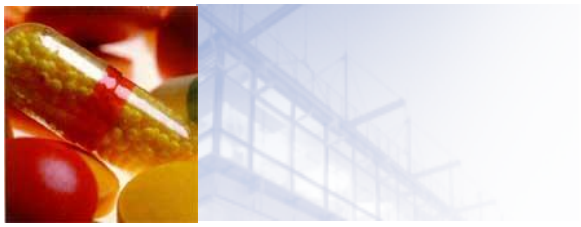

Isotretinoin and the effectiveness of the pregnancy prevention programme in Europe

Draft study report

July 2013

UNIVERSITY OF BATH

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1. Background / rationale

Isotretinoin is an effective pharmacological treatment for severe nodular acne vulgaris that is unresponsive to other, first-line therapies. However, it is highly teratogenic when used during the first trimester of pregnancy. Therefore, pregnancy prevention programs (PPPs) are in place across Europe, committing female isotretinoin users of childbearing potential to use at least two effective means of contraception just before, during, and immediately after isotretinoin use. Despite these PPPs, 'breakthrough' pregnancies still occur in females using isotretinoin.[1]

Research indicates that often, females are unaware of the requirement to use contraceptive measures when using isotretinoin[2] and the question arises as to why this should be the case. Thus far, no clear indications exist to suggest certain populations in Europe are at higher risk of failure to adhere to contraceptive advice given with isotretinoin prescriptions. One study from the Netherlands identified better adherence to the PPP when isotretinoin was prescribed by GPs than by dermatologists,[3] whereas another Dutch study suggested the opposite.[4] There was no indication of real differences in adherence between different age groups.[4]

This phenomenon observed with isotretinoin highlights the possibility that PPPs for other products may not be as effective as required. For PPPs in place with cancer treatments it could be argued the issue is less pressing than for acne treatment. However, more products with indications other than cancer are being introduced on the market that are teratogenic and for which PPPs will be introduced; a recent example being alitretinoin for severe chronic hand eczema refractory to corticosteroids.[5] To ensure efficacy of the PPPs, therefore, the question needs to be addressed as to what makes PPPs fail and what can be done to improve adherence to pregnancy prevention guidelines in users of teratogenic products who are of childbearing potential.

This document reports on the first two parts of a study carried out to achieve this.

2. Aims and objectives

2.1 Aims

1. To determine the prevalence of isotretinoin use in women of childbearing age.
2. To characterise the use of isotretinoin in terms of demographic and clinical characteristics of the treated population in Europe.
3. To estimate the risk of occurrence of pregnancies in women of childbearing age using isotretinoin and of factors associated with this risk.
4. To evaluate the main limiting and/or facilitating factors associated with the effectiveness of the PPP.
5. To provide practical recommendations for improving the effectiveness of PPPs in Europe.

2.2 Objectives addressed in this report

- To use data from population-based healthcare databases in the United Kingdom, Italy and Denmark (data from the Netherlands have already been published) to determine the prevalence of isotretinoin use in women of childbearing age.
- To use the databases to identify characteristics of isotretinoin users in terms of age, sex, comorbidity, socio-economic status, smoking status, alcohol use, body mass index, parity, gravidity and contraceptive history (oral as well as depot contraceptive preparations, emergency contraception, intra uterine devices, sterilisation, vasectomy of husband) where known as well as duration of use and the frequency of visits to their GP and to their dermatologist.
- To identify, within these databases, factors associated with a higher or lower likelihood of pregnancy occurrence such as age, socio-economic status, smoking status, alcohol use, pre-pregnancy body mass index, parity, gravidity, and contraceptive history (as above) as well as the frequency of visits to their GP and to their dermatologist where known.
- To update the literature review by Crijns *et al.* (2011) on Compliance with pregnancy prevention programmes of isotretinoin in Europe.

The update of the systematic literature review was subcontracted to the University of Groningen. For this reason, it is not incorporated in this document but it is submitted as a separate report (appendix I). The database studies are described below.

3. Methods

3.1 Study design and data sources

The study reported on in this document consisted of two main components

1. A drug utilisation study of isotretinoin use in women of childbearing age.
2. A risk assessment study to evaluate risk factors associated with a higher or lower likelihood of pregnancy occurrence in women of childbearing age using isotretinoin.

