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## **Angiotensin-Converting Enzyme (ACE) Inhibitors and Pregnancy**

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Angiotensin-converting enzyme (ACE) inhibitors are used to treat hypertension and congestive heart failure. ACE is a dipeptidyl-carboxypeptidase which catalyzes the conversion of the biologically inactive decapeptide angiotensin I to the active octapeptide angiotensin II. Angiotensin II is one of the most potent vasoconstrictors known.

The use of ACE inhibitors first started in 1977 with the introduction of captopril. Today there are over 15 agents that fall into the category of ACE inhibitors. These hypertensive agents have an advantage over other agents because they work by enhancing blood flow to vital organs without altering cardiac output or causing adverse metabolic consequences (Barr and Cohen 1991; Hanssens et al., 1991). Because of this characteristic, ACE inhibitors are becoming more frequently used in women of reproductive age. By 1989, over a million prescriptions for these drugs were dispensed annually with approximately 5% prescribed for women in their child bearing years (Piper, 1992). Over time case reports of women exposed to ACE inhibitors have accumulated and on March 13, 1992 the U.S. Federal Drug Administration issued a warning regarding the use of ACE inhibitors in pregnancy. Because of the associations between fetal complications and malformations and ACE inhibitors, the FDA recommended that women avoid taking ACE inhibitors during the second and third trimesters of pregnancy. This RISK||NEWSLETTER will address the use of these drugs and their effects on pregnancy.

### **RISK DURING THE FIRST TRIMESTER**

In the past ACE inhibitors were not considered to be significantly associated with risk of malformations when used during the first trimester. Recently there have been reports suggesting that their use during the first trimester, while not associated with malformation may not entirely safe.

Among 14 infants born to women who were treated with captopril during their first trimester, no malformations were found (Kreft-Jais et al., 1988). In another study Piper (1992) looked at 106,813 women. Nineteen women were found to have used ACE inhibitors during pregnancy. Seven of those women used the drug captopril during the first trimester and no association with congenital anomalies was found.

More recently, Hanssens et al. (1991) reviewed the literature and reported 4 spontaneous pregnancy losses (before 14 weeks) and 2 terminations in 47 pregnancies. These women were treated during the first trimester with ACE inhibitors along with other drugs. Of the 6 losses, two cases had no information on fetal normality, three were normal, and one case had fetal leg and skull abnormalities. Rabbour (1994) reported on a mother who was exposed to enalapril throughout the beginning of her

pregnancy. A cesarean was performed at 28 weeks because of acute distress syndrome. The infant then developed hypotension, anuria, and generalized edema. At 2 years unilateral kidney hypoplasia was diagnosed.

## RISKS DURING THE SECOND AND THIRD TRIMESTERS

Studies have shown that there is a risk associated with the use of ACE inhibitors during the second and third trimesters. Guignard et al. (1988) have shown that captopril and enalapril can cross the placenta in the developing fetus. These drugs are believed to have a pharmacological effect during the fetal period of development, stage of pregnancy from eight weeks after conception until term.

The risks of ACE inhibitors are mainly based on case reports and small studies gathered since use of the drugs began. Rosa et al. (1989) reported on four cases of neonatal anuria in infants born to women exposed to either captopril or enalapril during pregnancy.

In a case reported by Barr (1990), a 26 year-old woman gave birth to an infant with oligohydramnios, pulmonary hypoplasia, and skull defects after being treated throughout pregnancy with captopril and other drugs. This study did not take into account the use of other drugs, which may have confounded the results.

Piper et al. (1992) reported two serious outcomes when ACE inhibitors were used during the second and third trimesters or throughout pregnancy. One infant had prolonged anuria and another had occipital encephalocele. The authors stated that even though there were only two adverse outcomes, the small size of the cohort might indicate that the absolute risk could be high. The authors suggested as sources of bias the possibility of other teratogenic exposures and maternal characteristics linked to the use of ACE inhibitors.

Rhabbour et al. (1994) reported a case of a 24 year-old woman who gave birth to twins after exposure during the third trimester. The first infant, a boy, had hypotension and oliguria, and later developed chronic renal failure and hypertension. The second infant, a girl, suffered respiratory distress syndrome followed by hypotension and oliguria.

Lisinopril, another ACE inhibitor, has also been associated with renal failure, fetal skull hypoplasia, and oligohydramnios (Rosa and Bosco, 1991).

Hanssens et al. (1991) reported a high frequency of fetal growth retardation with exposure to ACE inhibitors, but commented that this finding may be associated with the underlying hypertension and not the ACE inhibitor treatments.

## OTHER FACTORS

Women who are treated with ACE inhibitors use these drugs because they usually have severe or resistant hypertension. Hypertension is associated with fetal and maternal complications during pregnancy. These complications include perinatal death, small for gestational age, and poor perinatal outcome (Sibai, 1992; Williams, 1995). Some of the fetal complications, e.g., intrauterine growth retardation (IUGR) and acute and chronic fetal distress, are similar to those seen in pregnant women treated with captopril (Hacker and Moore, 1986; Sibai, 1991). It is difficult therefore to determine if the problems result from the medications or the underlying condition of hypertension. Other studies are needed to determine how much of a risk is associated with the use of ACE inhibitors and how much risk may be due to the complications associated with hypertension.

## POSSIBLE MECHANISM

A definite mechanism for the pattern of developmental disturbances caused by ACE inhibitors is unknown. In lowering the fetal blood pressure, ACE inhibitors may cause IUGR as well as renal

problems. Low fetal blood pressure and low uterine pressure on the head due to oligohydramnios reportedly causes reduced blood circulation to the periphery of the skull. This may account for deformities and underdevelopment in skull formation (Brent and Beckman, 1991; Barr and Cohen, 1991).

#### RISKS WHEN BREAST FEEDING

Captopril is excreted in milk in very limited amounts (Devlin, 1981). The WHO Working Group on Drugs and Human Lactation showed that a maximum of 0.014% of the maternal dose of captopril would be ingested during breast-feeding. They, therefore, concluded that it was safe to use captopril during breast-feeding.

#### SUMMARY

Overall, ACE inhibitors are not associated with malformations or adverse outcomes when used during the first trimester, although isolated cases of anuria, skull deformities, hypotension and edema have been observed at this time. ACE inhibitors have been associated with oligohydramnios, fetal death, neonatal anuria and death, fetal skull hypoplasia, IUGR and pulmonary hypoplasia when used during the fetal stage of development. Controlled studies need to be conducted to determine the magnitude of the risk associated with these drugs when used during the second or third trimesters.

Because of the possible risks associated with ACE inhibitors, alternate medications should be used during the second and third trimesters of pregnancy. In some cases ACE inhibitors may be the only way to control hypertension during pregnancy. When hypertension cannot be controlled by any other means, the risks of the drug's usage and the teratogenic risks to the pregnancy need to be weighed and carefully considered.