Isotretinoin and the effectiveness of the pregnancy prevention programme in Europe

Appendix I

A former edition of this systematic review is published in 2010: *H Crijns, SM Straus, Ch Gispen – de Wied, LTW de Jong – van den Berg, Compliance with Pregnancy Prevention Programs of isotretinoin in Europe: a systematic review. Br J Dermatol 2011;164:238-244.*

We have updated this review with literature until April 1st 2013.

Compliance with Pregnancy Prevention Programs of isotretinoin in Europe: a systematic review

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Abstract

Introduction: The aim of this review is to identify publications describing the use of isotretinoin in humans and the compliance to the pregnancy prevention programme (PPP) in Europe.

Material and Method: Systematic search Medline (and Embase) using the terms 'isotretinoin, pregnancy (and Europe)'. Furthermore, manual search in publications was performed.

Results: A total of 24 publications were identified. Publications consist of case reports of exposed pregnancies, surveys among dermatologists or pharmacists and database studies evaluating the compliance of the PPP. The studies and surveys deal with groups of patients exposed to isotretinoin before or during pregnancy and/or compliance with the PPP of isotretinoin. If provided, in 6-26% isotretinoin was prescribed in full accordance with the PPP. Pregnancy incidence was seen in 0.2-1.0 per 1000 women of childbearing age using isotretinoin. Between 65-87% of these pregnancies were terminated.

Conclusions: Review of studies in Europe performed so far show failures in the implementation of this PPP. Therefore, the isotretinoin PPP has to be scrutinized to identify whether new measures should be taken or whether the failures in the implementation have to corrected. New measures should take into account the definition of the ultimate goal of a PPP and the acceptable burden. In the mean time, stakeholders could make a start with adjustments in the implementation of the PPP by taking their responsibility and enhancing the performance by explicit instructions, monitoring the performance and adjusting, if necessary.

Introduction

Isotretinoin was authorised in the US in 1982 and in the EU in 1983 and was marketed as Roaccutane® for severe acne by Roche. In 1983 the first reports of congenital malformations appeared[1] despite the warnings about the teratogenic risks in pregnancy. The retinoic acid embryopathy described by Lammer et al[2] (1985) has a relative risk of 26%. This embryopathy consists of craniofacial, cardiac, thymic and central nervous system malformations. The relative risk of congenital malformations due to isotretinoin exposure during pregnancy is comparable to the relative risk for thalidomide.

In 1988 the marketing authorisation holder implemented a Pregnancy Prevention Programme (PPP) for oral isotretinoin, which was included in the product information worldwide. In the US, studies on the compliance of the PPP were performed by research institutes[3,4], by the Food and Drug Administration (FDA)[5] and by Roche. Because of a lower than expected compliance a more strict PPP for isotretinoin has been implemented in the US in 2002, 'SMART' and an even stricter PPP was implemented in 2006, 'iPledge'.

In 1997, recommendations for prescription and dispensing of isotretinoin were strengthened in France. In 2001 the first generic of isotretinoin became available. Currently there are at least 70 generic oral isotretinoin formulations on the market in Europe[1]. Because of differences in the PPP between the different isotretinoin containing products, a harmonisation procedure for all products containing isotretinoin was approved by the European Commission in October 2003. During this harmonisation procedure not only the PPP was harmonised but also the indication for use was amended to a stricter second line indication for oral isotretinoin. Currently in Europe, Isotretinoin is indicated as treatment for severe forms of acne resistant to adequate courses of standard therapy with systemic anti-bacterial medication and topical therapy.

[1] Communication between European Union member states.

Literature search revealed that the majority of the publications on isotretinoin, pregnancy and compliance to the PPP originate from Northern America. Information specific for the European situation is very limited. The aim of the current study is therefore to perform a review of publications on use of isotretinoin in pregnancy and compliance of the PPP in Europe.

Materials and Methods

A search was performed in Medline with the Mesh terms 'isotretinoin, pregnancy, Europe' and 'isotretinoin, pregnancy'. The Searches identified 20 and 337 publications, respectively at 1 April 2013. A language selection made of publications in English, French, German or Dutch. Other selection criteria were studies, case reports, oral isotretinoin, and human data. The searches were supplemented with manual analyses of references of the leading publications and all identified European publications dealing with systemic use of isotretinoin and birth defects.

