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Isotretinoin Use and Compliance with the Dutch Pregnancy Prevention Programme

A Retrospective Cohort Study in Females of Reproductive Age Using Pharmacy Dispensing Data

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Abstract

Background: Isotretinoin is very effective in the treatment of severe acne. However, because of the teratogenic properties of this agent an isotretinoin Pregnancy Prevention Programme (PPP) was implemented in the Netherlands to guarantee that treatment is contraindicated in women of reproductive age unless at least one effective method of contraception is used. Furthermore, the PPP stipulates that isotretinoin treatment should be managed by physicians or specialists experienced in treatment with this drug and that only monthly prescriptions are issued.

Objective: To assess compliance with the Dutch isotretinoin PPP in women of reproductive age during the study period of 1 January 2005 to 31 December 2008.

Methods: Detailed information on dispensed medication and co-medication was available from the Dutch Foundation of Pharmaceutical Statistics. Four types of outcome were studied: concomitant dispensing of hormonal contraceptive with isotretinoin; the proportion of specialist prescribing of isotretinoin; prescribing of conventional acne therapy prior to isotretinoin initiation; and isotretinoin dispensing exceeding the maximum amount. The use of contraceptives in women aged between 15 and 45 years was defined as concomitant if the period of systemic contraceptive use overlapped the period of isotretinoin dispensing for at least 10 days, or if any dispensing of an intrauterine or intravaginal contraceptive was recorded since the

year 2000. Dispensings were separated into those prescribed by either specialists or general practitioners (GPs). The use of antibacterials, antiandrogens or topical agents against acne was checked 4 months prior to an isotretinoin dispensing, and a possible excess of the maximum amount of isotretinoin was defined as prescriptions of more than 100 defined daily doses.

Results: During the study period, data were available for 442 Dutch pharmacies encompassing 4881 women of reproductive age using isotretinoin at least once during study period. Among women of reproductive age, the use of isotretinoin increased during the study period. The proportion of isotretinoin initiation with concomitant oral hormonal or intrauterine contraceptives was low (59.3% [95% CI 57.6, 61.0]). Initiation of isotretinoin by a specialist increased the chance for concomitant contraception by 26% (95% CI 6.0, 49.0); in 78.2% (95% CI 76.8, 79.6) of women, isotretinoin was initiated by a specialist. Conventional acne therapy up to 16 months prior to isotretinoin initiation was found in 70% of the women (70.3% [95% CI 66.0, 74.6]). In 1.4% (95% CI 1.0, 1.8) of cases of treatment initiation, the amount of isotretinoin dispensed on one prescription seemed too high.

Conclusion: Attention should be paid to improving the implementation of the isotretinoin PPP. Despite clear guidelines and warnings in the product information, our study strongly suggests that concomitant use of isotretinoin and contraceptives is too low. Even though we will have missed non-pharmacological forms of contraception, these results raise doubts about the safe use of isotretinoin in women of reproductive age in the Netherlands. Furthermore, isotretinoin does not seem to be used in cases of severe acne only. Reserving isotretinoin prescribing to specialists may improve adherence to the PPP.

Background

Isotretinoin (13-cis-retinoic acid), a synthetic derivative of vitamin A (retinol), has been registered in the US since 1982 and in all European countries except Sweden since 1983 for the therapy of severe resistant nodular and scarring acne.[1] Isotretinoin is the only acne medication that affects all four pathogenic factors of acne, i.e. being comedolytic, reducing the sebaceous gland size, decreasing sebum production, and with some anti-inflammatory activity.[2,3] As isotretinoin leads to lasting remissions in the majority of acne patients with a relatively short treatment course of up to 6 months, it is an efficacious and cost-effective anti-acne drug.[2,4] However, results from animal studies conducted immediately after the drug was introduced onto the market suggested teratogenicity.[5,6] The exact mechanism of isotretinoin is unknown, but it is assumed that it alters DNA transcription, similar to other retinoids. In fetuses, it can lead to a vitamin A-like embryopathy with mental retardation, absence or malformation of ears and other facial malformations, ophthalmoplegia, maxillary bone malformations, teeth malformation, various cardiac malformations, limb reduction defects and skeletal hyperostosis.[7,8] The risk of spontaneous abortion is approximately 20%. In completed pregnancies, 65–82% of neonates appear normal at birth, but there is insufficient data to determine how many will develop isotretinoin-related problems later on.[7]

