

Possible long term teratogenic effect of isotretinoin in pregnancy

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Abstract. – The isotretinoin, a 13-cis-retinoic acid, has revolutionized the management of severe treatment-resistant acne and it has been widely used for a range of dermatological conditions, in 90% of the time in young women between 13 and 45 years of age. This agent has severe teratogenic effects, as serious craniofacial, cardiovascular, thymic and central nervous system malformations. The baseline population risk of malformations is 3-5%, but it increases to almost 30% in women exposed to isotretinoin during the first trimester of pregnancy. Generally, patients in treatment with isotretinoin avoid eventual pregnancy during assumption and, after its stopping, fertility and foetal development are normal once circulating isotretinoin levels return to normal. There are no known deleterious effects on male fertility and on long term teratogenic effect of isotretinoin. In this report, we suppose the possibility to develop a foetal malformations after a long term wash out from isotretinoin therapy. A 32 year-old healthy nullipara pregnant woman, with an uneventful past gynaecological history, was admitted in Hospital, with a severe depressive syndrome in a 18 weeks malformed pregnancy for thoraco-omphalopagus conjoined twins. She only assumed isotretinoin, at dose of 1 mg/kg a day, for a severe and scarring acne for 7 months. After 3 months of pharmacological wash out, patient become pregnant and manifested this severe malformation. Woman interrupted gestation, by labour induction.

Key Words:

Isotretinoin, Acne, Teratogenicity, Foetal malformations, Conjoined twins.

Introduction

The use of oral isotretinoin (13-cis-retinoic acid) has revolutionized the management of severe treatment-resistant acne and it has been

widely used for other dermatological conditions, such as gram-negative folliculitis, recalcitrant rosacea, pyoderma faciale, generalized lichen planus, psoriasis, cutaneous lupus erythematosus¹.

Isotretinoin major indication rests in severe nodular acne, but it is commonly used for severe acne that is resistant to oral antibiotics as well².

Isotretinoin is used 90% of the time in young people between 13 and 45 years of age and 50% of isotretinoin prescriptions are for women³. Since 1983, when the teratogenicity of isotretinoin was first documented in humans, the US Food and Drugs Administration (FDA)⁴ has met frequently to make recommendations to balance the needs of patients with severe cystic acne to receive isotretinoin with the need to protect foetus from exposure. Nevertheless, isotretinoin is currently the most broadly prescribed teratogenic drug in the USA and Canada⁵.

In case of isotretinoin prescription, two means of birth control, one either hormonal or surgical, are required for all fertile women taking the drug and should be continued for one menstrual period after the treatment is stopped. After a course of isotretinoin, fertility and foetal development are normal once circulating isotretinoin levels return to normal. There are no known deleterious effects on male fertility and on long term teratogenic effect of isotretinoin⁶.

In this paper we report a case of possible late teratogenic effect after isotretinoin assumption for severe and scarring acne.

Since the thalidomide disaster of the 1960s, physicians and the population as a whole have developed an increased awareness of the potential side-effects of drug exposure during pregnancy; nevertheless, it remains that known teratogenic pharmacologic agents are still being prescribed without a proper physician surveillance, as in the case of isotretinoin prescription.

The introduction of isotretinoin in 1982 was a milestone in the treatment of recalcitrant nodular acne; although the severe teratogenic effects of the drug quickly became evident³⁻⁵. Isotretinoin use rapidly increased and was inappropriately extended to patients with less severe forms of acne².

By molecular side, isotretinoin is a synthetic retinoid that inhibits the differentiation of sebaceous glands, corrects the keratinisation defect in the follicle, and has also some anti-inflammatory activity. However, along with its wide usage, there are growing concerns about its side-effects, and the most important side effect is the teratogenicity^{7,8}.

Despite clear labelling of isotretinoin is contraindicated during pregnancy, birth defects consequent to in utero exposure to isotretinoin are still reported soon after dispensing of the drug and they include serious craniofacial, cardiovascular, thymic and central nervous system malformations¹⁰.

The baseline risk of malformations in the population is from 3 to 5%, but it has been reported to increase to almost 30% in women exposed to isotretinoin during the first trimester of pregnancy, in an analysis of spontaneous report databases or self-report surveys⁸⁻¹⁰.

Isotretinoin utilization in women of childbearing age is a very important public health issue because of spontaneous and elective abortions, children with major malformations¹⁰. All of these will require continuous healthcare services throughout their lifetime. It is an even more important problem due to the fact that it is surely preventable with medical controls¹¹.

