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Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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ABSTRACT

Objective To estimate isotretinoin exposure in Dutch pregnant women and secondly, to analyse the occurrence of congenital anomalies and fetal death in these isotretinoin exposed pregnancies.

Design Population based study

Setting the Netherlands

Participants a cohort of 203,962 pregnancies with onset between 1 January 1999 and 1 September 2007 consisting of 208,161 fetuses (including multiple births)

Main outcome measures Isotretinoin exposure in the 30 days before or during the first, second or third trimester of pregnancy. The occurrence of fetal death and fetusus with congenital anomalies. Odds ratios (ORs) with 95% confidence intervals adjusted for maternal age were calculated to estimate the risk of congenital anomalies and fetal death after maternal isotretinoin exposure.

Results 45 pregnancies, 2.21 (1.63 to 2.93) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy. Sixty percent of isotretinoin exposed pregnancies started isotretinoin when already pregnant. Among the isotretinoin exposed pregnancies, the proportion of fetal death or congenital anomalies was 6.4% (1.7 to 16.4) and the OR for any congenital anomaly or fetal death was 1.48 (0.46 to 4.77) after adjustment for maternal age. For fetal death, the adjusted OR was 4.00 (1.25 to 12.91) and for congenital anomalies 0.70 (0.10 to 5.06). The risk was highest with exposure to isotretinoin during 30 days before conception or during the first trimester with an adjusted OR of 3.64 (1.41 to 9.39) for any congenital anomaly or fetal death.

Conclusions Although a pregnancy prevention programme was already implemented in 1988, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands and moreover, we showed that in these exposed pregnancies there was an elevated risk of congenital anomalies and fetal death.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based study in the EU on isotretinoin exposure during pregnancy in a large cohort of more than 200,000 pregnancies with virtual complete and detailed drug dispensing and pregnancy outcome data which enabled calculating accurate isotretinoin exposure rates among pregnant women and assessment of pregnancy outcomes.
- Statistical analysis should be interpreted with caution because the absolute number of isotretinoin exposed pregnancies was small.
- Our results might even underestimate the actual isotretinoin exposed pregnancies because pregnancies that ended in a spontaneous or elective abortion before gestational age of 16 weeks were not included in our cohort.
- With this study reasons for failure of the pregnancy prevention programme cannot be identified and only the period 1999 to 2007 has been evaluated. More recent data are necessary to further study the up to date situation of the isotretinoin PPP in the Netherlands.

INTRODUCTION

Isotretinoin, a vitamin A derivative, is licensed in the European Union (EU) since 1983 and is indicated for systemic treatment of severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) in patients resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.[1] However, the teratogenic potential is a known major adverse effect of treatment with isotretinoin. Animal studies already suggested teratogenic effects in humans and isotretinoin has been contraindicated for use during pregnancy since the very beginning of the marketing authorisation. Despite this contraindication, the first cases of congenital anomalies after isotretinoin use during pregnancy were documented already in 1983.[2] Systemic isotretinoin exposure during the first 10 weeks of pregnancy leads to congenital anomalies in approximately 26% of live births.[3] Isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects.[3] Exposure beyond the first 10 weeks of pregnancy can cause developmental delays and other CNS effects in approximately 40% of live births.[4 5] Furthermore, spontaneous abortion was observed in 7-20% of isotretinoin exposed pregnancies and elective termination of pregnancies occurred in more than 50% of exposed pregnancies.[3 4]

Reports of congenital anomalies after isotretinoin use accumulated and consequently, in 1988 the marketing authorisation holder of isotretinoin implemented a Pregnancy Prevention Programme (PPP) world-wide to better prevent pregnancies among systemic isotretinoin users.[6] The PPP included an educational programme for prescribers and patients including material to be used in counselling women about the need to prevent pregnancy while taking isotretinoin. Conditions for prescribing included a negative pregnancy test, the use of reliable contraception and a signed patient consent form.[6] In 2003, a review of isotretinoin by the European Medicine Agency (EMA) resulted in a compulsory European harmonised PPP for all isotretinoin containing products.[1] The elements of the European wide PPP are listed in box 1.

Box 1: Elements of the EU isotretinoin PPP

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up
2. Use of effective contraceptive measures from four weeks before isotretinoin initiation until four weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.
3. Pregnancy testing should be done before, during and five weeks after discontinuation of isotretinoin
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of seven days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the PPP.

The safe use of isotretinoin in women of reproductive age is in the interest of public health because of the potential risk of spontaneous and elective abortions, and, more importantly, children with major congenital anomalies require continuous healthcare throughout their life. Although a PPP has been implemented in the EU, pregnancies during isotretinoin therapy still occur.[7 8] The regulatory authorities of sixteen EU member states responded in 2009 to a survey that isotretinoin exposed pregnancies have occurred in their country.[9] A French study between 2003 and 2006 estimated a pregnancy rate from 0.4 to 1.2 per 1000 female isotretinoin users within reproductive age.[8] Studies in the Netherlands observed that only 52% to 59% of the female isotretinoin users of reproductive age used concomitant hormonal contraceptives, which was higher than the 39%-46% observed in the general female population of similar age, but lower than anticipated.[10 11] Although these studies show limited compliance with the isotretinoin PPP, it is not known whether isotretinoin exposure also occurs during pregnancy and what the outcome of these pregnancies is. Therefore, the objective of our study was to estimate isotretinoin exposure in Dutch pregnant women and secondly, to analyse the occurrence of congenital anomalies and fetal death in these isotretinoin exposed pregnancies.

METHODS

Data sources

For this population based study a cohort of 203,962 pregnancies consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort including, amongst other information, drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) that are collected since 1986.[12] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[13] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[14] The registry contains information about care before, during, and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The PRN includes information on congenital anomalies detected during pregnancy, at birth or within the first year after birth. The probabilistic linking method between PHARMO and PRN has been

described in detail elsewhere but was generally based on the birth date of the mother and fetus and their postal zip codes.[15] To be included in the cohort the mother should be registered in the community pharmacy database of PHARMO during the whole pregnancy. The start of pregnancy was based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

Isotretinoin dispensings

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in our cohort within the 12-months period before or during pregnancy were extracted from the PHARMO Database Network. Considering a daily dosage of 0.5 mg-1mg per kilogram daily,[1] isotretinoin prescriptions dispensed on the same day were pooled (e.g. the prescriptions of a 10 mg and 20 mg tablet to result in a daily dosage of 30mg were pooled). The length of all isotretinoin dispensings was calculated by dividing the total number of prescribed units by the number of units (doses) to be taken per day. In case the pooled dispensings had different lengths - in case every other day different strengths should be taken - the longest duration was taken (i.e. one day 20 mg tablet, the other day 20 mg and 10 mg tablet). To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

Drug exposure

For all pregnancies (n=203,962) > 16 weeks of gestational age included in the cohort, isotretinoin exposure before and during pregnancy was determined based on isotretinoin dispensing data (ATC D10BA01) filled by the mother during the 12-months period before and during pregnancy. Exposure in person time (days) was calculated by dividing the total number of prescribed units by the number of prescribed units per day. Isotretinoin exposure periods were defined considering a possible overlapping period but gaps between two isotretinoin dispensings were not permitted in one period. Using the start and end date of the isotretinoin , the number of days exposed during pregnancy was estimated for the following exposure windows: 30 days before conception, first 90 days of gestation (first trimester), day 90-179 of gestation (second trimester) and day 180 – delivery (third trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

Pregnancy outcomes

For each fetus (n=208,161), we determined whether congenital anomalies or fetal death was reported. Fetal death was defined as death before complete expulsion or extraction from the mother.[16] Congenital anomalies were categorised into nine sub-groups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. Description of the classification system for congenital anomalies used in our study are presented in the supplementary information Table S1. As we were interested in those congenital anomalies potentially induced by maternal drug exposure, chromosomal anomalies were excluded.

Analysis

The dispensing rate of isotretinoin among the pregnant women included in our study was calculated and stratified per exposure period. Exposure to isotretinoin per 10,000 pregnancies was calculated for the aforementioned exposure periods including their 95% confidence intervals (95% CIs). We used multiple logistic regression models to calculate odds ratios (ORs) and 95% CIs to estimate associations between congenital anomalies, fetal death and maternal isotretinoin exposure. We adjusted for maternal age at conception (<20, 20-24, 25-29, 30-34, ≥35), and if possible also for calendar time (year of conception) and gender of the infant. Analyses for specific congenital anomalies were performed when > 3 cases were observed. The t-test or Fisher exact test was used to derive p-values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided p-values <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203,962 pregnancies corresponding to 208,161 fetuses (including multiple births) were included in our study. The mean maternal age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days). Demographics for isotretinoin exposed and unexposed pregnancies are presented in table 1.

Table 1: Description of the study population

	Isotretinoin exposed*	Isotretinoin unexposed	*p-value*
Pregnancies (N=203,962)	51	203,911	
Mean (±SD) maternal age at conception in years (95% CI)	29.1 (4.9) (27.8 – 30.5)	30.3 (4.7) (30.3 – 30.3)	0.56
Mean (±SD) gestational age at delivery in weeks (95% CI)	39 (25 days) (38 – 40)	39, 3 days (19 days) (39. 3 days – 39. 3 days)	0.33
Fetuses (N=208,161)	53	208,108	
Gender (boy %)	47.2% (33.3 – 61.1)	51.5% (51.3 – 51.7)	0.53
Maternal age at conception in years, n, column %.			0.37
< 20 years of age	2 (3.8%)	4,063 (2.0%)	
≥ 20 -25 years of age	7 (13.2%)	22,144 (10.6%)	
≥ 25 -30 years of age	21 (39.6%)	68,366 (32.9%)	
≥ 30 -35 years of age	14 (26.4%)	81,581 (39.2%)	
≥ 35 years of age	9 (17.0%)	31,951 (15.4%)	
Gestational age at delivery, n, column %.			0.64
< 27 weeks	1 (1.9%)	2,198 (1.1%)	
27 – 30 weeks	1 (1.9%)	1,167 (0.6%)	
31-33 weeks	0 (0.0%)	2,008 (1.0%)	
34-36 weeks	3 (5.7%)	7,126 (3.4%)	
37-39 weeks	12 (22.6%)	50,854 (24.4%)	
>40 weeks	36 (67.9%)	144,755 (69.5%)	
Fetal death or congenital anomalies, n;% (95% CI)	5; 9.4% (1.3 -17.6)	9,041; 4.3% (4.3 – 4.4)	0.08
Fetal death, n; % (95% CI)	3; 5.7% (0 – 12.1)	3,404; 1.6% (1.6 – 1.7).	0.06
Congenital anomalies, n;% (95% CI)	3; 5.7% (0 – 12.1)	6,246; 3.0% (2.93 – 3.07)	0.21

*including 45 isotretinoin exposed pregnancies and 6 pregnancies occurred within 30 days after isotretinoin discontinuation

Isotretinoin dispensings

A total of 416 isotretinoin dispensings to 130 of the 203,962 women in the 12-months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of > 30 days of isotretinoin use. Figure 1 shows that the percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Overall, 45 pregnant women, 2.21 (95% CI 1.63 – 2.93) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six additional pregnancies were identified within one month after isotretinoin discontinuation. In 40 out of 203,962 pregnancies, 1.96 (95% CI

1.42 – 2.64) per 10,000 pregnancies, an isotretinoin prescription was filled during pregnancy. Thirty-two of these 40 pregnant women received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings ranged from 1 to 7, with a median of 2.50. Among the pregnancies exposed to isotretinoin during pregnancy (n=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. Figure 2 shows that the number of women exposed to isotretinoin during pregnancy was the highest in 2006 with 3.48 exposed pregnancies (95% CI 1.70 – 6.39) per 10,000 pregnancies.

Pregnancy outcomes

Independent of isotretinoin exposure, for 9,046 of the 208,161 fetuses (4.35%, 95% CI 4.26- 4.43) fetal death or a congenital anomaly excluding chromosomal anomalies was reported in the PRN. The proportion of fetal death was 1.64% (95% CI 1.58 – 1.69) and 3.00% (95% CI 2.93 – 3.08) for congenital anomalies.

The 45 pregnancies exposed to isotretinoin during pregnancy corresponded to 47 fetuses. Among these 47 fetuses, three were identified fetal deaths or had congenital anomalies (6.38%, 95%CI 1.65 – 16.39). The proportion of fetal death (n=3) and congenital anomalies (n=1) was 6.38% (95%CI 1.65 – 16.39) and 2.13% (95% CI 0.11 – 10.04) respectively. Considering also the six pregnancies that occurred within one month after isotretinoin discontinuation, a total of five out of 53 fetus (9.43%, 95CI 3.54 – 19.68) were identified as fetal death (n=3) or had a congenital anomaly (n=3). The isotretinoin exposed fetal deaths and infants born with congenital anomalies in different exposure period are presented in table 2.

Table 2: Isotretinoin exposed pregnancies and fetuses per exposure period

Isotretinoin exposure period*	Pregnancies (N=203,962)	Exposed pregnancies / 10,000 pregnancies (N, 95% CI)	Median number of days exposed per pregnancy (range)	Fetuses (N=208,161)	Fetuses with congenital anomalies or fetal death (N=53)**
30 days before conception (30 days period)	23	1.13 (0.73 – 1.67)	24 (range 3 – 30)	23	5; 21.74% (8.43 – 41.80)
1st trimester (90 days period)	28	1.37 (0.93 – 1.96)	31 (range 3 – 88)	28	3; 10.71% (2.80 – 2.65)
2nd trimester (90 days period)	25	1.23 (0.81 – 1.78)	57 (range 1 – 90)	26	2; 7.69% (1.31 – 23.16)
3rd trimester (90-103 days period)	26	1.28 (0.85 – 1.84)	62 (range 1 – 103)	28	2; 7.14% (1.22 – 21.65)
During pregnancy (270 days period)	45	2.21 (1.63 – 2.93)	63 (range 3 – 236)	47	3; 6.38% (1.65 – 16.39)
30 days before or during pregnancy (300 days period)	51	2.50 (1.88 – 3.26)	63 (range 7 – 236)	53	5; 9.43% (3.54 – 19.68)
30 days before or during 1st trimester (120 days period)	35	1.72 (1.24 – 2.36)	32 (range 7 – 114)	35	5; 14.29% (5.43 – 28.86)

CI=Confidence interval.
*Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that period
**51 pregnancies corresponded to 53 infants including two multiple births

For isotretinoin exposure during pregnancy, the odds ratio (OR) for any congenital anomaly or fetal death was 1.48 (95% CI 0.46 – 4.77) after adjustment for maternal age (see table 3). Considering the same exposure window, for fetal death, the adjusted OR was 4.00 (95% CI 1.25 – 12.91) and for congenital anomalies 0.70 (95% CI 0.10 – 5.06). The number of cases were too low to allow for adjustments in addition to maternal age. Adding the 30 days before conception to the exposure window (exposure 30 days before or during pregnancy), the adjusted OR for any congenital anomaly or fetal death was 2.28 (95% CI 0.91 – 5.72). A significantly increased OR of 3.64 (95% CI 1.41 – 9.39) was observed for any congenital anomaly or fetal death and isotretinoin exposure within 30 days before or first trimester of pregnancy. The ORs for fetal death were significantly increased in both these periods.

Table 3: Odds ratios for congenital anomalies and fetal death and isotretinoin exposure during pregnancy

Congenital anomalies	Unexposed fetuses (N=208,106)	Isotretinoin exposed fetuses								
		During pregnancy (N=47)			30 days before or during pregnancy (N=53)			30 days before or 1st trimester (N=35)		
		N	OR	Adjusted OR*	N	OR	Adjusted OR*	N	OR	Adjusted OR*
Any congenital anomaly or fetal death	9,041	3	1.51 (0.47 – 4.84)	1.48 (0.46 – 477)	5	2.30 (0.91 – 5.77)	2.28 (0.91 – 5.72)	3	3.68 (1.43 – 9.48)	3.64 (1.41 – 9.39)
Fetal death	3,404	3	4.10 (1.27 – 13.22)	4.00 (1.25 – 12.91)	3	3.61 (1.13 – 11.58)	3.57 (1.11 – 11.47)	3	5.64 (1.73 – 18.42)	5.55 (1.70 – 18.19)
Any congenital anomaly	6,246	1	0.70 (0.10 – 5.09)	0.70 (0.10 – 5.06)	3	1.94 (0.61 – 6.22)	1.93 (0.60 – 6.18)	1	3.03 (0.93 – 9.90)	3.02 (0.92 – 9.86)

*maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)

Description of cases

The pregnancies exposed to isotretinoin in the 30 days before or during pregnancy resulted in five cases of fetal death or congenital anomalies. The year of conception of these cases was 2002 (n=2), 2003 (n=2) and 2005 (n=1). Three of the five cases were exposed to isotretinoin during pregnancy and two cases were only exposed to isotretinoin in the 30 days before conception because conception occurred within 30 days after isotretinoin discontinuation and no new isotretinoin prescriptions were filled afterwards. All three pregnancies exposed to isotretinoin during pregnancy started while the mother was already using isotretinoin, and all three cases ended in fetal death. One pregnancy was exposed to isotretinoin 29 days following conception and no new isotretinoin prescriptions were filled after conception. The pregnancy ended in fetal death after 19 weeks. In the second pregnancy two isotretinoin prescriptions were filled during pregnancy resulting in a total of 166 days of isotretinoin exposure during pregnancy (19 days in the first trimester and 79 and 68 days in the second and third trimester of pregnancy, respectively). After 38 weeks, the pregnancy resulted in fetal death and cardiovascular anomalies (not further specified). In the third pregnancy, four isotretinoin prescriptions were filled during pregnancy resulting in a total of 163 days of isotretinoin exposure during pregnancy (73 in first, 51 and 39 in second and third trimester respectively). After 35 weeks the pregnancy ended in fetal death. The two remaining pregnancies were only exposed to isotretinoin in the 30 days before conception. Both fetusus were born with gestational age of 39 or 40 weeks and had congenital anomalies; one had a neural tube defect and for the other the anomaly was not further specified.