The safe use of isotretinoin in women of childbearing age is an important public health issue, as pregnancy is preventable. Children conceived while the mother is receiving isotretinoin treatment are at increased risk of being born with major malformations and will require continuous healthcare services throughout their life.[4] Despite the thalidomide disaster in the 1960s, known teratogens are still prescribed without proper physician surveillance, although, since 1982, many interventions to lower the number of pregnancies exposed to isotretinoin have been initiated.[4,9-11] Early interventions included letters from the manufacturer to physicians, and warning stickers on the label stressing the teratogenic risk of isotretinoin.[12,13] In 1986, these separate interventions were combined in the US into a Pregnancy Prevention Programme (PPP). For European countries the European Medicines Agency released clear guidelines for prescribers, pharmacists and patients regarding the safe use of isotretinoin in 2003.[14] These guidelines demanded harmonized, consistent and accurate product information as the increasing marketing of generic drugs with varying product information has caused uncertainty and confusion amongst users. The European guidelines had to be implemented under national responsibility in the member countries with a supporting PPP. Since 2003, the Dutch isotretinoin PPP has stated that isotretinoin is contraindicated in women of reproductive age unless they meet all of the following requirements, even if not sexually active: have severe acne; understand the teratogenic risk and the need of the PPP; use effective continuous contraception with one, preferably two, forms (of which one is a barrier method such as a condom) from 1 month before treatment initiation until 1 month after cessation of isotretinoin; are capable of taking effective contraceptive steps; are informed to immediately consult a doctor in case of pregnancy; pregnancy testing before, during and 5 weeks after cessation of treatment; sign informed consent on understanding the risks and agreement on the necessary ongoing precautionary measures with isotretinoin treatment. Furthermore, isotretinoin should be prescribed to this patient group by physicians experienced in treating patients with this drug. The maximum duration of a prescription is 30 days and dispensing of the drug by the pharmacy should take place within 7 days after prescription. In the Netherlands, items in the PPP were communicated to prescribers, pharmacists and patients via the product information,[15-18] national general practitioner (GP) standards on treatment of acne[19] and the common literature on drug information.[20-22]

Despite these clear guidelines, cases of unintended pregnancy during isotretinoin use ending in abortion or serious malformation have been reported to the Dutch authorities. A study carried out in Dutch community pharmacies showed that the requirements of the isotretinoin PPP were not fully adhered to in daily pharmaceutical practice.[23] Consequently, we investigated the degree of implementation of the isotretinoin PPP in the Netherlands, and trends in the quality of prescribing during the last 4 years. In this retrospective cohort study using pharmacy dispensing data, we investigated isotretinoin use in women of reproductive age, together with hormonal contraceptives and the degree of specialist prescribing. Furthermore, we assessed whether isotretinoin use was restricted to patients with severe acne after having tried conventional acne therapy and whether prescribing for a maximum of 30 days at a time was adhered to.

Methods

Settings and Inclusion Criteria

In this population-based study, detailed information on all dispensed medication was available from the Dutch Foundation of Pharmaceutical Statistics (SFK). The SFK routinely collects dispensing data from more than 90% of the approximately 1900 community pharmacies in the Netherlands. For each patient, dispensings are identified by a unique but anonymous code, together with sex and year of birth. The data include detailed information on drugs dispensed, such as the effective chemical substance using codes from the Anatomical Therapeutic

Chemical (ATC) system and the amount dispensed by defined daily doses (DDD), i.e. the recommended daily dose for a specific indication in an adult.[24] Together with the date of dispensing and information on the prescribed daily dose from the computerized system of the community pharmacies, this information enabled us to calculate periods of drug use. Each dispensing was labelled with the type of prescriber so that prescribing by GPs and specialists could be distinguished.

During the study period (1 January 2005 to 31 December 2008) we included data from all pharmacies that had delivered complete data since 1 January 2000 (figure 1). This long history of data was necessary in order to assess whether the isotretinoin dispensings during the study period accompanied dispensing of contraceptives for local intrauterine or intravaginal use placed up to at least 5 years earlier. Although local devices may be effective up to 10 years after placement, there would not have been enough data-delivering pharmacies with a complete history dating back to 1 January 1995, thus dispensing of dispensing of contraceptives for local intrauterine or intravaginal use in the 5 years prior to the start of the study was taken into account. Within the eligible community pharmacies, we included all women between 15 and 45 years of age who received at least one systemic isotretinoin prescription (ATC code D10BA01) during the study period.

