

D - DERMATOLOGICI

D01BA – Antimycotic drugs for systemic use

Griseofulvin – D01BA01

This agent shows a variable intestinal absorption. Its concentration level in fetal blood is the same as in maternal blood. Patented in 1956.

Case report

- Rosa et al (1987), FDA: 2 couples of conjoined twins exposed to griseofulvin in early pregnancy have been recorded, out of over 20,000 FDA reports of congenital anomalies in newborns exposed to drugs during the first trimester. This observation has given rise to further studies (see below).

Retrospective cohort studies without controls

- Rosa et al (1987): ad hoc study on prescriptions, and linkage to clinical records. During a survey of 55,736 pregnancies recorded in a single population, 37 first trimester exposures to griseofulvin were located. Among these, 2 newborns with congenital anomalies (5.4%) were detected, one single cardiopathy, and one non-specified defect. The preceding observation was not confirmed.

Case-control studies, specific

- Metneki and Czeizel (1987), Hungarian CCSCA. 39 couples of conjoined twins, none of them exposed, were matched with 6,786 control newborns showing other types of congenital anomalies. Cardiopathy and piloric stenosis were detected in 2 first-trimester exposures, vs. 3 exposures out of 10,962 controls: OR = 1.1 (CI 95%: 0.1-7.9).
- Knudsen (1987), ICBDMs: None of the 47 couples of conjoined twins out of over 3 million newborns collected by various birth defects registers located all over, including Italy, had been exposed to griseofulvin.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 34 first trimester exposures, 1 newborn with major defects, 1 expected. RR = 1.0 (CI 95%: 0.02-5.6).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: none of the 4 newborns exposed in the early 16 weeks had congenital anomalies.

Conclusions: The available studies on the use of griseofulvin during the first trimester of pregnancy do not point out any population background risk increase. The hypothesis of association with conjoined twinning, suggested by the two cases reported in 1987 has not been confirmed by further investigations.

Terbinafine – D01BA02

This inhibitor of squalene epoxidase is available in Italy since 1992.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Petranyi et al (1983): nonteratogenic in rats or rabbits (30,100 and 300 mg/kg per os).

Conclusions: No specific studies are available in literature consistent with the use of terbinafine in human pregnancy. Inadvertent exposure appears unlikely to increase the risk of adverse pregnancy outcome, due to a lack of reported anomalies over the long period of commercialization and considering that teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

D05B – Anti-psoriasis drugs for systemic use

D05AB – Psoralens for systemic use

They derive from the fusion of a furan and a coumarin. They can be found in lime, lemon and fig trees. They are quickly absorbed orally.

Methoxsalen (8-methoxypsoralen) – D05BA02

Originally extracted from Amni Majus, a plant the Egyptians used to treat vitiligo. It makes skin sensitive to ultraviolet rays, with which it is associated in the PUVA treatment (300-400 UVA). Patented in 1978.

Prospective cohort studies without controls

- Gunnarskog et al (1993): 14 healthy newborns were exposed at various stages of pregnancy to PUVA treatment.
- Garbis et al (1995), ENTIS: 31 healthy newborns exposed in the first trimester

Conclusions: Only limited information was available, making it difficult to show an association between methoxsalen and an increase in the background reproductive risk.

D05BB – Retinoids for the treatment of psoriasis

These synthetic derivatives of vitamin A influence cell proliferation and their differentiation, the immune system, inflammation, and sebum production.

Acitretin – D05BB02

Acitretin is a metabolite of etretinate (not available in Italy). Its mean half-life, in patients aged between 21 and 70 years is of 50 hours and 60 hours for its major metabolite, cis-acitretin. Over 99% of this agent are expected to be excreted within 36 days since the latest administration. The intake of acitretin along with alcohol causes the formation of an etretinate having a half-life of about 120 days (Roche 2000). It is available in Italy since 1998.

Case report (etretinate)

- Rosa et al (1986) has reported (also from the past literature) 7 cases of exposed infants to etretinate during pregnancy. 4 showed CNS abnormalities – 2 of them were spina bifida, 1 encefalophalocele – and 3 had craniofacial anomalies.

