Renin Angiotensin System Blocker Fetopathy: A Midwest Pediatric Nephrology Consortium Report

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Objectives Fetuses continue to be exposed to renin angiotensin system (RAS) blockers despite their known teratogenicity and a black box warning. We hypothesized that fetopathy from in utero exposure to RAS blockers has a broader spectrum of clinical manifestations than described previously and that there are a variety of clinical scenarios leading to such exposures.

Study design This was a retrospective study performed through the Midwest Pediatric Nephrology Consortium. Cases of RAS blocker fetopathy were identified, with determination of renal and extrarenal manifestations, timing of exposure, and the explanation for the fetal exposure.

Results Twenty-four cases were identified. RAS blocker exposure after the first trimester was associated with more severe renal manifestations. Chronic dialysis or kidney transplantation was required in 8 of 17 (47%) patients with RAS blocker exposure after the first trimester and 0 of 7 patients with exposure restricted to the first trimester (P = .05). Extrarenal manifestations, some not previously noted in the literature, included central nervous system anomalies (cystic encephalomalacia, cortical blindness, sensorineural hearing loss, arachnoid cysts) and pulmonary complications (pneumothorax, pneumomediastinum). RAS blocker exposure usually was secondary to absent or poor prenatal care or undiagnosed pregnancy.

Conclusion RAS blocker fetopathy continues to be a cause of considerable morbidity, with more severe renal manifestations associated with exposure after the first trimester. A variety of significant extrarenal manifestations occur in these patients. Clinicians should emphasize the risk of fetopathy when prescribing RAS blockers to women of childbearing age. *(J Pediatr 2015;167:881-5)*.

See editorial, p 792

Renin angiotensin system (RAS) blockers, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and direct renin inhibitors, are commonly used to treat hypertension.[1] In addition, they are effective in slowing the decline of kidney function in patients with chronic kidney disease, especially when proteinuria is present.[2]

The importance of the RAS for normal kidney development has been demonstrated by studies that use gene targeting or pharmacologic interference with the RAS.[3,4] RAS blockers have long been known to cause morbidity and mortality to the developing fetus, especially during the second or third trimester of pregnancy.[1] Exposure during the first trimester also can increase risk for malformations of the cardiovascular system and central nervous system (CNS).[5] Two of 15 newborns exposed to lisinopril during the first trimester had major birth defects.[5] On the basis of limited epidemiologic data, complications are estimated to occur in up to 10%-20% of fetuses exposed to ACEIs in the second and third trimesters of pregnancy.[6]

The most common adverse effect of RAS blocker exposure in utero is renal papillary atrophy with impaired urinary concentrating ability.[7] Other features of intrauterine exposure to RAS blockers include oligohydramnios, pulmonary hypoplasia, renal failure, neonatal hypotension, prematurity, small for

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
CNS	Central nervous system
eGFR	Estimated glomerular filtration rate
FDA	US Food and Drug Administration
RAS	Renin angiotensin system
RRT	Renal-replacement therapy

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gestational age newborns, and perinatal mortality.[8] ARBs used during pregnancy have similar effects on the fetus as ACEIs[9-11]; however, complications are more common and severe with exposure to ARB.[11]

Despite the US Food and Drug Administration (FDA) implementation of a black box warning in 1992 proscribing against the use of ACEIs during the second and third trimesters of pregnancy, the number of pregnant women exposed to ACEIs was nearly 3-fold greater in 2003 than in 1986-1988.[12,13] Ongoing exposure is well-documented.[14] There is a need for better methods to reduce fetal exposure to these teratogenic medications.[13]

We hypothesized that RAS blocker fetopathy has a broader spectrum of presentation than previously described in the literature and that there are a variety of clinical scenarios that lead to in utero exposure. Hence, we present a large cohort of patients with RAS blocker fetopathy, all exposed after the FDA black box warning, and provide an explanation for the in utero exposure.