For the first two components, the most recent systematic literature review (by Crijns *et al*) was updated to include the literature up to April 2013. In addition, we set out to use data from four population-based healthcare databases:

A. The United Kingdom's General Practice Research Database, which contains longitudinal medical records collected within UK primary care.
B. The Secure Anonymised Information Databank (SAIL), which covers the population of Wales and contains hospital admissions and medical records collected in general practice.
C. Statistik Denmark, which contains data on virtually all pregnancies and community pharmacy data for the whole of Denmark
D. Italian databases covering the Emilia Romagna and Tuscany regions which contain administrative prescription claims data, hospital discharge data and data on all hospital births (~99% of all births) in the region.

Holders from all data sources agreed to participate in the study. However, following this agreement and upon protocol finalisation, for each data source, problems were encountered:

1) For the GPRD, no ISAC approval could be obtained because ISAC claimed the study was not feasible in the GPRD as a consequence of isotretinoin prescribing characteristics (often by consultant dermatologists rather than GPs) and incomplete recording of contraceptive practice in the GPRD. These issues had been recognised in advance by the study investigators (as indicated in the grant proposal) and it had been made clear to ISAC the study limitations would be highlighted in the final study report. However, ISAC could not be convinced. As a solution, the study was carried out as a feasibility study of the evaluation of predictors of PPP failure for isotretinoin.
2) Despite having monthly conference calls, four face to face meetings as well as regular communications via email, no ethics approval could be obtained in time for the SAIL database to be included in this study.
3) It transpired that the holders of the Danish data did not have data on all women of childbearing age in Denmark, but only on pregnant women. This precluded the evaluation of prevalence of use or risk factors for breakthrough pregnancies in the Danish population. As a consequence, the Danish colleagues decided the anticipated value of their contribution to the study was too low to merit their participation.
4) Despite having monthly conference calls, four face to face meetings as well as regular communications via email, no data could be obtained in time for the database from Tuscany to be included in this study. Data from Emilia Romagna were included and, recognising the fact that oral contraceptive prescribing is not necessarily recorded in the Italian databases, they were supplemented with data obtained by manual searches through hospital records.

This report therefore only includes data from the UK GPRD and the Emilia Romagna region in Italy.

3.2 Source population and study populations

Source population

The source population consisted of all individuals registered on one of the databases, for a minimum time period of 12 months, between 1 January 2004 and 31 December 2010. In addition, all women prescribed isotretinoin in the St Anna Ospedale dermatology clinic in

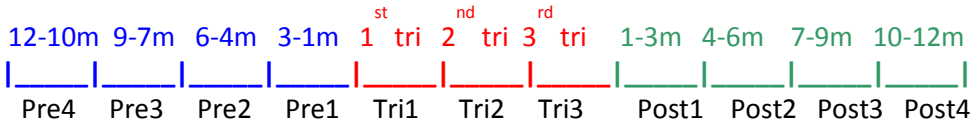
Emilia Romagna were identified and the hospital records searched manually. There was some, but incomplete overlap between the populations covered by the hospital clinic and the database in Emilia Romagna.

Study populations

- For the drug utilisation study the study population included all eligible individuals who had received ≥1 prescription for isotretinoin.
- For the risk factors of pregnancy study the study population included all females of child bearing age (11-50 years) who had received ≥1 prescription for isotretinoin.

3.3 Exposure definition and measurement

The exposure of interest was isotretinoin and exposure was defined as a record for ≥1 prescription for isotretinoin recorded in the relevant databases. For women who became pregnant during the study period, exposure was assessed during different time periods of interest:



3.4 Outcome definition and measurement

For the risk assessment component of the study the main outcome of interest was evidence of a pregnancy whilst being exposed to isotretinoin. The method of pregnancy identification was dependent on the country and database. For the United Kingdom all types of pregnancy outcome were identified (live births, stillbirths, spontaneous abortions and induced terminations). In Emilia Romagna only pregnancies resulting in a live birth or stillbirth could be captured.

3.5 Covariate definitions and measurement

Where available, information was collected on the following

- Age
- Sex
- Likely indication for isotretinoin prescribing
- Socio-economic status quintile
- Smoking status (non-smoker, smoker, ex-smoker, unknown)
- Alcohol use (teetotal, drinks alcohol, heavy/problem drinker, ex-drinker, unknown)
- BMI (≤19, 20-24, 25-29, 30-34, ≥35, unknown)
- Parity
- Gravidity
- Contraceptive history (oral as well as depot contraceptive preparations, emergency contraception, intra uterine devices, sterilisation, vasectomy of husband) where known as well as duration of use
- Frequency of visits to their GP
- Frequency of visits to their dermatologist

