

Taking angiotensin-converting enzyme inhibitors during pregnancy

Is it safe?

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Abstract

Question One of my 35-year-old pregnant patients has been treated with enalapril for primary hypertension. She learned she was pregnant at 11 weeks' gestation. I read somewhere that angiotensin-converting enzyme (ACE) inhibitors can cause malformations. What advice do you give to Motherisk callers?

Answer Most published studies have failed to show an effect of ACE inhibitors on congenital malformations. A recent systematic review and meta-analysis conducted by Motherisk does not suggest increased fetal risk of malformations. However, ACE inhibitors should be avoided in late pregnancy, as they might cause renal failure and acalvaria in the baby.

Les inhibiteurs de l'enzyme de conversion de l'angiotensine durant la grossesse

Sont-ils sécuritaires?

Résumé

Question L'une de mes patientes enceintes âgée de 35 ans est traitée avec de l'énalapril pour une hypertension primaire. Elle a appris qu'elle était enceinte après 11 semaines de gestation. J'ai lu quelque part que les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA) peuvent causer des malformations. Quels conseils donnez-vous à ceux qui posent des questions à ce sujet à Motherisk?

Réponse La plupart des études publiées n'ont pas réussi à révéler des effets attribuables aux inhibiteurs de l'ECA sur les malformations congénitales. Une récente synthèse critique et une méta-analyse réalisées par Motherisk n'indiquent pas qu'il puisse y avoir des risques fœtaux accrus de malformations. Toutefois, il faudrait éviter les inhibiteurs de l'ECA en fin de grossesse, car ils pourraient causer une insuffisance rénale et l'absence de voûte crânienne chez le bébé.

Essential hypertension is a common diagnosis among young women.¹ Depending on the population studied, the incidence during pregnancy ranges from 0.5% to 3.0%.² Different types of hypertensive disorders during pregnancy include chronic hypertension, gestational hypertension, and preeclampsia, accounting for most antenatal care provision.³ Risks to the mother include maternal death, stroke, heart failure, and pulmonary edema. The fetus is also at risk, and common fetal complications include intrauterine growth restriction, placental abruption, and prematurity.⁴

Angiotensin-converting enzyme (ACE) inhibitors are widely used as first-line therapy for chronic hypertension. They are frequently used in women of reproductive age; consequently, some women are bound to be taking ACE inhibitors at the time of conception, as more than half of all pregnancies are unplanned.⁴

Captopril, enalapril, and lisinopril cross the human placenta in pharmacologically significant amounts. It is

conceivable that other ACE inhibitors have similar placental transfer.^{5,6}

Animal studies

While the results of animal studies on the use of ACE inhibitors during pregnancy vary, most of them have failed to show increased malformation rates. However, animal data reveal increased morbidity and mortality in fetuses exposed to ACE inhibitors in utero. A prospective placebo-controlled study of baboons showed a significant increase in fetal death or fetal growth restriction (4 of 13) in the group treated with enalapril when compared with placebo ($P < .05$).⁷ Use of captopril in maternal sheep during late pregnancy caused low fetal blood pressure, and the risk of stillbirth was substantially elevated.⁸

First-trimester human exposure

Cooper and colleagues⁹ reported an increased risk of congenital malformations in fetuses exposed to

ACE inhibitors during the first trimester. They studied a cohort of 29 507 infants who were enrolled in Tennessee Medicaid, who were born between 1985 and 2000, and for whom there was no evidence of maternal diabetes. Out of this cohort, 209 infants with exposure to ACE inhibitors in the first trimester were identified. The risk ratio for major congenital malformations was 2.71 (95% CI 1.72 to 4.27). It has been argued that these findings were affected by confounding and ascertainment biases. These include the inability to exclude women with undiagnosed or diet-controlled type 2 diabetes mellitus, no adjustment for prepregnancy body mass, which is a considerable predictor of risk of type 2 diabetes mellitus, and uncontrolled hypertension.¹⁰ In infants, maternal obesity is an independent risk factor for neural tube defects and cardiac malformations.^{11,12}

Recently, Motherisk¹³ conducted a systematic review of the literature and meta-analysis evaluating the use of ACE inhibitors during the first trimester of pregnancy and their association with major congenital malformations. We identified 5 cohort studies for the meta-analysis and included 19 case reports, case series, or case-control studies in the descriptive part of the systematic review. The meta-analysis failed to demonstrate an increase in major malformations after use of ACE inhibitors or angiotensin II receptor blockers (ARBs) specifically, with no difference from exposure compared with other antihypertensive medications. The systematic review of the case reports and case series published in the past 25 years involved 424 pregnancies. These reports do not suggest a specific pattern of malformations.

Diav-Citrin et al recently studied 252 pregnancies exposed to ACE inhibitors and ARBs, 256 pregnancies exposed to other antihypertensive medications, and 495 control pregnancies from 2 teratology information services in Israel and Italy. They concluded that ACE inhibitors and ARBs are not major teratogens when used in the first trimester, and the risk of major congenital malformations was comparable between the groups ($P = .95$). In this study, women with known diabetes (both pre-existing and gestational) were not excluded, and there was no adjustment for maternal body mass index.¹⁴

Serreau et al reported on 10 cases of pregnant women exposed to ARBs during early pregnancy. One out of the 8 fetuses exposed exclusively during the first trimester was reported to have craniofacial dysmorphism, clinodactyly, and tubular dysplasia.¹⁵

In a cohort retrospective review of 348 989 infants or fetuses from all pregnancies in Finland ($N = 343\,324$), exposure of infants or fetuses to ACE inhibitors ($n = 137$) was associated with an increased risk of major congenital malformations, mostly cardiac. However, when adjusted for diabetes, the excess risk was nullified.¹⁶

Lenestål et al¹⁷ reported on a cohort of 1418 women from the Swedish Medical Birth Register who had used antihypertensive drugs in early pregnancy but who did not have diabetes. Cardiovascular defects occurred with an adjusted odds ratio of 2.59 (95% CI 1.92 to 3.51). However, the results were similar when the women had used ACE inhibitors or other antihypertensive drugs, without any clear drug specificity.

In France, data on 159 pregnancies with exposure to ACE inhibitors and 159 controls were obtained. Pregnancies with confirmed first-trimester exposure to ACE inhibitors were included. The rate of major malformations in live births or stillbirth was not different between the 2 groups (relative risk 1.5, 95% CI 0.3 to 6.5).¹⁸

Second and third trimesters

Second- and third-trimester exposure to ACE inhibitors is associated with oligohydramnios, hypocalvaria, anuria, renal failure, neonatal hypotension, and patent ductus arteriosus.¹⁹⁻²¹ It is also associated with aortic arch obstructive malformations.²² Some of these infants exhibit severely impaired renal function and hypoplastic lungs owing to oligohydramnios, and they might progress to death or end-stage renal failure. The cause of these defects appears to be related to inhibitory effects on the renin-angiotensin-aldosterone system.²³ The morbidity is estimated to be quite high; it is between 10% and 20% of infants exposed.⁴

Conclusion

The use of ACE inhibitors during the first trimester of pregnancy does not appear to increase the rate of congenital malformations; recent studies strongly suggest that the original report by Cooper et al⁹ might reflect uncontrolled confounding.

However, discontinuation of ACE inhibitors before the second trimester is recommended to avoid the well documented pattern of fetal risks. 

Competing interests

None declared

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Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future Motherisk Updates.

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