isotretinoin was prescribed.[11,13,14,16,19]

The research ethics committee of Laval University in Quebec approved the protocol. All statistical analyses were performed using SAS 8.1. Means with 95% confidence intervals were used in descriptive analysis of continuous variables, and proportions were used to study dichotomous values. Tests of statistical significance reported in this paper were based on $2 \times 2$ analyses with Fisher exact tests using a significance level of $<.05$.

## RESULTS

### Demographics

Forty-seven female isotretinoin users agreed to participate in the study. Two women were excluded because they had finished their treatment more than 6 months before the interview. Therefore, 45 women were included in the analysis. All the women who contacted us agreed to participate. The mean age was 25.9 ± 6.9 years (16-45 years). **Figure 1** shows the age distribution in the sample. More than half the women (55%) were living as part of a couple; the others were single. Forty-four women (98%) were from an urban area. More than two thirds (67%) of the women had a college or university degree. All the women who were interviewed stated that they were fertile to their knowledge, and 85% declared themselves sexually active during treatment.

### Prescribing physicians

Dermatologists were prescribing physicians in 78% of

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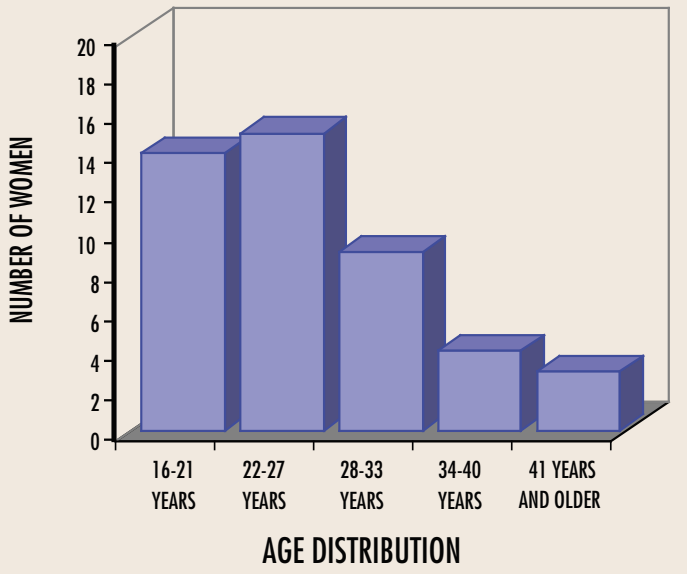
**Figure 1.** Age distribution of female participants using isotretinoin




cases and family practitioners for the remaining 22%. Pregnancy prevention measures taken by physicians, as reported by women, are summarized in **Table 1**. Sixteen women had a prescription for contraception written by the same physician who prescribed the isotretinoin.

**Table 1.** Physicians' actions reported by women taking isotretinoin

| PHYSICIANS' ACTIONS | % | NUMBER (N = 45) |
|---|---|---|
| Discussed teratogenic risks | 93.3 | 42 |
| Gave written information about teratogenic risks | 35.6 | 16 |
| Gave written information about contraception | 4.4 | 2 |
| Advised patient to use 2 effective contraceptive methods during treatment | 60.0 | 27 |
| Advised patient to begin effective double contraception 1 month before starting isotretinoin | 28.9 | 13 |
| Advised patient to wait for the next menstrual period before starting isotretinoin | 20.0 | 9 |
| Advised patient to continue effective double contraception for 1 month after the last dose | 40.0 | 12* |
| Prescribed a pregnancy test before starting isotretinoin | 44.4 | 20 |
| Prescribed monthly pregnancy testing | 13.3 | 6 |
| Used the consent form | 13.3 | 6 |

**Proportion calculated for the 30 women who had finished isotretinoin treatment at the time of the interview.*

Of the remaining 29 women, the physician prescribing isotretinoin asked whether they already had a contraception method in 75% of the cases. **Table 2** summarizes contraceptive methods prescribed or, if no refill was needed, verified and therefore approved by physicians prescribing isotretinoin. Some women spontaneously reported that their dermatologists asked them to see their family physicians for contraception and monthly monitoring related to isotretinoin (liver enzymes, side effects, pregnancy testing, etc).