DISCUSSION

This study showed that 2 per 10,000 pregnancies were exposed to isotretinoin during pregnancy despite the fact that a PPP is implemented to prevent isotretinoin use during pregnancy. In the majority of isotretinoin exposed pregnancies, women started isotretinoin when already pregnant. The risk of congenital anomalies or fetal deaths was increased in pregnancies that were exposed to isotretinoin during the 30 days prior or during the first trimester of pregnancy while the risk of fetal death was increased during all analysed time windows.

That there are still women who are using isotretinoin during pregnancy despite the implementation of the PPP is of major concern. Since the majority of the isotretinoin exposed women were already pregnant at the time of first isotretinoin prescription, it seems that pregnancy in isotretinoin users was not always excluded before drug dispensing (box 1). Furthermore, women of reproductive age treated with isotretinoin might not always

have used effective contraceptive measures. Our study showed that compliance with the maximum length of prescription of 30 days between 1999 and 2007 was limited since one third of isotretinoin dispensings exceeded 30 days. This decreased to 13% in 2007 which suggests a higher awareness. Based on this study, no conclusions can be drawn as to which elements of the PPP fail but it is obvious that the PPP is not completely effective. These findings are in line with previous Dutch studies that found that concomitant use of hormonal contraceptives in isotretinoin using women of reproductive age is limited to 52% - 59%.[10 11] Limited compliance with the PPP in the Netherlands was also observed in a survey among Dutch pharmacists which indicated that in 2007 and 2011, 44% and 49% of pharmacists respectively checked the use of contraception at every isotretinoin dispensing.[17] The percentage of pharmacists that asked for negative pregnancy tests was stable with 15% and 16% respectively and is in line with the results of our study which demonstrate that it seems that pregnancy is not always excluded before initiating isotretinoin. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP, especially since isotretinoin is used in young women of reproductive age. If that does not work, more strict measures might have to be considered.

In the United States (US), the most recent isotretinoin PPP, called iPLEDGE, has been implemented since 2006 and is stricter than the EU PPP. iPLEDGE is an internet-based system that requires registration of all stakeholders with monthly updates on prescription, pregnancy tests, contraceptive use, acknowledgement of risks.[18] The pregnancy rate among isotretinoin users in the US with the iPLEDGE PPP was estimated 2.7 per 1000 treatment courses and did not change compared to the previous PPP called SMART (System to Manage Accutane Related Teratogenicity) while only small improvements in compliance with contraceptive measures were observed.[18 19] Further restrictive measures as in iPLEDGE do not seem to improve the results and may contribute to the potential inefficiencies of the healthcare system.

The proportion of congenital anomalies or fetal death after isotretinoin exposure during pregnancy in our study was 6.4%. Comparable proportions were observed in a German study which also found that 76% of isotretinoin exposed pregnancies ended in an elective pregnancy termination.[7] No information on elective pregnancy termination was available in our study but the potentially high proportion of elective pregnancy termination may explain the lower proportions of congenital anomalies after isotretinoin exposure during pregnancy observed in our study (2.1%) as compared to earlier studies that reported 26%-28%.[3 4] The present study identified a total of five pregnancies of which the adverse pregnancy outcome, including three fetal deaths,

may be related to isotretinoin use. Although the statistical analysis should be interpreted cautiously due to low numbers, we observed an increased risk of fetal death whereas for congenital anomalies an increased risk could not be determined. The neural tube defect in one of the cases is not a known CNS defect typical for retinoid embryopathy[3] and furthermore, may be related to other factors since isotretinoin exposure was only identified in the 30 days period before conception. Nevertheless, according to the isotretinoin PPP, the pregnancy should not have occurred. Another pregnancy resulted in fetal death and also reported a cardiovascular anomaly (not further specified) after isotretinoin exposure during the first weeks after conception. This anomaly may be a typical symptom of retinoid embryopathy such as ventricular septic defect[3], but insufficient information on the congenital anomaly was available to draw these conclusions. Congenital anomalies identified in other cases were also coded on high level only (e.g. congenital anomaly not further specified). For the assessment of retinoid embryopathy, both detailed descriptions of the diagnosed congenital anomaly as well as detailed information on drug exposure preferably verified by the patient whether the drug was actually taken are necessary.

Strengths and weaknesses of the study

A strength of this study is that we used a population based study including virtual complete and detailed drug dispensing data and pregnancy outcome data, which enabled calculating accurate isotretinoin exposure rates among pregnant women which can be extrapolated to the national situation to indicate impact on public health. This would be more difficult and probably less accurate when using spontaneous reported cases or data from teratology information services, since these data sources do not provide clear denominators to calculate exposure rates and may suffer from substantial underreporting. Although our absolute numbers were small, all exposure and outcome information was prospectively gathered and unbiased because nobody was aware of the research hypothesis. Moreover, we simply confirmed an adverse reaction which is nowadays undisputed.

Our results might even underestimate the actual risk because no information can be provided on spontaneous and elective abortions that occurred before gestational age of 16 weeks because these data are not captured in the PRN database and these pregnancies were therefore not included in our cohort.

Implications and future research

In the Netherlands, approximately 180,000 pregnancies are reported annually.[20] When extrapolating the 2.21 (95% CI 1.63 – 2.93) per 10,000 women exposed to isotretinoin during pregnancy to a national level, there

would be 29 to 52 pregnancies receiving isotretinoin per year yielding unnecessary high risks for congenital anomalies and fetal deaths. Therefore, it is in the interest of public health to implement effective PPPs and improve these measures or their compliance as much as possible to reduce isotretinoin use during pregnancy to the lowest possible level.

With the present study reasons for PPP failure cannot be identified and only the period 1999 to 2007 has been evaluated. More recent data are necessary to further study the up to date situation of the isotretinoin PPP in the Netherlands in order to take appropriate action, especially since the last few years attention for the isotretinoin PPP might have improved the carefulness with which isotretinoin is prescribed and dispensed. In the Netherlands, the PPP is communicated to healthcare professionals via product information,[21] national general practitioner (GP) standards on treatment of acne,[22] drug prescription and dispensing systems,[23] the website of the Dutch Medicines Evaluation Board,[24] and the common (national) literature on drug information.[25] Furthermore, research on isotretinoin use in the Netherlands and the PPP is conducted and published in (inter)national scientific medical journals. [9-11 17 26-29]

Conclusions

The safe use of isotretinoin is important for public health to prevent unnecessary high risks of congenital anomalies and fetal deaths. Although a PPP was implemented almost 15 years ago, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands and moreover, we showed that in these exposed pregnancies there is an elevated risk of congenital anomalies and fetal death. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP. Before regulatory measures should be considered, the isotretinoin PPP requires further evaluation using more recent data to assess whether isotretinoin use among women with reproductive age has improved.

FIGURE LEGENDS

Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days per calendar year

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies per calendar year

——— Exposed to isotretinoin in 30 days before or during pregnancy

– – – – Exposed to isotretinoin during pregnancy

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Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that LH and RH are employees of the PHARMO Institute. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. MS is leading a research group that sometimes conducts research for pharmaceutical companies. None related to the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Details of contributors Each author participated actively and sufficiently in this study. IZ, RR, LH, MS and BS contributed to the study design and the interpretation of the data. IZ and LH collected and analysed the data. IZ, RR, LH, RH, MS, SS and BS participated in the development and critical review of the manuscript for important intellectual content and provided final approval of the version to be published. A statement that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval Not applicable. The research team did not have access to medical records.

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Data sharing No additional data available.

Transparency The lead author (IZ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

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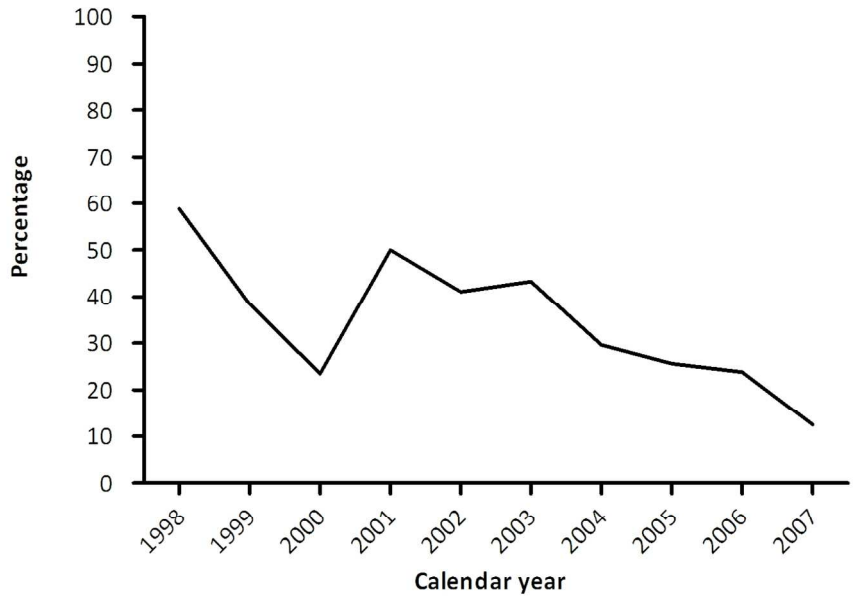
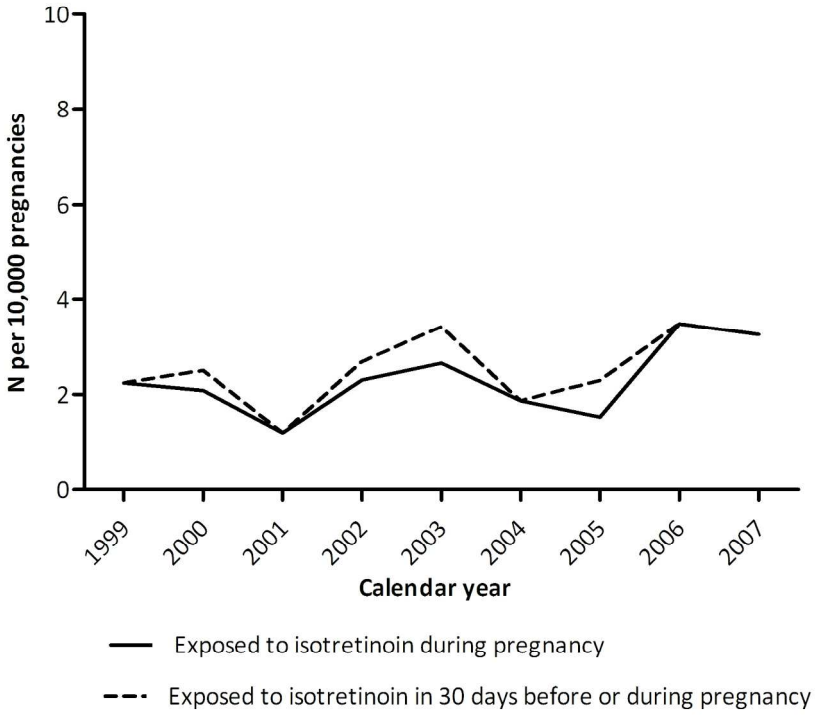
Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days per calendar year



Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days per calendar year
135x101mm (300 x 300 DPI)

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies per calendar year



Isotretinoin exposed pregnancies per 10,000 pregnancies per calendar year
186x160mm (300 x 300 DPI)

Supplementary information:

Table S1: Classification system for congenital anomalies

1. Abdominal wall disorders and skin disorders
Abdominal wall defects
Gastroschisis
Omphalocele
Hernia diaphragmatica
Hernia umbilicalis
Hernia inguinalis
Relaxation diaphragma
Skin anomalies
Congenital skin disorder
Hemangiome (>4cm2)
Naevus pigmentosus
Skin anomalies not further specified
Skin or abdominial wall defects not further specified
2. Cardiovascular defects
Conotruncal defects
Right ventricular outflow tract obstruction defects
Left ventricular outflow tract obstruction defects
Septal defects
Single artery umbilical
Cardiovascular defects not further specified
3. Defects in the digestive system
Oro-facial clefts
Oesophageal atresia with(out) tracheooesophageal fistula
Duodenal, small intestine, ano-rectal atresia and stenosis
Morbus Hirschsprung
Malrotation / volvulus
Defects in the digestive system not further specified
4. Defects in the nervous system
Neural tube defects
Anencephalus
Spina bifida / Meningo(myelo)cele
Encephalocele
Hydrocephaly / holoprosencephaly
Microcephaly
Nerveous-musculo defects
Eye anomalies
Microphthalmos
Other eye anomalies
Ear anomalies
Defects of nervous system not further specified
5. Musculoskeletal defects

Phocomelia
Club foot - talipes equinovarus
Polydactyly
Syndactyly
Hip dislocation and/or dysplasia
Muskuloskeletal defects not further specified
6. Respiratory defects
Choanal atresia
Cystic adenomatous malformation of the lung
Abnormal trachea
Lung hypoplasia
Congenital lobair emfysema
Hydro/chylo thorax
Defects in the respiratory system not further specified
7. Urogenital defects
Hypospadias /epispadias
Indeterminate sex
Cryptorchism
Urologic disorders
Exstrophia vesicae
Bilateral renal agenesis including Potter syndrome
Congenital kidney cyste
Obstructive uropathy
Urogenital defect not further specified
8. Multiple, syndrome or chromosomal anomalies
Down syndrome
Other chromosomal anomalies
Syndromes
Multiple anomalies (not specified previously)
9. Other congenital anomalies
Congenital anomalies not further specified

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-78
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	6

Continued on next page

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8; (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure	9 (Table 2)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11; (Table 3)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11;(Table 3)
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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key words: isotretinoin, pregnancy prevention programme, teratogens, congenital malformations

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ABSTRACT

Objective To estimate isotretinoin exposure in Dutch pregnant women despite the implemented pregnancy prevention programme (PPP) and secondly, to analyse the occurrence of adverse fetal or neonatal outcomes in these isotretinoin exposed pregnancies.

Design Population based study

Setting the Netherlands

Participants a cohort of 203,962 pregnancies with onset between 1 January 1999 and 1 September 2007 consisting of 208,161 fetuses or neonates.

Main outcome measures Isotretinoin exposure in the 30 days before or during pregnancy. Proportions of adverse fetal or neonatal outcomes, defined as intrauterine deaths ≥ 16 week of gestation and neonates with major congenital anomalies. Odds ratios (ORs) with 95% confidence intervals (CI) adjusted for maternal age were calculated to estimate the risk of adverse fetal or neonatal outcome after maternal isotretinoin exposure.

Results 51 pregnancies, 2.5 (95%CI 1.9 to 3.3) per 10,000 pregnancies, were exposed to isotretinoin despite the pregnancy prevention programme. 45 of these pregnancies, 2.2 (95%CI 1.6 to 2.9) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy and six additional women became pregnant within 30 days after isotretinoin discontinuation. In sixty percent of isotretinoin exposed pregnancies, women started isotretinoin while already pregnant. In five out of the 51 isotretinoin exposed pregnancies, 9.4% (95%CI 1.3 to 17.6), had an adverse fetal or neonatal outcome. The OR for adverse fetal or neonatal outcomes after isotretinoin exposure in 30 days before or during pregnancy was 2.3 (95%CI 0.9 to 5.7) after adjustment for maternal age.

Conclusions Although a PPP was already implemented in 1988, we showed that isotretinoin exposed pregnancies in the Netherlands and adverse fetal and neonatal events still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based study in the EU on isotretinoin exposure during pregnancy in a large cohort of more than 200,000 pregnancies which enabled estimating isotretinoin exposure rates among pregnant women and its consequences on a nationwide scale.
- From the virtually complete and detailed drug dispensing data, isotretinoin exposure could only be estimated since drug dispensing data does not ascertain actual drug use and precise exposure intervals. However, patients coming for refills are usually taking their drug.
- Spontaneous abortions before gestational age of 16 weeks and elective abortions were not included in our cohort and therefore our results probably underestimate the number of isotretinoin exposed pregnancies and its consequences.
- The analysis was restricted to adverse fetal and neonatal outcomes in general since specific teratogenic risk could not be estimated with data lacking information on pregnancies until 16 weeks of gestation and lacking detailed descriptions of adverse fetal and neonatal outcomes.

INTRODUCTION

Isotretinoin, a vitamin A derivative, is licensed in the European Union (EU) since 1983 and is indicated for systemic treatment of severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) in patients resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.[1] The teratogenic potential is an important characteristic of isotretinoin. Animal studies already suggested teratogenic effects in humans and isotretinoin has been contraindicated for use during pregnancy since the very beginning of the marketing authorisation. Despite this contraindication, the first cases of congenital anomalies after isotretinoin use during pregnancy were documented already in 1983.[2] As described by Lammer et al. in 1985, isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects.[3] They found a relative risk of 26 for this group of major congenital malformations after systemic isotretinoin exposure during some parts of the first 10 weeks after conception.[3] Elective termination of pregnancy (ETOP) was decided in more than 50% of exposed pregnancies and 20% of the remaining pregnancies ended in a first trimester spontaneous abortion.[3] Reports of congenital anomalies after isotretinoin use accumulated and consequently, in 1988 the marketing authorisation holder of isotretinoin implemented a world-wide Pregnancy Prevention Programme (PPP) to better prevent pregnancies among systemic isotretinoin users.[4] The PPP included an educational programme for prescribers and patients including material to be used in counselling women about the need to prevent pregnancy while taking isotretinoin. Conditions for prescribing included a negative pregnancy test, the use of reliable contraception and a signed patient consent form.[4] In 2003, a review of isotretinoin by the European Medicine Agency (EMA) resulted in a compulsory European harmonised PPP for all isotretinoin containing products.[1] The elements of the European wide PPP are listed in box 1.

Box 1: Elements of the EU isotretinoin PPP

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up
2. Use of effective contraceptive measures from four weeks before isotretinoin initiation until four weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.
3. Pregnancy testing should be done before, during and five weeks after discontinuation of isotretinoin
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of seven days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the PPP.

