Exposures during pregnancy

Isotretinoin cases in the Finnish TIS database

Isotretinoin exposures during pregnancy still occur despite pregnancy prevention programmes having been available for decades.

Maria Ellfolk[1], Melinda Gonzalez[1], Julia Reponen[1], Anna Korpelainen[1], Heli Malm[1,2,3,4].
[1]Teratology Information Service, Emergency Medicine and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[2]Department of Clinical Pharmacology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[3]Individualized Drug Therapy Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[4] Department of Child Psychiatry, University of Turku, Turku, Finland

Background

Isotretinoin is a known teratogen and causes malformations in up to 35% of exposed fetuses. Synthetic retinoids interfere with neural crest cell migration and typically affected organs are the heart and the central nervous system.

In order to prevent fetal exposure, a number of different pregnancy prevention measures have been introduced by regulating authorities over the years. The latest was introduced by EMA in March 2018 and passed as law in July 2018 by the European Commission and is legally binding in all EU member states (Table 1). In Finland additional measures are taken to minimize the risk of pregnancy during isotretinoin treatment (Table 2). The commission also requires the manufacturers to follow up the efficacy of the latest pregnancy prevention programs by following the amount of isotretinoin exposures during pregnancy.

Materials and methods

We performed a search of isotretinoin related inquiries in the Finnish TIS database. The search covered the period from June 1st 2006 to Jan 31st 2023.

Results

The total number of annual contacts to the Finnish TIS during the study period ranged between 6,000-9,000 contacts per year. During this time 234 isotretinoin inquiries have been reported in the database. Most of them concern the length of the washout period.

The number of pregnancies with isotretinoin exposure during organogenesis remained stable with an average of 1-2 cases each year and reaching a total of 26 cases through the study years (Figure 1).

Information concerning reasons for exposure during organogenesis was available in 17 cases, among them 15 cases with unreliable contraception or no use of any contraception (Table 3).

Conclusions

Despite pregnancy prevention programmes exposures to isotretinoin during pregnancy still occur. Further studies evaluating the effectiveness of the pregnancy prevention programs and reasons for their failure are needed.

Table 1. EMA isotretinoin pregnancy prevention programme (July 2018).

- assessment of each woman's **potential to become pregnant**
- **pregnancy tests** (before, during and after stopping treatment)
- need to use **at least one effective** method of **contraception** during and after treatment
- risk acknowledgement form to confirm that appropriate advice has been given (and understood) to the patient

Table 2. Additional isotretinoin pregnancy prevention measures in Finland (September 2018).

In addition to the EMA pregnancy prevention programme, the following measures are taken in Finland:

- **prescribed only by dermatologist**
- women who can become pregnant:
  - prescription for 30 days treatment (new prescription required for continuing treatment)
  - prescription valid only for 7 days from prescription date

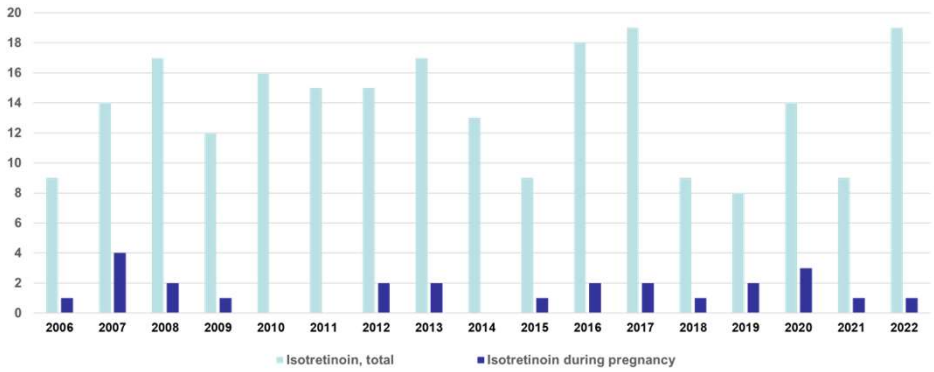

Figure 1. *Number of calls concerning isotretinoin, years 2006-2022.*

Table 3. Reasons for isotretinoin pregnancy exposure.

Reason	Number	Comment
Contraception failed	2	
Unreliable type of contraception	5	All cases before 2017
Did not use contraception	10	
• **Thought pregnancy not possible**	5	
• **Prescribed, refused using or use unknown**	2	
• **Prescribed, stopped using**	3	