What Is the Chance of a Normal Pregnancy in a Woman Whose Fetus Has Been Exposed to Isotretinoin?

Michael J. Sladden, MAE, MRCP(UK); Karen E. Harman, MD, MRCP; Department of Medicine, University of Tasmania, Launceston, Australia (Dr Sladden), and Department of Dermatology, Leicester Royal Infirmary, Leicester, England (Dr Harman)

Clinical Question: Recently, one of our patients who was taking isotretinoin became pregnant. This occurred despite appropriate counseling, a negative pregnancy test result before commencing treatment, and use of the combined oral contraceptive pill Microgynon 30 (Schering Health Care, West Sussex, England) (levonorgestrel, 150 µg, ethinylestradiol, 30 µg). The patient did not want to terminate her pregnancy. The aim of this Critically Appraised Topic is to explore the literature to determine the chance of delivering a healthy child after fetal exposure to isotretinoin; the types of fetal malformations associated with it; and what monitoring should be performed.

Background

Since introduction of the drug in 1982, over 2000 pregnancies in the United States have been affected by fetal exposure to isotretinoin,1 most resulting in spontaneous or elective abortions.2-6

Literature Search

We searched the Medline and EmBase databases from 1966 to March 2007 using the terms isotretinoin or Accutane or Roaccutane and pregnancy or birth defect.

Appraisal of the Evidence

We found 469 articles in the literature search and chose 2 case series3,4 that prospectively identified and followed up pregnancies in which the fetus was exposed to isotretinoin for which abortion was not elected.3,4 We extracted data from these 2 prospective studies to develop our clinical bottom line because these studies are likely to be less biased than the retrospective studies. These 2 studies collected data from a combined total of 151 pregnant women in the United States aged 14 years to older than 35 years whose fetuses were exposed to isotretinoin.

- In one study3 of 115 pregnancies, there were 21 spontaneous abortions (18%). Of the 94 live births, 61 were healthy infants (65% of births, 53% of pregnancies), 26 had congenital malformations consistent with isotretinoin embryopathy (95% confidence interval, 19%-37%).3
  - In the second study4 of 36 pregnancies, there were 8 spontaneous abortions (22%). Of the 28 live births, 23 were healthy infants (82% of births, 64% of pregnancies), and 5 had congenital malformations (18% of births, 14% of pregnancies).

The main abnormalities found in isotretinoin embryopathy are craniofacial, central nervous system, cardiovascular, and thymic.1,3,4,7,8
  - Craniofacial: ear defects, dysmorphism, cleft palate, depressed nasal bridge, hypertelorism;
  - Central nervous system: hydrocephalus, microcephaly, facial nerve palsy, cortical and cerebellar defects;
  - Cardiovascular: Fallot's tetralogy, transposition of great vessels, septal defects, aortic arch hypoplasia;
  - Thymic: ectopia, hypoplasia, aplasia; and
  - Miscellaneous: spina bifida, limb reduction.

In addition, fetal exposure to isotretinoin is associated with high risk of adverse outcome with respect to mental functioning.9 The United Kingdom National Teratology Information Service10 estimates that in fetal exposure to isotretinoin, 30% of infants with no gross malformations have mental retardation, and up to 60% have impaired neuropsychological function.

The National Teratology Information Service recommends that women who wish to continue their pregnancy after fetal exposure to isotretinoin should have alphafetoprotein testing at 16 to 19 weeks' gestation and undergo a targeted ultrasound scan and echocardiography at 20 to 21 weeks' gestation.10 These investigations would give some indication of the risks of structural malformations so that parents can plan support services and, in rare instances, in utero intervention could be performed, if appropriate.

The high rate of fetal exposure to isotretinoin and its serious teratogenicity are clearly illustrated. The US Food and Drug Administration has recently approved the “iPLEDGE” risk management program,11 which is designed to reduce the risk of fetal exposure to isotreti-
noin. However, it is also important that dermatologists prevent pregnant women from taking the medication (document proof of no pregnancy) and prevent women who are taking it from getting pregnant (use of 2 forms of birth control).

Limitations

There is no dose of oral isotretinoin that is safe for use in pregnant women,

and, consequently, there are no published studies of women who took isotretinoin throughout pregnancy. Therefore, information about safety must be obtained from studies in which isotretinoin was taken for acne during some portion of pregnancy.

Reported outcomes of retrospectively and prospectively ascertainment cases differ considerably. Therefore, we have based our conclusions on data from prospective studies because of the strong likelihood of bias (especially reporting bias) associated with retrospective studies. Published prospective outcome data are available for only a small proportion of pregnancies in which the fetus was exposed to isotretinoin because most of these pregnancies are not reported in the literature.

The level of fetal exposure to isotretinoin varies from pregnancy to pregnancy so it is possible that isotretinoin-related problems may be higher for women who continue taking isotretinoin for a longer period of time before discovering that they are pregnant. However, there is insufficient data to address this issue. There is little information about the timing of spontaneous abortions, either in weeks or trimesters. There is little follow-up data on infants with no gross malformation to determine the risk of developmental disabilities later in life.

Clinical Bottom Line

In pregnancies in which the fetus is exposed to isotretinoin,

• The risk of spontaneous abortion is approximately 20%;

• In pregnancies that progress, 65% to 82% of neonates appear normal at birth, but there is insufficient data to determine how many will later develop isotretinoin-related problems;

• There is an 18% to 28% risk of isotretinoin embryopathy;

• There is no safe level of exposure; any exposure can cause malformation;

• The main abnormalities are craniofacial, cardiac, central nervous system, and thymic; and

• Women who choose to continue their pregnancy require careful support and monitoring.

Finally, it is important that dermatologists prevent pregnant women from taking isotretinoin and prevent women who are taking it from getting pregnant.

What Happened to Our Patient?

Our patient ceased taking isotretinoin as soon as she discovered that she was pregnant, at approximately 6 to 7 weeks’ gestation. We discussed with her the evidence regarding isotretinoin and birth defects. She elected to continue with her pregnancy and underwent regular ultrasound scans, performed by her obstetrician. She delivered a healthy baby girl, with no apparent birth defect. At age 18 months, her daughter was developing normally.

REFERENCES


