Motherisk Update

Prolonged exposure to angiotensin-converting enzyme inhibitors during pregnancy

Fetal toxicity could be reversible

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ABSTRACT

QUESTION I read in a Motherisk Update that angiotensin-converting enzyme (ACE) inhibitors are contraindicated during pregnancy. Many women, however, do not know they are pregnant for quite some time after conception. One of my patients was taking ACE inhibitors for 3 to 4 months while she was pregnant. How should I advise her?

ANSWER The deleterious effects ACE inhibitors have on fetuses were seen only after exposure during the second and third trimesters and were mostly secondary to renal damage. These effects can be reversed, as described in this Motherisk Update.

RÉSUMÉ

QUESTION J'ai lu dans une mise à jour de Motherisk que les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA) sont contre-indiqués durant la grossesse. Par ailleurs, il faut à plusieurs femmes un certain temps après la conception pour se rendre compte qu'elles sont enceintes. L'une de mes patientes a pris des inhibiteurs de l'ECA pendant les trois ou quatre premiers mois de sa grossesse. Quels conseils devrais-je lui donner?

RÉPONSE Les effets néfastes des inhibiteurs de l'ECA sur les fœtus n'ont été observés qu'après une exposition durant les deuxième et troisième trimestres et ils étaient principalement reliés à des dommages rénaux. Ces effets peuvent être réversibles, comme il est décrit dans la présente mise à jour de Motherisk.

Angiotensin-converting enzyme (ACE) inhibitors are first-line medications in treatment of hypertension and cardiac and renal diseases. Investigators consistently report fetal toxicity after maternal exposure to ACE inhibitors during late pregnancy. Adverse effects include fetal renal dysplasia, oligohydramnios, intrauterine growth restriction, skull hypoplasia, patent ductus arteriosus, pulmonary hypoplasia, and deformities of the limbs.[1]

Approximately half of all pregnancies are unplanned,[2] so physicians should be prepared to give accurate information and counseling to women who take ACE inhibitors during pregnancy. We thought it would be useful to present a case where there were sonographic signs of fetal ACE-inhibitor toxicity and then a favourable outcome after the ACE inhibitor was discontinued.

Case

A 28-year-old woman in her second pregnancy was referred to Mount Sinai Hospital in Toronto, Ont, for evaluation at 25.5 weeks' gestation. Her medical history included chronic renal disease and hypertension secondary to mixed connective tissue disease. She was taking 60 mg of nifedipine,

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50 mg of atenolol, 200 mg of hydroxychloroquine, and 50 mg of ramipril (an ACE inhibitor) each day.

Her current pregnancy had been diagnosed only 3 weeks before the referral. At that time, she had had an ultrasound scan that demonstrated fetal biometry consistent with a fetus of 22 weeks' gestation. Fetal anatomy was normal, but severe oligohydramnios was noted. Otherwise, the pregnancy appeared to be uncomplicated. Following the scan, the ramipril was discontinued, and her dosage of atenolol was increased.

Three weeks later, a detailed ultrasound examination revealed that the amniotic fluid volume had returned to normal with an index of 15.3. Fetal anatomy was normal, except for the presence of a two-vessel cord. Appropriate fetal body and breathing movements were seen. Results of Doppler scans of the umbilical artery and the middle cerebral artery were normal. Estimated fetal weight was at the 15th percentile for 25 weeks' gestation. No further deterioration in the fetus's condition was noted, but at 30 weeks' gestation, the patient was admitted for cesarean section because of worsening hypertension and renal function.

An 880-g female infant was delivered, with Apgar scores of 8 and 9 at 1 and 5 minutes of age, respectively. Because of increasing respiratory distress, she was intubated at 90 minutes of age and received two doses of surfactant. She was ventilated for 6 days, and she needed continuous positive airway pressure for 14 days. She developed mild physiologic jaundice with a maximum bilirubin level of 197 µmol/L on day 8. Results of an ultrasound scan of her head were normal. She was passing 4 to 6 mL/kg of urine hourly from day 1. Her renal function tests showed abnormally high initial levels that eventually settled in the first 48 hours. Her creatinine levels were 188, 148, 112, 72, and 58 µmol/L and her urea level was 12.2, 17.4, 15.6, 7.3, and 5.8 mmol/L at 24, 36, 48, 60, and 120 hours old, respectively.

Mechanism

Studies in animals have shown a high incidence of fetal death and stillbirth with use of ACE inhibitors during pregnancy.[3,4] The deleterious fetal outcomes, namely oligohydramnios, intrauterine growth restriction, skull hypoplasia, patent ductus arteriosus, oligohydramnios-related pulmonary hypoplasia, and limb deformities, result from two mechanisms: damage to fetal kidneys and a decrease in uterine blood flow that leads to decreased oxygen delivery to the fetus.[5] These conditions are secondary to the direct effect of an ACE inhibitor on the fetal renin-angiotensin system.[6,7]

Epidemiology

Epidemiologic evidence regarding fetal ACE-inhibitor toxicity is based mostly on case reports and case studies. It is important to note that no teratogenic effects were noted in reports of infants exposed to ACE inhibitors (mainly captopril or enalapril) during only the first trimester.[8-10] In contrast, there is concern when use of ACE inhibitors continues into the second and third trimesters. This concern is increasing as reports of grave fetal outcomes are being published frequently.[11]

The exact rate of severe adverse fetal or neonatal outcomes can only be estimated in the absence of cohort studies. One obstacle in estimating the effect of ACE inhibitors on a fetus is the confounding effect of maternal disease. As in the case presented here, hypertension treated with ACE inhibitors might have various causes, including some very severe maternal conditions, such as lupus erythematosus and renal transplantation. These underlying conditions themselves could contribute to adverse fetal outcomes. Although data are limited, there does not appear to be a strong teratogenic risk for women exposed to ACE inhibitors when they conceive.[12]

Discontinuation of ACE inhibitors before the second trimester is recommended by the US Food

and Drug Administration because of the effects seen in both humans and animals. As our case demonstrates, however, poor neonatal outcome after prolonged exposure to ACE inhibitors is not inevitable, and the effect of long-term antenatal exposure to ACE inhibitors could be reversible.

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Dr Shrim is a member and Dr Koren is Director of the Motherisk Program. Dr Shrim, Dr Berger, Dr Kingdom, and Dr Hamoudi are physicians in the Maternal-Fetal Medicine Division of the Department of Obstetrics and Gynecology at the University of Toronto and Mount Sinai Hospital. Dr Shah practises in the Department of Pediatrics at Mount Sinai Hospital and teaches at the University of Toronto. Dr Koren is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

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