THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

Terminations of pregnancy associated with isotretinoin use in New Zealand

Peter Moodie, Richard Jaine, Jason Arnold, Scott Metcalfe, Mike Bignall, Bruce Arroll

Abstract

Aims Oral isotretinoin is a highly-effective treatment for severe acne. It is also highly teratogenic. Recently, funded access was widened (from vocationally registered dermatologists only) to include vocationally trained general practitioners and nurse practitioners acting within their scope of practice. This decision has caused some debate. While it is hoped that it will increase access to those living in more deprived areas, there are concerns that there will be an increase in the number of affected pregnancies. This study aims to report on terminations of pregnancy occurring while using isotretinoin in New Zealand.

Method Using NHI numbers, termination of pregnancy admissions were matched to recent isotretinoin prescriptions.

Results This study has revealed that there appears to have been more unintended pregnancies related to isotretinoin use than previously thought. A total of 39 terminations of pregnancy related to isotretinoin use were identified in the year ending June 2008. This gave a crude termination of pregnancy rate of 73 per 10,000 females aged 10–44 years.

Conclusions While there are some limitations to this study, the results are consistent with recent international research suggesting previous pregnancy rates on isotretinoin have been underestimates. Widening funding of isotretinoin will likely increase the absolute numbers of pregnancies but also has the potential to increase relative numbers. As such, it will be vital that primary care is alert to the risks of isotretinoin use and gain experience in its day-to-day usage. Although access has been widened, all requests for funding will now be recorded on a national database (Special Authority database) to enable closer monitoring of isotretinoin usage.

Oral isotretinoin is a highly-effective treatment for severe refractory cystic and conglobate acne that has been available for over 20 years. It is also highly teratogenic. Given that the medication was difficult to use and the risk of teratogenicity, until recently, funded access in New Zealand has been available only for prescriptions written by vocationally registered dermatologists. Despite this funding restriction, other prescribers have always been allowed to issue prescriptions, albeit with a patient having to pay the full direct cost of isotretinoin along with pharmacy markups and dispensing fees. Several other countries, including the United Kingdom and Australia, have similar restrictions.

In April 2009, the agency that manages New Zealand's community pharmaceutical budget, PHARMAC (Pharmaceutical Management Agency), widened funded access to oral isotretinoin such that vocationally trained general practitioners and nurse

practitioners acting within their scope of practice were able to write fully subsidised scripts for their patients.

The main impetus behind this decision was to address the inequities of access present under the funding restriction: those living in more deprived areas and Māori and Pacific people were less likely to access isotretinoin.[1]

Those opposed to widening funding cited several concerns including:

- The lack of expertise by non-dermatologist prescribers in managing isotretinoin;
- The potential increase in pregnancy exposures; and
- Pressure on GPs to prescribe isotretinoin.[2]

In response to these concerns, PHARMAC stated that: GPs would receive training in managing isotretinoin; although there is the potential to increase absolute numbers of affected pregnancies, the proportion of affected pregnancies may not increase; and prescribing pressure may be present for any type of doctor.[2]

Isotretinoin is teratogenic at all therapeutic doses. Malformations—characteristically ear defects, central nervous system defects and/or cardiovascular defects—have been reported following a single dose of the pharmaceutical.[3] Malformation rates for pregnancies that end in birth range from 11% to 30%, with most estimates at the upper end of this range.[4–7]

Most research on the pregnancy rate of women on isotretinoin has been completed in North America. One of the early studies reported a pregnancy rate of 8.8 per 1000 person-years of treatment.[5] Other figures quote a pregnancy rate for women taking isotretinoin of 0.04% in 1989 dropping to 0.02% in 1999.[8] However, given the not insignificant limitations of some of this research (such as self-reported surveys and spontaneous reporting of pregnancies), these rates are expected to be underestimates.[7,9]

A more recent retrospective cohort study found a pregnancy rate of 32.7 per 1000 person-years of treatment: a rate four times greater than what has been previously published.[7] Elective termination of pregnancy rates vary greatly from 36% to 84%.[4–7]

In New Zealand, there is very little data about pregnancy rates while on isotretinoin. An informal voluntary survey undertaken by dermatologists in New Zealand identified approximately 60 at risk pregnancies over a 20-year period (personal communication, 2008).

There is a lack of New Zealand-specific data on this issue and the current international literature (mostly from North America) is unlikely to be generalisable to New Zealand given differences in prescribing restrictions, pharmaceutical costs, pregnancy prevention programmes and overall demographics. As such, this study aims to report on terminations of pregnancy occurring while using isotretinoin in New Zealand.