**Table 2.** Contraception prescribed or verified and approved by the physician prescribing isotretinoin

| CONTRACEPTION | % | NUMBER (N = 38*) |
|---|---|---|
| Birth control pill | 57.9 | 22 |
| Condom | 18.4 | 7 |
| Intrauterine device | 7.9 | 3 |
| Medroxyprogesterone (Depo-Provera) | 7.9 | 3 |
| Vasectomy | 5.3 | 2 |
| Abstinence | 2.6 | 1 |

**Seven women did not remember having received a prescription for contraception or having their usual contraceptive method verified and approved.*

## Pharmacists

Thirty-five women (78%) declared that pharmacists gave them verbal information about teratogenesis and pregnancy prevention when they filled their Accutane prescription. Pharmacists also gave written information, other than the package insert, to 28 women (62%).

## Women's understanding of recommendations

Most women reported receiving verbal (42/45) information from physicians and a smaller proportion receiving written information (16/45). Virtually all participants found the information they received clear and easy to understand. Forty women (89%) read the package insert and 98% of them found it clear. All 45 women admitted knowing that they must avoid pregnancy while using this medication. They all remembered the warning symbol on the package insert and were able to explain its meaning adequately. Some women spontaneously reported that, if they had not been aware of the teratogenic potential of isotretinoin, they might have interpreted the symbol as meaning the drug could prevent a pregnancy.

## Women's compliance with recommendations

Only eight women (18%) waited for their next menstrual period to start isotretinoin. During treatment, 78% (n=35) reported not using two contraceptive methods all the time, as required. Moreover, three women (7%) reported

that they had had sexual intercourse using no contraception during the treatment, and two of them had done so repeatedly. Among the 21 women using only one contraceptive method, 33% were using condoms (**Table 3**).

**Table 3. Women's contraception use before, during, and after treatment with isotretinoin**

| | MONTH PRECEDING THERAPY (N = 44*) | | DURING THERAPY (N = 45) | | MONTH AFTER DISCONTINUATION (N = 23†) | |
|---|---|---|---|---|---|---|
| CONTRACEPTIVE METHOD | % | N | % | N | % | N |
| None | 18 | 8 | 7 | 3 | 17 | 4 |
| Sometimes 1 | 7 | 3 | 7 | 3 | 4 | 1 |
| Always 1 | 64 | 28 | 64 | 29 | 70 | 16 |
| Always 2‡ | 11 | 5 | 22 | 10 | 9 | 2 |

*One woman did not remember.
†Of the 45 women, 22 had not finished their treatment at the time of the interview.
‡As recommended by Accutane monograph and Pregnancy Prevention Program.

The association of women's use of double contraception with their recollection that physicians discussed pregnancy prevention during the interview was statistically significant ($P<.04$). The clinical significance of that relationship is important. One additional patient in three will comply with double contraception when physicians discuss that issue (number needed to treat =3, 95% confidence interval 0-14). The absolute risk reduction is 37%.

## DISCUSSION

In our study, female patients reported that physicians prescribing isotretinoin did not advise them according to the recommendation concerning pregnancy prevention. Yet women reported that they understood they clearly should avoid pregnancy during treatment and that they found the information provided clear and easy to understand. Despite this claim, women did not comply with the pregnancy prevention recommendations. This might be explained by their underestimation of the need to protect themselves against pregnancy.

Despite the fact that no women reported being pregnant in our study, many of them could have already been pregnant at treatment initiation because only 44% were tested for pregnancy. These findings are consistent with Autret et al,[18] who reported that 16% of the women who exposed their fetus to isotretinoin were already pregnant when the treatment began.