4. Analysis plan

- The prevalence of isotretinoin use in women of childbearing age was calculated separately for each country.
- The characteristics of isotretinoin users were described in terms of age, sex, comorbidity, socio-economic status, smoking status, alcohol use, body mass index, parity, gravidity and contraceptive history (oral as well as depot contraceptive preparations, emergency contraception, intra uterine devices, sterilisation, vasectomy of husband) where known as well as duration of use and the frequency of visits to their GP and to their dermatologist.
- The incidence of pregnancy among women of childbearing age using isotretinoin was calculated for each country separately.
- Characteristics of isotretinoin users who became pregnant were compared with those who did not in order to identify factors associated with a higher or lower likelihood of pregnancy. The number of breakthrough pregnancies identified was too low to allow for the evaluation of predictors of the risk of becoming pregnant in the isotretinoin user population through logistic regression.
- The literature review by Crijns *et al.* (2011) on compliance with pregnancy prevention programmes of isotretinoin in Europe was updated to include the published peer reviewed literature until April 2013.

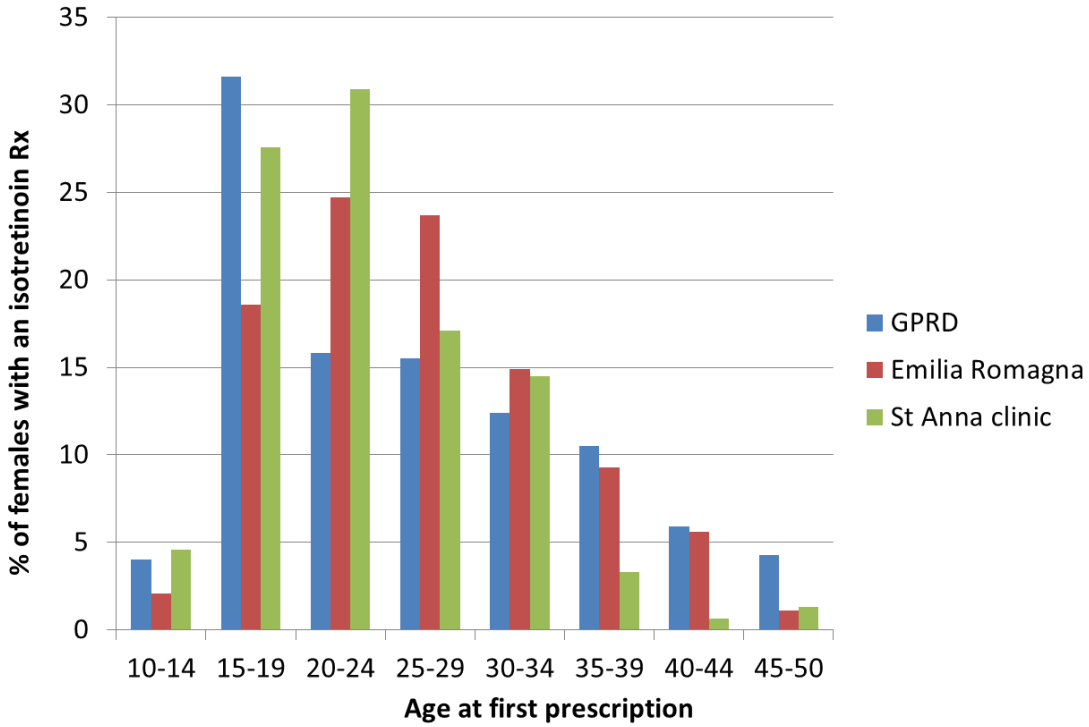
5. Results

In the GPRD, just under 1.8 million eligible women were identified; in Italy, at just under 900,000 the study population was about half the size. Prevalence of isotretinoin prescribing was 0.02% in the UK, compared with 0.7% in Italy. In the dermatology clinic, 152 women of childbearing age were identified who had been prescribed isotretinoin (Table 1). The study population in Emilia Romagna covered the entire region; in the GPRD the average amount of follow up before the first prescription was 8.2 years, with 85% of the study population having at least 3 years follow up before their first isotretinoin prescription. Age at first isotretinoin prescription in the different data sources is depicted in figure 1. As can be seen from this figure, females being prescribed isotretinoin in the UK were younger on average than in Italy.