Methods

Isotretinoin prescription data—Once a funded prescription is dispensed in New Zealand the data is collected in a national repository and available for analysis. In addition to prescriber details, the

medication name, strength, quantity and dosage are recorded, along with an encrypted National Health Index (NHI) number where this is available.

The NHI number is a unique identifier for virtually everybody in New Zealand who has ever had contact with the health service. As previously reported[1] only 60% of isotretinoin prescriptions had an NHI attached (potentially due to the non-routine use of NHI numbers by private specialists).

Prescription data for isotretinoin for the period year ending June 2008 was accessed through PharmHouse. The PharmHouse database is a subset of the New Zealand Health Information Service (NZHIS) database that contains records of all the claims for medicines dispensed within New Zealand.

Termination of pregnancy data—All public hospitals report to the NZHIS on surgical procedures carried out which are recorded as "disease related groups" (DRGs). All terminations of pregnancy carried out in a public hospital are recorded in this way along with an NHI number.

All legal terminations of pregnancy must be reported to the New Zealand Abortion Supervisory Committee. Termination of pregnancy data was obtained for this study for year ending June 2008. Not all records in this database have an NHI number available. By example, in 2008 the Abortion Supervisory Committee identified 18,382 terminations of pregnancy. However, 1592 (or 8.7%) were performed at a private clinic in Auckland and these cases would not have been identified in the NZHIS database. Therefore, no NHI data was available for these women.

Matching datasets—With the available NHI numbers, an attempt was made to match termination of pregnancy admissions obtained with recent (i.e. within the last 6 months) isotretinoin prescriptions using NHI numbers. A prescription within the preceding 6 months was chosen as the period during which a possible link between isotretinoin use and wish to terminate pregnancy could most likely be made. This period takes into account prescription length, one month post medication period, time to awareness of pregnancy and time to organise termination.

Deprivation level—Individuals were assigned the deprivation level of their area of residence based on the New Zealand Deprivation Index (NZDep). The NZDep Index is a population level index based on nine variables recorded on the 2001 New Zealand census.[10]

Analysis—Simple descriptive analysis of isotretinoin prescriptions and terminations of pregnancy by deprivation level were completed. Total number of terminations of pregnancy for those who had been given a prescription of isotretinoin in the preceding 6 months are given.

Ethics—Ethics approval was not sought as this work fits the exception criteria for secondary use of data without consent according to the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities (2006).*

Results

In the year ending June 2008, there were 27,056 funded isotretinoin prescriptions (approximately 3,000,000 capsules) dispensed. Over the same timeframe, there were 14,793 terminations of pregnancy identified from the databases.

Isotretinoin use was not evenly distributed across the deprivation quintiles (Figure 1). Those from the least deprived quintile are more than twice as likely to access isotretinoin compared with people from the most deprived quintile.

The opposite effect is present when terminations of pregnancy are analysed. There were three times as many terminations of pregnancy performed on individuals from the most deprived areas compared to those living in the least deprived areas (Figure 2).

Figure 1. Isotretinoin prescription rates by deprivation level, year ending June 2008