The relationship between physicians' behaviour and the regular use of double contraception demonstrates that the women's retention and their perception of the precautions taken by physicians are essential for their compliance. To our knowledge, this is the first study investigating that relation in this context. Our findings emphasized the fact that physicians must always use all the PPP elements. Merely informing women about the teratogenic risks of isotretinoin was insufficient to modify their sexual behaviour to use effective contraception.

Age distribution in our sample was similar to the findings of a recent American study[20] on women using isotretinoin. The proportion of dermatologists (78%) to family practitioners who prescribed isotretinoin is comparable to findings in other studies.[11,16-18] Our sample was mainly urban and highly educated; this could influence our results. In fact, dermatologists are more accessible in cities. Nevertheless, an increasing number of family physicians prescribe isotretinoin in Canada.[15] Moreover, even though our questionnaire was not designed to collect that specific information, some women spontaneously reported that dermatologists asked them to see their family doctors for contraception and monitoring related to isotretinoin.

In our study, 58% of women were using oral contraception as the main contraceptive method and, most of the time, as the unique contraceptive method. Considering that 60% of oral contraceptive users miss one or more pills during a 6-month period,[21,22] this could have dramatic consequences among women who use isotretinoin. Moreover, as 30% of condom users are intermittent users and typical use shows a 14% failure rate,[23] the finding that 18% of women participating in this study reported the use of condoms as their only contraceptive method is worrisome.

In general, proportions of physicians or women who did not comply with various recommendations of the monograph or PPP are in the same range as those found in other studies.[16-19] The important difference in the use of the consent form in our study (13%) compared with the Accutane survey (77%)[16] could be explained by the greater risk of lawsuits against physicians in the United States.

Fetal exposure to isotretinoin will continue to occur if patients use only one contraceptive method, use contraceptive methods with a high risk of failure, do not use any contraceptive method, or are not screened for pregnancy before and during treatment. More extensive measures should be taken to ensure that women are not pregnant before starting treatment and that contraceptive recommendations are understood and followed. The consent form should always be used, as it helps to ensure that women are aware of the teratogenic risks and pregnancy prevention recommendations. In light of our findings, certification and registration should be required for physicians who wish to prescribe and follow up on isotretinoin in Canada, as proposed by Koren et al.[15]

Moreover, pharmacists should be included in the process by verifying pregnancy testing and ongoing appropriate contraception before dispensing the drug monthly. They have the opportunity to reinforce information given by physicians because they are the last link in

the prescription-information-dispensing process. This study illustrates that women do not seem to understand the possible consequences of inadequate contraception; reinforced teamwork between pharmacists and physicians is needed to better involve these women.

We agree that physicians are only one element in the process of pregnancy prevention, even if they can and should be especially important. Many studies about isotretinoin, including the Accutane survey, used women's self-reports to assess physicians' behaviour.[11,13,14,16,19] This procedure probably underestimates information given by physicians, although we did not intend to measure this outcome. Instead, this study measured what women recall their physicians have said or done. In fact, the way the women feel about, perceive, and retain the information is an important factor influencing the way information will be used in real life thereafter. Further exploration of underlying reasons for women's noncompliance might show how to change such behaviour. Despite the small sample, our results confirm important failures in pregnancy prevention with Canadian women who use isotretinoin.

## CONCLUSION

From the perspective of female patients, physicians prescribing isotretinoin did not always advise them according to the recommendations concerning pregnancy prevention. The women stated they understood the information received but did not comply with pregnancy prevention measures. An important link between the extent of the pregnancy prevention measures taken by physicians and women's compliance was evident.

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### Contributors

*This paper is derived from* **Ms Boucher's** *Master's degree project; she took part in all steps of designing and implementing the study under the supervision of* **Dr Beaulac-Baillargeon,** *her research director. Questionnaires were designed and pretested conjointly, and both authors performed statistical analyses, interpreted results, and wrote the manuscript.* **Ms Boucher** *performed all interviews.*

### Competing interests

*None declared*

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