Before, Between & Beyond Pregnancy
The National Preconception Curriculum and Resources Guide for Clinicians

Annotated Articles Guiding Preconception Care of Women with Diabetes

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Exposure in First Trimester to ACE inhibitors

Cooper, WO., Hernandez-Diaz, S., Arbogast, PG., Dudley, JA., Dyer, S., Gideon, PS., Hall, K., Ray, WA. Major congenital malformations after first-trimester exposure to ACE Inhibitors. NEJM 2006; 354: 2443-2451. http://content.nejm.org/cgi/reprint/354/23/2443.pdf

Synopsis: ACE inhibitor fetopathy (oligohydramnios, IUGR, hypocalvaria, renal dysplasia, anuria, renal failure and death) have been associated with second and third trimester fetal exposure to ACE Inhibitors (ACE-I). The defects are thought to result from ACE inhibitor impairment of fetal renal function. Since this function develops later in pregnancy, first trimester use had not been thought to have adverse effect. The authors sought to evaluate outcomes associated with first trimester exposures.

The Tennessee Medicaid system is able to track prescriptions through a computerized system and through linkage with the vital records and hospitalization claims congenital anomalies are identifiable. This study investigated the likelihood of major congenital anomalies in infants divided into three groups: first trimester exposure to ACE-I; exposure to other anti-hypertensive agents in the first trimester and no exposure to hypertensive treatments in the first trimester. The researchers began their investigation with data on 33,810 infants (including fetal deaths). A number of exclusions, including diabetes, exposure to other known teratogens, and exposure to ACE-I beyond the first trimester resulted in a cohort of 29,507. The outcome of interest was presence of major congenital malformation not related to chromosomal or clinical genetic syndrome.

Of the study births, 411 infants were exposed to anti-HTN meds (209 ACE-I and 202 other agent exposures). In comparison to the infants without exposure to any agent, mothers of exposed infants were older, more educated, more likely to have ≥ 1 chronic illness, multigravid, live in a rural county, and less likely to have late prenatal care. In comparing the mothers of ACE-I exposed infants to those exposed to another agent, mothers of ACE-I exposed infants were slightly older and more educated. In the control group, major congenital malformations were diagnosed in 856 (2.9%) infants.

Among infants with ACE-I exposure in 1st trimester, the risk ratio for a major congental anomaly was 2.71 (95% CI: 1.72 – 4.27). ? Exposed infants had an increased risk of

malformation of the cardiovascular system (RR 3.72 95% CI: 1.89 – 7.3)) and CNS (RR 4.39 95% CI: 1.37 – 14.02)). Infants exposed to other anti-HTN medications during the 1st trimester demonstrated no increased risk for major congenital abnormalities.

Even when a secondary analysis was conducted to restrict ACE-I exposed group to mothers who filled their prescription ≥14 days after their LMP and broadening the definition of diabetes to exclude women who had a single outpatient visit with diagnosis of diabetes noted in the first trimester, the association of abnormalities with ACE-I exposure remained.

Limitations of this study include method of data ascertainment with medication exposure assumed by prescription filling; however, there is a biological plausibility for the findings.

This study suggests that, in addition to previously accepted risks of ACE-Inhibitor in the second and third trimesters, first trimester fetal exposure cannot be considered safe and should be avoided.

Posted March, 2008; reviewed April, 2009