Identifying studies on compliance of the use of oral isotretinoin, surveys and case reports resulted in 24 European publications. Finally, these publications will be discussed.

Results

A total of 24 publications were identified. These publications consist of case reports of exposed pregnancies (n=9), surveys among dermatologists or pharmacists and database studies evaluating the compliance of the PPP (n=15). The results of the studies and surveys are presented in table 1 and the case reports in table 2.

Taking into account the selected publications, France contributed for more than half of the publications (n=11) of which nine were in French, all other publications were in English.

Studies and surveys

The identified studies and surveys among dermatologists or pharmacists deal with groups of patients exposed to isotretinoin before or during pregnancy and/or compliance with the PPPs for isotretinoin. Parts of the results of these studies and surveys are presented in tables 3 and 4.

Four French studies were performed by the group of Autret-Leca et al [6,7,8,9,], using the same sources and database, and showing a development over time.

In France, the incidence of pregnancies with isotretinoin use remains stable between 0.2-1.0 per 1000 women of childbearing age. In the publication by Bensouda-Grimaldi et al[8], the covered period was divided because of authorisation of generic formulations of isotretinoin in 2001.

In the first study[6], a total of 318 pregnancies during or shortly after stopping isotretinoin were reported over a period of nine years (1987-1995). In 84% of these pregnancies, contraception was not prescribed or prescribed with poor compliance.

In the second study[7], 37 pregnancies were reported over a period of 22 months (March 1997-December 1998). Restricted measures for pregnancy prevention came to force in March 1997 and this study was to evaluate the new procedures.

The third study[8], 103 pregnancies exposed to isotretinoin occurred over a period of four years (1999-2002). In their recent study[9] 147 spontaneously reported cases of isotretinoin exposure during the teratogenic risk period, were evaluated. Detailed information about contraception was available of 88 women, of whom 32% did not take any contraceptives, in 48% the contraception failed, in 17% there was a poor compliance and 3% of the women stopped the contraception.

The rate of spontaneously reported isotretinoin exposure during pregnancy has increased from 0.3 (from 1999 -2002) to 0.41 in the most recent study[9] (2003-2006).

The second part of these four studies concerned prescription surveys on the recommendations of the PPP current at that time. Questionnaires were filled in by the pharmacist, who interviewed female patients with isotretinoin prescriptions.

In the first study[6], 230 pharmacies were selected and 102 actually participated in the questionnaire survey. A total of 173 questionnaires were analysed. The prescriptions covered 3 months (range 1-16 months) for isotretinoin and in 13 cases (8%) accompanied with a prescription for a contraceptive.

In the second study[7], of the 310 selected pharmacies actually 105 pharmacies participated for the questionnaire survey. A total of 165 questionnaires were completed. In 27 cases the contraceptive method did not fulfil the PPP criteria, for instance Diane® was prescribed in 19 cases and in 17 cases the contraceptive method was poorly described.

In the third study[8], 45 pharmacies participated and 68 questionnaires were analysed. In 47% the prescription concerned Roaccutane® and in the other cases generic formulations of isotretinoin.

A questionnaire survey with dermatologists practising in Scotland[10] was performed. Sixty-four of the ninety dermatologists completed the questionnaire of which a similar proportion of men and women, clinical experience and age. Patients were asked about the possibility of a pregnancy in 95% of the women older than 16 years and in 70% of the women younger than 16 years. In patients younger than 16 years, only in 41% this test was routinely performed. Verbal and written advice on avoiding pregnancy was given in 97%. In general oral contraceptives were considered an adequate form of contraception, for 75% of the physicians progestagen-only or IUD was also suitable and for 15% barrier methods such as condoms were also acceptable. In 67% the dermatologists asked the general practioner to prescribe an oral contraceptive and in 27% Diannette® was suggested. With 79% of the physicians, isotretinoin was started after at least one month of oral contraceptive use. Only in 6% a pregnancy test was performed at each visit. Ten per cent of the physicians did not warn their patients to avoid pregnancy for one month after discontinuation of isotretinoin, a number of physicians recommended avoidance for two months after stopping of isotretinoin.

