Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers

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CRD summary
The review concluded that infants exposed to antihypertensives during the first trimester (first 12 weeks) of pregnancy were at increased risk of major congenital malformation than infants not exposed, but high quality studies were needed to corroborate the findings. Given the limitations of the observational studies, the authors' conclusions seem too strong and are not justified by the data.

Authors' objectives
To examine the risks associated with exposure to angiotensin converting enzyme inhibitors or receptor blockers in the first trimester of pregnancy.

Searching
MEDLINE (1950 to 2009) and EMBASE (inception to February 2011) were searched with no language restrictions for published studies; search terms were reported. Reference lists of relevant articles were manually searched. Meeting abstracts and proceedings were searched for unpublished studies.

Study selection
Cohort studies that compared exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers during the first trimester of pregnancy versus no exposure or exposure to other antihypertensives were eligible for inclusion. Eligible studies were required to provide sufficient data for meta-analysis. Studies that reported on minor malformations, growth retardation, death or functional abnormalities were not eligible for inclusion. Case control and cohort studies not providing sufficient data for meta-analysis were eligible for inclusion in the qualitative analysis.

The primary outcome was presence of major congenital malformation (defined as serious or major structural or mental defect that could have adverse effects on health or development).

Some included cohort studies excluded mothers with diabetes, previous exposure to known teratogens, or a history of chromosomal/genetic defects. Other antihypertensives included calcium channel blockers, beta blocking agents, anti-adrenergic drugs, drugs acting on arteriolar smooth muscles, and diuretics. Mothers treated with antihypertensives were reported to be older, more likely to smoke, have a higher body mass index, and be more likely to take other medications for comorbid conditions.

Two reviewers independently screened studies for inclusion, with disagreements resolved through consensus.

Assessment of study quality
Two reviewers independently assessed study quality using the Newcastle-Ottawa Scale, which assessed selection bias, comparability and ascertainment of the outcomes of interest. Scores ranged from 0 to 4 on selection, 0 to 2 on comparability, and 0 to 3 on outcome. Discrepancies were resolved through discussion.

Data extraction
Outcome data on each infant or foetus were extracted into a 2x2 contingency table and used to calculate odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals. Primary authors were contacted for clarification where necessary.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Data were pooled using a random-effects model to calculate effect sizes (pooled ORs or RRAs) and associated 95% confidence intervals (CIs). Adjustments were made for body mass index; women with a history of diabetes were excluded from the analysis. Heterogeneity was assessed using $X^2$, $T^2$ and $I^2$. Sensitivity analyses were conducted to assess the effects of quality and effect size on the results.
Publication bias was assessed through the visual inspection of funnel plots.

**Results of the review**

Five cohort studies (n=786 infants exposed to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; n=1,723 infants exposed to other antihypertensives; n=1,091,472 infants not exposed) were included in the review. Two studies were retrospective and three were prospective (there were some discrepancies in data reported in tables and text; the figures reported in this abstract were taken from the table). Two cohort studies scored the maximum on selection, all scored the maximum on comparability, and one scored the maximum on outcome.

Compared with infants not exposed to antihypertensives, infants exposed to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers showed a statistically significant increase in risk of major congenital malformations (RR 1.78, 95% CI 1.07 to 2.94; five studies; I²=41%). Similarly, infants exposed to other antihypertensives showed statistically significantly greater risk of malformations compared to infants not exposed to antihypertensives (RR 1.45, 95% CI 1.15 to 1.83; four studies; I²=11%). There were no statistically significant risk differences between infants exposed to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and those exposed to other antihypertensives (four studies; I²=52%).

Sensitivity analyses showed that removal of the study with the highest effect size from the first comparison resulted in a non-significant risk ratio of 1.44 (95% CI 0.78 to 2.67). No other sensitivity analyses significantly altered the findings.

Results from the qualitative analysis (including 19 studies) were reported in the review.

**Authors’ conclusions**

Infants exposed to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the first trimester of pregnancy were not at significantly increased risk of major congenital malformation compared with exposure to other antihypertensives. However, there was an increased risk of malformations in infants exposed to antihypertensives compared with infants not exposed. High quality studies were needed to corroborate the findings.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. A satisfactory search of the literature was undertaken with attempts to minimise language and publication bias. The authors acknowledged that there may be some risk of publication bias. Study selection and quality assessment were performed in duplicate, but it was unclear whether this was applied to data extraction, so there was the potential risk of reviewer error and bias.

Appropriate criteria were used to assess the quality of cohort studies. One retrospective study scored highly on quality, but it should still be borne in mind that only observational studies were analysed. The authors acknowledged the limitations of observational studies, the clinical and methodological heterogeneity, and potential methodological limitations relating to the meta-analysis. There were also large differences in the number of infants exposed to antihypertensives compared with those not exposed.

Given the methodological issues associated with the evidence, the authors’ conclusions seem too strong and are not justified by the data. However, their recommendation for further high quality research seems appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that high quality studies were needed.

**Funding**

Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation.

**Bibliographic details**


**PubMedID**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.