Cohort studies without controls (etretinate)

- Grote et al (1985): here are the outcomes 1-6 months after the drug was suspended: 11 healthy newborns, 2 spontaneous abortions, 1 fetus with hypoplasia of the lower limb.

Case report (acitretin)

- De Die-Smulders et al (1995): 1 stillbirth who had been exposed starting 10 days after conception throughout the first trimester had upper and lower limbs defects and craniofacial anomalies, ear malformations and atrioventricular defect.

Cohort studies without controls (acitretin)

- Geiger et al (1994), Manufacturer, preliminary data – see Maradit and Geiger (1999).
- Maradit and Geiger (1999), Manufacturer: review of 123 reported exposures to acitretin before or during pregnancy, collected from all over the world (see table below).

Conclusions: Etretinate, acitretin precursor, induces a malformative syndrome characterized by myelomeningocele, multiple synostosis, facial dysmorphism, syndactyly, and skull and cervical vertebra dysfunction (Roche 1986). Their frequency is shown in the table below. Acitretin can possibly metabolize to etretinate, mainly if taken along with alcohol, thus increasing the teratogenic risk. Manufacturer recommends strict alcohol abstinence during acitretin treatment and for at least 2 months after stopping therapy. Residual acitretin and/or etretinate in body fat and in plasma have been detected in women as long as 29 months after stopping therapy (Sturkenboom et al 1994). Manufacturer also recommends a post-therapy contraceptive period of 2-3 years (Roche 2000).

D10AD – Retinoids used in the topic treatment of acne

Tretinoin – D10AD01

Only 5-7% of the applied dose is absorbed (van Hoogdalem 1998). The absorbed dose following daily intake is less than 0.015 mg/kg that is 30 times less than the lowest teratogenic dose used in humans (Nau 1993). It is available in Italy since 1989.

Case report

- Camera and Pregliasco (1992): 1 newborn exposed in the early 11 weeks of gestation with ear malformations.
- Lipson et al (1993): 1 first trimester exposure with multiple malformations: omphalocele, diaphragmatic hernia, cardiopathy, reduced upper limb defect.
- Navarre-Belhassen et al (1998): 1 first trimester exposure with multiple malformations.
- Selcen et al (2000): 1 first trimester exposure with ear malformations and CNS abnormalities.

Retrospective cohort studies without controls

- Rosa et al (1994), FDA: of 25 spontaneous records concerning infants with congenital anomalies exposed in the first trimester to topic tretinoin, 5 had holoprosencephaly, while only 19 holoprosencephalies had been recorded among 8,700 newborns exposed to other drugs. This suspicious association has not been confirmed by the study of 1,120 first trimester exposures, where none of the 49 surveyed newborns with major defects showed (as expected) holoprosencephaly.

Prospective cohort studies without controls

- Johnson et al (1994), TIS: 53 exposures. One single newborn, also exposed to isotretinoin per os, had a classical embryopathy.

Retrospective cohort studies with internal controls

- Rosa (1998), Michigan MSS: of 441 first trimester exposures, 272 VIP, 22 spontaneous abortions, 7 newborns had major defects (none of which consistent with isotretinoin syndrome), 9 expected (RR = 0.8; CI 95%: 0.3-1.6).

- Jick et al (1993), Seattle GHC: 215 first trimester exposed pregnancies and 430 controls. RR as per major congenital anomalies in first trimester exposures = 0.7 (CI 95%: 0.2-2.3).

Prospective cohort studies with internal controls

- Shapiro et al (1997), TIS Motherisk Program: 94 first trimester exposures and 133 controls. No difference was detected in terms of stillbirth and abortion. 2 exposed newborns (2/86) had congenital anomalies (aortic bicuspid valve and renal dysplasia), vs. 2 controls (2/119) (aortic stenosis and imperforate anus): RR = 1.4 (CI 95%: 0.2-9.6).

Case-control studies, specific

- De Wals et al (1991), Eurocat: none of the 16 cases of holoprosencephaly with no identified chromosomal anomalies studied by various European registers of birth defects, including Italy, had been exposed to topic or systemic retinoids.

