ONLINE SUPPLEMENT

Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review

Short title
Fetal renin-angiotensin system blockade syndrome

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Expanded Results

General aspects and prevalence
The first case of suspected ACE-Is fetopathy was published in 1981.¹ The same year, another case characterized by the voluntary termination of the pregnancy was described in South Africa by Duminy et al, although this case was excluded from our analysis because it did not fulfill the inclusion criteria.² The first case of ARB fetopathy was reported nearly 20 years later in 1999.³ The number of publications over the years concerning the consequences of intrauterine exposure to ACE-Is or ARBs is depicted on Figure S2A. Interestingly, the number of published cases of ACE-Is fetopathy has declined during the most recent years (Figure S2B) despite the increased prenatal exposure to these drugs over the years.⁴, ⁵ Pharmacovigilance studies dealing with the post-marketing safety of ARBs (losartan and valsartan) during the late 90s demonstrate that approximately three pregnancies will occur in 10,000 treated individuals.³, ⁶ In contrast, the prenatal exposure to ACE-Is is between 2 and 70 per 10,000 pregnant women and increased between 1984 and 2003.⁴, ⁵, ⁷ The prevalence of exposure during the first trimester was considerably higher than the exposure at the end or during the entire pregnancy.⁴, ⁵

Intrauterine exposure to ACE-Is
The mean maternal age of the 118 well-documented cases of intrauterine exposure to ACE-Is was 31.3 ± 6.6 years, and the indications for maternal antihypertensive treatment mainly included essential hypertension (58 cases), followed by secondary causes for hypertension (mainly renal diseases; 28 cases), pregnancy-induced hypertension (15 cases) and diabetes mellitus (11 cases). In six cases, no corresponding information was available.

Intrauterine exposure to ARBs
The mean maternal age of the 68 well-documented cases of intrauterine exposure to ARBs was 36.1 ± 5.8 years, and the indications for maternal antihypertensive treatment were mainly essential hypertension (38 cases). Other indications included secondary causes for hypertension (largely renal diseases; 7 cases) and diabetes mellitus (5 cases). In 17 mothers, the indication for antihypertensive treatment was not known. Only one mother was treated with an ARB because of pregnancy-induced hypertension.
Literature


Table S1: Outcome following exposition during pregnancy to drugs that inhibit the renin-angiotensin system

<table>
<thead>
<tr>
<th>Fetal RAS-blockade syndrome</th>
<th>Exposition during the beginning of pregnancy (only first, only second, first and second trimester)</th>
<th>exposition at the end of pregnancy (second and third or only third trimester) or during the entire pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angiotensin-Converting Enzyme Inhibitors (Total 58 infants)</td>
<td>Angiotensin-Receptor Blockers (Total 37 infants)</td>
</tr>
<tr>
<td>Oligohydramnion</td>
<td>6 (10%)</td>
<td>16 (43%)*</td>
</tr>
<tr>
<td>Anuria</td>
<td>2 (3%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Renal failure or need for dialysis</td>
<td>1 (2%)</td>
<td>11 (30%) *</td>
</tr>
<tr>
<td>Arterial hypotension</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>3 (5%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Persistent patent ductus arteriosus</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Hypocalvaria</td>
<td>1 (2%)</td>
<td>6 (16%) *</td>
</tr>
<tr>
<td>Limbs defect</td>
<td>0 (0%)</td>
<td>9 (24%) *</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>6 (10%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Cerebral complications</td>
<td>1 (2%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Death, miscarriage or intrauterine fetal death</td>
<td>15 (26%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>Newborns without fetal RAS-blockade syndrome</td>
<td>36 (62%)</td>
<td>9 (24%) *</td>
</tr>
</tbody>
</table>

* significantly (p<0.05) different from the respective value of Angiotensin-Converting Enzyme Inhibitors; † significantly different (p<0.05) when compared to the exposition during the first and second trimester (Fisher exact test)
Records identified through database search (n=3639)

Records searched after duplicates removed (n=1685)

Studies excluded after abstract or title review (n=1568)

Citations assessed in detail for eligibility (n=117)

Article excluded (n=56)
  language (n=8)
  duplicate cases of other reports (n=3)
  articles without cases or not described in detail (n=45)

Reports found in reference lists (n=11)

Eligible reports (n=72)

The flow of the studies through the review
The number of the considered publications dealing with exposure during pregnancy to drugs that inhibit the renin-angiotensin system. Angiotensin converting enzyme inhibitors: Black bar; angiotensin receptor blockers: Grey bar.
The number of the considered newborns per year of publication. Angiotensin converting enzyme inhibitors: Black bar; angiotensin receptor blockers: Grey bar.