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Retinoids and teratogenicity

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ABSTRACT

For more than 30 years, retinoids have been used for acne treatment also their teratogenic effects are widely known. For any woman at a fertility age and under retinoid treatment, a contraception programme should be in place. Pregnancy should be postponed until the completion of treatment and one month afterwards. Multiple foetal abnormalities are directly linked to isotretinoin.

Keywords: retinoids, pregnancy, teratogen

INTRODUCTION

Retinoids are the preferred treatment for acne and are highly teratogenic. Whenever prescribed in a fertile woman, a form of contraception should be recommended to prevent pregnancy during treatment and for one month afterwards. However, undergoing termination for many patients is an excruciating decision to pursue an abortion. Unfortunately, literature data regarding retinoid teratogenicity are scarce, making counselling and managing antenatal care difficult for doctors.

RETINOIDS

Retinoids encompass a class of complexes that are connected to vitamin A. Discovered in the 1970s, isotretinoin was launched as a treatment in the 1980s, being known as Accutane. It lowers sebum secretion, a drug effect that is helpful in the systemic therapy of serious acne, scarring acne, nodulocystic and conglobate acne, which has not responded to systemic antibacterial, or acne associated with psychological issues [1].

Isotretinoin elimination can take two weeks of the last dose, but some researchers have shown that some persons have an elimination half-life of 167.4 hours, meaning 35 days period until safe levels were reached.

The dose usually given is 0.5-1.0 mg/kg/day once a day or twice a day, but this is related to the weight of the patient severity of the condition. The treatment lasts for four to 6 months, and the cumulative dose is of 120-150 mg/kg [2,3].

TERATOGENICITY

Ample evidence has shown that the main worry of isotretinoin, is teratogenicity when used systematically in pregnancy. Exposure to any teratogenic substance from day of conception to day 17 is associated with intact survival or death. Serious and permanent malformations can occur during the embryonic phase [4,5]. A theory that gain ground looking into isotretinoin toxicity, is hypervitaminosis A which is an artificial retinoid or vitamin A by-product. Retinoids are engaged in the HOX signalling gene lanes that are involved in the branchial arches (pharyngeal arches) during the fourth week of gestation. Subsequently, it is the derivatives of the pharyngeal arches that are most prone to de-

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fects caused by isotretinoin effects during pregnancy (Table 1) [6-9].

TABLE 1. Fetal consequences of isotretinoin use

Craniofacial abnormalities
• ear abnormalities
• eye abnormalities
• cleft palate
• retrognathia/small jaw
• depressed nasal bridge
• eye malformation (ocular hypertelorism)
Neurologic abnormalities
• small head (microcephaly)
• facial nerve palsy
• hydrocephalus and ventriculomegaly
• cortical and cerebellar abnormalities
Cardiovascular deficiencies
• Fallot's tetralogy
• ventricular and atrial septal defects
• TGA (transposition of the great arteries) and aortic arch narrowing
Thymic malformations
• hypoplasia
• aplasia and ectopia

Anotia, microtia and narrowing of the exterior part of the ear canal are all consequences of systemic administration of retinoids. Limb reduction has also been reported in isotretinoin. Up to 60% of children born with a normal appearance at birth may present neurological deficit, mental retardation (< 30%), and behavioural dysfunction. In fetuses exposed to retinoin the chances of fetal malformations are around 20-35% alongside an incidence of spontaneous miscarriage of 20-35%.This fact should be disclosed to parent [4,10]. Termination of pregnancy is frequently deemed as the safest option due to the known strong teratogenicity of retinoids. In a study published by Berard et al., 84% of women who fell pregnant on isotretinoin have chosen not to carry on with the pregnancy [11]. A common opinion is that safe levels are attained after two weeks of the last dose [1,12]. It is the authors' personal view that at the current stage, more evidence is necessary before recommending pregnancy at less than four weeks since the end of the treatment. After a comprehensive counselling majority of couples will choose to end the pregnancy. This fact was showed by Bernard et al., with 84% of couples choosing to stop the pregnancy. As it was alluded, safe amounts of isotretinoin are attained 2 weeks after the last dose. It is the authors' personal view that at the current stage, more evidence is necessary before recommending pregnancy at less than four weeks since the end of the treatment.

CONCLUSIONS

Isotretinoin is an efficient treatment for a troubling disorder. Unfortunately, it is particularly teratogenic. The effect on the foetus results in severe, permanent and untreatable conditions. To prevent these teratogenic effects, contraception is strongly recommended. If pregnancy occurs, while the patient is on treatment with isotretinoin, a personalised antenatal pathway should be tailored.

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