

MOTHERISK UPDATE

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Taking ACE inhibitors during pregnancy

Is it safe?

ABSTRACT

QUESTION A pregnant patient is taking enalapril for primary hypertension. How safe are angiotensin-converting enzyme inhibitors (ACEI) during pregnancy?

ANSWER Evidence of whether ACEIs cause problems during the first trimester of pregnancy is reassuring. There is evidence that they cause severe renal and other problems during the second and third trimesters, however. These drugs should be avoided during pregnancy.

RÉSUMÉ

QUESTION Une patiente enceinte prend de l'énalapril pour une hypertension primaire. Les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) sont-ils sans risque durant la grossesse?

RÉPONSE Les données probantes à savoir si les IECA causent des problèmes durant le premier trimestre de la grossesse sont rassurantes. Par ailleurs, il est démontré qu'ils causent de graves problèmes néphrologiques et d'autres problèmes durant le deuxième et le troisième trimestres. Ces médicaments devraient être évités durant la grossesse.

Incidence of chronic hypertension during pregnancy ranges from 0.5% to 3.0% depending on the population studied.¹ Maternal and perinatal morbidity and mortality are generally not increased when patients have uncomplicated mild chronic hypertension. Risks to both mother and fetus increase dramatically, however, when pregnancy is complicated by severe uncontrolled hypertension or other risk factors, such as older maternal age, hypertension lasting more than 15 years, diabetes, renal disease, cardiac disease, or connective tissue disease.¹ Some reported complications of uncontrolled hypertension during pregnancy are maternal death, stroke, heart failure, and

pulmonary edema; common fetal complications are intrauterine growth restriction, abruption of the placenta, and prematurity and its adverse effects.¹

Angiotensin-converting enzyme inhibitors are excellent antihypertensive agents with few side effects (Table 1). They are becoming widely used as first-line therapy for chronic hypertension in women of reproductive age. They are also

used in treatment of renovascular hypertension, autoimmune diseases, and diabetes mellitus in this age group. Because 50% of all pregnancies are unplanned, some women are bound to be taking ACEIs at the time of conception.

Animal studies

Animal studies of rats and rabbits given ACEIs during organogenesis showed no increased incidence of major malformations in offspring. Animal data reveal, however, increased morbidity and mortality in fetuses exposed to ACEIs in utero. Decreased uteroplacental blood flow, low birth weight, hypotension, preterm delivery, and fetal death were noted.² A prospective placebo-controlled

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Table 1. Angiotensin-converting enzyme inhibitors

AGENT	TRADE NAME
Benazepril	Lotensin
Captopril	Capoten
Cilazapril	Inhibace
Enalapril	Vasotec
Enalaprilat	Vasotec IV
Fosinopril	Monopril
Lisinopril	Prinivil, Zestril
Perindopril	Coversyl
Quinapril	Acupril
Ramipril	Altace

study of baboons showed a significant increase in fetal death or fetal growth restriction (four of 13) in the group treated with enalapril compared with no instances among the controls.³

Placental transfer

Captopril, enalapril, and lisinopril have been shown to cross the human placenta in pharmacologically significant amounts; other ACEIs probably do the same.^{4,6} Once in a fetus, most ACEIs are excreted renally in their active form (when there is urine production) and could be recirculated through swallowed amniotic fluid.

First-trimester exposure

Postmarketing surveillance of ACEI use during the first trimester of pregnancy in the United States, Canada, and Israel followed the outcomes of 79 women who had been exposed to ACEIs. Among the 66 women exposed during only the first trimester (<14 weeks), there were 48 live births (including two sets of twins), 15 spontaneous abortions, and five therapeutic abortions. Among the 48 live births, three cases of intrauterine growth restriction were documented. One case involved twins delivered at 36 weeks' gestation; the other

two cases involved full-term infants. Another child had a patent ductus arteriosus that required surgical ligation at 18 months. This infant was born at 40 weeks' gestation to a mother who discontinued ACEI treatment at 7½ weeks' gestation and was treated with digoxin throughout the pregnancy and warfarin sodium for the first 5 weeks followed by heparin for the remainder of the pregnancy. No babies who had been exposed to ACEIs during only the first trimester had renal tubular dysplasia. Among the 13 mothers who continued ACEI treatment beyond 14 weeks' gestation, there were 13 live births with one major malformation (renal tubular dysplasia).⁷

A surveillance study of Michigan Medicaid recipients involved 86 newborns exposed to captopril during the first trimester. Four newborns (4.7%) had major birth defects, including one cardiovascular anomaly, one polydactyly, one limb reduction defect, and one hypospadias. In a review by Briggs et al,⁸ among 40 newborns exposed to enalapril during the first trimester, four (10%) had major birth defects, including two cardiovascular anomalies and one polydactyly, and among 15 newborns exposed to

lisinopril during the first trimester, two (13.3%) had major birth defects, including one polydactyly.

