Cleft Palate and Toe Malformations in a Child With Fetal Methotrexate Exposure

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Methotrexate, a commonly administered chemotherapeutic agent, is a well-known human teratogen. Exposure of a fetus between 6 and 8 weeks of gestation is postulated to cause birth defects. However, fetal exposure to this drug after this critical period is thought to have little to no effect on eventual fetal development and growth. The authors report a case of an infant whose mother was exposed to methotrexate during pregnancy. The infant was evaluated at their clinic for an incomplete cleft palate and associated asymmetric deformities of the toes on both feet.

CASE REPORT

A 38-day-old infant presented to the cleft/craniofacial clinic for evaluation of an incomplete cleft palate and associated bilateral deformities of the toes. The baby’s mother had taken methotrexate for the management of a molar pregnancy at approximately the eighth week of gestation.

The infant presented with a cleft of the soft palate. The remainder of the head and neck examination and examination of both upper extremities were normal.

The right foot revealed an agenesis of the fifth toe with a foreshortened second toe. The remainder of the foot was apparently normal on physical examination. Examination of the left foot revealed fusion of the third, fourth, and fifth toes with clinodactyly of the second toe. The remainder of the left foot and lower extremity was also normal on physical examination.

DISCUSSION

Methotrexate is a medication commonly administered as part of cancer chemotherapy protocols and for the management of rheumatoid arthritis.
It also can be used to manage molar or ectopic pregnancies and as an abortifacient.

Methotrexate and its active metabolites compete for the folate-binding site of dihydrofolate reductase, an enzyme critical in the production of DNA, RNA, and ultimately in protein synthesis. Embryonic exposure to methotrexate has been shown to cause birth defects in chicks, mice, rats, and rabbits.

The key period of teratogenicity for methotrexate is thought to occur between the sixth and eighth weeks of gestation. One case of a milder set of birth defects possibly related to methotrexate given in the eleventh week of gestation has been reported.1 The minimum dose needed to produce birth defects is thought to be more than 10 mg a week.2 Typical patterns of birth defects that have been associated with methotrexate include growth deficiency; micrognathia; hypoplastic supraorbital ridges; small, low-set ears; and limb abnormalities. Developmental delay has also been reported.3 A previous report describes an adult with physical attributes of fetal methotrexate syndrome who has apparently normal mental development.4

While it can be used as a safe chemotherapeutic agent, such cases serve as a reminder that significant defects can and do occur if methotrexate is given during pregnancy.

REFERENCES