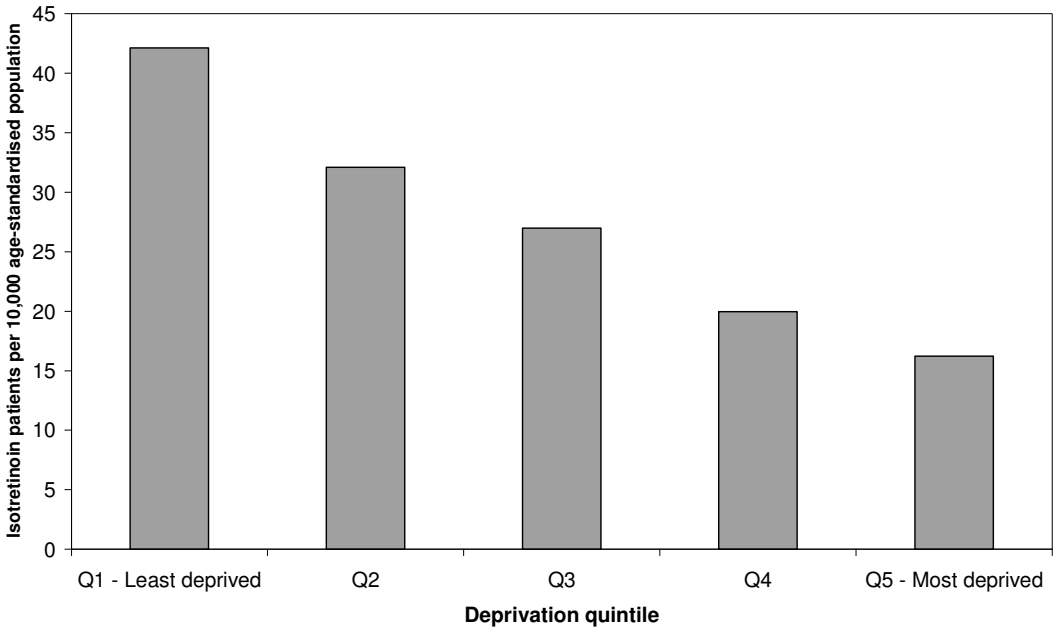
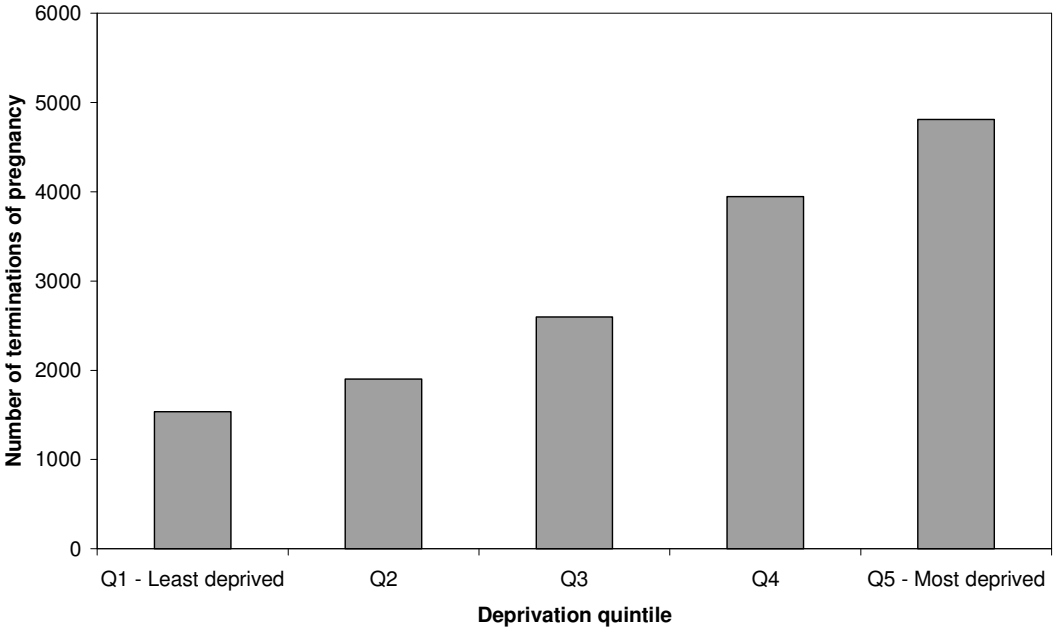
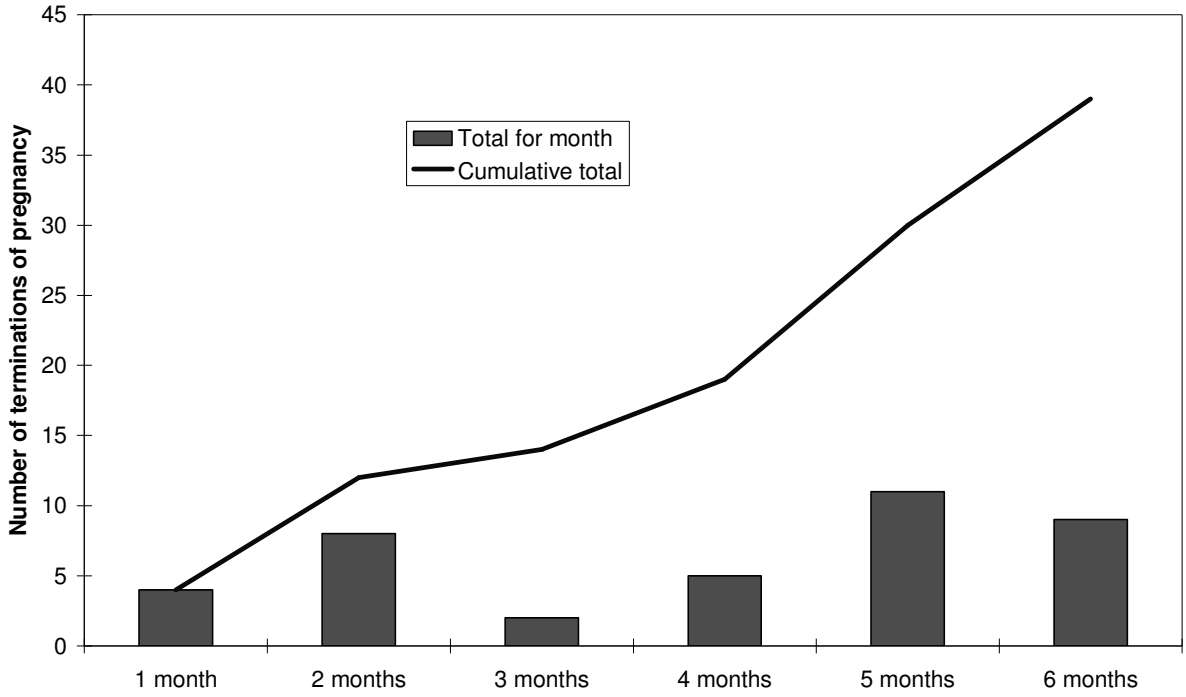