A Swedish study[11] was performed on the Medical Birth Registry for infants born during 1982 through 1989. In Sweden isotretinoin may only be prescribed on a named patient basis. A total of 301 pregnancies were identified of women who had received isotretinoin. There were 173 infants (including 8 twins) whose mothers had been treated with isotretinoin before pregnancy, of which two infants had major birth defects, one child with a ventricular septum defect and one child with preaxial polydactyly. Of the 132 infants (6 twins) which were born before isotretinoin was given, one child had a cleft lip and palate. Only three women were identified who had used isotretinoin during pregnancy; all three infants were normal. These three women did not use oral contraceptives or IUDs during isotretinoin treatment.

In Denmark[12] a questionnaire was circulated to 185 dermatologists 20 years after introduction of isotretinoin. 132 questionnaires were returned with a response rate of 71%. Post-treatment advice on avoiding pregnancy differed from one month in 29% to two months in 42%, three months in 15% and more than three months in 11%.

A prospective survey was performed in France[13] in 2001. In 50% of the 182 pharmacies of the Côte d'Or. Of these pharmacies, 37 (41%) collected prescriptions of isotretinoin. Sixty-seven patients filled out a questionnaire of which 74% lived in urban environment and 26% lived in rural or semi-rural environment. The prescriber of isotretinoin was a dermatologist in 60 cases (89.5%). Isotretinoin was prescribed for acne in 66 cases and in one case for cutaneous lupus. In 53 (79.1%) cases the prescription was the first prescription, in 12 cases (17.9%) it was the second prescription and in two cases (3%) it was the third prescription. Five women did not have a pregnancy test. Teratogenic risk was known in 48 women (71%) through friends before consulting the physician. Seventeen women (25.3%) never received an information leaflet. Of the women who have read the information before, 87% did have the pregnancy test within in accordance with the PPP, compared to the women who had read the information later or who did not receive an information leaflet, 57% did have a pregnancy test in accordance with the PPP (p=0.007). Thirty-eight women (50%) were not aware that

contraception should continue after stopping isotretinoin; however they continued the contraception for even more than one month (median of 3 months).

The Italian study[14], evaluated the system on the isotretinoin PPP in Italy and was performed by Telefono Rosso (TR) a member of the European Network of Teratology Information Services (ENTIS). Over the period of July 2002-October 2005, 52 patients contacted TR, including 19 requests (36.5%) for information preconception, 29 pregnancies (55.8%) including four pregnancies concerning paternal exposure. The 29 pregnancies consisted of pregnancies in which the patient discontinued isotretinoin one month or more before pregnancy. Data from 35 of the 52 women could be used for evaluation with the following additional results (not presented in table 4): indication was not followed correctly in 10 women (28.6%), claim of not receiving clear and precise information on teratogenicity in 5 women (14.3%), and treatment started on 2nd or 3rd day of menstruation in 9 women (25.7). In addition to the study, a case was reported of a child with complex cardiopathy and bilateral anotia born to a woman using isotretinoin until the 5th week of pregnancy, see table 2.

A prospective observational study was performed in France[15] covering the period October 2005 through January 2007. A total of 1263 patients were included of which 56% male (n=709) and 44% female (n=554). 296 dermatologists participated of which 72% female. The mean age of the physicians was 48 ±7 years. A pregnancy test five weeks after stopping isotretinoin was not evaluated. One month before starting treatment with isotretinoin 548 women used effective contraception. An oral contraceptive was used by 98% and the remaining 2% an implantable progestagen, IUD or was menopausal. In 13% of the women contraceptives were temporarily interrupted with a maximum duration of one cycle.

The German study[16] evaluated pregnancy outcome of pregnancies occurring during isotretinoin use recorded between 1993 through 2008. In total 230 information requests on oral isotretinoin were received during the covered period at this Teratology Information Service (TIS). In 108 out of these 230 cases, isotretinoin was used during the period of one month prior conception and/or during

pregnancy. If information on contraceptive measures was available (n= 69), 69.9% did not use contraceptive measurements, 30.4% (n=21) used contraception that failed. None of the patients did use two complementary contraceptive measures as recommended by the isotretinoin PPP. The 91 known pregnancy outcomes were compared with controls, prospective enrolled pregnancies of women who have been exposed to non-teratogenic agents during the study period. There were 5.5% spontaneous abortions vs. 10.1% in the control group, 75.8% elective terminations vs. 1.9%, and 18 live births (19.8%) including a pair of twins vs. 88.0%. Three (16.9%) of the 18 live born infants had congenital malformations vs. 8.5% consisting of major birth defects 5.6% (n=1) vs. 3.7% (n=12).