The safe use of isotretinoin in women of reproductive age is in the interest of public health because of the potential risk of spontaneous and elective abortions, and, more importantly, children with major congenital anomalies require continuous healthcare throughout their life. Although a PPP has been implemented in the EU, pregnancies during isotretinoin therapy still occur.[5 6] The regulatory authorities of sixteen EU member states responded in 2009 to a survey that isotretinoin exposed pregnancies have occurred in their country.[7] A French study between 2003 and 2006 estimated a pregnancy rate from 0.4 to 1.2 per 1000 female isotretinoin users within reproductive age.[6] Studies in the Netherlands observed that only 52% to 59% of the female isotretinoin users of reproductive age used concomitant hormonal contraceptives, which was higher than the 39%-46% observed in the general female population of similar age, but lower than anticipated.[8 9] Although these studies show limited compliance with the isotretinoin PPP, it is not known whether isotretinoin exposure also occurs during pregnancy and what the outcome of these pregnancies is. Therefore, the objective of our study was to estimate isotretinoin exposure in Dutch pregnant women despite the implemented PPP and secondly, to analyse the occurrence of adverse fetal and neonatal outcomes in these isotretinoin exposed pregnancies.

METHODS

Data sources

For this population based study a cohort of 203,962 pregnancies consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort including, amongst other information, drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) that are collected since 1986.[10] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[11] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[12] The registry contains information about care before, during, and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The PRN includes information on pregnancy outcome including congenital anomalies

detected during pregnancy, at birth or within the first year after birth. The probabilistic linking method between PHARMO and PRN has been described in detail elsewhere but was generally based on the birth date of the mother and child and their postal zip codes.[13] To be included in the cohort the mother should be registered in the community pharmacy database of PHARMO during the whole pregnancy. The date of conception was estimated based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

Isotretinoin dispensings

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in our cohort within the 12-months period before or during pregnancy were extracted from the PHARMO Database Network. Considering a daily dosage of 0.5 mg-1mg per kilogram daily,[1] isotretinoin prescriptions dispensed on the same day were assumed to be used simultaneously and therefore these dispensings were pooled and considered as one dispensing (e.g. the prescriptions of a 10 mg and 20 mg tablets dispensed at the same time to reach a daily dosage of 30mg). For each isotretinoin dispensing, the length of the dispensing was calculated by dividing the total number of prescribed units by the number of units (doses) to be taken per day. In case isotretinoin dispensings that were pooled together had different lengths, the length of the single dispensing with the longest duration was used. To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

Drug exposure interval

For all pregnancies (n=203,962) with of gestational age of at least 16 weeks included in the cohort, isotretinoin exposure was estimated based on isotretinoin dispensing data (ATC D10BA01) filled by the mother during the 12-months period before and during pregnancy. Exposure in person time (days) was calculated by dividing the total number of prescribed units by the number of prescribed units per day. Isotretinoin exposure periods were defined considering a possible overlap of isotretinoin dispensings. Gaps, isotretinoin free periods between two isotretinoin dispensings, were not permitted meaning that an isotretinoin exposure period ends once an isotretinoin free period was identified. Using the start and end date of the isotretinoin exposure period, the number of days exposed was estimated for the following exposure intervals: 30 days before conception, first 90 days of gestation (first trimester), day 90-179 of gestation (second trimester) and day 180 – delivery (third

trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

Adverse fetal or neonatal outcomes

For each fetus (n=208,161), we determined whether adverse fetal or neonatal outcomes were reported. Adverse fetal or neonatal outcomes were defined as all intrauterine deaths ≥ 16 week of gestation and live born infants with major congenital anomalies. If possible, congenital anomalies were categorised into nine sub-groups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. As we were interested in adverse fetal outcomes potentially induced by maternal drug exposure, chromosomal anomalies were not considered as an adverse outcome in the analyses.

Analysis

Potential exposure to isotretinoin in the 30 days before or during pregnancy was calculated per 10,000 pregnancies for the aforementioned exposure intervals including their 95% confidence intervals (95% CIs). The proportions of adverse fetal outcome among isotretinoin exposed and unexposed fetuses or neonates were calculated including their 95% CIs. We used multiple logistic regression models to calculate odds ratios (ORs) and 95% CIs to estimate associations between adverse fetal or neonatal outcome and maternal isotretinoin exposure. We adjusted for maternal age at conception (<20, 20-24, 25-29, 30-34, ≥35), and if possible also for calendar time (year of conception) and gender of the infant. Analyses for specific congenital anomalies were performed when > 3 cases were observed. The t-test or Fisher exact test was used to derive p-values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided p-values <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203,962 pregnancies corresponding to 208,161 fetuses (including multiple births) were included in our study. The mean maternal

age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days).

Isotretinoin dispensings

A total of 416 isotretinoin dispensings to 130 of the 203,962 women in the 12-months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of > 30 days of isotretinoin use. Figure 1 shows that the percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Isotretinoin exposed pregnancies

Demographics for isotretinoin exposed and unexposed pregnancies are presented in table 1.

Table 1: Description of the study population

	Isotretinoin exposed*	Isotretinoin unexposed	*p-value*
Pregnancies (N=203,962)	51	203,911	
Mean (±SD) maternal age at conception in years (95% CI)	29.1 (4.9) (27.8 – 30.5)	30.3 (4.7) (30.3 – 30.3)	0.56
Mean (±SD) gestational age at delivery in weeks (95% CI)	39 (25 days) (38 – 40)	39, 3 days (19 days) (39, 3 days – 39, 3 days)	0.33
Fetuses (N=208,161)	53	208,108	
Gender (boy %)	47.2% (33.3 – 61.1)	51.5% (51.3 – 51.7)	0.53
Maternal age at conception in years, n, column %.			0.37
< 20 years of age	2 (3.8%)	4,063 (2.0%)	
≥ 20 -25 years of age	7 (13.2%)	22,144 (10.6%)	
≥ 25 -30 years of age	21 (39.6%)	68,366 (32.9%)	
≥ 30 -35 years of age	14 (26.4%)	81,581 (39.2%)	
≥ 35 years of age	9 (17.0%)	31,951 (15.4%)	
Gestational age at delivery, n, column %.			0.64
< 27 weeks	1 (1.9%)	2,198 (1.1%)	
27 - 30 weeks	1 (1.9%)	1,167 (0.6%)	
31-33 weeks	0 (0.0%)	2,008 (1.0%)	
34-36 weeks	3 (5.7%)	7,126 (3.4%)	
37-39 weeks	12 (22.6%)	50,854 (24.4%)	
> 39 weeks	36 (67.9%)	144,755 (69.5%)	
Adverse fetal outcome, n;% (95% CI)	5; 9.4% (1.3 -17.6)	9,041; 4.3% (4.3 – 4.4)	0.08

*in the 30 days before conception or during pregnancy

Overall, 51 pregnancies, 2.5 (95%CI 1.9 to 3.3) per 10,000 pregnancies, were potentially exposed to isotretinoin in the 30 days before conception or during pregnancy, despite the implemented pregnancy prevention programme. Forty-five pregnant women, 2.2 (95%CI 1.6 – 2.9) per 10,000 pregnancies, were estimated to be exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six pregnancies were identified within one month after isotretinoin discontinuation and were estimated to be exposed only before conception. In 40 out of 203,962 pregnancies, 2.0 (95% CI 1.4 – 2.6) per 10,000 pregnancies, an isotretinoin prescription was filled during pregnancy and 32 pregnancies, 1.6 (95% CI 1.1 – 2.2) per 10,000 pregnancies, received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings per pregnancy ranged from 1 to 7, with a median of 2.5. The estimated isotretinoin exposure per exposure interval is presented in table 2.

Table 2: Potential isotretinoin exposed pregnancies per exposure interval

Isotretinoin exposure interval*	Exposed pregnancies (N=203,962)	Exposed pregnancies per 10,000 pregnancies (95% CI)	Median number of days exposed per pregnancy (range)
30 days before conception (30 days period)	23	1.1 (0.7 – 1.7)	24 (range 3 – 30)
1st trimester (90 days period)	28	1.4 (0.9 – 2.0)	31 (range 3 – 88)
2nd trimester (90 days period)	25	1.2 (0.8 – 1.8)	57 (range 1 – 90)
3rd trimester (90-103 days period)	26	1.3 (0.9 – 1.8)	62 (range 1 – 103)
During pregnancy (270 days period)	45	2.2 (1.6 – 2.9)	63 (range 3 – 236)
30 days before or during pregnancy (300 days period)	51	2.5 (1.9 – 3.3)	63 (range 7 – 236)
30 days before or during 1st trimester (120 days period)	35	1.7 (1.2 – 2.4)	32 (range 7 – 114)

CI=Confidence interval.
*Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that exposure interval

Among the pregnancies estimated to be exposed to isotretinoin during pregnancy (n=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. Figure 2 shows that the number of women estimated to be exposed to isotretinoin during pregnancy was the highest in 2006 with 3.5 pregnancies (95% CI 1.7 – 6.4) per 10,000 pregnancies.

Adverse fetal or neonatal outcomes

Independent of isotretinoin exposure, adverse fetal or neonatal outcomes were observed for 9,046 of the 208,161 fetuses (4.4%, 95% CI 4.3 – 4.4). The 51 pregnancies potentially exposed to isotretinoin in 30 days before conception or during pregnancy corresponded to 53 fetuses or neonates including two multiple births. Five of these, all singletons, had an adverse fetal or neonatal outcome (9.4% [95% CI 3.5 – 19.7]). These included three intrauterine deaths and two live born infants with major congenital anomalies (see table 3). Among those potentially exposed during pregnancy only (n=47), 6.4% (95% CI 1.7 – 16.4) had an adverse fetal or neonatal outcome. The odds ratio (OR) for adverse fetal or neonatal outcome after potential isotretinoin exposure in the 30 days before or during pregnancy was 2.3 (95% CI 0.9 – 5.7) after adjustment for maternal age (see table 3). Restricting the analysis to the potential isotretinoin exposure during pregnancy, the adjusted OR of an adverse fetal outcome was 1.5 (95% CI 0.5 – 4.8). The number of cases was too low to allow for adjustments in addition to maternal age. The adjusted OR of any fetal or neonatal outcome was significantly increased at 3.6 (95%CI 1.4-9.4) for isotretinoin exposure during the 30 days before or first trimester of pregnancy.

Table 3: Odds ratios for adverse fetal and neonatal outcomes and isotretinoin exposure in 30 days before or during pregnancy

Isotretinoin exposed fetuses	Exposed fetuses with adverse outcomes	OR (95% CI)	Adjusted OR* (95% CI)
During pregnancy (N=47)	3†	1.5 (0.5 – 4.8)	1.5 (0.5 – 4.8)
30 days before or during pregnancy (N=53)	5†‡	2.3 (0.9 – 5.8)	2.3 (0.9 – 5.7)
30 days before or 1st trimester (N=35)	5†‡	3.7 (1.4 – 9.5)	3.6 (1.4 – 9.4)

CI=confidence interval
* maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)
† Includes three intrauterine deaths.
1) in week 19, potentially exposed first 29 days following conception;
2) in week 35, potentially exposed 10 weeks following conception and from week 18 until week 32;
3) in week 38, also reported an unspecified septal defect; potentially exposed first 8 days following conception, during week 12 until 24, during week 28 until 38.
‡ Includes two live born infants with major congenital anomalies.
1) Neural tube defect, potentially exposed all 30 days before conception, not after conception.
2) Major congenital anomaly not further specified, potentially exposed the first 15 days of the 30 days before conception, not after conception.

DISCUSSION

This study shows that 2 per 10,000 pregnancies were exposed to isotretinoin despite the PPP which is implemented to prevent isotretinoin use during pregnancy. Although this study was not intended to estimate

the teratogenic risks of isotretinoin, adverse fetal and neonatal outcomes among these exposed pregnancies were observed. That there are still women who are using isotretinoin during pregnancy despite the implementation of the PPP is of major concern. Especially since the majority of isotretinoin exposed women (60%) were already pregnant at the time of first isotretinoin prescription and it seems that pregnancy was not always excluded before isotretinoin dispensing (box 1). These exposed pregnancies could probably have been prevented when appropriate pregnancy testing would have been performed. Furthermore, it was earlier demonstrated that women of reproductive age treated with isotretinoin did not always use effective contraceptive measures because only up to 59% of these women concomitantly used hormonal contraceptives.[8 9] Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days, which however decreased from 50% in 1999 to 13% in 2007. Based on these findings it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. Limited compliance with the PPP was also observed in a survey among Dutch pharmacists which indicated that in 2007 and 2011, 44% and 49% of pharmacists respectively checked the use of contraception at every isotretinoin dispensing.[14] The percentage of pharmacists that asked for negative pregnancy tests was stable with 15% and 16% respectively and is in line with our study which demonstrated that pregnancy is not always excluded before initiating isotretinoin and result in isotretinoin exposed pregnancies that could have been prevented. Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days which however decreased from 50% in 1999 to 13% in 2007, Based on these results it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP, especially since isotretinoin is mostly used in young women of reproductive age.

Previous studies on isotretinoin use during pregnancy in other Western countries showed comparable results indicating that the limited compliance to the PPP is not restricted to the Netherlands.[6 15-17] In the United States (US), the most recent isotretinoin PPP, called iPLEDGE, has been implemented since 2006 and is stricter than the EU PPP. iPLEDGE is an internet-based system that requires registration of all stakeholders with monthly updates on prescription, pregnancy tests, contraceptive use, and acknowledgement of risks.[17] The pregnancy rate among isotretinoin users in the US with the iPLEDGE PPP was estimated at 2.7 per 1,000 treatment courses and did not change compared to the previous PPP called SMART (System to Manage Accutane Related

Teratogenicity) while only small improvements in compliance with contraceptive measures were observed.[17 18] Apparently, also iPLEDGE does not bring complete security because further restrictive measures as in iPLEDGE do not seem to improve the results and may add unnecessary burden to the healthcare system since healthcare professionals and patients need to register and verify information on a monthly basis.[4]

Strengths and weaknesses of the study

A strength of this study is that we used a population based design including virtually complete and detailed drug dispensing data and pregnancy outcome data of a large cohort, which enabled estimating nationwide isotretinoin exposure rates among pregnant women. A known limitation of using drug dispensing data is that it does not confirm the actual use of the drug under study and does not provide information on the precise time window of drug use. In addition, it is likely that women may change or stop their medication use when they become aware of pregnancy. However, it should be noted that our data show that the majority (80%) of pregnant women who filled prescriptions for isotretinoin came back for refills, suggesting that they really used the drug.

This study provides no information on spontaneous abortions that occurred until gestational age of 16 weeks and ETOPs because these data are not captured in the PRN database and these pregnancies were thus not included in our cohort. This resulted in an underestimation of the number of pregnancies that were potentially exposed to isotretinoin in the 30 days before or during pregnancy and the adverse fetal and neonatal outcomes. Studies that estimated the teratogenic risk of isotretinoin using prospectively documented isotretinoin exposed pregnancies found much higher proportions of pregnancies resulting in spontaneous abortion, stillbirth or reported congenital malformations i.e. 36% (13 of the 36 fetuses)[3] and 26% (6 of the 23 fetuses)[5].

Without detailed information on drug exposure preferably verified by the patient whether the drug was actually taken and detailed descriptions of the diagnosed fetal outcome as well as on spontaneous abortions, the teratogenic risk of isotretinoin could not be accurately estimated. However, the primary aim of this study was to show that adverse fetal and neonatal outcomes still occur in isotretinoin exposed pregnancies, despite the implemented PPP. Unfortunately, due to the low number of cases it was not possible to adjust in the statistical analysis for important confounding factors other than maternal age such as smoking, alcohol intake, previous pregnancy outcomes and exposure to other potentially teratogenic drugs. Detection bias may also

have influenced the incidence and estimated risks of congenital anomalies since more detailed diagnostics might have been used in pregnancies exposed to isotretinoin compared to the unexposed pregnancies. Nevertheless, the results of our study are in line with the undisputed embryotoxicity of isotretinoin and indicate that such events still occur despite the implemented PPP.

Implications and future research

In the Netherlands, approximately 180,000 pregnancies are reported annually.[19] When extrapolating the 2.2 (95% CI 1.6 – 2.9) per 10,000 women potentially exposed to isotretinoin during pregnancy to a national level, there would be 29 to 52 isotretinoin-exposed pregnancies per year yielding unnecessary risks for congenital anomalies and fetal deaths. Therefore, it is in the interest of public health to implement effective PPPs and improve these measures or their compliance as much as possible to reduce isotretinoin use during pregnancy to the lowest possible level.

With the present study only the period 1999 to 2007 has been evaluated. The past years in the Netherlands, the PPP is communicated to healthcare professionals via product information,[20] national general practitioner (GP) standards on treatment of acne,[21] drug prescription and dispensing systems,[22] the website of the Dutch Medicines Evaluation Board,[23] and the common (national) literature on drug information.[24] Furthermore, research on isotretinoin use in the Netherlands and the PPP is conducted and published in (inter)national scientific medical journals.[7-9 14 25-28] Consequently, data after 2007 are needed to judge if attention for the isotretinoin PPP during recent years has improved the carefulness with which isotretinoin is prescribed and dispensed.

Conclusions

Although a PPP was implemented almost 15 years ago, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands which could have been prevented if appropriate exclusion of pregnancy before isotretinoin initiation would have been performed. Moreover, adverse fetal outcomes were reported among these pregnancies. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

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Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that LH and RH are employees of the PHARMO Institute. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. MS is leading a research group that sometimes conducts research for pharmaceutical companies. None related to the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Details of contributors Each author participated actively and sufficiently in this study. IZ, RR, LH, MS and BS contributed to the study design and the interpretation of the data. IZ and LH collected and analysed the data. IZ, RR, LH, RH, MS, SS and BS participated in the development and critical review of the manuscript for important intellectual content and provided final approval of the version to be published. A statement that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval Not applicable. The research team did not have access to medical records.

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Data sharing No additional data available.

Transparency The lead author (IZ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

FIGURE LEGENDS

Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days by calendar year

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies by calendar year

——— Exposed to isotretinoin in 30 days before or during pregnancy

– – – – Exposed to isotretinoin during pregnancy

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Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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ABSTRACT

Objective To estimate isotretinoin exposure in Dutch pregnant women despite the implemented pregnancy prevention programme (PPP) and secondly, to analyse the occurrence of ~~congenital anomalies and~~adverse fetal ~~death~~or neonatal outcomes in these isotretinoin exposed pregnancies.