Outcomes

We addressed four different outcomes as indicators for the degree of implementation of the isotretinoin PPP. These were analysed annually to detect trends in the quality of isotretinoin prescribing during the last 4 years. In addition, first isotretinoin prescriptions during the whole study period were analysed. An isotretinoin dispensing was considered as a first dispensing if no prior isotretinoin dispensing was found during the foregoing 12 months. We excluded 'drop in' patients, i.e. those who, apart from a single systemic isotretinoin dispensing, had no dispensing of any other medication in the previous 2 years.

Concomitant Use of Contraceptives with Isotretinoin

As the main outcome, we first estimated the proportion of women within the reproductive age of between 15 and 45 years who used systemic isotretinoin without a concomitant dispensing of

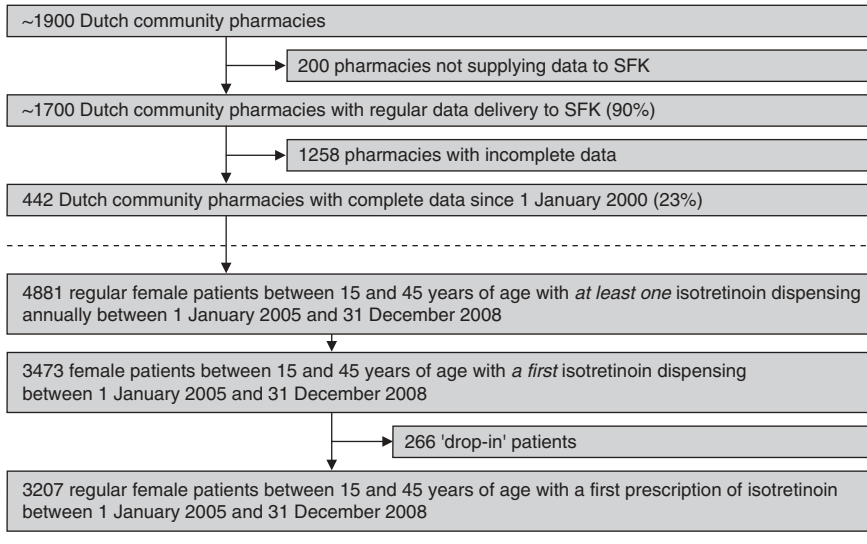

Fig. 1. Pharmacies and patients included in the study. **SFK** = Foundation of Pharmaceutical Statistics.

contraceptives from their community pharmacy. Two forms of contraception were searched for in the pharmacy data: contraceptives for local use (intrauterine or intravaginal devices [IUDs], by ATC code G02B) and systemic hormonal contraceptives (the 'pill', by ATC code G03A for hormonal, systemic contraceptives, and G03H for the anti-androgen cyproterone). Concomitant use of a local contraceptive with isotretinoin was defined as any dispensing of this contraceptive, as of 1 January 2000, prior to or together with isotretinoin initiation. For systemic hormonal contraceptives, periods of drug use were calculated by the number of pills dispensed within 25 months prior to the isotretinoin dispensing, with a standard monthly prolongation of 7 days to adjust for 1 week of cessation. Absence of concomitant use of systemic contraceptives was stated if no days of oral contraceptives were found during the period of isotretinoin use. For concomitant use of systemic contraceptives with isotretinoin, we defined 'partial overlap' if use of the contraceptive covered at least 10 days of the isotretinoin period, and 'total overlap' if use of the oral contraceptive lasted for at least 30 days after the dispensing of isotretinoin, as isotretinoin should be dispensed monthly. For the use of systemic contraceptives we used the two categories of 'partial' and 'total' overlap with isotretinoin dispensing in order to vary the specificity of our findings. The date of actual treatment initiation cannot be determined from dispensing data, and therefore criteria that are too restrictive could lead to under-estimation of the real use of concomitant hormonal contraception. Concomitant use of contraception with isotretinoin use was defined if a local contraceptive was detected before or with the isotretinoin dispensing, or if at least a period of partial or total overlap, respectively, with a systemic contraceptive was detected during usage of isotretinoin. If a woman had more than one period of isotretinoin use annually, at least one period with concomitant hormonal contraception was regarded as effective pregnancy prevention in the annual analysis. We also analyzed contraception concomitant with isotretinoin within age categories and we used logistic regression analysis to assess the contribution of specialist prescribing to the use of concomitant contraception.