Conclusions: None of the available studies suggest that topic use of tretinoin (normally barely absorbed) induce an increase in malformations. Occasional recorded association between malformations (in particular with holoprosencephaly and with malformations similar to those observed in systemic retinoids) and topic use of tretinoin has not been confirmed by further studies.

D10B – Anti-acne compounds for systemic use

D10BA – Retinoids used in the treatment of acne

Isotretinoin (13-cis-retinoic acid) – D10AD04 – D10AD54 – D10BA01

Its chemical structure is similar to Vitamin A. It was first marketed in the US in September 1982 for the treatment of cystic acne resisting other conventional therapies. Pregnant women are advised against this drug, due to its teratogenic action in experimental animals.

Case records, review

- Lynberg et al (1990): review of 61 published cases thoroughly described so as to help setting out characteristics and also a quantitative analysis of isotretinoin embryopathy.

Lynberg et al (1990)	Percentage (n=61)
Congenital anomalies	71%
Ear: micro-anotia or absence – stenosis of auricular canal	
CNS: microcephaly, hydrocephalus, other malformations	49%
Heart : common trunk, transposition of the great vessels, tetralogy of Fallot, single ventricle, coarctation or other anomalies of aorta	33%
Association of:	
Ear malformation + CNS + Heart	18%
Ear Malformations + CNS	39%
Ear Malformations + Heart	25%
CNS Malformations + Heart	23%

The study of the case record also suggests that the critical period for embryopathy is between 28 and 70 days following the latest menstruation, in particular between 35 and 49 days.

- Rosa (1991): review of case record published between 1983 and 1990 (including earlier reviews by Chen 1984 and Zarowny 1984). 95 isotretinoin embryopathies, 93 of which detected among isolated records, and 2 in a cohort of 1,120 women in Michigan Medicaid.
- Further case records, following Rosa review 1991, not changing the already well known characteristics of embryopathy: Rizzo et al (1991), Balliu Badia et al (1997), Ishijma and Sando (1999), Ceviz et al (2000), and Moerike and Pantzar (2002).

Cohort studies

- Lammer et al (1985): A study based on 154 pregnancies exposed in the first trimester and spontaneously reported to Roche, FDA and CDCs between 1982 and 1984. This number included the cases published by Rosa 1983, Lott et al 1983, Braun et al 1984, Hill 1984, Stern et al 1984, Fernhoff and Lammer 1984, De la Cruz et al 1984, and Marwick 1984. The entire case record of 154 pregnancies has been divided according to the gestational week of the record as follows:
 1. prospective cohort, when the exposed pregnancy was recorded prior to week 12 (36): 5 newborns with malformations (14%), useful to assess the relative risk of those defects in comparison with what had been observed in the Registry for congenital anomalies in Atlanta = 25.6 (CI 95%: 11.4-57.5).
 2. retrospective cohort, when the pregnancy was recorded later, often supported by an old echography (118). The retrospective cohort helped setting out the type of malformation associated to isotretinoin exposure, globally classified as "migration impairments of cranial neural crest cells" (see conclusions).
- Lammer et al (1987): the previous study has been enriched with 21 more first-trimester exposures, for a total of 57 prospective exposures: 37 healthy newborns, 11 showing congenital anomalies (23%).
- Dai et al (1989): a prospective cohort study analyzed cases spontaneously reported to the Manufacturer, in order to set out the risk following the end of the treatment (see table).
- Dai et al (1992): a prospective cohort study analyzed cases spontaneously reported to the Manufacturer, in order to set out the risk of congenital anomalies due to exposures during pregnancy (see table). The study probably comprehends some of the cases analyzed by Lammer (1987).

Retrospective cohort studies without controls

- MMWR (2000) and Honein et al (2001): a survey has been carried out in California in the course of the evaluation of preventive campaigns against retinoid embryopathy in the years 1989-1999. The monitoring system had revealed 900 pregnancies out of around 177,000 fertile-aged treated women (5 per thousand). This study reports in details 14 first trimester exposures, out of a total of 23 eligible, occurred in California in the period 1997-1999: 4 spontaneous abortions, 5 VIP (unknown reason), 4 healthy newborns, 1 newborn with dextrocardia, aortic atresia, hydrocephaly, and facial dysmorphism (risk estimate, 1/5 as expected).