Figure 2. Total number of terminations of pregnancy by deprivation level, year ending June 2008



This study identified 39 patients who had a termination of pregnancy as well as an isotretinoin prescription within the preceding 6 months. This gives a crude termination of pregnancy rate of 73 per 10,000 females aged 10–44 years. The crude termination of pregnancy rate for the total population of females aged 10–44 years is 139 per 10,000. The monthly distribution is shown in Figure 3.

Figure 3. Monthly total and cumulative number of terminations of pregnancy by months following isotretinoin prescription, year ending June 2008



Discussion

This study has identified a far greater number of pregnancies related to isotretinoin use than was previously suspected. A total of 39 terminations of pregnancy were identified where a prescription of isotretinoin had been given in the previous 6 months.

While the termination of pregnancy rate for those taking isotretinoin was approximately half that for the total population, it is still higher than previously assumed. There had been concern that early estimates of pregnancy rates for people using isotretinoin had been significantly underestimated.[7,9]

The results of this study support this concern in the New Zealand setting and are consistent with recent international literature.[7] We suspect that, on an international scale, pregnancy rates while using isotretinoin are far higher than previously recognised.

There are some limitations to this analysis. Both datasets used were incomplete. Forty percent of the isotretinoin prescriptions did not have an NHI number attached, while almost 9% of the termination of pregnancy data did not have an NHI number. However, if the percentage of isotretinoin prescriptions or terminations of pregnancy with NHI numbers increased, it would be expected that there would have been a greater absolute number of terminations of pregnancy associated with isotretinoin use identified. Hence these results are almost certainly an underestimate of the number of at risk pregnancies. It is unknown how an increase in NHI recording would affect the termination of pregnancy rate.

A further limitation of this study is the use of isotretinoin prescriptions in the 6 months preceding a termination of pregnancy. Not all of these pregnancies would necessarily have been at risk and could have occurred later than a month after stopping therapy. It is also possible that terminations may have resulted for other reasons independent of known isotretinoin usage and associated risks of teratogenicity.

This study only examined terminations of pregnancy and does not attempt to identify other pregnancies, such as spontaneous abortions and pregnancies carried through to birth, that may have occurred while using isotretinoin. Given that previous international studies identify that elective terminations of pregnancy account for between 36% and 84% of all pregnancies related to isotretinoin use, this study is very likely an underestimate of the total number of pregnancies occurring while using isotretinoin. There was also no attempt to identify reasons for the terminations of pregnancy.

Given these results, what effect may the widening of funded access to isotretinoin have on the number of pregnancies occurring while using the pharmaceutical? It is expected that widening funding access will increase the total number of people using isotretinoin, particularly those living in the more deprived areas, and potentially Māori and Pacific people.[1]

Further analysis of the termination of pregnancy data showed that those in the most deprived areas were overrepresented in termination of pregnancy figures overall. This suggests that if access is widened such that those in the more deprived areas achieve greater access, there is also a greater risk not only in absolute numbers of pregnancies but also in relative numbers. This will be a very real challenge for primary care providers to ensure that contraception is managed well in this group. However the new decision support mechanism and the GP experience with birth control could potentially reduce the relative pregnancy numbers.