Specialist Prescribing of Isotretinoin

As the secondary outcome, we calculated the proportion of isotretinoin dispensings prescribed by medical specialists. Amongst these, dermatologists or internists are regarded as physicians being familiar with isotretinoin treatment. As our data did not contain information on the type of specialist, we were not able to specifically assess isotretinoin prescriptions by the type of specialist. In the annual analysis we defined isotretinoin as being prescribed by a specialist if at least one specialist prescription was detected. Treatment initiation by specialists during the whole study period was also assessed.

Conventional Acne Therapy Prior to Isotretinoin Initiation

As isotretinoin should be reserved for serious therapy-resistant acne after having tried benzoylperoxide or local or systemic antibacterials,[19] the absence of prior conventional therapy might indicate inappropriate prescribing. We calculated the proportions of isotretinoin users in our study population who had not been prescribed prior conventional anti-acne medication (the systemic antibacterials tetracyclines [J01A] or macrolides [J01FA], anti-androgens [G03H] or topical agents [D06, D07, D10A]). For the annual analysis, we searched for conventional acne therapy from September of the prior year up until the isotretinoin prescription. For the analysis of first dispensings during the whole study period, we checked for conventional acne therapy within 4 months prior to the first dispensing of isotretinoin.

Isotretinoin Dispensings Possibly Exceeding the Maximum Amount

Isotretinoin is to be dispensed for a maximum of 30 days. One DDD of isotretinoin corresponds to 30 mg, and the maximal daily dose is 1 mg/kg. Thus, for a person with a bodyweight of 100 kg, a prescription should be restricted to a maximum of 100 DDD (3000 mg) isotretinoin. We calculated annually how many females of reproductive age filled at least one prescription

exceeding 100 DDD of isotretinoin, and determined the number of first dispensings exceeding this maximum amount during the whole study period.

Analysis

Descriptive statistics were used to summarize patient characteristics and prescribing behaviour. We described prescription patterns of isotretinoin during the study period from 1 January 2005 to 31 December 2008 for females within the reproductive age (excluding 'drop-in' patients). This was done annually for the four outcomes and also for isotretinoin treatment initiation during the whole study period. SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

Results

During the study period and the previous 5 years, complete data were available at the SFK for 442 community pharmacies, comprising approximately 23% of the total of nearly 1900 community pharmacies in the Netherlands in 2008.[25] In the eligible pharmacies, a total of 4881 women of reproductive age (between 15 and 45 years) had annually received at least one prescription of isotretinoin between 1 January 2005 and 31 December 2008 (figure 1). During the study period, 3473 women had first prescriptions and 266 (8%) were 'drop-in' patients, leaving a total of 3207 women of reproductive age as regular patients within a pharmacy who initiated isotretinoin during the study period. The average age of women of reproductive age initiating isotretinoin was 27.6 years (SD 7.4 years). During the 4 years of our study period, the number of women of reproductive age treated with isotretinoin increased steadily from 1097 in 2005 to 1428 in 2008 within the 442 pharmacies (table I). The annual proportions of first prescriptions of isotretinoin within women of reproductive age ranged between 66.5% (95% CI 62.1, 70.9) in 2006 to 71.9% (95% CI 67.7, 76.1) in 2008.

Concomitant Use of Contraceptives with Isotretinoin

The annual percentage of women of reproductive age using isotretinoin without any local contraceptive since 1 January 2000, and without at least a partial overlap of systemic hormonal contraceptives was between 39.9% (95% CI 35.3, 44.5) in 2007 and 44.0% (95% CI 39.4, 48.6) in 2006 (table I). Sub-analysis for partial and total overlap of concomitant use of systemic hormonal contraceptives showed that between 44.4% (95% CI 39.8, 49.0) and 48.2% (95% CI 43.5, 52.9) of the women had a partial overlap with systemic contraceptives for at least 10 days (years 2006 and 2007, respectively). A more stringent analysis for total overlap of the pill with an isotretinoin dispensing for 30 days resulted in proportions of female isotretinoin users with concomitant hormonal contraceptives of between 37.6% (95% CI 33.1, 42.1) in 2006 and 40.8% (95% CI 36.2, 45.4) in 2007. Within the female isotretinoin users, 11.6% (95% CI 8.6, 14.6) in 2006 and 12.3% (95% CI 9.2, 15.4) in 2008 had a local contraceptive prior to or in conjunction with isotretinoin treatment. Sub-analysis elucidated that one-third of the local contraceptives were started at the same time as isotretinoin treatment initiation. The other two-thirds of IUDs were placed up to 8 years earlier. During our study period, no trends were seen for an increase or decrease in concomitant use of the different forms of hormonal contraceptives in conjunction with isotretinoin. In our analysis of first dispensings during the whole study period, 59.3% (95% CI 57.6, 61.0) of the women initiating isotretinoin had concomitant use of a systemic hormonal contraceptive for at least 10 days, or a local contraceptive since 1 January 2000 (table II). Figure 2 shows that isotretinoin is started mostly in women aged between 18 and 30 years. However, the proportion of women lacking concomitant use of contraceptives was consistent for the age categories of women starting isotretinoin; age did not increase the chance of the patient receiving concomitant contraceptives at commencement of isotretinoin. A first isotretinoin prescription from a specialist increased the

