

Bilateral Anotia with Exposure to Retinoic Acid during Pregnancy

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Introduction

Isotretinoin (13-cis retinoic acid) is the most potent known inhibitor of sebum production and is by far one of the most effective antiacne medications for the treatment of severe and scarring acne, but it has been shown to be teratogenic when used during pregnancy. The risk of malformations in the population is 3-5%, but it has been reported to increase to almost 30% in women exposed to isotretinoin during the first trimester of pregnancy.

Congenital malformations associated with isotretinoin-exposed pregnancies include serious craniofacial, cardiovascular and central nervous system malformations. It is possible that a major mechanism of isotretinoin teratogenesis is a deleterious effect on cranial neural-crest cell activity that results in the observed craniofacial, cardiac, thymic and major auricular malformations including anotia and severe microtia, micrognathia, cleft palate, conotruncal heart defects and aortic-arch abnormalities, thymic defects, retinal or optic-nerve abnormalities (anophthalmia, microphthalmia, defects of the retina), and central nervous system malformations. The pattern of malformations closely resemble that are produced in animal studies of retinoid teratogenesis malformations [1,2]. Here we present a case of major auricular malformations with bilateral anotia after isotretinoin exposure during pregnancy.

Case Report

A 24 year old woman G1P0 has given birth of a term child without external ear folds. When her pregnancy history was checked, she told that when she got pregnant, she had been on acne vulgaris therapy (Ro-Accutane 2x1) because of her acneic lesions, as soon as she learned her pregnancy (after one week of missed days), she had discontinued the drug and forgot to tell her doctor about it. Her first and second trimester scans reported no major anomalies. After birth, bilateral anotia was detected, A CT (computerized tomography) scan was done to determine the anatomy of the bony structures and middle and inner ears. Tomography of the fetal cranium showed no external or inner ear structures only including hypoplastic lateral semicircular canals (Figures 1 and 2). She was discharged from the hospital with bookings from genetics, cardiology, plastic surgery and head, neck surgery (otolaryngology), for the baby.

Discussion

Isotretinoin is an orally active retinoic acid derivative for the



Figure 1: Left ear fold.

treatment of refractory nodulocystic acne. The pharmacological profile of isotretinoin suggests that it acts primarily by reducing sebaceous gland size and sebum production. The drug is widely distributed throughout body tissues. Despite clear labelling of isotretinoin as contraindicated during pregnancy, birth defects consequent to inutero exposure are still reported even after dispensing of the drug because it is deposited in the adipose tissue. The critical period for exposure appears to be two to five weeks postconception, although this is clinically inexact. Isotretinoin's half life is less than a day, although a teratogenic metabolite, 4-oxo-isotretinoin, has a half life of several days [3,4].

The most frequently reported severe birth defects involved in the central nervous system are microcephaly or hydrocephalus), in the cardiovascular system are anomalies of the great vessels. The major mechanism of isotretinoin teratogenesis is a effect on the development of cephalic neural-crest cell activity [3-5].

Isotretinoin should be used with two forms of birth control in reproductive years and some authors recommend even six months of birth control after discontinuation of the drug [4,5].

Lammer et investigated 154 human pregnancies with fetal exposure to isotretinoin. They found a characteristic pattern of malformations involving craniofacial, cardiac, thymic, and central nervous system structures. The number of malformations included microtia/anotia [5] infants), micrognathia [6], cleft palate [3], conotruncal heart defects and aortic-arch abnormalities, thymic defects [7], retinal or optic-nerve abnormalities [4], and central nervous system malformations [8]. He pointed out that exposure to isotretinoin was associated with an unusually high relative risk for a group of selected major malformations (RR=25.6; 95%CI interval, 11.4-57.5) [5].



Figure 2: Right ear fold.

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In literature, microtia or absence of external ears were also noted in majority of cases like our case [6,7] but there are also rare expressions of the drug like a newborn with asymmetric crying face whose mother had taken isotretinoin during the first month of pregnancy. Asymmetric crying face is a rare finding of retinoic acid embryopathy and results from the intrauterine effects of retinoic acid on the development of the depressor anguli oris muscle or the mandibular branch of the facial nerve [8]. Another study reported that gestational isotretinoin exposure induces long-term cognitive deficits in the offspring [9].

Isotretinoin use in women of child bearing age is still a very important public health issue because of the risk of spontaneous and elective abortions and malformations. Children exposed to isotretinoin with major malformations will require continuous healthcare services throughout their lifetime; it is an even more important problem due to the fact that it is preventable. Women having this drug should not be pregnant at least two months after cessation of drug.

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