Methods

This retrospective study was conducted by 14 pediatric nephrology centers belonging to the Midwest Pediatric Nephrology Consortium (www.mwpnc.com). The centers received approval from their local Institutional Review Boards. Cases that presented over 10 years were included. Children with renal involvement secondary to intrauterine exposure to ACEIs or to ARBs were identified. Renal involvement attributable to ACEIs or ARBs was defined on the basis of the presence of acute kidney injury, chronic kidney disease, or tubular dysfunction (eg, nephrogenic diabetes insipidus) and the absence of an alternative explanation.

Patients were selected on the basis of a clinical constellation of findings among infants and children whose mothers reported exposure to an ACEI or ARB during pregnancy. Fetal exposure to these agents was validated through the child's medical record, and the child was classified as having RAS blocker fetopathy by the treating nephrologist. Case identification was accomplished through a combination of searching electronic databases and physician recall of specific patients. Data collected included renal and extrarenal complications, timing of RAS blocker exposure, and reason for RAS blocker exposure during pregnancy. An estimated glomerular filtration rate (eGFR) was determined at last follow-up with the modified Schwartz formula.[15] Data are presented as a mean and SD or as a median and IQR. Comparisons between groups were performed with the Fisher exact test.

Results

Twenty-four patients with in utero exposure to RAS blockers were identified. Patient characteristics are shown in Table I. The mean age at last follow-up was 4.7 ± 3.2 years (range 0.03-13). Most of the mothers had chronic hypertension and/or diabetes mellitus with minimal or no prenatal care. In one case, a mother was inadvertently started on an ARB during the second trimester because of a pharmacy error (wrong medication given to the mother). The mean gestational age at birth was 34.6 ± 2.7 weeks (range 28-40), and the median hospitalization duration at birth was 27.5 days (IQR 20.5-44.25; duration was not available in 2 patients). Twelve patients were intubated with mean duration of 10.7 ± 8.6 days (range 2-30 days; duration unavailable in 1 patient). The exposure was to an ACEI in 14 cases and an ARB in 10 cases. Seven cases had exposure only during the first trimester. Seventeen patients had exposure after the first trimester (all 3 trimesters in 8 patients; first and second trimester in 6 patients; second trimester in 1 patient; third trimester in 2 patients).

Table I. Patient characteristics

Patient age, y	Name of RAS blocker used	Reason for intrauterine exposure
0.03	Lisinopril	HTN, unknown pregnancy
0.58	Candesartan	HTN, unknown pregnancy
0.66	Lisinopril	HTN, morbid obesity
1.75	Enalapril	DM, unknown pregnancy
2	Valsartan	Chronic HTN, late prenatal care
2	Valsartan	HTN
2	Valsartan	HTN
2	Olmesartan	HTN, DM, unknown pregnancy
3	Olmesartan	Chronic HTN
3	Lisinopril	HTN, DM, dialysis dependent, unknown pregnancy
4	Olmesartan	HTN, no prenatal care
4	Lisinopril	HTN
4	Enalapril	HTN
5	Lisinopril	Unknown pregnancy
5	Moexipril	HTN
5	Lisinopril	HTN
6	ACEI (name unknown)	Inadvertently started during second trimester
7	Irbesartan	HTN, type 2 DM, unknown pregnancy
8	Valsartan	Unknown pregnancy
8	Lisinopril	Unknown pregnancy
9	Candesartan	HTN, late prenatal care
10	Ramipril	DM, HTN, unknown pregnancy
10	ACEI (name unknown)	HTN
13	Captopril	Lupus nephritis, unknown pregnancy

DM, diabetes mellitus; *HTN*, hypertension.

Clinical manifestations are summarized in the Figure. There was no major difference in renal complications or oligohydramnios based on type of RAS blocker exposure. There were 12 CNS complications in 4 patients from the ARB group and 3 complications in 3 patients in the ACEI group. Two patients in each group had patent ductus arteriosus. Pulmonary hypoplasia occurred in 7 patients with ACEI exposure and 6 patients with ARB exposure. All 6 instances of pneumothorax occurred in the patients with a history of ACEI exposure. In each group, we noted 5 cases of hypocalvaria (poor growth of the membranous bones of the skull). The mean gestational age was 34.8 ± 2.6 weeks in the ARB group and 34.9 ± 2.8 weeks in the ACEI group.