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# ACEIs/ARBs IN THE FIRST TRIMESTER OF PREGNANCY

Fetal toxicity has been reported in conjunction with angiotensin converting enzyme Inhibitor (ACEI) and angiotensin receptor blocker (ARB) use throughout gestation.[1,2,3] Recent evidence however, suggests that ACEI/ARB use during the first trimester may not pose a greater risk than other antihypertensives or hypertension itself.[4,5] This information has important implications for treatment of hypertension in women of childbearing age and for pregnant women who have been inadvertently exposed to ACEIs.

**Hypertension in Pregnancy**

Hypertension during pregnancy is associated with an increased risk of adverse effects for both the mother and the fetus (Table 1). Approximately one percent of pregnant women have pre-existing hypertension and may be on antihypertensive therapy at the time of conception.[6] Blood pressure drops during the first two trimesters returning to pre-pregnancy level in the third trimester.[7] Women with mild hypertension may be able to reduce or discontinue antihypertensive therapy during this time.[7] There is concern that low blood pressure (DBP < 80 mmHg) could compromise placental perfusion. Canadian criteria for blood pressure control during pregnancy are outlined in Table 2.[8]

**Mechanism of ACEI teratogenicity**

ACEIs and ARBs are contraindicated during the second and third trimesters of pregnancy because they have been associated with serious adverse effects in the fetus.[1,2,7,8] They affect the fetal angiotensin renin system which does not become active until the second trimester.[9,10] It is proposed that fetal hypotension and decreased fetal renal blood flow cause renal impairment and oligohydramnios (deficient amniotic fluid).[9,19] This can lead to a variety of adverse effects including pulmonary hypoplasia (incomplete lung tissue development), hypocalvaria (underdevelopment of the skull), limb deformities, persistent patent ductus arteriosus (failure to close fetal bypass duct between descending aorta and pulmonary artery), and neonatal death.[7,9,10]

**Table 1: Adverse effects associated with uncontrolled hypertension in pregnancy** [4,7]

| Maternal effects | Fetal effects |
|---|---|
| • Stroke<br>• Pulmonary edema<br>• Retinopathy<br>• Renal failure<br>• Hypertensive encephalopathy<br>• Cesarean delivery<br>• Post-partum hemorrhage | • Premature birth<br>• Intrauterine growth restriction<br>• Placental abruption<br>• Fetal death<br>• Neonatal death |

**Table 2: Recommendations for blood pressure control for pregnant women with hypertension** [8]

| **Not Severe** |
|---|
| Without comorbidities*<br>SBP 130 – 155 mmHg; DBP 80 –105 mmHg<br>With comorbidities*<br>SBP 130 – 139 mmHg; DBP 80 – 89 mmHg |
| **Severe** |
| SBP < 160 mmHg; DBP < 110 mmHg |

* diabetes mellitus, renal disease, cerebrovascular disease

**First trimester exposure**

An epidemiologic study published in 2006 observed an increase in risk of major cardiovascular and central nervous system malformations with the use of ACEI in comparison to other antihypertensives in the first trimester.[3] This prompted a Health Canada Advisory warning women not to use ACEIs during pregnancy or if planning a pregnancy.[11] The risk was also extrapolated to include ARBs[12]. However, major confounders in this study have been flagged,[9,12]

casting doubt on the results of the study. Serious confounding variables include the difference in average age of women between the cohorts and inability to exclude obesity, undiagnosed or diet-controlled diabetes mellitus, and unaccounted detailing of stillbirths and terminations.[9,12]

Further to this, recent observational studies[9,13] and a meta-analysis[5] suggest ACEI/ARBs do not have an elevated risk of major malformations when compared to other antihypertensives. There was a two-fold increase in pre-term deliveries and a shorter median gestational age of two weeks in the groups exposed to any antihypertensive compared to the non-antihypertensive group.[9] Hypertension itself appears to increase the risk of birth defects[13]. Characteristics of antihypertensive candidates (older, obese, multiple comorbidities) may contribute to the heightened risk of malformation in comparison to healthy controls.[5]

One study by Motherisk observed an increased risk of miscarriage in the ACEI/ARB exposed group (18 %) versus the other antihypertensive (8.9 %) and healthy non-exposed (11.8%) groups ($p < 0.001$). The authors speculate this result might be misleading as there was a higher proportion of comorbidities such as diabetes in the ACE/ARB group. However they were unable to do a subanalysis because of the small number of diabetic patients who had miscarriages and the ACE/ARB association could not be ruled out. [4] Previously, an increased incidence of spontaneous abortion with ACEIs had only been demonstrated in animal studies.[4]

**Pre-conception management:**

- Advise women on ACEI/ARBs planning a pregnancy to consult with their physicians regarding their medications.[7,8]
    - If the indication is hypertension, the physician & patient may decide to switch to a safer alternative (Table 3) prior to conception, or wait until pregnancy is confirmed.
    - If the indication is for proteinuria, a condition in which there are no other alternatives, continue the ACEI or ARB until pregnancy is confirmed.
    - Drugs of choice for treatment of hypertension in pregnancy are labetalol, methyldopa, and nifedipine.[7,8] (See Table 3.)
- Given the potential role of hypertension in fetal abnormalities ,[13] women should be encouraged to optimize blood pressure control prior to conception as recommended by the CHEP guidelines.[14]

**Table 3: Drugs recommended for use during pregnancy**[7,8]

| Drug | Usual Dose |
|---|---|
| Labetalol | 100 – 400 mg BID – TID<br>Max: 1200 mg/d |
| Methyldopa | 250 – 500 mg BID – QID<br>Max: 2000 mg/d |
| Nifedipine | XL 20 – 50 mg once daily<br>Max: 120 mg/d |

**Post-conception management**

- Once pregnancy is confirmed, ACEI/ARBs should be discontinued. If antihypertensive therapy is indicated, a safer alternative (Table 3) can be recommended.[7,8]
- Exposure to ACEI/ARB is not an indication for termination of the pregnancy, nor an indication for invasive diagnostics.[1] Based on the evidence above, women can be reassured that exposure to ACE/ARBs in early pregnancy does not appear to put the fetus at a higher risk than other antihypertensives.

**Postpartum management:**

- If an ACEI/ARB was being used pre-pregnancy for the purpose of renal protection, it should be restarted.[8]
- ACEIs can be considered as an option to treat postpartum hypertension in breastfeeding mothers.[8]
- ACEIs are unlikely to reach clinically significant levels in breast milk; however the selection of a well-studied ACEI such as captopril, enalapril, benazepril or quinapril is preferred.[15,16]
- There are no human data on ARB use while breastfeeding. They are classified as probably compatible with breastfeeding.[2,15,16]

**Bottom Line: It is commonly accepted that ACEIs and ARBs are contraindicated during pregnancy; however, considerable evidence suggests that this contraindication applies predominantly to the 2nd and 3rd trimester. For women considering becoming pregnant, it is acceptable to wait until conception is confirmed before switching to an alternate antihypertensive.**

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