In the Netherlands three online questionnaires related to the adherence to the PPP of acitretinoin were send to health care professionals (two to pharmacists (n=1000 and n=556) and one to dermatologists (n=567) [17]. The response was low, being 20% for both pharmacists questionnaires and 28% for the questionnaire to dermatologists. Most pharmacists (82%) checked the limited supply for isotretinoin for 30 days and the 7 day validity of the prescription (53-61%). However only 15% of the pharmacists asked for a negative pregnancy test before each dispensing and 44-49% checked before delivery the use of contraceptives. The majority of the pharmacists (73%) considered that the main responsibility of the PPP lies with the dermatologist/prescriber.

Although 93% of the dermatologists were of the opinion that he/she performed the isotretinoin PPP and adhered to the PPP, only 25% were compliant to all the different elements of the PPP as stated in the product information. Three-quarter of the responding dermatologists has the opinion that both prescriber and patient are responsible for pregnancy prevention, while 25% considered the patient solely responsible for the PPP.

Two Dutch drug utilization studies [18,19] were published both using pharmacy prescription databases to assess the compliance with the Dutch isotretinoin PPP in women of childbearing potential. The first study (2005-2008) [18] included 4881 women aged 15-45 using isotretinoin at least once during the study period. Among women of childbearing potential the proportions of first prescription of

isotretinoin increased during the study period from 66.5% to 71.9%. Almost 80% of the isotretinoin first prescriptions was prescribed by the specialist. Of the women who started isotretinoin, 59% received concomitantly either an oral hormonal systemic or a local (intrauterine) contraceptive. Conventional acne therapy up to 16 months prior to isotretinoin initiation was prescribed to 70% of the women. The second study[19] was much smaller and included 651 women of childbearing potential using isotretinoin. The use of prescribed contraceptives among female isotretinoin users using the strict definition of the PPP (use of contraceptives before start, during and after discontinuation of isotretinoin) was 52-54%. A more liberal definition of a minimum of one contraceptive prescription showed 61-62% use of contraceptives among isotretinoin users. Both percentages were higher than the 39-46% use in reference population (women aged 15-45, not taking isotretinoin). Compliance with contraceptive use among isotretinoin users was higher in rural versus urban areas (55-67% vs. 43-53%, respectively) as well as with preceding therapy of conventional anti-acne treatment compared with no preceding therapy (66% vs. 41%, respectively). This study also found a higher compliance with contraceptives when isotretinoin was prescribed by the general practitioner compared with the specialist (63% vs. 37%, respectively).

The final article[20] we will discuss is a questionnaire survey among European Regulatory Agencies aimed to get an impression on the implementation of the harmonized PPP of isotretinoin in the European member states. In 2009 a questionnaire (request for Non-Urgent Information or NUI) was send to all 25 EU member states plus Norway and Iceland. The response rate was 82% (22 out of the 27 countries). In 21 of these member states isotretinoin is marketed and the PPP is in force. In 18 countries all 7 elements, required following a formal EU review (see box 1), are incorporated in the PPP. Seven member states had additional measures in place. In spite of the implementation of the PPP and additional measures, in 16 out of the 22 responding European member states information on a total of 143 isotretinoin exposed pregnancies was available since implementation of the harmonized PPP.

Box 1: seven elements of the EU PPP

I.	Pharmacist's Guide to dispensing isotretinoin
II.	Physician's Guide to prescribing isotretinoin
III.	Checklist for prescribing to female patients
IV.	Educational material for the male and/or female patients
V.	Patient Information Brochure
VI.	Brochure on contraception
VII.	An acknowledgement form for female patients

Case Reports

Nine case reports and their outcome are presented in table 2, of which one case report was presented in a publication on a study. The case reports originate mostly from France (n=5), two reports from Italy, and single reports from Belgium and Greece.

