Fetal risk from angiotensin converting enzyme inhibitors in the first trimester

In 1980, published animal data in *The Lancet* flagged concerns with the angiotensin converting enzyme (ACE) inhibitor captopril.¹ Publications on the safety of ACE inhibitors followed in the 1980s.

By 1993, ACE inhibitor fetopathy had been described in the offspring of patients who took these drugs in the second and third trimesters. The adverse outcomes were deliberately called fetopathy rather than teratogenicity at that time.²

A 2006 report raised further concerns by demonstrating an association of ACE inhibitors used in the first trimester of pregnancy with an increased rate of birth defects, in particular cardiac malformations and neural tube defects. Other antihypertensive drugs were not associated with increased risks in birth defects.³

However, in 2011 Li *et al.*, in a retrospective cohort study with a much larger population base and a more ethnically diverse population, did not confirm the reported findings. The study showed that hypertension itself appears to be a modest risk for birth defects, particularly cardiac.⁴ Similar findings were reported in a smaller Swedish cohort study⁵ and a large case-control US study.⁶

Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study

Li *et al.* *BMJ* 2011;**343**:d5931

Researchers examined 465,754 mother–infant pairs for the reported link between the use of ACE inhibitors in the first trimester and birth defects. This population based, retrospective cohort study linked automated clinical and pharmacy databases, including comprehensive electronic medical records. The subjects were pregnant women and their live born offspring in the Health Care Plan of Kaiser Permanente Northern California from 1995 to 2008.

The analysis estimated risks in pregnant women who had received only ACE inhibitors in the first trimester, and separately, in women who had received other antihypertensive drugs. Comparison was made with two unexposed groups – women with a diagnosis of hypertension who had received no antihypertensive drugs in the first trimester, and women without hypertension who did not receive antihypertensives.

There were two main conclusions of this study: (1) ‘Maternal use of ACE inhibitors in the first trimester has a risk profile similar to the use of other antihypertensives regarding malformations in live offspring.’ (2) ‘The apparent increased risk of malformations with the use of ACE inhibitors (and other antihypertensives) in the first trimester is likely due to the underlying hypertension rather than the medications.’⁴

There was an increased rate of congenital heart defects compared with that found in normal controls, and a similar association of the rate of heart defects with the use of other antihypertensives.

Use of ACE inhibitors in the first trimester was only 0.9/1000, while the use of other antihypertensive medications in the first trimester was 2.4/1000. After adjustment for maternal age, ethnicity, parity and obesity, when used in the first trimester only, use of ACE inhibitors was associated with a trend to increased risk of congenital heart defects in offspring (the odds ratio [OR] confidence interval [CI] crosses 1.0), but not of neural tube defects (NTDs), when compared with the risk in normal controls (those with neither hypertension nor use of any antihypertensives during pregnancy) (15/381 [3.9%] versus 6232/400,021 [1.6%] cases, OR 1.54 [95% CI 0.90–2.62]).

A similar and more definite association was observed for use of other antihypertensives (28/1090 [2.6%] in respect of the risk of congenital heart defects, odds ratio 1.52 [1.04–2.21]).

However, when compared with controls with a diagnosis of hypertension but who were not using antihypertensive therapy (708/29,735 [2.4%] cases of congenital heart defects), neither use of ACE inhibitors nor of other antihypertensives in the first trimester was associated with an increased risk of congenital heart defects (odds ratios 1.14 [0.65–1.98] and 1.12 [0.76–1.64], respectively).

‘Hypertension controls’ were those women with a diagnosis of hypertension at any time from one year before their last menstrual period to the end of their pregnancy but who were not prescribed any antihypertensive drugs. The similar increased risk of malformations in the offspring of women who had used any antihypertensive drugs in the first trimester, compared with that in women who had untreated hypertension, suggests it may be the underlying condition of hypertension that increases the risk of birth defects.

The 1993 study of second and third trimester exposure showed that most patients reported pre-existing hypertension and other vascular conditions, and suggested that ‘underlying microvascular disease *per se*’ may have resulted in adverse fetal outcomes. Additional pathological mechanisms postulated were fetal hypotension and renal hypoperfusion.²

Correspondence to the *BMJ* following the 2011 article included the question that as congenital malformations in live births was the main outcome measured, would malformations in any terminations of pregnancy have changed the results. As a safe alternative to the ACE inhibitors, calcium channel blockers were advocated for use in the first trimester.

What these studies show us

Li’s⁴ study has not confirmed an association between maternal use of ACE inhibitors in the first trimester and an increased risk of malformations, but has confirmed the known fetal toxicity due to ACE inhibitor use in the second and third trimesters.

An accompanying editorial to Li’s article concludes ‘Evidence is reassuring, but risks remain from the hypertension itself.’ It also points to possible future research as to ‘whether there is a “pre-hypertensive” condition that may affect the fetus before an increase in maternal blood pressure is detected, or even detectable’.⁷

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Neil Hotham BPharm

Pharmacist, Affiliate Lecturer at the University of Adelaide, Formerly, Senior Specialist Drug Information Pharmacist, Women's and Children's Hospital, Adelaide, Australia

Email: neil.hotham@adelaide.edu.au

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