Prospective cohort studies with internal controls

- Adams and Lammer (1993): IQ evaluation in 31 children (5.3 mean age) exposed to isotretinoin during the early 60 days of gestation, 30 controls not exposed of the same age: half of them revealed an IQ below 85 and one third of them also had congenital anomalies. This study, although preliminary and never published, proves that isotretinoin is also causative of cognitive deficit, regardless of CNS existing abnormalities.

Conclusions: Exposure to 0.5-1.5 mg/kg/die of isotretinoin in the early weeks of pregnancy (critical period 2-5 weeks after conception) can cause:

1. spontaneous abortion, at a risk of 40%
2. malformative syndrome at a risk of 26% (see table), characterized by CNS abnormalities (hydrocephalous, paresis of the 7th cranial nerve, cerebellar defects, encephalocele, cortical blindness, hypoplasia of the optical nerve, retinal defects, and microphthalmia), craniofacial abnormalities (micro-anotia, micrognathia, cleft lip, facial asymmetry, and facial dysmorphisms), cardiac septal defects and, more frequently, cono-truncali (TGV, Fallot, right ventricle with double exit, truncus arteriosus communis), interruption or hypoplasia of arcus aortae. Rhythm hypoplasia with immunodeficiency, hypo-agenesia of the limbs, mental retardation or borderline intelligence with learning difficulties. See also the table by Lynberg et al 1990.
3. borderline intelligence without evident malformations, with deficiency in the visual-motor integration and in the attention and organizing capabilities, with a risk around 30%

Risk of teratogenic action associated to oral retinoids, in relationship with the exposure period (Dai et al 1989, 1992).

Retinoid and Period of exposure	Author (year)	Type of study	Infants with defect on total	Risk of defects (IC 95%)
Isotretinoin in pregnancy	Lammer et al (1987)	Prospective cohort	11 / 48	23% (12-37%)
Isotretinoin in pregnancy	Dai et al (1992)	Prospective cohort	26 / 94	28% (19-37%)
Isotretinoin within one month since the end of treatment	Dai et al (1989)	Prospective cohort	2 / 48	4 % (1-14%)
Etretinate in pregnancy	Geiger et al (1994)	Retro-prospective cohort	11 / 43	26% (14-41%)
Etretinate within two years since the end of treatment	Geiger et al (1994)	Prospective cohort	1 / 45	2% (0-12%)
acitretin in pregnancy	Maradit e Geiger (1999)	Prospective cohort	1 / 1	n.c
acitretin prior to pregnancy	Maradit e Geiger (1999)	Prospective cohort	2 / 47	4 % (1-14%)

The teratogenic action of isotretinoin performs the differentiation and migration of neural crest cells. Following the failure of various prevention programs in the United States (MMWR 2000) and elsewhere (Atanakovic and Koren 1999, Autret et al 1997, Chan et al 1996), aiming at warning about teratogenic effects of isotretinoin, FDA has promoted a program concerning the handling of teratogenic risk associated to the use of retinoids (Lowenstein 2002). The aim being no treatment during pregnancy, and no pregnancy during treatment, the program is based on the following items:

- doctors must not prescribe isotretinoin as drug of first choice, but only for severe, nodular acne not responding to any other treatment;
- doctors are due to study Roche "SMART (System to Manage Accutane-Related Teratogenicity) – Guide to Best Practice" handbook, sign a letter of "comprehension of the subject" and mail it back to Roche;
- FDA encourages doctors to follow an half-a-day ECM course organized by Roche;
- doctors who have attended the course receive a sticker to put on prescription and tell the pharmacist that the woman proved negative to the pregnancy

test and that she has been adequately informed about checking her fertility and making a monthly pregnancy test;

- the validity of a prescription cannot exceed one month;
- women should follow the doctor's recommendations, find out the most suitable way to check their fertility, make the monthly pregnancy test on blood, sign the informed consent, and have the opportunity to be included in the monitoring program;
- pharmacists should provide women with an informative handbook, give the drug only when the prescription bears the sticker, and only within one month since the date of the prescription itself.