Design Population based study

Setting the Netherlands

Participants a cohort of 203,962 pregnancies with onset between 1 January 1999 and 1 September 2007 consisting of 208,161 fetuses ~~(including multiple births)~~or neonates.

Main outcome measures Isotretinoin exposure in the 30 days before or during ~~the first, second or third trimester of~~ pregnancy. ~~The occurrence~~Proportions of adverse fetal or neonatal outcomes, defined as intrauterine deaths ≥ 16 week of ~~fetal death~~gestation and ~~fetusus~~neonates with major congenital anomalies. Odds ratios (ORs) with 95% confidence intervals (CI) adjusted for maternal age were calculated to estimate the risk of ~~congenital anomalies and~~ adverse fetal ~~death~~or neonatal outcome after maternal isotretinoin exposure.

Results ~~45~~51 pregnancies, 2.~~21 (~~5 (95%CI 1.~~63~~9 to 3.3) per 10,000 pregnancies, were exposed to isotretinoin despite the pregnancy prevention programme. 45 of these pregnancies, 2.~~93~~2 (95%CI 1.6 to 2.9) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy~~. Sixty~~ and six additional women became pregnant within 30 days after isotretinoin discontinuation. In sixty percent of isotretinoin exposed pregnancies, women started isotretinoin ~~when~~while already pregnant. ~~Among~~ In five out of the 51 isotretinoin exposed pregnancies, ~~the proportion of~~9.4% (95%CI 1.3 to 17.6), had an adverse fetal ~~death or congenital anomalies was 6.4% (1.7 to 16.4) and the~~ or neonatal outcome. The OR for ~~any congenital anomaly or~~ adverse fetal ~~death was 1.48 (~~or neonatal outcomes after isotretinoin exposure in 30 days before or during pregnancy was 2.3 (95%CI 0.~~46~~9 to ~~4.77~~5.7) after adjustment for maternal age.~~ For fetal death, the adjusted OR was 4.00 (1.25 to 12.91) and for congenital anomalies 0.70 (0.10 to 5.06). The risk was highest with exposure to isotretinoin during 30 days before conception or during the first trimester with an adjusted OR of 3.64 (1.41 to 9.39) for any congenital anomaly or fetal death.~~

Conclusions Although a ~~pregnancy prevention programme~~PPP was already implemented in 1988, we showed that isotretinoin exposed pregnancies in the Netherlands and adverse fetal and neonatal events still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin

PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance. ~~still pregnancies exposed to isotretinoin in the Netherlands and moreover, we showed that in these exposed pregnancies there was an elevated risk of congenital anomalies and fetal death.~~

~~-~~ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based study in the EU on isotretinoin exposure during pregnancy in a large cohort of more than 200,000 pregnancies ~~with virtual complete and detailed drug dispensing and pregnancy outcome data~~ which enabled ~~calculating accurate~~estimating isotretinoin exposure rates among pregnant women and ~~assessment of pregnancy outcomes~~its consequences on a nationwide scale.
- ~~Statistical analysis should be interpreted with caution because the absolute number of isotretinoin exposed pregnancies was small.~~
- ~~Our results might even underestimate the actual isotretinoin exposed pregnancies because pregnancies that ended in a spontaneous or elective abortion~~From the virtually complete and detailed drug dispensing data, isotretinoin exposure could only be estimated since drug dispensing data does not ascertain actual drug use and precise exposure intervals. However, patients coming for refills are usually taking their drug.
- Spontaneous abortions before gestational age of 16 weeks and elective abortions were not included in our cohort and therefore our results probably underestimate the number of isotretinoin exposed pregnancies and its consequences.
- The analysis was restricted to adverse fetal and neonatal outcomes in general since specific teratogenic risk could not be estimated with data lacking information on pregnancies until 16 weeks of gestation and lacking detailed descriptions of adverse fetal and neonatal outcomes.

INTRODUCTION

Isotretinoin, a vitamin A derivative, is licensed in the European Union (EU) since 1983 and is indicated for systemic treatment of severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) in patients resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.[1] ~~However, the~~The teratogenic potential is ~~a known major adverse effect~~an important characteristic of ~~treatment with~~ isotretinoin. Animal studies already suggested teratogenic effects in humans and isotretinoin has been contraindicated for use during pregnancy since the very beginning of the marketing authorisation. Despite this contraindication, the first cases of congenital anomalies after isotretinoin use during pregnancy were documented already in 1983.[2] ~~Systemic isotretinoin exposure during the first 10 weeks of pregnancy leads to congenital anomalies in approximately 26% of live births~~As described by Lammer et al. in 1985, isotretinoin~~,~~ ~~Isotretinoin~~ embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects.[3] They found a relative risk of 26 for this group of major congenital malformations after systemic isotretinoin exposure during some parts of the first 10 weeks after conception.[3] Elective termination of pregnancy (ETOP) was decided in more than 50% of exposed pregnancies and 20% of the remaining pregnancies ended in a first trimester spontaneous abortion.[3] ~~Exposure beyond the first 10 weeks of pregnancy can cause developmental delays and other CNS effects in approximately 40% of live births.[4,5] Furthermore, spontaneous abortion was observed in 7-20% of isotretinoin exposed pregnancies and elective termination of pregnancies occurred in more than 50% of exposed pregnancies.[3,4]~~

Reports of congenital anomalies after isotretinoin use accumulated and consequently, in 1988 the marketing authorisation holder of isotretinoin implemented a world-wide Pregnancy Prevention Programme (PPP) ~~world-wide~~ to better prevent pregnancies among systemic isotretinoin users.[6,4] The PPP included an educational programme for prescribers and patients including material to be used in counselling women about the need to prevent pregnancy while taking isotretinoin. Conditions for prescribing included a negative pregnancy test, the use of reliable contraception and a signed patient consent form.[6,4] In 2003, a review of isotretinoin by the European Medicine Agency (EMA) resulted in a compulsory European harmonised PPP for all isotretinoin containing products.[1] The elements of the European wide PPP are listed in box 1.

Box 1: Elements of the EU isotretinoin PPP

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up
2. Use of effective contraceptive measures from four weeks before isotretinoin initiation until four weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.

3. Pregnancy testing should be done before, during and five weeks after discontinuation of isotretinoin
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of seven days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the PPP.

The safe use of isotretinoin in women of reproductive age is in the interest of public health because of the potential risk of spontaneous and elective abortions, and, more importantly, children with major congenital anomalies require continuous healthcare throughout their life. Although a PPP has been implemented in the EU, pregnancies during isotretinoin therapy still occur.[~~7~~ ~~8~~5 6] The regulatory authorities of sixteen EU member states responded in 2009 to a survey that isotretinoin exposed pregnancies have occurred in their country.[~~9~~7] A French study between 2003 and 2006 estimated a pregnancy rate from 0.4 to 1.2 per 1000 female isotretinoin users within reproductive age.[~~8~~6] Studies in the Netherlands observed that only 52% to 59% of the female isotretinoin users of reproductive age used concomitant hormonal contraceptives, which was higher than the 39%-46% observed in the general female population of similar age, but lower than anticipated.[~~10~~ ~~11~~8 9] Although these studies show limited compliance with the isotretinoin PPP, it is not known whether isotretinoin exposure also occurs during pregnancy and what the outcome of these pregnancies is. Therefore, the objective of our study was to estimate isotretinoin exposure in Dutch pregnant women despite the implemented PPP and secondly, to analyse the occurrence of ~~congenital anomalies and~~ adverse fetal ~~death~~and neonatal outcomes in these isotretinoin exposed pregnancies.

METHODS

Data sources

For this population based study a cohort of 203,962 pregnancies consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort including, amongst other information, drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) that are collected since 1986.[~~12~~10] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[~~13~~11] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric

database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[~~14~~12] The registry contains information about care before, during, and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The PRN includes information on pregnancy outcome including congenital anomalies detected during pregnancy, at birth or within the first year after birth. The probabilistic linking method between PHARMO and PRN has been described in detail elsewhere but was generally based on the birth date of the mother and ~~fetus~~ child and their postal zip codes.[~~15~~13] To be included in the cohort the mother should be registered in the community pharmacy database of PHARMO during the whole pregnancy. The ~~start~~date of ~~pregnancy~~conception was estimated based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

Isotretinoin dispensings

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in our cohort within the 12-months period before or during pregnancy were extracted from the PHARMO Database Network. Considering a daily dosage of 0.5 mg-1mg per kilogram daily,[1] isotretinoin prescriptions dispensed on the same day were ~~pooled~~assumed to be used simultaneously and therefore these dispensings were pooled and considered as one dispensing (e.g. the prescriptions of a 10 mg and 20 mg ~~tablet to result in~~tablets dispensed at the same time to reach a daily dosage of 30mg ~~were pooled). The length of all~~). For each isotretinoin ~~dispensings~~ dispensing, the length of the dispensing was calculated by dividing the total number of prescribed units by the number of units (doses) to be taken per day. In case ~~the pooled~~isotretinoin dispensings that were pooled together had different lengths ~~– in case every other day different strengths should be taken –~~, the length of the single dispensing with the longest duration was ~~taken (i.e. one day 20 mg tablet, the other day 20 mg and 10 mg tablet).~~ used. To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

Drug exposure interval

For all pregnancies (n=203,962) ~~> 16 weeks~~with of gestational age of at least 16 weeks included in the cohort, isotretinoin exposure ~~before and during pregnancy~~ was ~~determined~~estimated based on isotretinoin dispensing data (ATC D10BA01) filled by the mother during the 12-months period before and during pregnancy. Exposure in person time (days) was calculated by dividing the total number of prescribed units by the number of

prescribed units per day. Isotretinoin exposure periods were defined considering a possible ~~overlapping period but gaps~~overlap of isotretinoin dispensings. Gaps, isotretinoin free periods between two isotretinoin dispensings, were not permitted ~~in one~~meaning that an isotretinoin exposure period ends once an isotretinoin free period~~.~~ was identified. Using the start and end date of the isotretinoin exposure period, the number of days exposed ~~during pregnancy~~ was estimated for the following exposure ~~windows~~intervals: 30 days before conception, first 90 days of gestation (first trimester), day 90-179 of gestation (second trimester) and day 180 – delivery (third trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

~~Pregnancy~~Adverse fetal or neonatal outcomes

For each fetus (n=208,161), we determined whether ~~congenital anomalies or~~ adverse fetal ~~death was~~or neonatal outcomes were reported. ~~Fetal death was~~ Adverse fetal or neonatal outcomes were defined as ~~death before complete expulsion or extraction from the mother.[15] Congenital~~all intrauterine deaths ≥ 16 week of gestation and live born infants with major congenital anomalies. If possible, congenital anomalies were categorised into nine sub-groups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. ~~Description of the classification system for congenital anomalies used in our study are presented in the supplementary information Table S1. As we were interested in those congenital anomalies~~As we were interested in adverse fetal outcomes potentially induced by maternal drug exposure, chromosomal anomalies were ~~excluded.~~ not considered as an adverse outcome in the analyses.

Analysis

~~The dispensing rate of isotretinoin among the pregnant women included in our study was calculated and stratified per~~Potential exposure ~~period. Exposure~~ to isotretinoin in the 30 days before or during pregnancy was calculated per 10,000 pregnancies ~~was calculated~~ for the aforementioned exposure ~~periods~~intervals including their 95% confidence intervals (95% CIs). The proportions of adverse fetal outcome among isotretinoin exposed and unexposed fetuses or neonates were calculated including their 95% CIs. We used multiple logistic regression models to calculate odds ratios (ORs) and 95% CIs to estimate associations between ~~congenital anomalies,~~adverse fetal ~~death~~or neonatal outcome and maternal isotretinoin exposure. We adjusted for maternal age at conception (<20, 20-24, 25-29, 30-34, ≥35), and if possible also for calendar time (year of

conception) and gender of the infant. Analyses for specific congenital anomalies were performed when > 3 cases were observed. The t-test or Fisher exact test was used to derive p-values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided p-values <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203,962 pregnancies corresponding to 208,161 fetuses (including multiple births) were included in our study. The mean maternal age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days). ~~Demographics for isotretinoin exposed and unexposed pregnancies are presented in table 1.~~

Isotretinoin dispensings

A total of 416 isotretinoin dispensings to 130 of the 203,962 women in the 12-months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of > 30 days of isotretinoin use. Figure 1 shows that the percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Isotretinoin exposed pregnancies

Demographics for isotretinoin exposed and unexposed pregnancies are presented in table 1.

Table 1: Description of the study population

	Isotretinoin exposed*	Isotretinoin unexposed	*p-value*
Pregnancies (N=203,962)	51	203,911	
Mean (±SD) maternal age at conception in years (95% CI)	29.1 (4.9) (27.8 – 30.5)	30.3 (4.7) (30.3 – 30.3)	0.56
Mean (±SD) gestational age at delivery in weeks (95% CI)	39 (25 days) (38 – 40)	39, 3 days (19 days) (39- 3 days – 39- 3 days)	0.33
Fetuses (N=208,161)	53	208,108	
Gender (boy %)	47.2% (33.3 – 61.1)	51.5% (51.3 – 51.7)	0.53
Maternal age at conception in years, n, column %.			0.37
< 20 years of age	2 (3.8%)	4,063 (2.0%)	
≥ 20 -25 years of age	7 (13.2%)	22,144 (10.6%)	
≥ 25 -30 years of age	21 (39.6%)	68,366 (32.9%)	
≥ 30 -35 years of age	14 (26.4%)	81,581 (39.2%)	
≥ 35 years of age	9 (17.0%)	31,951 (15.4%)	

Gestational age at delivery, n, column %.			0.64
< 27 weeks	1 (1.9%)	2,198 (1.1%)	
27 ~~–~~ 30 weeks	1 (1.9%)	1,167 (0.6%)	
31-33 weeks	0 (0.0%)	2,008 (1.0%)	
34-36 weeks	3 (5.7%)	7,126 (3.4%)	
37-39 weeks	12 (22.6%)	50,854 (24.4%)	
>~~40~~ 39 weeks	36 (67.9%)	144,755 (69.5%)	
~~Fetal death or congenital anomalies~~Adverse fetal outcome, n;% (95% CI)	5; 9.4% (1.3 -17.6)	9,041; 4.3% (4.3 – 4.4)	0.08
~~Fetal death, n; % (95% CI)~~	~~3; 5.7% (0 – 12.1)~~	~~3,404; 1.6% (1.6 – 1.7).~~	~~0.06~~
~~Congenital anomalies, n;% (95% CI)~~	~~3; 5.7% (0 – 12.1)~~	~~6,246; 3.0% (2.93 – 3.07)~~	~~0.21~~

~~*including 45 isotretinoin exposed pregnancies and 6 pregnancies occurred within 30 days after isotretinoin discontinuation~~*in the 30 days before conception or during pregnancy

Overall, ~~45 pregnant women~~51 pregnancies, 2.~~21~~5 (95% CI 1.~~63 – 2.93~~9 to 3.3) per 10,000 pregnancies, were potentially exposed to isotretinoin in the 30 days before conception or during pregnancy, despite the implemented pregnancy prevention programme. Forty-five pregnant women, 2.2 (95%CI 1.6 – 2.9) per 10,000 pregnancies, were estimated to be exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six ~~additional~~ pregnancies were identified within one month after isotretinoin discontinuation~~.~~ and were estimated to be exposed only before conception. In 40 out of 203,962 pregnancies, ~~1.96~~2.0 (95% CI 1.~~42~~4 – 2.~~64~~6) per 10,000 pregnancies, an isotretinoin prescription was filled during pregnancy~~.~~ ~~Thirty-two of these 40 pregnant women~~ and 32 pregnancies, 1.6 (95% CI 1.1 – 2.2) per 10,000 pregnancies, received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings per pregnancy ranged from 1 to 7, with a median of 2.~~50.~~5. The estimated isotretinoin exposure per exposure interval is presented in table 2.

Table 2: Potential ~~i~~isotretinoin exposed pregnancies ~~and fetuses~~ per exposure period

Isotretinoin exposure ~~period~~interval*	Exposed ~~P~~pregnancies (N=203,962)	Exposed pregnancies ~~per~~/ 10,000 pregnancies (N, 95% CI)	Median number of days exposed per pregnancy (range)	~~Fetuses (N=208,161)~~	~~Fetuses with congenital anomalies or fetal death (N=53)**~~
30 days before conception (30 days period)	23	1.13 (0.73 – 1.67)	24 (range 3 – 30)	~~23~~	~~5; 21.74% (8.43 – 41.80)~~
1st trimester (90 days period)	28	1.37 (0.93 – 1.96)	31 (range 3 – 88)	~~28~~	~~3; 10.71% (2.80 – 2.65)~~
2nd trimester (90 days period)	25	1.23 (0.81 – 1.78)	57 (range 1 – 90)	~~26~~	~~2; 7.69% (1.31 – 23.16)~~
3rd trimester (90-103 days period)	26	1.28 (0.85 – 1.84)	62 (range 1 – 103)	~~28~~	~~2; 7.14% (1.22 – 21.65)~~
During pregnancy (270 days period)	45	2.21 (1.63 – 2.93)	63 (range 3 – 236)	~~47~~	~~3; 6.38% (1.65 – 16.39)~~
30 days before or during pregnancy (300 days period)	51	2.50 (1.88 – 3.26)	63 (range 7 – 236)	~~53~~	~~5; 9.43% (3.54 – 19.68)~~
30 days before or during 1st trimester (120 days period)	35	1.72 (1.24 – 2.36)	32 (range 7 – 114)	~~35~~	~~5; 14.29% (5.43 – 28.86)~~

CI=Confidence interval.
*Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that exposure interval~~period~~
~~**51 pregnancies corresponded to 53 infants including two multiple births~~

Among the pregnancies estimated to be exposed to isotretinoin during pregnancy (n=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. Figure 2 shows that the number of women estimated to be exposed to isotretinoin during pregnancy was the highest in 2006 with 3.~~48 exposed~~5 pregnancies (95% CI 1.~~70~~7 – 6.~~39~~4) per 10,000 pregnancies.