Table I. Annual assessment of the quality of prescribing, according to the Dutch isotretinoin Pregnancy Prevention Programme (PPP), in women of reproductive age (between 15 and 45 years)[a]

Prescribing	Year			
	2005	2006	2007	2008
Isotretinoin dispensings (n)	1097	1139	1217	1428
Systemic hormonal contraceptives, partial overlap with isotretinoin {n (% [95% CI])}	509 (46.4 [41.8, 51.0])	506 (44.4 [39.8, 49.0])	587 (48.2 [43.5, 52.9])	657 (46.0 [41.4, 50.6])
Systemic hormonal contraceptive, total overlap with isotretinoin {n (% [95% CI])}	433 (39.5 [34.9, 44.1])	428 (37.6 [33.1, 42.1])	496 (40.8 [36.2, 45.4])	566 (39.6 [35.0, 44.2])
Local intrauterine or intravaginal contraceptive {n (% [95% CI])}	128 (11.7 [8.7, 14.7])	135 (11.6 [8.6, 14.6])	144 (11.8 [8.8, 14.8])	176 (12.3 [9.2, 15.4])
Isotretinoin dispensings without any systemic or local contraceptive concomitant with isotretinoin {n (% [95% CI])}	460 (42.0 [37.4, 46.6])	437 (44.0 [39.4, 48.6])	486 (39.9 [35.3, 44.5])	595 (41.7 [37.1, 46.3])
Specialist prescription of isotretinoin at least once annually {n (% [95% CI])}[b]	840 (76.6 [72.7, 80.5])	864 (75.9 [71.7, 79.9])	958 (78.7 [74.9, 82.50])	1167 (81.7 [78.1, 85.3])
First dispensings of isotretinoin {n (% [95% CI])}	763 (69.6 [65.3, 73.9])	757 (66.5 [62.1, 70.9])	834 (68.5 [62.1, 70.9])	1027 (71.9 [67.7, 76.1])
First dispensings by a specialist {n (% within annual first dispensings of isotretinoin [95% CI])}[b]	584 (69.5 [65.2, 73.8])	558 (73.7 [69.6, 77.8])	653 (78.3 [74.5, 82.1])	824 (80.2 [76.5, 83.9])
Conventional acne therapy prior to an isotretinoin dispensing {n (% within annual first dispensings of isotretinoin [95% CI])}[c]	526 (68.9 [64.6, 73.2])	553 (73.1 [69.0, 77.2])	612 (73.4 [69.3, 77.5])	675 (65.7 [61.3, 70.1])
Isotretinoin dispensing >100 defined daily doses occurring at least once {n (% [95% CI])}	33 (3.0 [1.4, 4.6])	25 (2.2 [0.8, 3.6])	37 (3.0 [1.4, 4.6])	36 (2.5 [1.0, 4.0])

a Comprises 442 Dutch community pharmacies ('drop-in' patients have been excluded).

b The Dutch PPP recommends that isotretinoin is prescribed by a physician or specialist experienced in the use of this drug in women of reproductive age.

c Previous conventional acne treatment since September of the previous year is determined and comprises the following Anatomical Therapeutic Chemical codes: J01A, J01FA, G03H, D10A, D06 or D07.