In two case reports of French origin [21,22], concentrations of isotretinoin and its metabolites were determined in foetal tissue. The first case was described in both publications.

Discussion

This systematic literature review was performed on studies and case reports using Mesh terms isotretinoin, pregnancy and Europe. A total of 24 publications were identified of which 15 studies and nine publications on case reports. The studies evaluated the compliance to the PPP of isotretinoin in these countries. A common conclusion all studies is that the compliance was regarded insufficient and that the PPP should be strengthened. The case reports indicate that pregnancies occurred despite a PPP for isotretinoin was in place.

A limiting factor in the four French studies could be the fact that pharmacists performed the interviews. Pharmacists are actors in the control process and the answers might concern also their compliance with the programme. Possible bias can therefore not be excluded.

Due to the different periods of data collection and the changes over time in the PPPs, the introduction of generic drugs, and the regulatory referral of isotretinoin, a comparison of the results of the studies and surveys and comparison of the routine risk minimisation activities in different countries is difficult.

This review reveals deficiencies in the implementation of the isotretinoin PPP. Poor compliance was shown among others by failure of contraceptive measures causing 30% of the pregnancies.

Responsible for this poor compliance seems to be prescribers, patients, pharmacists but also regulatory authorities.

It can be discussed whether use of Diane-35®/Diannette are acceptable contraceptives. These medicinal products are authorised for treatment of acne in women and have also contraceptive action. Prescribing these products for contraceptive use should not be thought little of, because of the high thrombosis risk, which may be even higher than the third generation oral contraceptives.

The efficacy of the PPP in prevention of pregnancies is important since more and more teratogenic drugs become available, for instance lenalidomide and thalidomide. However, these drugs have mostly oncologic indications and are not likely prescribed to women of childbearing age. Isotretinoin on the other hand is prescribed for an aesthetic problem that is not life-threatening or causing disability in the age group of childbearing potential, and therefore having a high risk for congenital malformations when used just before or during pregnancy.

The EU pregnancy prevention programme was evaluated in 2002-2003 during a regulatory procedure and because of pregnancies reported throughout Europe. The Pharmacovigilance Working Party (PhVWP) of the Committee of Human Medicinal Products (CHMP) of the European Commission is monitoring the current PPP for isotretinoin on a regular basis. The regulatory authority of the United Kingdom (UK), being the 'Reference Member State' in Europe for Roaccutane, reported as such in January 2010, 105 pregnancies spontaneously reported only in the UK. This was mentioned in a recent publication on the Guideline for isotretinoin use in the UK[29]. This publication presents also results from an audit performed by the British Association of Dermatologists (BAD) on isotretinoin use and three out of the four audit points concerned the PPP.

Recently, another tretinoin has been approved for the European market, namely Alitretinoin for the indication of eczema. This product's PPP will be closely monitored because this product will also be prescribed for a relatively young population including women of childbearing age. Adherence to a

strict programme as iPledge is a burden for all stakeholders and there is no way of completely avoiding human-related failure.

Isotretinoin pregnancy prevention programme has to be evaluated and closely monitored in all countries but also better designed studies should be performed to gain insight in the full picture before taking any new measures. Review of studies in Europe performed so far show failures in the implementation of this PPP. Therefore, the isotretinoin PPP has to be scrutinised to identify whether new measures should be taken or whether the failures in the implementation have to be corrected. New measures should take into account the definition of the ultimate goal of a PPP and the acceptable burden. In the mean time, stakeholders could make a start with adjustments in the implementation of the PPP by taking their responsibility and enhancing the performance by explicit instructions, monitoring the performance and adjusting, if necessary.