~~Pregnancy~~Adverse fetal or neonatal outcomes

Independent of isotretinoin exposure, adverse fetal or neonatal outcomes were observed for 9,046 of the 208,161 fetuses (4.~~35~~4%, 95% CI 4.~~26 – 4.43) fetal death or a congenital anomaly excluding chromosomal anomalies was reported in the PRN.~~3 – 4.4). The ~~proportion of fetal death was 1.64% (95% CI 1.58 – 1.69) and 3.00% (95% CI 2.93 – 3.08) for congenital anomalies.~~

~~The 45~~51 pregnancies potentially exposed to isotretinoin in 30 days before conception or during pregnancy corresponded to ~~47~~53 fetuses~~. Among~~ or neonates including two multiple births. Five of these ~~47 fetuses, three were identified~~, all singletons, had an adverse fetal or neonatal outcome (9.4% [95% CI 3.5 – 19.7]). ~~deaths or had congenital anomalies (6.38%, 95%CI 1.65 – 16.39). The proportion of fetal death (n=3) and congenital anomalies (n=1) was 6.38% (95%CI 1.65 – 16.39) and 2.13% (95% CI 0.11 – 10.04) respectively. Considering also the six pregnancies that occurred within one month after isotretinoin discontinuation, a total~~

~~of five out of 53 fetus (9.43%, 95CI 3.54 – 19.68) were identified as fetal death (n=3) or had a congenital anomaly (n=3). The isotretinoin exposed fetal deaths and~~ These included three intrauterine deaths and two live born infants ~~born~~ with ~~congenital anomalies in different~~ major congenital anomalies (see table 3). Among those potentially exposed during pregnancy only (n=47), 6.4% (95% CI 1.7 – 16.4) had an adverse fetal or neonatal outcome. The odds ratio (OR) for adverse fetal or neonatal outcome after potential isotretinoin exposure ~~period are presented~~in the 30 days before or during pregnancy was 2.3 (95% CI 0.9 – 5.7) after adjustment for maternal age (see table 3). Restricting the analysis to the potential isotretinoin exposure during pregnancy, the adjusted OR of an adverse fetal outcome was 1.5 (95% CI 0.5 – 4.8). The number of cases was too low to allow for adjustments in ~~table 2.~~addition to maternal age. The adjusted OR of any fetal or neonatal outcome was significantly increased at 3.6 (95%CI 1.4-9.4) for isotretinoin exposure during the 30 days before or first trimester of pregnancy. ~~For isotretinoin exposure during pregnancy, the odds ratio (OR) for any congenital anomaly or fetal death was 1.48 (95% CI 0.46 – 4.77) after adjustment for maternal age (see table 3). Considering the same exposure window, for fetal death, the adjusted OR was 4.00 (95% CI 1.25 – 12.91) and for congenital anomalies 0.70 (95% CI 0.10 – 5.06). The number of cases were too low to allow for adjustments in addition to maternal age. Adding the 30 days before conception to the exposure window (exposure 30 days before or during pregnancy), the adjusted OR for any congenital anomaly or fetal death was 2.28 (95% CI 0.91 – 5.72). A significantly increased OR of 3.64 (95% CI 1.41 – 9.39) was observed for any congenital anomaly or fetal death and isotretinoin exposure within 30 days before or first trimester of pregnancy.~~

Table 3: Odds ratios for adverse fetal and neonatal outcomes and isotretinoin exposure in 30 days before or during pregnancy

Isotretinoin exposed fetuses	Exposed fetuses with adverse outcomes	OR (95% CI)	Adjusted OR* (95% CI)
During pregnancy (N=47)	3†	1.5 (0.5 – 4.8)	1.5 (0.5 – 4.8)
30 days before or during pregnancy (N=53)	5†‡	2.3 (0.9 – 5.8)	2.3 (0.9 – 5.7)
30 days before or 1st trimester (N=35)	5†‡	3.7 (1.4 – 9.5)	3.6 (1.4 – 9.4)

CI=confidence interval
* maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)
† Includes three intrauterine deaths.
1) in week 19, potentially exposed first 29 days following conception;
2) in week 35, potentially exposed 10 weeks following conception and from week 18 until week 32;
3) in week 38, also reported an unspecified septal defect; potentially exposed first 8 days following conception, during week 12 until 24, during week 28 until 38.
‡ Includes two live born infants with major congenital anomalies.
1) Neural tube defect, potentially exposed all 30 days before conception, not after conception.
2) Major congenital anomaly not further specified, potentially exposed the first 15 days of the 30 days before conception, not after conception.

Table 3: Odds ratios for congenital anomalies and fetal death and isotretinoin exposure during pregnancy

Congenital anomalies	Unexposed fetuses (N=208,106)	Isotretinoin-exposed fetuses								
		During pregnancy (N=47)			30 days before or during pregnancy (N=53)			30 days before or 1st trimester (N=3		
		N	OR	Adjusted OR*	N	OR	Adjusted OR*	N	OR	Adjusted OR*
Any congenital anomaly or fetal death	9,041	3	1.51 (0.47 – 4.84)	1.48 (0.46 – 477)	5	2.30 (0.91 – 5.77)	2.28 (0.91 – 5.72)	3	3.68 (1.43 – 9.48)	3.64 (1.41 – 9.39)
Fetal death	3,404	3	4.10 (1.27 – 13.22)	4.00 (1.25 – 12.91)	3	3.61 (1.13 – 11.58)	3.57 (1.11 – 11.47)	3	5.64 (1.73 – 18.42)	5.55 (1.70 – 18.19)
Any congenital anomaly	6,246	1	0.70 (0.10 – 5.09)	0.70 (0.10 – 5.06)	3	1.94 (0.61 – 6.22)	1.93 (0.60 – 6.18)	1	3.03 (0.93 – 9.90)	3.02 (0.92 – 9.86)

*maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)

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~~**Description of cases**~~

~~The pregnancies exposed to isotretinoin in the 30 days before or during pregnancy resulted in five cases of fetal death or congenital anomalies. The year of conception of these cases was 2002 (n=2), 2003 (n=2) and 2005 (n=1). Three of the five cases were exposed to isotretinoin during pregnancy and two cases were only exposed to isotretinoin in the 30 days before conception because conception occurred within 30 days after isotretinoin discontinuation and no new isotretinoin prescriptions were filled afterwards. All three pregnancies exposed to isotretinoin during pregnancy started while the mother was already using isotretinoin, and all three cases ended in fetal death. One pregnancy was exposed to isotretinoin 29 days following conception and no new isotretinoin prescriptions were filled after conception. The pregnancy ended in fetal death after 19 weeks. In the second pregnancy two isotretinoin prescriptions were filled during pregnancy resulting in a total of 166 days of isotretinoin exposure during pregnancy (19 days in the first trimester and 79 and 68 days in the second and third trimester of pregnancy, respectively). After 38 weeks, the pregnancy resulted in fetal death and cardiovascular anomalies (not further specified). In the third pregnancy, four isotretinoin prescriptions were filled during pregnancy resulting in a total of 163 days of isotretinoin exposure during pregnancy (73 in first, 51 and 39 in second and third trimester respectively). After 35 weeks the pregnancy ended in fetal death. The two remaining pregnancies were only exposed to isotretinoin in the 30 days before conception. Both fetusus were born with gestational age of 39 or 40 weeks and had congenital anomalies; one had a neural tube defect and for the other the anomaly was not further specified.~~

DISCUSSION

This study ~~showed~~shows that 2 per 10,000 pregnancies were exposed to isotretinoin ~~during pregnancy~~ despite the ~~fact that a~~ PPP which is implemented to prevent isotretinoin use during pregnancy. ~~In~~Although this study was not intended to estimate the ~~majority~~teratogenic risks of isotretinoin, adverse fetal and neonatal outcomes among these exposed pregnancies~~, women started isotretinoin when already pregnant. The risk of congenital anomalies or fetal deaths was increased in pregnancies that~~ were ~~exposed to isotretinoin during the 30 days prior or during the first trimester of pregnancy while the risk of fetal death was increased during all analysed time windows.~~

observed. That there are still women who are using isotretinoin during pregnancy despite the implementation of the PPP is of major concern. ~~Since~~ Especially since the majority of ~~the~~ isotretinoin exposed women (60%) were already pregnant at the time of first isotretinoin prescription~~,~~ and it seems that pregnancy ~~in isotretinoin users~~ was not always excluded before ~~drug~~isotretinoin dispensing (box 1). These exposed pregnancies could probably have been prevented when appropriate pregnancy testing would have been performed. Furthermore, it was earlier demonstrated that women of reproductive age treated with isotretinoin ~~might~~did not always ~~have used~~use effective contraceptive measures~~.~~ because only up to 59% of these women concomitantly used hormonal contraceptives.[8 9] Our study showed that compliance with the recommended maximum length of prescription of 30 days ~~between 1999 and 2007~~ was limited since one third of isotretinoin dispensings exceeded 30 days~~. This~~, which however decreased from 50% in 1999 to 13% in 2007. Based on these findings it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. ~~which suggests a higher awareness. Based on this study, no conclusions can be drawn as to which elements of the PPP fail but it is obvious that the PPP is not completely effective. These findings are in line with previous Dutch studies that found that concomitant use of hormonal contraceptives in isotretinoin using women of reproductive age is limited to 52% - 59%.~~[10 11] Limited compliance with the PPP ~~in the Netherlands~~ was also observed in a survey among Dutch pharmacists which indicated that in 2007 and 2011, 44% and 49% of pharmacists respectively checked the use of contraception at every isotretinoin dispensing.[17 14] The percentage of pharmacists that asked for negative pregnancy tests was stable with 15% and 16% respectively and is in line with ~~the results of~~ our study which ~~demonstrate that it seems~~demonstrated that pregnancy is not always excluded before initiating isotretinoin and result in isotretinoin exposed pregnancies that could have been prevented. Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days which however decreased from 50% in 1999 to 13% in 2007, Based on these results it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP, especially since isotretinoin is mostly used in young women of reproductive age. ~~If that does not work, more strict measures might have to be considered.~~

Previous studies on isotretinoin use during pregnancy in other Western countries showed comparable results indicating that the limited compliance to the PPP is not restricted to the Netherlands.[6 15-17] In the United States

(US), the most recent isotretinoin PPP, called iPLEDGE, has been implemented since 2006 and is stricter than the EU PPP. iPLEDGE is an internet-based system that requires registration of all stakeholders with monthly updates on prescription, pregnancy tests, contraceptive use, and acknowledgement of risks.[~~18~~17] The pregnancy rate among isotretinoin users in the US with the iPLEDGE PPP was estimated at 2.7 per 1,000 treatment courses and did not change compared to the previous PPP called SMART (System to Manage Accutane Related Teratogenicity) while only small improvements in compliance with contraceptive measures were observed.[~~18~~ ~~19~~17 ~~18~~] ~~Further~~ Apparently, also iPLEDGE does not bring complete security because further restrictive measures as in iPLEDGE do not seem to improve the results and may ~~contribute to the potential inefficiencies of~~ add unnecessary burden to the healthcare system since healthcare professionals and patients need to register and verify information on a monthly basis.[4]

~~The proportion of congenital anomalies or fetal death after isotretinoin exposure during pregnancy in our study was 6.4%. Comparable proportions were observed in a German study which also found that 76% of isotretinoin exposed pregnancies ended in an elective pregnancy termination.[7] No information on elective pregnancy termination was available in our study but the potentially high proportion of elective pregnancy termination may explain the lower proportions of congenital anomalies after isotretinoin exposure during pregnancy observed in our study (2.1%) as compared to earlier studies that reported 26% 28%.[3 4] The present study identified a total of five pregnancies of which the adverse pregnancy outcome, including three fetal deaths, may be related to isotretinoin use. Although the statistical analysis should be interpreted cautiously due to low numbers, we observed an increased risk of fetal death whereas for congenital anomalies an increased risk could not be determined. The neural tube defect in one of the cases is not a known CNS defect typical for retinoid embryopathy[3] and furthermore, may be related to other factors since isotretinoin exposure was only identified in the 30 days period before conception. Nevertheless, according to the isotretinoin PPP, the pregnancy should not have occurred. Another pregnancy resulted in fetal death and also reported a cardiovascular anomaly (not further specified) after isotretinoin exposure during the first weeks after conception. This anomaly may be a typical symptom of retinoid embryopathy such as ventricular septic defect[3], but insufficient information on the congenital anomaly was available to draw these conclusions. Congenital anomalies identified in other cases were also coded on high level only (e.g. congenital anomaly not further specified). For the assessment of retinoid embryopathy, both detailed descriptions of the diagnosed congenital~~

~~anomaly as well as detailed information on drug exposure preferably verified by the patient whether the drug was actually taken are necessary.~~

Strengths and weaknesses of the study

A strength of this study is that we used a population based ~~study~~design including virtually complete and detailed drug dispensing data and pregnancy outcome data of a large cohort, which enabled ~~calculating accurate~~estimating nationwide isotretinoin exposure rates among pregnant women ~~which can be extrapolated to the national situation to indicate impact on public health. This would be more difficult and probably less accurate when using spontaneous reported cases or data from teratology information services, since these data sources do not provide clear denominators to calculate exposure rates and may suffer from substantial underreporting. Although our absolute numbers were small, all exposure and outcome information was prospectively gathered and unbiased because nobody was aware of the research hypothesis. Moreover, we simply confirmed an adverse reaction which is nowadays undisputed.~~

~~Our results might even underestimate the actual risk because no information can be provided on spontaneous and elective abortions that occurred before gestational age of 16 weeks because these data are not captured in the PRN database and these pregnancies were therefore not included in our cohort.~~

A known limitation of using drug dispensing data is that it does not confirm the actual use of the drug under study and does not provide information on the precise time window of drug use. In addition, it is likely that women may change or stop their medication use when they become aware of pregnancy. However, it should be noted that our data show that the majority (80%) of pregnant women who filled prescriptions for isotretinoin came back for refills, suggesting that they really used the drug.

This study provides no information on spontaneous abortions that occurred until gestational age of 16 weeks and ETOPs because these data are not captured in the PRN database and these pregnancies were thus not included in our cohort. This resulted in an underestimation of the number of pregnancies that were potentially exposed to isotretinoin in the 30 days before or during pregnancy and the adverse fetal and neonatal outcomes. Studies that estimated the teratogenic risk of isotretinoin using prospectively documented isotretinoin exposed pregnancies found much higher proportions of pregnancies resulting in spontaneous abortion, stillbirth or reported congenital malformations i.e. 36% (13 of the 36 fetuses)[3] and 26% (6 of the 23 fetuses)[5].

Without detailed information on drug exposure preferably verified by the patient whether the drug was actually taken and detailed descriptions of the diagnosed fetal outcome as well as on spontaneous abortions, the teratogenic risk of isotretinoin could not be accurately estimated. However, the primary aim of this study was to show that adverse fetal and neonatal outcomes still occur in isotretinoin exposed pregnancies, despite the implemented PPP. Unfortunately, due to the low number of cases it was not possible to adjust in the statistical analysis for important confounding factors other than maternal age such as smoking, alcohol intake, previous pregnancy outcomes and exposure to other potentially teratogenic drugs. Detection bias may also have influenced the incidence and estimated risks of congenital anomalies since more detailed diagnostics might have been used in pregnancies exposed to isotretinoin compared to the unexposed pregnancies. Nevertheless, the results of our study are in line with the undisputed embryotoxicity of isotretinoin and indicate that such events still occur despite the implemented PPP.

Implications and future research

In the Netherlands, approximately 180,000 pregnancies are reported annually.[~~20~~19] When extrapolating the 2.~~21~~2 (95% CI 1.~~63~~6 – 2.~~93~~9) per 10,000 women potentially exposed to isotretinoin during pregnancy to a national level, there would be 29 to 52 isotretinoin-exposed pregnancies ~~receiving isotretinoin~~ per year yielding unnecessary ~~high~~ risks for congenital anomalies and fetal deaths. Therefore, it is in the interest of public health to implement effective PPPs and improve these measures or their compliance as much as possible to reduce isotretinoin use during pregnancy to the lowest possible level.

With the present study ~~reasons for PPP failure cannot be identified and~~ only the period 1999 to 2007 has been evaluated. ~~More recent data are necessary to further study the up-to-date situation of the isotretinoin PPP in the Netherlands in order to take appropriate action, especially since the last few years attention for the isotretinoin PPP might have improved the carefulness with which isotretinoin is prescribed and dispensed.~~

The past years i~~I~~n the Netherlands, the PPP is communicated to healthcare professionals via product information,[~~21~~20] national general practitioner (GP) standards on treatment of acne,[~~22~~21] drug prescription and dispensing systems,[~~23~~22] the website of the Dutch Medicines Evaluation Board,[~~24~~23] and the common (national) literature on drug information.[~~25~~24] Furthermore, research on isotretinoin use in the Netherlands and the PPP is conducted and published in (inter)national scientific medical journals.[~~9 11 17 26 29~~7-9 14 25-28] Consequently, data

after 2007 are needed to judge if attention for the isotretinoin PPP during recent years has improved the carefulness with which isotretinoin is prescribed and dispensed.

Conclusions

~~The safe use of isotretinoin is important for public health to prevent unnecessary high risks of congenital anomalies and fetal deaths.~~ Although a PPP was implemented almost 15 years ago, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands ~~and moreover, we showed that in these exposed pregnancies there is an elevated risk of congenital anomalies and fetal death. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP. Before regulatory measures should be considered, the isotretinoin PPP requires further evaluation using more recent data to assess whether isotretinoin use among women with reproductive age has improved.~~

which could have been prevented if appropriate exclusion of pregnancy before isotretinoin initiation would have been performed. Moreover, adverse fetal outcomes were reported among these pregnancies. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

FIGURE LEGENDS

Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days ~~per~~by calendar year

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies ~~per~~by calendar year

——— Exposed to isotretinoin in 30 days before or during pregnancy

- - - - Exposed to isotretinoin during pregnancy

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Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that LH and RH are employees of the PHARMO Institute. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. MS is leading a research group that sometimes conducts research for pharmaceutical companies. None related to the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Details of contributors Each author participated actively and sufficiently in this study. IZ, RR, LH, MS and BS contributed to the study design and the interpretation of the data. IZ and LH collected and analysed the data. IZ, RR, LH, RH, MS, SS and BS participated in the development and critical review of the manuscript for important intellectual content and provided final approval of the version to be published. A statement that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval Not applicable. The research team did not have access to medical records.