A European survey⁹ reviewed pregnancy outcome of 22 women treated with captopril and nine women treated with enalapril. Twenty-one women conceived while they were taking ACEIs and 15 continued therapy until the end of pregnancy. Most women (27 of 31) had chronic essential hypertension, and three were proteinuric before pregnancy. No malformations were reported among the 14 pregnancies exposed to captopril during the first trimester. In the enalapril group, there were two spontaneous abortions in two women exposed during the first trimester, one at 7 weeks and the other at 11 weeks, both attributed to other causes. In a third case where enalapril was started at 24 weeks for severe glomerulopathy, a stillborn infant was delivered after 2 weeks. In six cases where women were taking enalapril at the time of conception, four discontinued treatment at 7 weeks, one discontinued at 28 weeks, and one continued throughout pregnancy (40 weeks): two infants were small for dates (one exposed throughout pregnancy, the other during only the first trimester). No other anomalies were mentioned.

Second- and third-trimester exposure

In contrast to first-trimester exposure to ACEIs, second- and third-trimester exposure appears to be fetotoxic, producing fetal hypocalvaria and renal defects. The cause of these defects appears to be related to fetal hypotension and reduced renal blood flow. Anuria associated with oligohydramnios can produce fetal limb contractures, craniofacial deformations, and pulmonary hypoplasia. Intrauterine growth restriction, prematurity, persistence of patent ductus arteriosus, severe neonatal hypotension, neonatal anuria, and

neonatal or fetal death have all been observed with use of these drugs.¹⁰

Infants affected by use of ACEIs during pregnancy have been born to mothers with hypertension of varying etiology. Although maternal hypertension might produce oligohydramnios, fetal growth restriction, and fetal distress, the evolution of oligohydramnios followed by delivery of a hypotensive anuric infant has not been described as one of the complications of maternal hypertension and is probably drug induced. There are case reports of resolution of oligohydramnios after discontinuation of ACEIs, and angiotensin-converting enzyme activity in exposed neonates was found to be profoundly blunted and normalized only after the renally excreted drug was removed by dialysis.¹⁰⁻¹²

There are several cases of oligohydramnios, fetal hypocalvaria, fetal renal damage, and fetal death reported in association with use of ACEIs during the second and third trimesters of pregnancy.⁸⁻¹² Twenty-nine cases of perinatal renal failure in association with maternal use of ACEIs were listed by the United States Federal Drug Administration in 1991.¹³

In a 1991 summary of 85 pregnancies during which women were exposed to ACEIs, 11 deaths (perinatal mortality rate 13%), including six stillbirths and five neonatal deaths, were reported.¹⁴ Based on limited epidemiologic data, the morbidity from exposure to ACEIs in the second and third trimesters of pregnancy is estimated to be as high

as 10% to 20%. Another article published in 1998 reporting pregnancy outcome in 20 prospective cases and reviewing 85 published cases stated that reported anomaly rates were lower in a larger series.¹⁵

Some women with severe uncontrolled hypertension might have to take ACEIs during pregnancy.¹⁶ In a small series of 10 patients with severe unresponsive hypertension, low-dose captopril was shown to improve maternal well-being with no fetal or neonatal compromise.¹⁷ The small sample size, however, might not have been able to detect a 5% to 10% risk of fetal morbidity or mortality. Case reports of use of angiotensin-2 receptor inhibitors during pregnancy show fetal effects similar to those observed with ACEIs.¹⁸

Conclusion

It is advisable not to prescribe ACEIs for pregnant women. Although there is insufficient evidence to ensure that ACEIs are safe if taken during the first trimester, they do not appear to be major teratogens. If women have to be treated with ACEIs during the second or third trimesters of pregnancy, close monitoring with serial sonograms for assessing amniotic fluid volume and fetal growth are necessary. Although oligohydramnios has been observed to reverse once ACEIs are discontinued, it should be remembered that oligohydramnios often does not appear until after a fetus has sustained irreversible injury. Renal function and blood pressure should be closely

monitored in newborns exposed to ACEIs in utero. ❖

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