Renin–angiotensin system blockers exposure *in utero*: a life-long risk for the offspring health

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The effect of renin–angiotensin system (RAS) inhibition on the growing fetus has been fist described in 1981 in neonates exposed to captopril *in utero* [1,2]. Main features of RAS fetopathy syndrome include oligohydramnios, renal failure, anuria, arterial hypotension, intrauterine growth retardation, pulmonary hypoplasia, hypocalvaria and limb defects, while cardiac and cerebral abnormalities may exist. The effect on the kidney is responsible for the major manifestations in exposed fetuses during the second and third trimester of pregnancy, in which nephrogenesis is more active and RAS plays a crucial role. RAS inhibition in the fetus may result in hypotension, renal hypoperfusion and ischemia, causing fetal kidney damage. Fetal anuria/oliguria-induced oligohydramnios may further result in pulmonary hypoplasia and other Potter sequence defects. Some studies provided evidence of major cerebral and cardiovascular congenital malformations in those exposed to RAS treatment in the first trimester of pregnancy [3,4]. However, the evidence was not consistent in further reports [5], whereas several pregnancy cohort studies showed an association of hypertension itself with birth defects rather than RAS blockers treatment in the first trimester [6].

The main body of evidence for RAS fetopathy comes from case reports or case series, and retrospective studies with significant risk of selection bias and heterogeneity of reporting [4,7]. However, common reporting results among studies are severe manifestations if exposure was continued throughout pregnancy or present after the first trimester of pregnancy and greater deleterious impact of angiotensin II receptor blockers (ARBs) compared with angiotensin converting enzyme inhibitors (ACE-I). The latter finding has been attributed to a longer inhibition of angiotensin II actions on its type 1 receptors by the ARBs.

In the current issue of *Journal of Hypertension*, Weber-Schoendorfer *et al.* [8] reported both retrospective and prospective data on RAS fetopathy in a large series ($n = 190$) of exposed pregnancies from the databases of six teratology information services. The estimating rate of fetopathy in the prospective cases was 3.2% for ACE-I, and 29.2% for ARBs with exposure after 20 gestational weeks. The rates for the retrospective cases from this study, as well as those previously reported in the literature, are significantly higher with rates greater than 90% for the ARBs [7]. The presence of fetopathy is critical for short-term pregnancy outcomes with preterm birth, death or pregnancy termination being more frequent in pregnancies with diagnosed fetopathy. Neonatal renal failure with or without need of dialysis is also a common reported outcome [4,7]. Weber-Schoendorfer *et al.* also examined several maternal risk factors for fetopathy including maternal age, obesity status, underlying hypertensive disease cause, medication dosage and concomitant other antihypertensive medication use. Notably, supporting previous literature the only factor that reached statistical significance was the use of ARBs compared with ACE-I. The age of women on ARBs was older in line with the results of previous studies. Moreover, in one case there was combined exposure to RAS blocker and aliskiren.

One issue to be concerned is the use of RAS blockers in pregnancy despite their well known teratogenic effect. Although RAS blockers treatment account for less than 1% of pregnancies in population studies, it not negligible among hypertensive pregnancies reaching up to 30% [9–11]. Unattended or unknown pregnancy and poor prenatal care was reported in most studies as an explanation of RAS blockers treatment in pregnant women with chronic hypertension [4]. In the United States, about 4.4% of pregnancies were reported to be exposed to antihypertensive treatment [9]. Pregnant women on antihypertensive medication are older with higher rates of obesity, diabetes and chronic kidney disease. Among those with chronic hypertension, 19.1% were exposed to RAS blockers during the first trimester of pregnancy, 5.9 and 1.3% during the second and third trimester. Of note, one-third of women on antihypertensive medication before pregnancy continued their treatment during the first trimester of pregnancy. The prevalence of hypertension in the women of reproductive age 20–44 years was reported 10.2% based on the 2011–2012 and the 2013–2014 National Health and Nutrition Examination Surveys. The application of the 2017 American

Journal of Hypertension 2020, 38:35–37

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DOI:10.1097/HJH.0000000000002259

College of Cardiology/American Heart Association hypertension guidelines would double this prevalence and result in an additional 4.5 million hypertensive women aged 20–44 years [12]. The implications of this increase on pregnancy outcomes are currently unknown.