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Data sharing No additional data available.

Transparency The lead author (IZ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days by calendar year

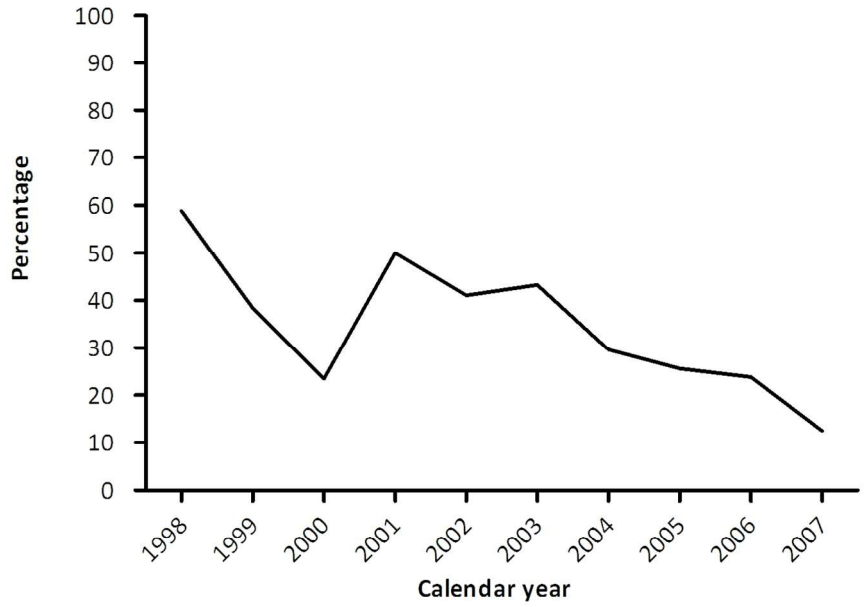

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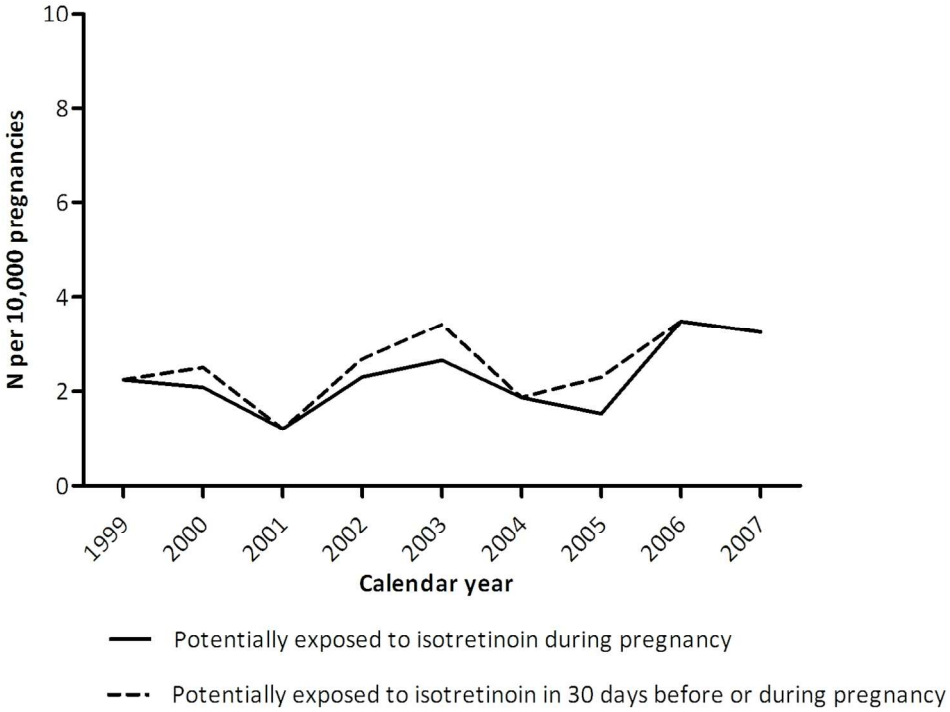
Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies by calendar year



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-78
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	6

Continued on next page

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8; (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure	9 (Table 2)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11; (Table 3)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11;(Table 3)
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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key words: isotretinoin, pregnancy prevention programme, teratogens, congenital malformations

Word count: 3580 words

ABSTRACT

Objective To estimate isotretinoin exposure in Dutch pregnant women despite the implemented pregnancy prevention programme (PPP) and secondly, to analyse the occurrence of adverse fetal or neonatal outcomes in these isotretinoin exposed pregnancies.

Design Population based study

Setting the Netherlands

Participants a cohort of 203,962 pregnancies with onset between 1 January 1999 and 1 September 2007 consisting of 208,161 fetuses or neonates.

Main outcome measures Isotretinoin exposure in the 30 days before or during pregnancy. Proportions of adverse fetal or neonatal outcomes, defined as intrauterine deaths ≥ 16 week of gestation and neonates with major congenital anomalies. Odds ratios (ORs) with 95% confidence intervals (CI) adjusted for maternal age were calculated to estimate the risk of adverse fetal or neonatal outcome after maternal isotretinoin exposure.

Results 51 pregnancies, 2.5 (95%CI 1.9 to 3.3) per 10,000 pregnancies, were exposed to isotretinoin despite the pregnancy prevention programme. 45 of these pregnancies, 2.2 (95%CI 1.6 to 2.9) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy and six additional women became pregnant within 30 days after isotretinoin discontinuation. In sixty percent of isotretinoin exposed pregnancies, women started isotretinoin while already pregnant. In five out of the 51 isotretinoin exposed pregnancies, 9.4% (95%CI 1.3 to 17.6), had an adverse fetal or neonatal outcome. The OR for adverse fetal or neonatal outcomes after isotretinoin exposure in 30 days before or during pregnancy was 2.3 (95%CI 0.9 to 5.7) after adjustment for maternal age.

Conclusions Although a PPP was already implemented in 1988, we showed that isotretinoin exposed pregnancies and adverse fetal and neonatal events potentially related to the exposure still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based study in the EU on isotretinoin exposure during pregnancy in a large cohort of more than 200,000 pregnancies which enabled estimating isotretinoin exposure rates among pregnant women and its consequences on a nationwide scale.
- From the virtually complete and detailed drug dispensing data, isotretinoin exposure could only be estimated since drug dispensing data does not ascertain actual drug use and precise exposure intervals. However, patients coming for refills are usually taking their drug.
- Spontaneous abortions before gestational age of 16 weeks and elective abortions were not included in our cohort and therefore our results probably underestimate the number of isotretinoin exposed pregnancies and its consequences.
- Specific teratogenic risks could not be estimated with data lacking information on pregnancies until 16 weeks of gestation and lacking detailed descriptions of adverse fetal and neonatal outcomes.

INTRODUCTION

Isotretinoin, a vitamin A derivative, is licensed in the European Union (EU) since 1983 and is indicated for systemic treatment of severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) in patients resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.[1] The teratogenic potential is an important characteristic of isotretinoin. Animal studies already suggested teratogenic effects in humans and isotretinoin has been contraindicated for use during pregnancy since the very beginning of the marketing authorisation. Despite this contraindication, the first cases of congenital anomalies after isotretinoin use during pregnancy were documented already in 1983.[2] As described by Lammer et al. in 1985, isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects.[3] They found a relative risk of 26 for this group of major congenital malformations after systemic isotretinoin exposure during some parts of the first 10 weeks after conception.[3] Elective termination of pregnancy (ETOP) was decided in more than 50% of exposed pregnancies and 20% of the remaining pregnancies ended in a first trimester spontaneous abortion.[3] Reports of congenital anomalies after isotretinoin use accumulated and consequently, in 1988 the marketing authorisation holder of isotretinoin implemented a world-wide Pregnancy Prevention Programme (PPP) to better prevent pregnancies among systemic isotretinoin users.[4] The PPP included an educational programme for prescribers and patients including material to be used in counselling women about the need to prevent pregnancy while taking isotretinoin. Conditions for prescribing included a negative pregnancy test, the use of reliable contraception and a signed patient consent form.[4] In 2003, a review of isotretinoin by the European Medicine Agency (EMA) resulted in a compulsory European harmonised PPP for all isotretinoin containing products.[1] The elements of the European wide PPP are listed in box 1.

Box 1: Elements of the EU isotretinoin PPP

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up
2. Use of effective contraceptive measures from four weeks before isotretinoin initiation until four weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.
3. Pregnancy testing should be done before, during and five weeks after discontinuation of isotretinoin
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of seven days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the PPP.

The safe use of isotretinoin in women of reproductive age is in the interest of public health because of the potential risk of spontaneous and elective abortions, and, more importantly, children with major congenital anomalies require continuous healthcare throughout their life. Although a PPP has been implemented in the EU, pregnancies during isotretinoin therapy still occur.[5 6] The regulatory authorities of sixteen EU member states responded in 2009 to a survey that isotretinoin exposed pregnancies have occurred in their country.[7] A French study between 2003 and 2006 estimated a pregnancy rate from 0.4 to 1.2 per 1000 female isotretinoin users within reproductive age.[6] Studies in the Netherlands observed that only 52% to 59% of the female isotretinoin users of reproductive age used concomitant hormonal contraceptives, which was higher than the 39%-46% observed in the general female population of similar age, but lower than anticipated.[8 9] Although these studies show limited compliance with the isotretinoin PPP, it is not known whether isotretinoin exposure also occurs during pregnancy and what the outcome of these pregnancies is. Therefore, the objective of our study was to estimate isotretinoin exposure in Dutch pregnant women despite the implemented PPP and secondly, to analyse the occurrence of adverse fetal and neonatal outcomes in these isotretinoin exposed pregnancies.

METHODS

Data sources

For this population based study a cohort of 203,962 pregnancies consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort including, amongst other information, drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) that are collected since 1986.[10] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[11] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[12] The registry contains information about care before, during, and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The PRN includes information on pregnancy outcome including congenital anomalies

detected during pregnancy, at birth or within the first year after birth. The probabilistic linking method between PHARMO and PRN has been described in detail elsewhere but was generally based on the birth date of the mother and child and their postal zip codes.[13] To be included in the cohort the mother should be registered in the community pharmacy database of PHARMO during the whole pregnancy. The date of conception was estimated based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

Isotretinoin dispensings

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in our cohort within the 12-months period before or during pregnancy were extracted from the PHARMO Database Network. Considering a daily dosage of 0.5 mg-1mg per kilogram daily,[1] isotretinoin prescriptions dispensed on the same day were assumed to be used simultaneously and therefore these dispensings were pooled and considered as one dispensing (e.g. the prescriptions of a 10 mg and 20 mg tablets dispensed at the same time to reach a daily dosage of 30mg). For each isotretinoin dispensing, the length of the dispensing was calculated by dividing the total number of prescribed units by the number of units (doses) to be taken per day. In case isotretinoin dispensings that were pooled together had different lengths, the length of the single dispensing with the longest duration was used. To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

Drug exposure interval

For all pregnancies (N=203,962) with of gestational age of at least 16 weeks included in the cohort, isotretinoin exposure was estimated based on isotretinoin dispensing data (ATC D10BA01) filled by the mother during the 12-months period before and during pregnancy. Exposure in person time (days) was calculated by dividing the total number of prescribed units by the number of prescribed units per day. Isotretinoin exposure periods were defined considering a possible overlap of isotretinoin dispensings. Gaps, isotretinoin free periods between two isotretinoin dispensings, were not permitted meaning that an isotretinoin exposure period ends once an isotretinoin free period was identified. Using the start and end date of the isotretinoin exposure period, the number of days exposed was estimated for the following exposure intervals: 30 days before conception, first 90 days of gestation (first trimester), day 90-179 of gestation (second trimester) and day 180 – delivery (third

trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

Adverse fetal or neonatal outcomes

For each fetus (N=208,161), we determined whether adverse fetal or neonatal outcomes were reported. Adverse fetal or neonatal outcomes were defined as all intrauterine deaths ≥ 16 week of gestation and live born infants with major congenital anomalies. If possible, congenital anomalies were categorised into nine sub-groups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. As we were interested in adverse fetal outcomes potentially induced by maternal drug exposure, chromosomal anomalies were not considered as an adverse outcome in the analyses.

Analysis

Potential exposure to isotretinoin in the 30 days before or during pregnancy was calculated per 10,000 pregnancies for the aforementioned exposure intervals including their 95% confidence intervals (95% CIs). The proportions of adverse fetal outcome among isotretinoin exposed and unexposed fetuses or neonates were calculated including their 95% CIs. We used multiple logistic regression models to calculate odds ratios (ORs) and 95% CIs to estimate associations between adverse fetal or neonatal outcome and maternal isotretinoin exposure. We adjusted for maternal age at conception (<20, 20-24, 25-29, 30-34, ≥35), and if possible also for calendar time (year of conception) and gender of the infant. Analyses for specific congenital anomalies were performed when > 3 cases were observed. The t-test or Fisher exact test was used to derive p-values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided p-values <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203,962 pregnancies corresponding to 208,161 fetuses (including multiple births) were included in our study. The mean maternal

age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days).

Isotretinoin dispensings

A total of 416 isotretinoin dispensings to 130 of the 203,962 women in the 12-months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of > 30 days of isotretinoin use. Figure 1 shows that the percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Isotretinoin exposed pregnancies

Demographics for isotretinoin exposed and unexposed pregnancies are presented in table 1.

Table 1: Description of the study population

	Isotretinoin exposed*	Isotretinoin unexposed	*p-value*
Pregnancies (N=203,962)	51	203,911	
Mean (±SD) maternal age at conception in years (95% CI)	29.1 (4.9) (27.8 – 30.5)	30.3 (4.7) (30.3 – 30.3)	0.56
Mean (±SD) gestational age at delivery in weeks (95% CI)	39 (25 days) (38 – 40)	39, 3 days (19 days) (39, 3 days – 39, 3 days)	0.33
Fetuses (N=208,161)	53	208,108	
Gender (boy %)	47.2% (33.3 – 61.1)	51.5% (51.3 – 51.7)	0.53
Maternal age at conception in years, N, column %.			0.37
< 20 years of age	2 (3.8%)	4,063 (2.0%)	
≥ 20 -25 years of age	7 (13.2%)	22,144 (10.6%)	
≥ 25 -30 years of age	21 (39.6%)	68,366 (32.9%)	
≥ 30 -35 years of age	14 (26.4%)	81,581 (39.2%)	
≥ 35 years of age	9 (17.0%)	31,951 (15.4%)	
Gestational age at delivery, N, column %.			0.64
< 27 weeks	1 (1.9%)	2,198 (1.1%)	
27 - 30 weeks	1 (1.9%)	1,167 (0.6%)	
31-33 weeks	0 (0.0%)	2,008 (1.0%)	
34-36 weeks	3 (5.7%)	7,126 (3.4%)	
37-39 weeks	12 (22.6%)	50,854 (24.4%)	
> 39 weeks	36 (67.9%)	144,755 (69.5%)	
Adverse fetal outcome, N; % (95% CI)	5; 9.4% (1.3 – 17.6)	9,041; 4.3% (4.3 – 4.4)	0.08

*in the 30 days before conception or during pregnancy

Overall, 51 pregnancies, 2.5 (95% CI 1.9 to 3.3) per 10,000 pregnancies, were potentially exposed to isotretinoin in the 30 days before conception or during pregnancy, despite the implemented pregnancy prevention programme. Forty-five pregnant women, 2.2 (95% CI 1.6 – 2.9) per 10,000 pregnancies, were estimated to be exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six pregnancies were identified within one month after isotretinoin discontinuation and were estimated to be exposed only before conception. In 40 out of 203,962 pregnancies, 2.0 (95% CI 1.4 – 2.6) per 10,000 pregnancies, an isotretinoin prescription was filled during pregnancy and 32 pregnancies, 1.6 (95% CI 1.1 – 2.2) per 10,000 pregnancies, received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings per pregnancy ranged from 1 to 7, with a median of 2.5. The estimated isotretinoin exposure per exposure interval is presented in table 2.

Table 2: Potential isotretinoin exposed pregnancies per exposure interval

Isotretinoin exposure interval*	Exposed pregnancies (N=203,962)	Exposed pregnancies per 10,000 pregnancies (95% CI)	Median number of days exposed per pregnancy (range)
30 days before conception (30 days period)	23	1.1 (0.7 – 1.7)	24 (range 3 – 30)
1st trimester (90 days period)	28	1.4 (0.9 – 2.0)	31 (range 3 – 88)
2nd trimester (90 days period)	25	1.2 (0.8 – 1.8)	57 (range 1 – 90)
3rd trimester (90-103 days period)	26	1.3 (0.9 – 1.8)	62 (range 1 – 103)
During pregnancy (270 days period)	45	2.2 (1.6 – 2.9)	63 (range 3 – 236)
30 days before or during pregnancy (300 days period)	51	2.5 (1.9 – 3.3)	63 (range 7 – 236)
30 days before or during 1st trimester (120 days period)	35	1.7 (1.2 – 2.4)	32 (range 7 – 114)

CI=Confidence interval.
*Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that exposure interval

Among the pregnancies estimated to be exposed to isotretinoin during pregnancy (N=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. Figure 2 shows that the number of women estimated to be exposed to isotretinoin during pregnancy was the highest in 2006 with 3.5 pregnancies (95% CI 1.7 – 6.4) per 10,000 pregnancies.