Since the drug was approved in 1982 and until 2000, the manufacturer has documented 1995 isotretinoin-exposed pregnancies, which it is obviously believed is an under-representation of the total number of exposed pregnancies¹².

Likely the patients in treatment for dermatologic conditions assumed adequate contraception methods during the isotretinoin therapy, to avoid the eventual pregnancy insurgence. In literature, few reports are on late teratogenic complications after the isotretinoin stopping of assumption.

Short Report

A 32 year-old healthy pregnant woman, 0 Para, with an uneventful past gynaecological history, was admitted in Hospital in the beginning of the year, with a severe depressive syndrome in a

18 weeks malformed pregnancy for thoraco-omphalopagus conjoined twins (Figure 1).

In the clinical history, she had a menarche at 12 years, regular meshes and she didn't assume estro-progestin contraception or other medical treatment in the last year. Patient only assumed isotretinoin (Roaccutane, F. Hoffmann-La Roche Ltd, Basle, Switzerland) at dose of 1 mg/kg a day (her's weight was about 60 kg) for a severe and scarring acne for 7 months, stopping at the end of may of 2008. After 3 months, in September 2008, patient become spontaneously pregnant and followed the routinely medical and ultrasonographical checks.

Woman requested to interrupt gestation, as conceded by the Italian law. She received an abortive labour induction after 5 gemeprost application (1 for each 3 hours), and delivered thoraco-omphalopagus female conjoined twins (Figures 2 and 3).

The post-operative recovery was normal, the patient had regularly discharged from the Hospital the day after abortive delivery, with no additive therapy.

Discussion

Although investigations have studied the use and pharmacological impact of isotretinoin in young women^{14,15}, it has been solely done in restricted populations with low participation rates, small sample sizes, self-reports or retrospective data collection schemes. The inconclusive dates of the studies are thus prone to various biases, in-



Figure 1. Median sagittal transabdominal sonographic foetal image of two stomachs (*stomaco*) in a unique abdomen.



Figure 2. Photo of the thoraco-omphalopagus conjoined twins: two bodies are fused from the upper chest to the lower chest, with four arms and two legs.

cluding selection bias, and leading to unknown absolute pregnancy exposure and early and late malformation rates in the population.

On foetal malformations evidenced in the case reports, the conjoined twins, identical twins with



Figure 3. A particular of genital part of conjoined twins: it is recognizable the female sex of twins.

bodies joined in utero, is a rare malformation. Its occurrence is estimated from 1 in 50,000-200,000 births, approximately half are stillborn, the overall survival rate is approximately 25%, and a smaller fraction of pairs born alive have abnormalities incompatible with the life. This malformation is more frequently found among the females, with a ratio of 3:1, and conjoined twins are typically classified by the point at which their bodies are joined¹³.

The most common types of conjoined twins are showed in Table I. This malformation, in absence of risk factor, should be included in a general estimation occurrence. However, after a isotretinoin therapy, she could be strongly linked to the long

Table I. SMost common types of conjoined twins, percentage in general population and characteristics.

Type of conjoined twins	Percentage	Characteristics
Thoraco-omphalopagus	28% of cases	Two bodies fused from the upper chest to the lower chest, usually share a heart, and may also share the liver or part of the digestive system
Thoracopagus	18.5% of cases	Two bodies fused from the upper thorax to lower belly and the heart is always involved in these cases
Omphalopagus	10% of cases	Two bodies fused at the lower chest, the heart is never involved in these cases; however, the twins often share a liver, digestive system, diaphragm, and other organs
Parasitic twins	10% of cases	Twins that are asymmetrically conjoined, resulting in one twin that is small, less formed, and dependent on the larger twin for survival
Craniopagus	6% of cases	Fused skulls, but separate bodies; these twins can be conjoined at the back of the head, the front of the head, or the side of the head, but not on the face or the base of the skull

term teratogenic effect of this agent. Therefore, by these evidences, we hypothesize for this case report a possible connection between the isotretinoin assumption for 7 months and the insurgence of malformed pregnancy with conjoined twins after 3 months of wash out from medicine.

In conclusion, even if it is stated that the isotretinoin causes malformation in pregnancy¹⁶, nobody has reported the long term risk of malformation after isotretinoin therapy stopping. In this report, we suppose the possibility to develop a foetal malformations also after a long term wash out from isotretinoin therapy.

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