The majority of women on RAS blockers treatment would discontinue treatment or change to another medication during the first or second trimester of pregnancy [9]. The impact of RAS inhibition on the fetus could be reversible and discontinuation of the drug during the first trimester of pregnancy would result in favorable outcomes [8]. The study by Weber-Schoendorfer *et al.* [8] showed significantly higher rates of recovery of oligohydramnios in those that cessation of drug was early in course of pregnancy. Furthermore, a relative longer period between drug cessation and delivery associated with lower rates of fetopathy possibly allowing to restore RAS inhibition-induced fetal abnormalities, but it could also reflect less severe fetopathy. However, recovery of urine output, regression of oligohydramnios and even normal renal function after birth may not accurately reflect existing renal damage [8,13,14]. In an autopsy study examining renal lesions in 14 fetuses exposed to RAS blockers who died soon after birth, the main finding was absence or poor differentiation of proximal tubules suggesting renal tubular dysgenesis [13]. The lesions were present in fetuses even after drug cessation and restoration of renin levels. In two cases with oligohydramnios reversed 2 weeks after drug cessation and kidney histology was evaluated at 4 and 7 weeks later. The striking feature in both cases was the presence of numerous cortical cysts and interstitial fibrosis, but normal differentiated proximal tubules, suggesting possible recovery of tubular lesions. Nevertheless, the remaining histological damage could affect long-term favorable outcome. Vascular lesions characterized by thickening and disorganization of the arteriolar muscular layer were also present in all exposed cases and could further interfere with the evolution of renal disease and hypertension.

The long-term outcome of fetuses exposed to RAS treatment born alive has been evaluated by very few studies, reporting outcome mainly in terms of kidney endpoints. In a systematic review including 118 cases of ACE-I and 68 cases of ARBs in-utero exposure, six out of 26 cases with available follow-up for more than 6 months presented chronic renal disease and two cases need for dialysis [7]. Arterial hypertension was reported in four (15%) patients. Persisting proteinuria, acidosis and polyuria were also reported. In a retrospective case series of 21 cases exposed to RAS blockers during the second or third trimester of pregnancy, among six patients who survived beyond the neonatal period five developed chronic kidney disease [15]. One more study provided long follow-up data, showing a 33% rate of chronic dialysis or transplantation in those exposed after the first trimester of pregnancy [4].

Treatment of hypertension with RAS blockers is the first choice for many physicians. Given the secular trends of increasing maternal age the number of pregnant women with hypertension would increase [9]. Teratology information services provide advice in cases of RAS blockers exposure in pregnancy. Weber-Schoendorfer *et al.* [8] reported that in most cases advice was seek early in pregnancy probably explaining the lower fetopathy rates in the prospective group. Awareness of caring physicians and future mothers on the fetotoxic effect of RAS blockers during pregnancy is of crucial importance. Whether prescription of ACE-I should be preferred over ARBs in women of reproductive age needs to be assessed by the benefit over risk, taking into account both the woman's individual clinical conditions and the possibility of future pregnancy. Cessation of medication as soon as possible in pregnancy course or preferably avoid RAS blockers treatment without contraception in women of reproductive age may prevent poor offspring outcomes. In the absence of data from large patient cohorts and established biomarkers long-term follow-up of exposed *in utero* to RAS blockers children is necessary. Renal ultrasound may show small or enlarged kidneys, increased echogenicity, with loss of corticomedullary differentiation and presence of renal cysts but could also be normal [7,13]. Regular assessment of blood pressure measurement, proteinuria and tubular function should be recommended even in those with normal renal function at birth.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

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