Table II. Quality of prescribing at initiation of isotretinoin treatment, according to the Dutch isotretinoin Pregnancy Prevention Programme (PPP), in women of reproductive age[a]

Prescribing	No. of women (% [95% CI])
Total no. of women	3207 (100)
Systemic or local contraceptives concomitant with isotretinoin initiation[b]	1903 (59.3 [57.6, 61.0])
Specialist prescribing of isotretinoin initiation[c]	2507 (78.2 [76.8, 79.6])
Conventional acne therapy within 4 months prior to isotretinoin initiation[d]	1834 (57.2 [55.5, 58.9])
Isotretinoin initiation with dispensing >100 defined daily doses	45 (1.4 [1.0, 1.8])

a First dispensings of isotretinoin to women in women between 15 and 45 years of age in 442 Dutch community pharmacies during 1 January 2005 and 31 December 2008; 'drop-in' patients were excluded.

b Concomitant use of systemic contraceptives with isotretinoin initiation was defined if the systemic contraceptive covered at least 10 days of the isotretinoin period.

c The Dutch PPP recommends that isotretinoin is prescribed by a physician or specialist experienced in the use of this drug in women of reproductive age.

d Previous conventional acne treatment is checked within the 4 months prior to the isotretinoin dispensing and comprises the following Anatomical Therapeutic Chemical codes: J01A, J01FA, G03H, D10A, D06 or D07.

chance of receiving concomitant contraceptives by 26% (95% CI 6.0, 49.0).

Specialist Prescribing of Isotretinoin

The annual proportion of women with at least one specialist prescription within all isotretinoin prescriptions was 75.9% (95% CI 71.7, 79.9) in 2006 and 81.7% (95% CI 78.1, 85.3) in 2008 (table I). In 78.2% (95% CI 76.8, 79.6) of women, isotretinoin was started by a specialist (tables I and II).

Conventional Acne Therapy Prior to Isotretinoin Initiation

In the annual analysis, we checked for prior conventional acne therapy up to September of the year preceding the first isotretinoin prescription within one calendar year. Consequently, the preceding use of conventional therapy was studied for a period of at least 4 months (16 months at the most) prior to an isotretinoin dispensing. In 2008 and 2007, we found that 65.7% (95% CI 61.3, 70.1) and 73.4% (95% CI 69.3, 77.5), respectively, of isotretinoin users had earlier used conventional acne therapy (table I). In a more stringent analysis during the whole study period for conventional therapy detected within 4 months prior to isotretinoin initiation, 57.2% (95% CI 55.5, 58.9) of the women were undergoing conventional acne therapy (table II).

Isotretinoin Dispensings Possibly Exceeding the Maximum Amount

Up to 3.0% (95% CI 1.4, 4.6) of women of reproductive age had received at least one prescription of isotretinoin exceeding 100 DDD (table I). 1.4% (95% CI 1.0, 1.8) of isotretinoin treatment initiation was above this maximum amount (table II).

Discussion

Our results suggest that the isotretinoin PPP of 2003 was not successfully implemented in clinical practice in the Netherlands. This PPP considers one contraceptive form as mandatory, and recommends two forms of contraception – a condom or diaphragm as well.[1] In 41% of women of reproductive age, we were unable to detect any dispensing of a concomitant hormonal systemic or local contraceptive by their regular pharmacy in conjunction with isotretinoin treatment initiation. As the teratogenic risk of isotretinoin is comparable to that of thalidomide, this proportion seems too high.[7,10,26-29] The proportional lack of hormonal contraceptives was consistently low over various age categories, a remarkable finding as isotretinoin is used primarily by women between 18 and 30 years of age and the average age of women in the Netherlands giving birth to their first child is 28.6 years.[30] The urgency for improving the implementation of the PPPs is high considering that the use of isotretinoin during pregnancy is still reported to the authorities, the number of female isotretinoin users of reproductive age in the Netherlands steadily increases and the average number of babies born to women in the Netherlands (1.98) is

relatively high compared with other European countries.

