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Renin-Angiotensin System Blocker Fetopathy

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Chronic hypertension in pregnant women is associated with significant maternal and fetal morbidity and mortality, and is thought to complicate approximately 5% of the 4 million pregnancies in the US annually.[1] Pregnant women with chronic hypertension are at risk for developing adverse complications, such as maternal preeclampsia, stroke, renal failure, and death.[2] In addition, adverse fetal outcomes, such as intrauterine growth restriction, preterm birth, and death, are more likely among pregnant women with chronic hypertension than those without. For example, in one study, the risk of cardiac congenital malformations was increased in pregnancies of women with both treated (OR 1.6, 95% CI 1.4-1.9) and untreated hypertension (OR 1.5, 95% CI 1.3-1.7).[3] The prevalence of chronic hypertension (7.7%) and use of antihypertensive agents (4.2%) in women of childbearing age (20-44 years) is relatively low.[4] However, among those who use antihypertensive agents, the use of angiotensin converting enzyme inhibitors (ACEIs) (44%) or angiotensin receptor blockers (ARBs) (20.4%) is prevalent and greater than that of diuretics (47.9%), thus, increasing the potential risk of inadvertent first trimester exposure of the fetus.[4] Given the recent changes in hypertensive guideline recommendations[5] and the prevalence of underlying risk factors in the general population, such as chronic kidney disease and diabetes,[1] the potential for exposure of a fetus to ACEIs or ARBs during the first trimester is substantial among women of child-bearing age with chronic hypertension, diabetes, or kidney disease.

In this issue of *The Journal*, Nadeem et al[6] describe a series of 24 children with acute kidney injury, chronic kidney disease, or tubular dysfunction, and a history of intrauterine exposure to renin-angiotensin system (RAS) blockers including ACEIs or ARBs. These cases of RAS fetopathy presented over a 10-year period to 14 pediatric nephrology centers belonging to the Midwestern Pediatric Nephrology Consortium. Primary findings from this report include: (1) a higher frequency of severe renal complications among children with RAS

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exposure in the second and/or third trimesters compared with children exposed during the first trimester, which is consistent with previous observations from laboratory, clinical, and epidemiologic studies[7-10]; (2) the occurrence of a number of extra-renal complications not previously reported as associated with RAS fetopathy; and (3) the fact that RAS blocker exposure occurred among pregnancies with absent or late prenatal care (n = 4) or that were unrecognized at the time of exposure (n = 11), as well as among recognized pregnancies (n = 9). These findings highlight issues common to studies that evaluate the risk of adverse fetal outcomes following medication use during pregnancy and suggest opportunities for prevention and education of women and healthcare providers about use of RAS blockers during pregnancy.

Methodological Issues in Studies of Adverse Effects in Offspring from Maternal Medication Use during Pregnancy

Case reports, case series, pregnancy exposure cohorts, and case-control studies can provide useful information about the effects of maternal medication use during pregnancy, but all face a number of methodological challenges. One common challenge relates to the potential for selection bias. This can result from evaluation of a select sample of pregnancies exposed to a medication of concern. If the criteria for inclusion in a study are exposure to the medication of interest and the presence of a certain disease or clinical findings, such as evidence of renal disease in the report by Nadeem et al,[6] exposed children who have no evidence of renal disease at birth will not be captured. The reported case series may either overestimate the frequency and severity of effects of the drug, or will not detect other unanticipated complications that arise at some point after birth. This can limit the study's ability to assess the spectrum of extra-renal complications that might result from intrauterine RAS blocker exposure. One way to address this type of selection bias is to follow all or a representative sample of exposed pregnancies and children through delivery and beyond the newborn period.

Further complicating the ability to ascertain potential extra-renal complications is the limited statistical power that can be achieved from evaluation of a small number of cases. This is particularly difficult for outcomes that are relatively rare in the general population. Overall, congenital malformations occur in 2%-3% of births,[11] and individual malformations are much rarer. It can be difficult to accrue sufficient numbers of exposed infants to evaluate such conditions in case reports. In particular, it is worth noting that none of the children in the case series by Nadeem et al[6] had any of the types of congenital heart defects previously reported as possibly associated with intrauterine exposure to RAS blockers (eg, pulmonary valve stenosis, Ebstein anomaly, coarctation of the aorta).[3,10,12-14] The extent to which a lack of such cases in the study by Nadeem et al[6] could be due to the limited sample size, selection bias, or lack of a real effect is unclear.

Two other challenges in case series assessing possible risks from use of medications during pregnancy are: (1) the need for a comparison or reference group; and (2) the need to address confounding by indication. To assess whether the finding of extra-renal complications might be due to intrauterine exposure to the RAS blockers in the case series by Nadeem et al,[6] it is necessary to compare the occurrence of observed events in the exposed infants with the

occurrence of such events in unexposed infants or in the general population. Ideally, this would involve assessing a cohort of offspring from unexposed pregnancies with comparable methods and length of follow-up. However, because there was no comparison or reference group in the study by Nadeem et al,[6] it is difficult to determine whether the findings regarding nonrenal complications could be related to RAS blocker exposure or coincidental.