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Table 1: Identified studies and surveys

Author(s)	Title	Country	Year	Source
Autret E, et al [6]	Isotrétinoïne (Roaccutane) chez la femme en âge de procréer : insuffisance de suivi des recommandations de prescription.	France	1997	Questionnaires to pharmacovigilance organisations and pharmacists
Holmes S, et al [9]	The prescription of isotretinoin to women: is every precaution taken?	United Kingdom	1998	Questionnaire survey of dermatologists
Källén B. [10]	Restriction of the use of drugs with teratognic properties : Swedish experiences with isotretinoin.	Sweden	1999	Medical Birth Registry for infants in Sweden
Autret-Leca E, et al[7]	Roaccutane chez la femme en âge de procréer : étude de l'impact du renforcement des recommandations de prescription.	France	2000	All pregnancies from several sources in France, such as pharmacovigilance centers, Roche and TIS* and sample of drug prescriptions
Wildfang I, et al [11]	Isotretinoin in Denmark – 20 years on.	Denmark	2002	Questionnaire survey of dermatologists
Dutronc Y, et al [12]	Modalités de prescription et de surveillance de l'isotrétinoïne den Côte d'Or : étude prospective chez 67 femmes en âge de procréer.	France	2004	Questionnaire to randomly selected pharmacies
Bensouda-Grimaldi L, et al [8]	Isotrétinoïn : suivi de l'application des recommandations des prescriptions chez les femmes en âge de procréer.	France	2005	All pregnancies from several sources in France, such as pharmacovigilance centers, Roche and other MAH** and TIS* and sample of drug prescriptions
De Santis M, et al[13]	The need for restricted prescription of retinoid acid derivative isotretinoin to prevent retinoid teratogenicity.	Italy	2007	TIS database
Jeanmougin M, et al [14]	Aide au bon usage de l'isotrétinoïn en pratique libérale : observatoire prospectif de 1263 patients acnéiques.	France	2009	Prospective observational, national, multicentre study.

Author(s)	Title	Country	Year	Source
Schaefer Ch, et al [15]	Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy.	Germany	2009 (ePub)	TIS database with prospective and retrospective cohorts compared with controls.
Teichert M. et al [18]	Isotretinoin use and compliance wth the dutch pregnancy prevention programme. A retrospective cohort study in females of reproductive age using pharmacy dispensing data.	The Netherlands	2010	Dispensed medication of the Dutch Foundation of Pharmaceutical Statistics.
Autret-Leca E. et al [9]	Isotretinoin exposure during pregnancy. Assessment of spontaneous reports in France.	France	2010	All spontaneous reported exposed pregnancies to pharmaco-vigilance centers, TIS*, and pharmaceutical companies.
Crijns H. et al [20]	Implementation of the harmonized EU isotretinoin pregnancy prevention programme. A questionnaire survey among European regulatory agencies.	Europe	2012	Questionnaire survey (request for Non-Urgent Information (NUI)) among EU member states plus Norway and Iceland.
Crijns H., et al [19]	Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilization study.	The Netherlands	2012	Pharmacy prescription database: IADB.nl
Crijns H., et al [17]	Healthcare professional surveys to investigate the implementation of the isotretinon pregnancy prevention programme. A descriptive study.	The Netherlands		Questionnaire survey among dermatologists and pharmacists

* TIS: Teratology Information Services

** MAH: Marketing Authorisation Holder(s)

Table 2: Identified case reports

Author(s)	Title	Country	Year	Source	Features infant	Exposure to isotretinoin
van Maldergem L, et al [23]	Morphological features of a case of retinoic acid embryopathy.	Belgium	1992	One case	Female foetus with enlarged and elongated head, low-set microtic ears, hypertelorism and a flat and depressed nasal bridge. Ventriculomegaly of lateral ventricles and cerebellar hypoplasia. Dextrocardia, with enlarged heart, VSD and single truncus arteriosus	Three months before conception and during first months of pregnancy.
Heckel S, et al [24]	Tératogénicité des rétinoïdes. Un cas et revue de la littérature.	France	1993	One case	A healthy female infant was delivered	Conception probably took place 10 days after stopping isotretinoin
Benifla J, et al [21]	Fetal tissue of retinoid. Experimental study concerning a case of isotretinoin (Roaccutan) administration and pregnancy.	France	1995	Therapeutic abortion in isotretinoin pregnancy and determination of concentrations in foetal tissues.	Terminated pregnancy at 17 weeks gestation: macroscopic normal foetus. Tissue concentrations ofisotretinoin and its metabolites showed transplacental crossing of isotretinoin and/or its metabolites.	Isotretinoin was used before and during pregnancy
Pilorget H, et al [25]	Embryopathie liée à l'isotretinoïne (Roaccutane®). A propos d'une observation.	France	1995	One Case	Agenesia of both external ears, a systolic cardiac murmur and paralysis of the right facial nerve	Isotretinoin use until one week before presumed conception