Adverse fetal or neonatal outcomes

Independent of isotretinoin exposure, adverse fetal or neonatal outcomes were observed for 9,046 of the 208,161 fetuses (4.4% [95% CI 4.3 – 4.4]). The 51 pregnancies potentially exposed to isotretinoin in 30 days before conception or during pregnancy corresponded to 53 fetuses or neonates including two multiple births. Five of these, all singletons, had an adverse fetal or neonatal outcome (9.4% [95% CI 3.5 – 19.7]). These included three intrauterine deaths and two live born infants with major congenital anomalies (see table 3). Among those potentially exposed during pregnancy only (N=47), 6.4% (95% CI 1.7 – 16.4) had an adverse fetal or neonatal outcome. The odds ratio (OR) for adverse fetal or neonatal outcome after potential isotretinoin exposure in the 30 days before or during pregnancy was 2.3 (95% CI 0.9 – 5.7) after adjustment for maternal age (see table 3). Restricting the analysis to the potential isotretinoin exposure during pregnancy, the adjusted OR of an adverse fetal outcome was 1.5 (95% CI 0.5 – 4.8). The number of cases was too low to allow for adjustments in addition to maternal age. The adjusted OR of any fetal or neonatal outcome was significantly increased at 3.6 (95% CI 1.4 – 9.4) for isotretinoin exposure during the 30 days before or first trimester of pregnancy.

Table 3: Odds ratios for adverse fetal and neonatal outcomes and isotretinoin exposure in 30 days before or during pregnancy

Isotretinoin exposed fetuses	Exposed fetuses with adverse outcomes	OR (95% CI)	Adjusted OR* (95% CI)
During pregnancy (N=47)	3†	1.5 (0.5 – 4.8)	1.5 (0.5 – 4.8)
30 days before or during pregnancy (N=53)	5†‡	2.3 (0.9 – 5.8)	2.3 (0.9 – 5.7)
30 days before or 1st trimester (N=35)	5†‡	3.7 (1.4 – 9.5)	3.6 (1.4 – 9.4)

CI=confidence interval

* maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)

† Includes three intrauterine deaths.

1) in week 19, potentially exposed first 29 days following conception.
2) in week 35, potentially exposed 10 weeks following conception and from week 18 until week 32.
3) in week 38, also reported an unspecified septal defect; potentially exposed first 8 days following conception, during week 12 until week 24 and during week 28 until week 38.

‡ Includes two live born infants with major congenital anomalies.

1) Neural tube defect, potentially exposed all 30 days before conception, not after conception.
2) Major congenital anomaly not further specified, potentially exposed the first 15 days of the 30 days before conception, not after conception.

DISCUSSION

This study shows that 2 per 10,000 pregnancies were exposed to isotretinoin despite the PPP which is implemented to prevent isotretinoin use during pregnancy. Although this study was not intended to estimate

the teratogenic risks of isotretinoin, adverse fetal and neonatal outcomes potentially related to isotretinoin exposure were observed. That there are still women who are using isotretinoin during pregnancy despite the implementation of the PPP is of major concern. Especially since the majority of isotretinoin exposed women (60%) were already pregnant at the time of first isotretinoin prescription and it seems that pregnancy was not always excluded before isotretinoin dispensing (box 1). These exposed pregnancies could probably have been prevented when appropriate pregnancy testing would have been performed. Furthermore, it was earlier demonstrated that women of reproductive age treated with isotretinoin did not always use effective contraceptive measures because only up to 59% of these women concomitantly used hormonal contraceptives.[8 9] Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days, which however decreased from 50% in 1999 to 13% in 2007. Based on these findings it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. Limited compliance with the PPP was also observed in a survey among Dutch pharmacists which indicated that in 2007 and 2011, 44% and 49% of pharmacists respectively checked the use of contraception at every isotretinoin dispensing.[14] The percentage of pharmacists that asked for negative pregnancy tests was stable with 15% and 16% respectively and is in line with our study which demonstrated that pregnancy is not always excluded before initiating isotretinoin and result in isotretinoin exposed pregnancies that could have been prevented. Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days which however decreased from 50% in 1999 to 13% in 2007. Based on these results it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP, especially since isotretinoin is mostly used in young women of reproductive age.

Previous studies on isotretinoin use during pregnancy in other Western countries showed comparable results indicating that limited compliance to the PPP is not restricted to the Netherlands.[6 15-17] In the United States (US), the most recent isotretinoin PPP, called iPLEDGE, has been implemented since 2006 and is stricter than the EU PPP. iPLEDGE is an internet-based system that requires registration of all stakeholders with monthly updates on prescription, pregnancy tests, contraceptive use, and acknowledgement of risks.[17] The pregnancy rate among isotretinoin users in the US with the iPLEDGE PPP was estimated at 2.7 per 1,000 treatment courses and did not change compared to the previous PPP called SMART (System to Manage Accutane Related

Teratogenicity) while only small improvements in compliance with contraceptive measures were observed.[17 18] Apparently, also iPLEDGE does not bring complete security because further restrictive measures as in iPLEDGE do not seem to improve the results and may add unnecessary burden to the healthcare system since healthcare professionals and patients need to register and verify information on a monthly basis.[4]

Strengths and weaknesses of the study

A strength of this study is that we used a population based design including virtually complete and detailed drug dispensing data and pregnancy outcome data of a large cohort, which enabled estimating nationwide isotretinoin exposure rates among pregnant women. A known limitation of using drug dispensing data is that it does not confirm the actual use of the drug under study and does not provide information on the precise time window of drug use. In addition, it is likely that women may change or stop their medication use when they become aware of pregnancy. However, it should be noted that our data show that the majority (80%) of pregnant women who filled prescriptions for isotretinoin came back for refills, suggesting that they really used the drug.

This study provides no information on spontaneous abortions that occurred until gestational age of 16 weeks and ETOPs because these data are not captured in the PRN database and these pregnancies were thus not included in our cohort. This resulted in an underestimation of the number of pregnancies that were potentially exposed to isotretinoin in the 30 days before or during pregnancy and the adverse fetal and neonatal outcomes. Studies that estimated the teratogenic risk of isotretinoin using prospectively documented isotretinoin exposed pregnancies found much higher proportions of pregnancies resulting in spontaneous abortion, stillbirth or reported congenital malformations i.e. 36% (13 of the 36 fetuses)[3] and 26% (6 of the 23 fetuses)[5].

Without detailed information on drug exposure preferably verified by the patient whether the drug was actually taken and detailed descriptions of the diagnosed fetal outcome as well as on spontaneous abortions, the teratogenic risk of isotretinoin could not be accurately estimated. With regard to the adverse fetal outcomes observed in our study, we cannot exclude that they had an other aetiology than isotretinoin exposure. Due to the low number of cases it was also not possible to adjust in the statistical analysis for important confounding factors other than maternal age such as smoking, alcohol intake, previous pregnancy outcomes and exposure to other potentially teratogenic drugs. Detection bias may also have influenced the

incidence and estimated risks of congenital anomalies since more detailed diagnostics might have been used in pregnancies exposed to isotretinoin compared to the unexposed pregnancies. Nevertheless, the results of our study are in line with the undisputed embryotoxicity of isotretinoin and suggestive of an increased risks of adverse fetal or neonatal events when isotretinoin is dispensed for use in the 30 days period before or during pregnancy.

Implications and future research

In the Netherlands, approximately 180,000 pregnancies are reported annually.[19] When extrapolating the 2.2 (95% CI 1.6 – 2.9) per 10,000 women potentially exposed to isotretinoin during pregnancy to a national level, there would be 29 to 52 isotretinoin-exposed pregnancies per year yielding unnecessary risks for congenital anomalies and fetal deaths. Therefore, it is in the interest of public health to implement effective PPPs and improve these measures or their compliance as much as possible to reduce isotretinoin use during pregnancy to the lowest possible level.

With the present study only the period 1999 to 2007 has been evaluated. The past years in the Netherlands, the PPP is communicated to healthcare professionals via product information,[20] national general practitioner (GP) standards on treatment of acne,[21] drug prescription and dispensing systems,[22] the website of the Dutch Medicines Evaluation Board,[23] and the common (national) literature on drug information.[24] Furthermore, research on isotretinoin use in the Netherlands and the PPP is conducted and published in (inter)national scientific medical journals.[7-9 14 25-28] Consequently, data after 2007 are needed to judge if attention for the isotretinoin PPP during recent years has improved the carefulness with which isotretinoin is prescribed and dispensed.

Conclusions

Although a PPP was implemented almost 15 years ago, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands which could have been prevented if appropriate exclusion of pregnancy before isotretinoin initiation would have been performed. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

FIGURE LEGENDS

Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days by calendar year

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies by calendar year

——— Exposed to isotretinoin in 30 days before or during pregnancy

– – – – Exposed to isotretinoin during pregnancy

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Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that LH and RH are employees of the PHARMO Institute. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. MS is leading a research group that sometimes conducts research for pharmaceutical companies. None related to the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Details of contributors Each author participated actively and sufficiently in this study. IZ, RR, LH, MS and BS contributed to the study design and the interpretation of the data. IZ and LH collected and analysed the data. IZ, RR, LH, RH, MS, SS and BS participated in the development and critical review of the manuscript for important intellectual content and provided final approval of the version to be published. A statement that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval Not applicable. The research team did not have access to medical records.

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Data sharing No additional data available.

Transparency The lead author (IZ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Isotretinoin exposure during pregnancy: a population-based study in the Netherlands

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ABSTRACT

Objective To estimate isotretinoin exposure in Dutch pregnant women despite the implemented pregnancy prevention programme (PPP) and secondly, to analyse the occurrence of adverse fetal or neonatal outcomes in these isotretinoin exposed pregnancies.

Design Population based study

Setting the Netherlands

Participants a cohort of 203,962 pregnancies with onset between 1 January 1999 and 1 September 2007 consisting of 208,161 fetuses or neonates.

Main outcome measures Isotretinoin exposure in the 30 days before or during pregnancy. Proportions of adverse fetal or neonatal outcomes, defined as intrauterine deaths ≥ 16 week of gestation and neonates with major congenital anomalies. Odds ratios (ORs) with 95% confidence intervals (CI) adjusted for maternal age were calculated to estimate the risk of adverse fetal or neonatal outcome after maternal isotretinoin exposure.

Results 51 pregnancies, 2.5 (95%CI 1.9 to 3.3) per 10,000 pregnancies, were exposed to isotretinoin despite the pregnancy prevention programme. 45 of these pregnancies, 2.2 (95%CI 1.6 to 2.9) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy and six additional women became pregnant within 30 days after isotretinoin discontinuation. In sixty percent of isotretinoin exposed pregnancies, women started isotretinoin while already pregnant. In five out of the 51 isotretinoin exposed pregnancies, 9.4% (95%CI 1.3 to 17.6), had an adverse fetal or neonatal outcome. The OR for adverse fetal or neonatal outcomes after isotretinoin exposure in 30 days before or during pregnancy was 2.3 (95%CI 0.9 to 5.7) after adjustment for maternal age.

Conclusions Although a PPP was already implemented in 1988, we showed that isotretinoin exposed pregnancies ~~in the Netherlands~~ and adverse fetal and neonatal events potentially related to the exposure still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based study in the EU on isotretinoin exposure during pregnancy in a large cohort of more than 200,000 pregnancies which enabled estimating isotretinoin exposure rates among pregnant women and its consequences on a nationwide scale.
- From the virtually complete and detailed drug dispensing data, isotretinoin exposure could only be estimated since drug dispensing data does not ascertain actual drug use and precise exposure intervals. However, patients coming for refills are usually taking their drug.
- Spontaneous abortions before gestational age of 16 weeks and elective abortions were not included in our cohort and therefore our results probably underestimate the number of isotretinoin exposed pregnancies and its consequences.
- ~~The analysis was restricted to adverse fetal and neonatal outcomes in general since S~~specific teratogenic risks could not be estimated with data lacking information on pregnancies until 16 weeks of gestation and lacking detailed descriptions of adverse fetal and neonatal outcomes.

INTRODUCTION

Isotretinoin, a vitamin A derivative, is licensed in the European Union (EU) since 1983 and is indicated for systemic treatment of severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) in patients resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.[1] The teratogenic potential is an important characteristic of isotretinoin. Animal studies already suggested teratogenic effects in humans and isotretinoin has been contraindicated for use during pregnancy since the very beginning of the marketing authorisation. Despite this contraindication, the first cases of congenital anomalies after isotretinoin use during pregnancy were documented already in 1983.[2] As described by Lammer et al. in 1985, isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects.[3] They found a relative risk of 26 for this group of major congenital malformations after systemic isotretinoin exposure during some parts of the first 10 weeks after conception.[3] Elective termination of pregnancy (ETOP) was decided in more than 50% of exposed pregnancies and 20% of the remaining pregnancies ended in a first trimester spontaneous abortion.[3] Reports of congenital anomalies after isotretinoin use accumulated and consequently, in 1988 the marketing authorisation holder of isotretinoin implemented a world-wide Pregnancy Prevention Programme (PPP) to better prevent pregnancies among systemic isotretinoin users.[4] The PPP included an educational programme for prescribers and patients including material to be used in counselling women about the need to prevent pregnancy while taking isotretinoin. Conditions for prescribing included a negative pregnancy test, the use of reliable contraception and a signed patient consent form.[4] In 2003, a review of isotretinoin by the European Medicine Agency (EMA) resulted in a compulsory European harmonised PPP for all isotretinoin containing products.[1] The elements of the European wide PPP are listed in box 1.

Box 1: Elements of the EU isotretinoin PPP

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up
2. Use of effective contraceptive measures from four weeks before isotretinoin initiation until four weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.
3. Pregnancy testing should be done before, during and five weeks after discontinuation of isotretinoin
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of seven days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the PPP.

The safe use of isotretinoin in women of reproductive age is in the interest of public health because of the potential risk of spontaneous and elective abortions, and, more importantly, children with major congenital anomalies require continuous healthcare throughout their life. Although a PPP has been implemented in the EU, pregnancies during isotretinoin therapy still occur.[5 6] The regulatory authorities of sixteen EU member states responded in 2009 to a survey that isotretinoin exposed pregnancies have occurred in their country.[7] A French study between 2003 and 2006 estimated a pregnancy rate from 0.4 to 1.2 per 1000 female isotretinoin users within reproductive age.[6] Studies in the Netherlands observed that only 52% to 59% of the female isotretinoin users of reproductive age used concomitant hormonal contraceptives, which was higher than the 39%-46% observed in the general female population of similar age, but lower than anticipated.[8 9] Although these studies show limited compliance with the isotretinoin PPP, it is not known whether isotretinoin exposure also occurs during pregnancy and what the outcome of these pregnancies is. Therefore, the objective of our study was to estimate isotretinoin exposure in Dutch pregnant women despite the implemented PPP and secondly, to analyse the occurrence of adverse fetal and neonatal outcomes in these isotretinoin exposed pregnancies.

METHODS

Data sources

For this population based study a cohort of 203,962 pregnancies consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort including, amongst other information, drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) that are collected since 1986.[10] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[11] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[12] The registry contains information about care before, during, and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The PRN includes information on pregnancy outcome including congenital anomalies

detected during pregnancy, at birth or within the first year after birth. The probabilistic linking method between PHARMO and PRN has been described in detail elsewhere but was generally based on the birth date of the mother and child and their postal zip codes.[13] To be included in the cohort the mother should be registered in the community pharmacy database of PHARMO during the whole pregnancy. The date of conception was estimated based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

Isotretinoin dispensings

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in our cohort within the 12-months period before or during pregnancy were extracted from the PHARMO Database Network. Considering a daily dosage of 0.5 mg-1mg per kilogram daily,[1] isotretinoin prescriptions dispensed on the same day were assumed to be used simultaneously and therefore these dispensings were pooled and considered as one dispensing (e.g. the prescriptions of a 10 mg and 20 mg tablets dispensed at the same time to reach a daily dosage of 30mg). For each isotretinoin dispensing, the length of the dispensing was calculated by dividing the total number of prescribed units by the number of units (doses) to be taken per day. In case isotretinoin dispensings that were pooled together had different lengths, the length of the single dispensing with the longest duration was used. To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

Drug exposure interval

For all pregnancies (N=203,962) with of gestational age of at least 16 weeks included in the cohort, isotretinoin exposure was estimated based on isotretinoin dispensing data (ATC D10BA01) filled by the mother during the 12-months period before and during pregnancy. Exposure in person time (days) was calculated by dividing the total number of prescribed units by the number of prescribed units per day. Isotretinoin exposure periods were defined considering a possible overlap of isotretinoin dispensings. Gaps, isotretinoin free periods between two isotretinoin dispensings, were not permitted meaning that an isotretinoin exposure period ends once an isotretinoin free period was identified. Using the start and end date of the isotretinoin exposure period, the number of days exposed was estimated for the following exposure intervals: 30 days before conception, first 90 days of gestation (first trimester), day 90-179 of gestation (second trimester) and day 180 – delivery (third

trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

Adverse fetal or neonatal outcomes

For each fetus (N=208,161), we determined whether adverse fetal or neonatal outcomes were reported. Adverse fetal or neonatal outcomes were defined as all intrauterine deaths ≥ 16 week of gestation and live born infants with major congenital anomalies. If possible, congenital anomalies were categorised into nine sub-groups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. As we were interested in adverse fetal outcomes potentially induced by maternal drug exposure, chromosomal anomalies were not considered as an adverse outcome in the analyses.

Analysis

Potential exposure to isotretinoin in the 30 days before or during pregnancy was calculated per 10,000 pregnancies for the aforementioned exposure intervals including their 95% confidence intervals (95% CIs). The proportions of adverse fetal outcome among isotretinoin exposed and unexposed fetuses or neonates were calculated including their 95% CIs. We used multiple logistic regression models to calculate odds ratios (ORs) and 95% CIs to estimate associations between adverse fetal or neonatal outcome and maternal isotretinoin exposure. We adjusted for maternal age at conception (<20, 20-24, 25-29, 30-34, ≥35), and if possible also for calendar time (year of conception) and gender of the infant. Analyses for specific congenital anomalies were performed when > 3 cases were observed. The t-test or Fisher exact test was used to derive p-values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided p-values <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203,962 pregnancies corresponding to 208,161 fetuses (including multiple births) were included in our study. The mean maternal

age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days).