Because of the limitations of data derived from pharmacies, it is possible that we may have missed other contraceptive methods such as condoms, tubal sterilization or vasectomy. This may explain some, but not all, lack of contraceptives. As the current Dutch isotretinoin PPP states only that one effective contraceptive form is obligatory and only advises on the concomitant use of a second form, it is less stringent than the American programmes, which explicitly demand two contraceptive methods for female users of isotretinoin of reproductive age. In the case of the US PPP, the additional contraceptive method should have been registered at the pharmacy, even with the use of a condom. According to European standards, our data cannot exclude the fact that condoms, also considered as adequate concomitant contraception, were the contraception form of first choice in some female isotretinoin users who were not using oral, intrauterine or intravaginal hormonal contraceptives. For tubal sterilization or vasectomy, national data show that 11% of Dutch couples choose these forms of contraception.[31] Unfortunately, no data were available for the whole population and it is to be expected that childless single people are less likely to choose these forms of contraception. We may have also underestimated the use of intrauterine devices containing copper without progestogens as these are classified as medical devices that might also be supplied outside the pharmacy and thus may not fully be covered by our data. Furthermore, we may have missed some concomitant use of intrauterine or intravaginal contraceptives as our data only covered a history of pharmacy data for 5 years, whereas these local contraceptives are effective for up to 10 years. However, as the average history of prior use in the last year of our study period was 8 years, such misclassification may be modest. In addition, according to national reimbursement data, in 2007 IUDs were only used by 1.6% of all users of hormonal contraceptives.[32] In order to avoid misclassification by women who filled contraceptives prescriptions in one pharmacy and isotretinoin in another, we excluded those patients from our analysis as 'drop-in' patients. Although this comprised only 8% of the women in our study population, it might include women with concomitant contraceptives and might lead to an estimate that is too conservative. Also, we may have underestimated the lack of concomitant hormonal contraception, as we counted at least one period of partial overlap with systemic contraceptives as sufficient protection. According to the PPP, women should be protected during the entire period of isotretinoin use and up to 1 month after cessation. Analysis of total concomitant use of systemic contraceptives increased the proportion of women without adequate hormonal protection to 60%.

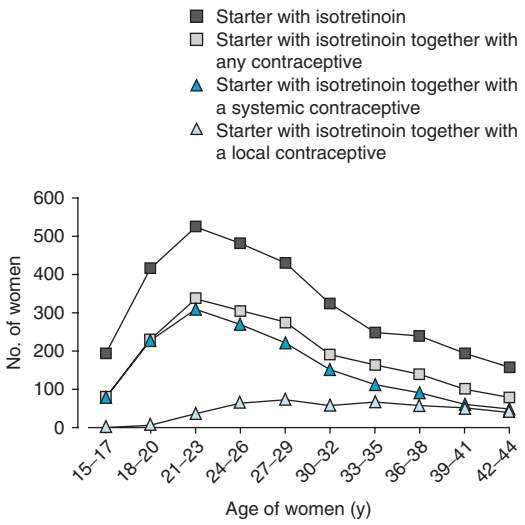

Fig. 2. Use of isotretinoin and concomitant contraceptives for women of reproductive age in the Netherlands, by age category. Includes 3207 females initiating isotretinoin within 442 Dutch community pharmacies between 1 December 2005 and 31 December 2008, and excludes 'drop-in' patients.

According to the Dutch PPP, isotretinoin treatment should be left to experienced prescribers. Although we could not focus on dermatologists or internists within the group of specialists, women prescribed isotretinoin by a specialist had a 26% increased chance of receiving contraception compared with prescriptions dispensed by GPs. Our results further suggest that prescribing of oral isotretinoin is not fully restricted to patients with severe therapy-resistant

acne. The Dutch treatment guideline on acne therapy only mentions isotretinoin at step four, after first trying local means such as benzoyl-peroxide, followed by local retinoids and then local or systemic antibacterials. However, we were able to detect prior use of conventional acne therapy in only 57% of females of reproductive age initiating isotretinoin. When increasing the timeframe for detection of prior use of conventional acne therapy from 4 months to up to 16 months, however, the percentages for prior conventional treatment increased to about 70%, but still left a substantial proportion of women starting isotretinoin without having tried conventional medication first. Because of the nature of our data, we were unable to detect the use of anti-acne therapy apart from that dispensed from pharmacies. However, amongst these drugs only benzoyl-peroxide is available over the counter and all other anti-acne drugs were thus captured by our data retrieval. These percentages were higher than in a Canadian study, where only 36% of patients had conventional anti-acne treatment before initiating isotretinoin.[3]

The Dutch Guidelines of GPs restrict the duration of each isotretinoin prescription to a maximum of 30 days.[19] This guidance was generally adhered to and we found only 2% of women of reproductive age receiving at least one isotretinoin dispensing of more than 100 DDD. Beside the possibility that these women weighed more than 100 kg, this could mean that the dosage was too high or that the dispensing was for longer than the maximum treatment duration of 30 days.