					and poor spontaneous movements	date
Pons J, et al [22]	Dosages maternels et foetaux de rétinoïdes. A propos de 2 cas d'exposition à l'isotrétinoïne (Roaccutane®).	France	1996	Two cases of which one was already reported in the publication of Benifla et al.	First case, see Benifla et al. Second case, concerns a foetus with a spina bifida and myelomenigocèle. Again high concentration of isotretinoin and its metabolites in the foetal tissue.	Isotretinoin use during first trimester of pregnancy in both cases
Dos Santos A, et al [26]	Tératogénicité de l'isotrétinoïne.	France	1998	Two cases	1) male infant with plagiocephalia and asymmetric face with ptosis of the right eyelid. Lateron the child had psychomotor retardation. 2) male infant with microcephalia and psychomotor retardation	1) oral isotretinoin use during first trimester of pregnancy 2) topical isotretinoin use on chest and back during the first month of pregnancy
Giannoulis C, et al [27]	Isotretinoin (Ro-Accutane) teratogenesis. A case report.	Greece	2005	One case	No cephalic skull up to the frontal bone, absent stomach, oesophagus atresia and small VSD	Isotretinoin use until 16th week of gestation
De Santis, et al [14]	The need for restricted prescription of retinoid acid derivative isotretinoin to prevent retinoid teratogenicity.	Italy	2007	One case	complex cardiopathy and bilateral anotia	Isotretinoin use until the 5th week of pregnancy
Malvasi M, et al [28]	Possible long term teratogenic effect of isotretinoin in pregnancy.	Italy	2009	One case	Thoraco-omphalopagus conjoined twins.	Isotretinoin use for 7 months until 3 months before gestation. Induced termination.

Table 3: information on pregnancies associated with isotretinoin use

	Autret[6]	Autret-Leca[7]	Bensouda-Grimaldi[8]	Schaefer[15]	Autret-Leca[9]
Period	1987-1995	March 1997-December 1998	1999-2002	1993-2008	2003-2006
Pregnancy incidence (per 1000)*	0.2-0.7	0.4-0.8	0.3-1.0 / 0.3-0.8**		0.41
Terminated pregnancies (%)	81	65	87	76	71
Pregnancies during treatment of isotretinoin (%)	16	49	29	47[$]	61
Pregnancies during first month of termination isotretinoin treatment (%)	33	22	45		23

*per 1000 women of childbearing age using isotretinoin

** period was divided because of authorization of generic formulations of isotretinoin in 2001

[$] database of Teratology Information Services, requests for information

Table 4: Results from studies on the compliance of the isotretinoin PPP

	Autret[6] (n=173)	Holmes[10] (n=64)	Autret-Leca[7] (n=165)	Wildfang[12] (n=132)	Dutronc[13] (n=67)	Bensouda-Grimaldi[8] (n=68)	De Santis[14] (n=35)	Jeanmougin[15] (n=554)	Autret-Leca[9] (n=147)
Mean age (range)	24 years (12-47)		26 years (± 8)		24 years (15-45)	25 years (14-45)		21 years (± 7)	27.3 years (16-44)
Prescription by dermatologists (%)	93	100**	89	100**	89	90		100**	86
Contraception in accordance with PPP (%)		75	70	85	72	78	57	99	48
Contraception not used (%)	28		12		11	4			32
Correctly prescribed isotretinoin (%)[$]	14		18			6	26		
Contraception continued during first month of termination isotretinoin (%)			93			82	57	96	
Pregnancy test before start isotretinoin (%)	29	55	85	60	78	96	37	98	
Pregnancy test at 5 weeks after termination isotretinoin (%)			64			62			
Signed acknowledgment form (%)		95	87			88			
Monthly pregnancy test (%)		6	88*	32		96		99	

$ isotretinoin prescribed in full accordance with the PPP for women of childbearing potential

* every second month instead of monthly.

** survey in dermatologists