In attempting to effectively manage contraception in those using isotretinoin several countries have implemented risk management approaches.[5,11] These programmes have tended to differ in their complexity and approach used.[11] Unfortunately, there is limited evidence of the effectiveness of some risk management approaches in preventing pregnancies.[11,12]

In New Zealand, current recommendations for starting and maintaining a patient on isotretinoin include: obtaining a current sexual history; giving appropriate advice and information on contraception and the risks of isotretinoin; the use of two forms of contraception; and pregnancy tests prior to initiating and monthly at each prescription.

It will be important to audit or monitor prescribers and their adherence to these recommendations. This will help in assessing the effectiveness of these recommendations and whether further pregnancy prevention approaches would be required.

The funding for isotretinoin was initially restricted due to the potential difficulty in managing this highly teratogenic pharmaceutical. However, given the results of this study, it appears that restricting access may not have prevented unwanted pregnancies as much as had been anticipated. Although primary care has not had a great deal of experience in the management of patients using isotretinoin, they have a great deal of experience and understanding of the management of contraception.

Primary care clinicians are also well placed to have an excellent understanding of the overall clinical and social circumstances of their patient. Now that funding has been widened to primary care, it will be vital that they are alert to the risks of isotretinoin use and gain experience in its day-to-day usage, while appropriately applying their broad experience in contraception management and their understanding of patients' clinical circumstances. It will be equally important for dermatologists to act as a backup to primary care in this area. To add further support to primary care, PHARMAC has arranged for training seminars along with a number of publications on the matter.

Now that funding has been widened, it is vital to robustly monitor isotretinoin use. To this effect, PHARMAC requires that funded access to isotretinoin be recorded on a "Special Authority" database. This will guarantee that NHI numbers are recorded on prescriptions and allow prescribing data to be accurately correlated to New Zealand termination of pregnancy data. It will be important to regularly review this data to ensure that the widening of funded access does not have any unexpected negative effects on the health of the population.

As a final step it would seem sensible to require private termination of pregnancy clinics to supply not only termination of pregnancy numbers to the Abortion Supervisory Committee but also include NHI numbers. In this way accurate statistics can be kept for the whole country.

Competing interests: None, including no external funding sources.

Author information: Peter Moodie, Medical Director PHARMAC, Wellington; Richard Jaine, Public Health Physician, Department of Public Health, University of Otago, Wellington; Jason Arnold, Senior Analyst, PHARMAC, Wellington; Scott Metcalfe, Chief Advisor Population Medicine/Public Health Physician, PHARMAC, Wellington; Mike Bignall, Therapeutic Group Manager, PHARMAC, Wellington; Bruce Arroll, Head of Department, Dept of General Practice and Primary Health Care, School of Population Health, University of Auckland

Acknowledgements: Dilky Rasiah (PHARMAC) assisted in finalising the manuscript. Coonwa Emmanuel Jo (NZ Ministry of Health) provided the data matching.

Correspondence: Peter Moodie, PHARMAC, PO Box 10-254, Wellington 6011, New Zealand. Fax: +64 (0)4 4604995; email: peter.moodie@pharmac.govt.nz

References:

1. Moodie P, Jaine R, Arnold J, et al. Usage and equity of access to isotretinoin in New Zealand by deprivation and ethnicity. BMJ (in press NZMJ).
2. bpac nz. The isotretinoin debate. Best Practice Journal. 2009;20:4-6.
3. James WD. Clinical practice. Acne. N Engl J Med. 2005;352(14):1463-72.
4. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol. 1992;26(4):599-606.
5. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. N Engl J Med. 1995;333(2):101-6.
6. Honein MA, Paulozzi LJ, Erickson JD. Continued occurrence of Accutane-exposed pregnancies. Teratology. 2001;64(3):142-7.
7. Bérard A, Azoulay L, Koren G, et al. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Clin Pharmacol. 2007;63(2):196-205.
8. Ellison RH, Leach EE. In reply: Isotretinoin and pregnancy. JAMA. 2001;285(16):2079-81.
9. Jones KL, Adams J, Chambers CD, et al. Isotretinoin and pregnancy. JAMA. 2001;285(16):2079-81.
10. Salmond C, Crampton P. NZDep2001 Index of Deprivation. Wellington: Department of Public Health, Wellington School of Medicine and Health Sciences, 2002.
11. Abroms L, Maibach E, Lyon-Daniel K, Feldman SR. What is the best approach to reducing birth defects associated with isotretinoin? PLoS Med. 2006;3(11):e483.
12. Atanackovic G, Koren G. Fetal exposure to oral isotretinoin: failure to comply with the Pregnancy Prevention Program. CMAJ. 1999;160(12):1719-20.