Our results are in line with other evaluations that, since 1983, have reported limited effects of PPPs. In the US, this led to a step-by-step development of more stringent programmes. After a front-page story in The New York Times in 1988 had suggested that hundreds of fetal malformations had occurred because of isotretinoin exposure, the US FDA launched a PPP in 1989 asking healthcare providers to carry out prior pregnancy testing, provide adequate contraception and patient information and obtain written consent from women prescribed isotretinoin.[11,12] In the US in 2002, the PPP was modified into a 'System to Manage Accutane-Related Teratogenicity' (SMART), which not only focused on pregnant women avoiding isotretinoin therapy but also on preventing pregnancy during treatment.[12,33] This programme targeted both healthcare providers and patients. It demanded two pregnancy tests prior to the start of treatment, required pharmacists to give medication guides with the isotretinoin prescription and stated the use of stickers for evidence of the qualification of registered prescribers. Last but not least, prescriptions were only to be dispensed if they were no more than 7 days old and dispensing was limited to a 30-day supply.[28] In 2003, this programme was evaluated and dismissed as a 'total failure' because the number of pregnant isotretinoin users had actually grown, together with the number of spontaneous or elective abortions. Furthermore, the number of children born with typical isotretinoin-induced birth defects had increased during release of the programme.[34] The failure was partially attributed to the lack of mandatory record-keeping and the fact that slightly different PPPs were started by the registration holders of three newly released generic isotretinoin brands.[13] Consequently, in the US, the so-called iPLEDGE programme was launched in March 2006.[35] This is one of the most rigorous risk management programmes for therapeutic agents, including a comprehensive monitoring system of the prescribing, dispensing and distribution of isotretinoin.[13] In a joint effort by the FDA and manufacturers, this programme allows the starting or continuation of isotretinoin treatment only in conjunction with monthly pregnancy tests and monthly identification of contraceptive methods by patients and doctors. Furthermore, it requires a thorough registration in a comprehensive computer-based programme by prescribers, pharmacists and wholesalers for each step within the chain of prescribing, dispensing and using isotretinoin. First evaluations of this programme report impressively low pregnancy rates of less than 1% under isotretinoin treatment.[13] However, the programme has been criticized as being too paternalistic and for potentially withholding effective treatment from those women who benefit

from it.[13] It exposes women of childbearing potential to undue burdens because it forces all women of reproductive age to enter a stringent process of pregnancy testing and prescribing without taking a women's individual situation into account.[35]

Earlier studies indicated an important role for physicians and pharmacists in the implementation of PPPs by patient counselling. The use of double contraception improved when physicians counselled patients and also gave verbal and written advice on the use of contraceptives when dispensing isotretinoin.[11] In a study on common practice of Dutch community pharmacies, 78% of the pharmacists reported providing information on the teratogenic risk of isotretinoin, but only 39% also gave additional information on contraception.[23] This was in line with the results of a study in the US and Canada among women becoming pregnant when taking isotretinoin, where only 30% recalled their pharmacists providing information about the potential teratogenic risk of isotretinoin.[33] The Dutch study furthermore showed that the pharmacists regarded the prescribers as primarily responsible for the safe use of isotretinoin. However, because of current legislation and standards, pharmacists and prescribers are equally responsible for patient counselling.[19]

Conclusion

Together with the fact that pregnancies and abortions are still reported in patients receiving isotretinoin treatment, our results strongly suggest that measurements should be taken in order to improve the implementation of the isotretinoin Dutch PPP into clinical practice. Extrapolating our results to the whole country indicates that annually about 4500 women of reproductive age undergo isotretinoin treatment, of whom about 2000 may not use effective contraceptives. Annually, about 1500 women of reproductive age may receive isotretinoin for milder forms of acne. Although our findings pertain to the Netherlands, it is doubtful whether the situation in other European countries is much better. Only more restrictive programmes, such as iPLEDGE in the US, have been shown to be effective. Earlier studies indicate achievements in effectively avoiding pregnancies under isotretinoin treatment by stating that two contraceptive methods are obligatory rather than one. Implementation might also be improved by explicit statements of responsibilities for prescribers as well as for pharmacists regarding patient counselling. The results of our study indicate that implementation could be improved by effectively restricting isotretinoin prescribing to specialists. The question of whether authorities will opt for a restrictive programme such as iPLEDGE or for an upgrade of the existing PPP is a political one.

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