Table 1. Isotretinoin prescribing prevalence

		GPRD		Emilia Romagna database		St Anna Ospedale dermatology clinic	
Source Population		1,768,602		860,900			
Number who received ≥ 1 prescription		323 (0.02%)		5,882 (0.7%)		152	
Number of prescriptions received		N	(%)	N	(%)	N	(%)
	1	140	(43.3)	133	(22.6)	Unknown	
	2	73	(22.6)	964	(16.4)	Unknown	
	3	28	(8.7)	900	(15.3)	Unknown	
	4	34	(10.5)	881	(15.0)	Unknown	
	5	11	(3.4)	632	(10.7)	Unknown	
	6	17	(5.3)	445	(7.6)	Unknown	
	>6	20	(6.0)	730	(12.4)	Unknown	

Figure 1. Age at first isotretinoin prescription in the different data sources



Further patient characteristics of females prescribed isotretinoin are provided in Table 2. From this Table it can be clearly seen that most information regarding patient characteristics was missing from the Italian data. Similarly, information regarding the indication for prescribing was not available from the Italian databases; according to the data from the dermatology clinic all 152 females had been prescribed isotretinoin for the treatment of acne. In the UK, 73.9% of prescriptions was for acne, for 24.1% no skin condition had been recorded as an indication and for the remaining prescriptions, the indications of hidradenitis suppurativa (1.9%) and other skin disorders (3.1%) were recorded. Of these, 10 cases had a concomitant diagnosis of acne.

Table 2. Characteristics of females prescribed isotretinoin

Status at time of first isotretinoin prescription		GPRD		Emilia Romagna		St Anna Ospedale Dermatology clinic	
Smoking status		N	(%)	N	(%)	N	(%)
	Non-smoker	209	(64.7)	-	-	-	-
	Current smoker	55	(17.0)	-	-	-	-
	Ex-smoker	46	(14.2)	-	-	-	-
	Unknown	13	(4.3)	-	-	-	-
Alcohol drinking status	Teetotal	45	(13.9)	-	-	-	-
	Drinks alcohol	159	(49.2)	-	-	-	-
	Heavy drinker	3	(0.9)	-	-	-	-
	Ex-drinker	9	(2.8)	-	-	-	-
	Unknown	107	(33.1)	-	-	-	-
Body mass index	<20	71	(22.0)	-	-	-	-
	20-24	136	(42.1)	-	-	-	-
	25-29	35	(10.8)	-	-	-	-
	30-34	15	(4.6)	-	-	-	-
	>34	8	(2.5)	-	-	-	-
	Unknown	58	(18.0)	-	-	-	-
Socio-economic status quintile	1 – least deprived	56	(17.3)	-	-	-	-
	2	60	(18.6)	-	-	-	-
	3	82	(25.4)	-	-	-	-
	4	82	(25.4)	-	-	-	-
	5 – most deprived	43	(13.3)	-	-	-	-

Contraceptive recording differed between the data sources, too. In the dermatology clinic, all females prescribed isotretinoin had notes in their records to confirm they used oral contraceptives. However, the records did not routinely capture prescription data. No information on contraceptive use was available from the Emilia Romagna database. In the UK GPRD, contraceptive practice is recorded although not necessarily completely so because females have the option of going to family planning clinics for their contraception and not all contraceptives are recorded on the GPRD. For 41.2% of prescriptions, no evidence was recorded of contraceptive practice. Details on the type of contraceptive are presented in Table 3.

Table 3. Contraceptive practice records

Contraception method	**GPRD**		**Emilia Romagna**		**St Anna Ospedale Dermatology clinic**	
	N of Rxs	(%)	N of Rxs	(%)	N of Rxs	(%)
Number of Rxs issued	861	----	21,816	----	Not available	
Hysterectomy	5	(0.6)	Not available		0	(0.0)
Oopherectomy	4	(0.5)	Not available		0	(0.0)
Sterilisation	34	(3.9)	Not available		0	(0.0)
Vasectomy of partner	0	(0.0)	Not available		0	(0.0)
Intrauterine device	85	(9.9)	Not available		0	(0.0)
Record of Depo-Provera	9	(1.0)	Not available		0	(0.0)
Record of Noristerat	0	(0.0)	Not available		0	(0.0)
Record of implanon	1	(0.1)	Not available		0	(0.0)

Table 3 continued on next page

Table 3. Contraceptive practice records continued

Contraception method	GPRD		Emilia Romagna	St Anna Ospedale Dermatology clinic
Oral contraceptive in 1m before Rx	144	16.7	Not available	All patients took oral contraceptives but records are not available as prescribed by GPs
Oral contraception in 3m before Rx	333	38.7	Not available	
Oral contraception in 6m before	413	48.0	Not available	
Code 'contraceptive advice'	73	1.9	Not available	
Code 'not sexually active'	1	0.1	Not available	

Table 4 provides more insight into the age distribution of those with and without evidence of contraception. From this Table it can be seen that especially in the teenage age group, contraceptive practice was less likely to be recorded. This may indicate less use of contraception in younger isotretinoin users or it may indicate that teenagers are more likely to receive their contraception elsewhere than the GP.

