

Retinoic Acid Embryopathy

Retinoic acid is a derivative of vitamin A and is presently used effectively to treat a variety of skin disorders, including serious acne. It has long been recognized from animal studies that retinoic acid and isotretinoin are teratogens, but when isotretinoin came into general use for cystic acne in human patients, many pregnant women were exposed to it. A "retinoic acid embryopathy syndrome" is now recognized among babies whose mothers took vitamin A derivative during pregnancy. Features of the syndrome include abnormalities of the cranium and face, central nervous system, heart, and thymus. The authors point out that it is difficult to conduct a proper prospective study because most women on treatment elect termination of pregnancy. However, among 36 pregnancies studied prospectively, eight resulted in spontaneous abortions, 23 in normal infants at birth, and five in malformed infants.

This paper reports 21 malformed infants with a characteristic pattern of malformations. Cranial and facial

abnormalities include microtia and anotia, micrognathia, and cleft palate; cardiac anomalies include conotruncal heart defects and aortic arch abnormalities; central nervous system abnormalities include hydrocephalus, fourth-ventricle cyst, holoprosencephaly and microcephaly, as well as major errors in cortical and cerebellar neuronal migration; and thymus abnormalities include ectopia, hypoplasia, and aplasia.

The exact timing and mechanism of teratogenesis are unknown. The authors speculate that exposure to isotretinoin may produce abnormal cephalic-neural-crest-cell activity around the 28th day of gestation. This would imply that early exposure is of greatest concern. Isotretinoin has a short half-life of between 16 to 20 hours. Thus, it would appear that there is no long-term effect of isotretinoin ingestion, and nonpregnant women need not worry about an effect after discontinuing this medication. The exact dose that may produce anomalies has not yet been determined.

The data in this report suggest an increased risk for spontaneous abortions and a risk of about 20%

for having a child with obvious congenital anomalies at birth among women who have taken isotretinoin acid early in pregnancy.

Lammer EJ, Chen DT, Hoar RM, et al. *N Engl J Med* 1985;313:837-841.

Editor's comment—*It is quite clear from animal and now human studies that vitamin A and its analogues are teratogenic in humans and cause a characteristic pattern of anomalies. It is extremely important that physicians make this potential side effect clear to women of childbearing age when prescribing isotretinoin or other vitamin A preparations. If a woman has been inadvertently exposed, she must be offered the option of prenatal diagnosis because many of the structural defects can be identified prenatally. Many fetuses exposed to vitamin A derivatives will spontaneously abort. To date, over half the reported children who have been exposed to isotretinoin during the early stages of gestation appear normal at birth. However, long-term follow-up of their intellectual development has not yet been possible.*