Isotretinoin dispensings

A total of 416 isotretinoin dispensings to 130 of the 203,962 women in the 12-months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of > 30 days of isotretinoin use. Figure 1 shows that the percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Isotretinoin exposed pregnancies

Demographics for isotretinoin exposed and unexposed pregnancies are presented in table 1.

Table 1: Description of the study population

	Isotretinoin exposed*	Isotretinoin unexposed	*p-value*
Pregnancies (N=203,962)	51	203,911	
Mean (±SD) maternal age at conception in years (95% CI)	29.1 (4.9) (27.8 – 30.5)	30.3 (4.7) (30.3 – 30.3)	0.56
Mean (±SD) gestational age at delivery in weeks (95% CI)	39 (25 days) (38 – 40)	39, 3 days (19 days) (39, 3 days – 39, 3 days)	0.33
Fetuses (N=208,161)	53	208,108	
Gender (boy %)	47.2% (33.3 – 61.1)	51.5% (51.3 – 51.7)	0.53
Maternal age at conception in years, N, column %.			0.37
< 20 years of age	2 (3.8%)	4,063 (2.0%)	
≥ 20 -25 years of age	7 (13.2%)	22,144 (10.6%)	
≥ 25 -30 years of age	21 (39.6%)	68,366 (32.9%)	
≥ 30 -35 years of age	14 (26.4%)	81,581 (39.2%)	
≥ 35 years of age	9 (17.0%)	31,951 (15.4%)	
Gestational age at delivery, N, column %.			0.64
< 27 weeks	1 (1.9%)	2,198 (1.1%)	
27 - 30 weeks	1 (1.9%)	1,167 (0.6%)	
31-33 weeks	0 (0.0%)	2,008 (1.0%)	
34-36 weeks	3 (5.7%)	7,126 (3.4%)	
37-39 weeks	12 (22.6%)	50,854 (24.4%)	
> 39 weeks	36 (67.9%)	144,755 (69.5%)	
Adverse fetal outcome, N; % (95% CI)	5; 9.4% (1.3 – 17.6)	9,041; 4.3% (4.3 – 4.4)	0.08

*in the 30 days before conception or during pregnancy

Overall, 51 pregnancies, 2.5 (95% CI 1.9 to 3.3) per 10,000 pregnancies, were potentially exposed to isotretinoin in the 30 days before conception or during pregnancy, despite the implemented pregnancy prevention programme. Forty-five pregnant women, 2.2 (95% CI 1.6 – 2.9) per 10,000 pregnancies, were estimated to be exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six pregnancies were identified within one month after isotretinoin discontinuation and were estimated to be exposed only before conception. In 40 out of 203,962 pregnancies, 2.0 (95% CI 1.4 – 2.6) per 10,000 pregnancies, an isotretinoin prescription was filled during pregnancy and 32 pregnancies, 1.6 (95% CI 1.1 – 2.2) per 10,000 pregnancies, received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings per pregnancy ranged from 1 to 7, with a median of 2.5. The estimated isotretinoin exposure per exposure interval is presented in table 2.

Table 2: Potential isotretinoin exposed pregnancies per exposure interval

Isotretinoin exposure interval*	Exposed pregnancies (N=203,962)	Exposed pregnancies per 10,000 pregnancies (95% CI)	Median number of days exposed per pregnancy (range)
30 days before conception (30 days period)	23	1.1 (0.7 – 1.7)	24 (range 3 – 30)
1st trimester (90 days period)	28	1.4 (0.9 – 2.0)	31 (range 3 – 88)
2nd trimester (90 days period)	25	1.2 (0.8 – 1.8)	57 (range 1 – 90)
3rd trimester (90-103 days period)	26	1.3 (0.9 – 1.8)	62 (range 1 – 103)
During pregnancy (270 days period)	45	2.2 (1.6 – 2.9)	63 (range 3 – 236)
30 days before or during pregnancy (300 days period)	51	2.5 (1.9 – 3.3)	63 (range 7 – 236)
30 days before or during 1st trimester (120 days period)	35	1.7 (1.2 – 2.4)	32 (range 7 – 114)

CI=Confidence interval.
*Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that exposure interval

Among the pregnancies estimated to be exposed to isotretinoin during pregnancy (N=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. Figure 2 shows that the number of women estimated to be exposed to isotretinoin during pregnancy was the highest in 2006 with 3.5 pregnancies (95% CI 1.7 – 6.4) per 10,000 pregnancies.

Adverse fetal or neonatal outcomes

Independent of isotretinoin exposure, adverse fetal or neonatal outcomes were observed for 9,046 of the 208,161 fetuses (4.4% [95% CI 4.3 – 4.4]). The 51 pregnancies potentially exposed to isotretinoin in 30 days before conception or during pregnancy corresponded to 53 fetuses or neonates including two multiple births. Five of these, all singletons, had an adverse fetal or neonatal outcome (9.4% [95% CI 3.5 – 19.7]). These included three intrauterine deaths and two live born infants with major congenital anomalies (see table 3). Among those potentially exposed during pregnancy only (N=47), 6.4% (95% CI 1.7 – 16.4) had an adverse fetal or neonatal outcome. The odds ratio (OR) for adverse fetal or neonatal outcome after potential isotretinoin exposure in the 30 days before or during pregnancy was 2.3 (95% CI 0.9 – 5.7) after adjustment for maternal age (see table 3). Restricting the analysis to the potential isotretinoin exposure during pregnancy, the adjusted OR of an adverse fetal outcome was 1.5 (95% CI 0.5 – 4.8). The number of cases was too low to allow for adjustments in addition to maternal age. The adjusted OR of any fetal or neonatal outcome was significantly increased at 3.6 (95% CI 1.4 – 9.4) for isotretinoin exposure during the 30 days before or first trimester of pregnancy.

Table 3: Odds ratios for adverse fetal and neonatal outcomes and isotretinoin exposure in 30 days before or during pregnancy

Isotretinoin exposed fetuses	Exposed fetuses with adverse outcomes	OR (95% CI)	Adjusted OR* (95% CI)
During pregnancy (N=47)	3†	1.5 (0.5 – 4.8)	1.5 (0.5 – 4.8)
30 days before or during pregnancy (N=53)	5†‡	2.3 (0.9 – 5.8)	2.3 (0.9 – 5.7)
30 days before or 1st trimester (N=35)	5†‡	3.7 (1.4 – 9.5)	3.6 (1.4 – 9.4)

CI=confidence interval
* maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)
† Includes three intrauterine deaths.
1) in week 19, potentially exposed first 29 days following conception.
2) in week 35, potentially exposed 10 weeks following conception and from week 18 until week 32.
3) in week 38, also reported an unspecified septal defect; potentially exposed first 8 days following conception, during week 12 until week 24 and during week 28 until week 38.
‡ Includes two live born infants with major congenital anomalies.
1) Neural tube defect, potentially exposed all 30 days before conception, not after conception.
2) Major congenital anomaly not further specified, potentially exposed the first 15 days of the 30 days before conception, not after conception.

DISCUSSION

This study shows that 2 per 10,000 pregnancies were exposed to isotretinoin despite the PPP which is implemented to prevent isotretinoin use during pregnancy. Although this study was not intended to estimate

the teratogenic risks of isotretinoin, adverse fetal and neonatal outcomes potentially related to isotretinoin exposure ~~among these exposed pregnancies~~ were observed. That there are still women who are using isotretinoin during pregnancy despite the implementation of the PPP is of major concern. Especially since the majority of isotretinoin exposed women (60%) were already pregnant at the time of first isotretinoin prescription and it seems that pregnancy was not always excluded before isotretinoin dispensing (box 1). These exposed pregnancies could probably have been prevented when appropriate pregnancy testing would have been performed. Furthermore, it was earlier demonstrated that women of reproductive age treated with isotretinoin did not always use effective contraceptive measures because only up to 59% of these women concomitantly used hormonal contraceptives.[8 9] Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days, which however decreased from 50% in 1999 to 13% in 2007. Based on these findings it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. Limited compliance with the PPP was also observed in a survey among Dutch pharmacists which indicated that in 2007 and 2011, 44% and 49% of pharmacists respectively checked the use of contraception at every isotretinoin dispensing.[14] The percentage of pharmacists that asked for negative pregnancy tests was stable with 15% and 16% respectively and is in line with our study which demonstrated that pregnancy is not always excluded before initiating isotretinoin and result in isotretinoin exposed pregnancies that could have been prevented. Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one third of isotretinoin dispensings exceeded 30 days which however decreased from 50% in 1999 to 13% in 2007. Based on these results it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP, especially since isotretinoin is mostly used in young women of reproductive age.

Previous studies on isotretinoin use during pregnancy in other Western countries showed comparable results indicating that limited compliance to the PPP is not restricted to the Netherlands.[6 15-17] In the United States (US), the most recent isotretinoin PPP, called iPLEDGE, has been implemented since 2006 and is stricter than the EU PPP. iPLEDGE is an internet-based system that requires registration of all stakeholders with monthly updates on prescription, pregnancy tests, contraceptive use, and acknowledgement of risks.[17] The pregnancy rate among isotretinoin users in the US with the iPLEDGE PPP was estimated at 2.7 per 1,000 treatment

courses and did not change compared to the previous PPP called SMART (System to Manage Accutane Related Teratogenicity) while only small improvements in compliance with contraceptive measures were observed.[17 18] Apparently, also iPLEDGE does not bring complete security because further restrictive measures as in iPLEDGE do not seem to improve the results and may add unnecessary burden to the healthcare system since healthcare professionals and patients need to register and verify information on a monthly basis.[4]

Strengths and weaknesses of the study

A strength of this study is that we used a population based design including virtually complete and detailed drug dispensing data and pregnancy outcome data of a large cohort, which enabled estimating nationwide isotretinoin exposure rates among pregnant women. A known limitation of using drug dispensing data is that it does not confirm the actual use of the drug under study and does not provide information on the precise time window of drug use. In addition, it is likely that women may change or stop their medication use when they become aware of pregnancy. However, it should be noted that our data show that the majority (80%) of pregnant women who filled prescriptions for isotretinoin came back for refills, suggesting that they really used the drug.

This study provides no information on spontaneous abortions that occurred until gestational age of 16 weeks and ETOPs because these data are not captured in the PRN database and these pregnancies were thus not included in our cohort. This resulted in an underestimation of the number of pregnancies that were potentially exposed to isotretinoin in the 30 days before or during pregnancy and the adverse fetal and neonatal outcomes. Studies that estimated the teratogenic risk of isotretinoin using prospectively documented isotretinoin exposed pregnancies found much higher proportions of pregnancies resulting in spontaneous abortion, stillbirth or reported congenital malformations i.e. 36% (13 of the 36 fetuses)[3] and 26% (6 of the 23 fetuses)[5].

Without detailed information on drug exposure preferably verified by the patient whether the drug was actually taken and detailed descriptions of the diagnosed fetal outcome as well as on spontaneous abortions, the teratogenic risk of isotretinoin could not be accurately estimated. With regard to the adverse fetal outcomes observed in our study, we cannot exclude that they had an other aetiology than isotretinoin exposure. ~~However, the primary aim of this study was to show that adverse fetal and neonatal outcomes still occur in isotretinoin exposed pregnancies, despite the implemented PPP. Unfortunately, D~~due to the low

number of cases it was also not possible to adjust in the statistical analysis for important confounding factors other than maternal age such as smoking, alcohol intake, previous pregnancy outcomes and exposure to other potentially teratogenic drugs. Detection bias may also have influenced the incidence and estimated risks of congenital anomalies since more detailed diagnostics might have been used in pregnancies exposed to isotretinoin compared to the unexposed pregnancies. Nevertheless, the results of our study are in line with the undisputed embryotoxicity of isotretinoin and suggestive of an increased risks of adverse fetal or neonatal events when isotretinoin is dispensed for use in the 30 days period before or during pregnancy. ~~indicate that such events still occur despite the implemented PPP.~~

Implications and future research

In the Netherlands, approximately 180,000 pregnancies are reported annually.[19] When extrapolating the 2.2 (95% CI 1.6 – 2.9) per 10,000 women potentially exposed to isotretinoin during pregnancy to a national level, there would be 29 to 52 isotretinoin-exposed pregnancies per year yielding unnecessary risks for congenital anomalies and fetal deaths. Therefore, it is in the interest of public health to implement effective PPPs and improve these measures or their compliance as much as possible to reduce isotretinoin use during pregnancy to the lowest possible level.

With the present study only the period 1999 to 2007 has been evaluated. The past years in the Netherlands, the PPP is communicated to healthcare professionals via product information,[20] national general practitioner (GP) standards on treatment of acne,[21] drug prescription and dispensing systems,[22] the website of the Dutch Medicines Evaluation Board,[23] and the common (national) literature on drug information.[24] Furthermore, research on isotretinoin use in the Netherlands and the PPP is conducted and published in (inter)national scientific medical journals.[7-9 14 25-28] Consequently, data after 2007 are needed to judge if attention for the isotretinoin PPP during recent years has improved the carefulness with which isotretinoin is prescribed and dispensed.

Conclusions

Although a PPP was implemented almost 15 years ago, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands which could have been prevented if appropriate exclusion of pregnancy before isotretinoin initiation would have been performed. ~~Moreover, adverse fetal outcomes were reported among these pregnancies.~~ These findings from the Netherlands add to the evidence that there is no full compliance to

the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

FIGURE LEGENDS

Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days by calendar year

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies by calendar year

——— Exposed to isotretinoin in 30 days before or during pregnancy

– – – – Exposed to isotretinoin during pregnancy

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Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that LH and RH are employees of the PHARMO Institute. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. MS is leading a research group that sometimes conducts research for pharmaceutical companies. None related to the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Details of contributors Each author participated actively and sufficiently in this study. IZ, RR, LH, MS and BS contributed to the study design and the interpretation of the data. IZ and LH collected and analysed the data. IZ, RR, LH, RH, MS, SS and BS participated in the development and critical review of the manuscript for important intellectual content and provided final approval of the version to be published. A statement that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval Not applicable. The research team did not have access to medical records.

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Data sharing No additional data available.

Transparency The lead author (IZ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1: Percentage of isotretinoin dispensings exceeding the maximum duration of 30 days by calendar year

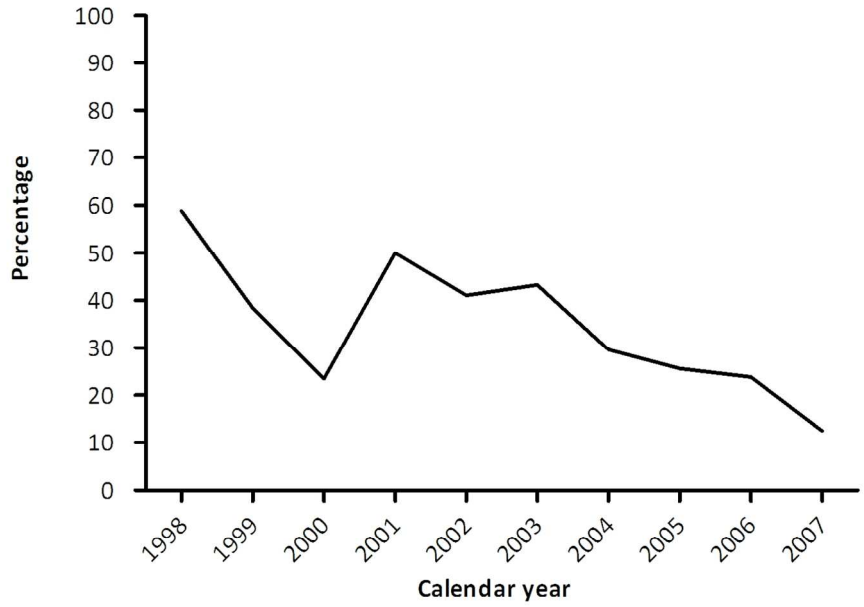

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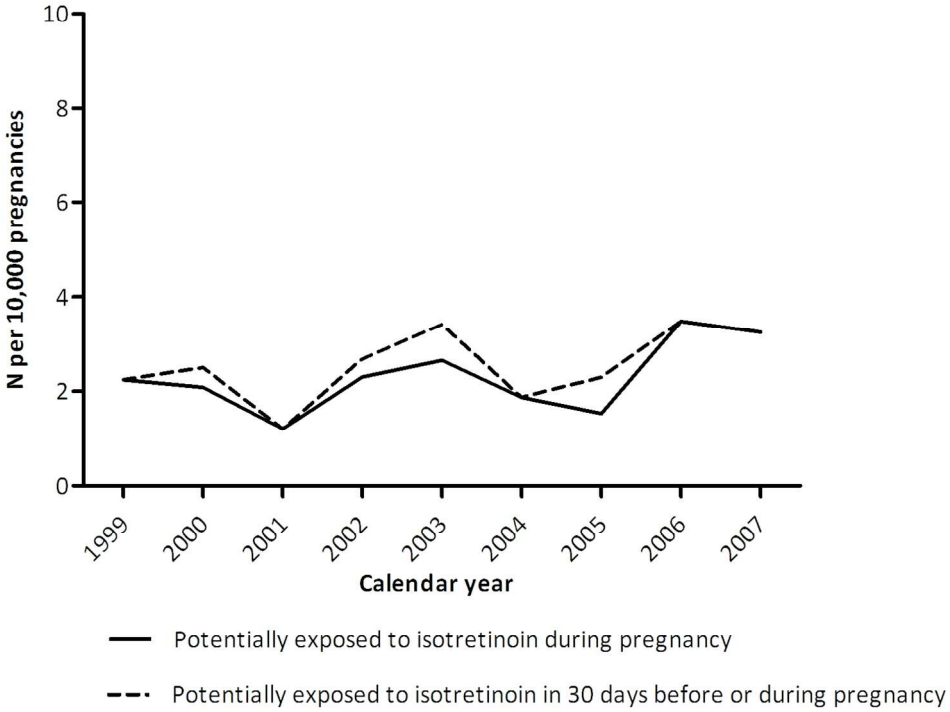
Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies by calendar year



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-78
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	6

Continued on next page

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8; (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure	9 (Table 2)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11; (Table 3)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11;(Table 3)
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.