Table 4. Contraceptive coverage amongst isotretinoin users by age group

Age at time of Rx	Covered by contraception		Not covered by contraception	
	N	%	N	%
11-14	12	(2.4)	18	(5.1)
15-19	126	(24.9)	136	(38.3)
20-24	93	(18.4)	50	(14.1)
25-29	85	(16.8)	48	(13.5)
30-34	68	(13.4)	44	(12.4)
35-39	50	(9.9)	25	(7.0)
40-44	48	(9.5)	22	(6.2)
45-50	24	(4.7)	12	(3.4)
Total Rxs	506		355	

Finally, no breakthrough pregnancies were identified in the GPRD, with no prescriptions issued during pregnancy and one prescription issued in the pre-pregnancy period which ended before the female's date of last menstrual period. In the Italian database it appeared isotretinoin had been prescribed during the second and third trimester of one pregnancy (figure 2). This is against guidance in the PPP although it is after embryogenesis.

Figure 2. Isotretinoin prescription patterns around pregnancy in the different data sources

Time period	Pre4	Pre3	Pre2	Pre1	Tri1	Tri2	Tri3	Post1	Post2	Post3	Post4	Any Tri
GPRD	1	5	4	1	0	0	0	0	0	4	0	0
Emilia Romagna	2	4	4	3	0	1	1	1	1	3	2	2
Dermatology Clinic	Not available											

6. Discussion

Despite successes within the team in conducting drug use in pregnancy studies using a common protocol and delivering study results as per agreed deadlines, it became clear in this particular study that sensitivities arise when aiming to identify pregnancy terminations. This raised ethical issues that proved to be an inhibition for the study. In addition, lack of study feasibility, even when acknowledged at study outset and with caveats included in the study protocol, proved to be a major barrier for some centres. It could be argued that, while it may be disappointing for study funders and investigators, this may not be entirely inappropriate.

From those centres that did participate, the following conclusions can be drawn. No breakthrough pregnancies and hence, PPP failures were identified in the UK and in one pregnancy in Italy, isotretinoin had been prescribed in the later stages of pregnancy. However, isotretinoin prescription records were incomplete in both databases analysed. In addition, early pregnancy losses will not have been identifiable in either database, and in Italy pregnancy losses or terminations could not be captured for this study.

Records of contraceptive practice from the Italian hospital records suggest 100% compliance with the PPP whereas the database records suggest a different picture. However, it is acknowledged the databases are incomplete with respect to contraceptive practice recording. The limitations of these data sources are described in more detail below.

<u>Limitations</u>

The contributing data sources were population based, however, given that isotretinoin prescribing is accompanied by a PPP it often is prescribed by dermatologists rather than by general practitioners. This will mean that not all prescribing will have been captured in automated healthcare databases and this study will not have captured all exposures, resulting in incorrect estimates of exposure frequency as well as an underestimate of the incidence of pregnancy amongst users. The differences in prevalence of use observed between Italy and the UK may reflect differences in clinical practice management (which healthcare practitioner prescribes) rather than true differences in prescribing frequency.

The database analyses were based on the issue or dispensing of a prescription and it was not possible to know whether the product was actually consumed and the timing at which it was taken.

Information on some of the covariates of interest were not routinely collected within some of the data sources and where they were collected they were not recorded for some patients, however, in these instances this information is likely to have been missing at random. Very limited data was available regarding pregnancy testing in relation to isotretinoin prescribing. Although the hospital records from the dermatology clinic all reported oral contraceptive use, this could not be verified through identification of prescriptions. Notably, within the records from the clinic no records of other contraceptive practice such as vasectomy of husband, sterilisation of female, etc. were recorded even in older women. As with all electronic healthcare databases, pregnancies that resulted in an early loss, before the pregnancy was clinically recognised, will not have been captured.

As anticipated therefore, this study remains inconclusive regarding the efficacy of the PPP for isotretinoin.

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