Even in instances where it can be established that the occurrence of observed events in exposed children is different than might be expected, it may be difficult to separate the effects of the medication from the effects of the condition for which the medication was administered. An example of this type of confounding by indication is the observed association of congenital heart defects among mothers with hypertension regardless of medication use.[3,12] Isolating the effects of a medication from those of the underlying condition requires studies of pregnancy outcomes among large numbers of women with and without exposure to medications with sufficient numbers of adverse events in each comparison group for robust inferences. However, women who do not require treatment with medication for conditions, such as hypertension, may have a different type of disease or different disease severity that may not result in the same frequency of adverse outcomes as women whose disease requires treatment.

Interpreting Outcomes following Medication Use during Pregnancy

The potential effects of medication use on the fetus and newborn infant can be many and varied. The abnormalities described by Nadeem et al[6] following fetal exposure to RAS blocking agents demonstrate several key points when interpreting pregnancy outcomes after medication use. First, the best documented manifestation of RAS fetopathy is impaired renal function rather than overt malformation of the kidneys. This effect is most evident with exposure during the second and particularly third trimester of pregnancy rather than the first.[10] Many observational studies of medication use focus on the occurrence of malformations following exposure during the first trimester when organ formation occurs. However, for many organs, development and maturation of function continues throughout gestation. RAS fetopathy is an example where more severe damage to organ function occurs with exposure in the second one-half of pregnancy. This could be expected from the known critical role of angiotensin II in the development of renal function later in gestation.[15] Second, the finding that ARBs adversely affect the kidney more frequently and earlier in pregnancy than ACEIs demonstrates that not all medications within the same general class of drugs have the same effect or level of effect on the fetus. Differences in the mechanism of action between ACEIs and ARBs and their half-lives may explain this.[16] New medications within a class often are developed specifically because they have a different or more targeted effect than alternatives.

Third, it is important to consider that not all adverse effects observed in an infant or fetus exposed prenatally to a medication may necessarily be related to that exposure. It is impossible to attribute cause definitively when only 1 infant in a small case series has a malformation. In addition, a number of the adverse events described by Nadeem et al[6] potentially arise secondary to associated factors rather than directly from the medication exposure. For example, oligohydramnios resulting from impaired production of fetal urine

can lead to pulmonary hypoplasia from compression of the fetus in utero. Prematurity, which has been associated with maternal hypertension,[12] can result in complications that are not a direct effect of the medication. These can include intracranial hemorrhage, cerebral palsy, seizure disorder, pneumothorax and pneumomediastinum secondary to mechanical ventilation, necrotizing enterocolitis, and possibly microcephaly, sensorineural hearing loss, cortical blindness, or cystic encephalomalacia in some instances. Patent ductus arteriosus, atrial septal defect, and tricuspid regurgitation are not uncommon in preterm infants and many term infants in the first days of life. Correlation of these abnormalities with the length of gestation, the age at which the infant was diagnosed, and the overall clinical setting might be helpful in interpreting their occurrence in the setting of maternal medication use.

Opportunities for Prevention and Education of Women of Childbearing Age and Healthcare Providers on Use of Medications during Pregnancy

Regardless of whether the observed abnormalities represent primary effects of the drug, secondary effects of the exposure, or associated conditions, it is critical for clinicians caring for pregnant women and their infants to be aware of the full range of potential complications experienced by infants exposed to RAS blocking drugs in utero. The article by Nadeem et al[6] highlights these complications. A unique finding of this study is that more than one-half of the exposures to RAS blockers occurred among pregnancies with absent or late prenatal care or that were unrecognized at the time of exposure. This underscores that advising against use of these medications beyond the first trimester is insufficient for prevention of such exposures. About 7% of pregnant women in the US receive no prenatal case or begin care in the third trimester, and about 37% of pregnancies in the US each year are unintended.[17,18] The known adverse effects of use of RAS blockers on kidney function in the offspring and the current prevalence of their use among women of child-bearing age who have hypertension make it imperative that healthcare providers consider whether a woman of child-bearing age might become pregnant while taking one of these drugs. Before prescribing RAS blockers, healthcare providers should screen prospective users for pregnancy, and discuss the risks and benefits of use of these drugs including the risks of unplanned pregnancy and fetal exposure, the use of effective birth control, and the various therapeutic options available.

The study by Nadeem et al[6] in this issue of *The Journal* adds to the body of literature on the occurrence of severe renal disorders among offspring of women who use RAS blockers during pregnancy and supports the indication from other studies of a higher frequency of such disorders among offspring exposed after the first trimester.[6] This study, based on a case series, also describes the range of clinical conditions that exposed infants may have and raises questions about what the absolute risk of RAS fetopathy might be among exposed pregnancies and whether additional extra-renal complications result from use of these medications during pregnancy. However, without appropriate comparison cohorts of exposed and unexposed pregnancies that have similar periods of follow-up, the absolute risk of RAS fetopathy remains undetermined. Although further studies are warranted to examine the absolute risk, the current evidence on adverse effects of RAS blockers use during pregnancy on infant outcomes suggests that the wisest course of action is to prevent use of

these drugs during pregnancy to the extent possible and to carefully consider their use among all women of childbearing age.

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Glossary

ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
RAS	Renin-angiotensin system

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