Human fetal malformations associated with the use of an angiotensin II receptor antagonist: Case Report

Malformações fetais associadas ao uso de antagonista dos receptores de angiotensina II: Relato de Caso

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Abstract

Introduction: The potential risks related to drug exposure during pregnancy represent a vast chapter in modern obstetrics and data regarding the safety of antihypertensive drugs during pregnancy are relatively scarce. **Case report:** A 37-year-old patient discovered her fifth pregnancy at our hospital after 26 weeks and 4 days of gestation. She reported a history of hypertension and was currently being treated with Losartan. Hospitalization was recommended for the patient and further evaluation of fetal vitality was performed. On the fourth day an ultrasound was performed, resulting in a severe oligohydramnios, fetal centralization and abnormal ductus venosus. After 36 hours, the newborn died. Pathologic evaluation: At autopsy, the skullcap had large fontanels and deficient ossification. The kidneys were slightly enlarged. A microscopic examination detected underdevelopment of the tubules and the presence of some dilated lumens. Immunohistochemical detection of epithelial membrane antigen was positive. Immunoreactivity of CD 15 was also assayed to characterize the proximal tubules, and lumen collapse was observed in some regions. **Discussion:** Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor antagonists (ARAs) are among the most widely prescribed drugs for hypertension. They are often used by hypertensive women who are considering become pregnant. While their fetal toxicity in the second or third trimesters has been documented, their teratogenic effect during the first trimester has only recently been demonstrated. **Conclusion:** Constant awareness by physicians and patients should be encouraged, particularly in regard to the prescription of antihypertensive drugs in women of childbearing age who are or intend to become pregnant.

Keywords: angiotensin receptor antagonists; hypertension; pregnancy complications; toxicity.

Resumo

Introdução: Os riscos relacionados à exposição de drogas durante a gestação representam um vasto capítulo na obstetrícia moderna e dados sobre a segurança de drogas anti-hipertensivas são relativamente escassos. **Relato do caso:** Paciente de 37 anos, hipertensa crônica, descobriu a gravidez com 26 semanas e 4 dias de gestação. Estava em uso regular de Losartana. Durante avaliação fetal ultrassonográfica, foi relatada a presença de grave oligoâmnio associado ao quadro de centralização fetal com alteração de ducto venoso, e, após 36 horas, verificou-se óbito neonatal. Necrópsia: Observou-se calota craniana com fontanelas amplas e ossificação deficiente. Rins levemente aumentados de volume e, à microscopia, hipodesenvolvimento de túbulos com presença de lúmen dilatado. Imunohistoquímica com expressão em túbulos distais de antígeno epitelial de membrana. Imunoperoxidade com expressão em túbulos proximais de CD 15 em células epiteliais e colapso de alguns lúmens fora observado. **Discussão:** Inibidores da conversão de angiotensina e antagonistas de receptor de angiotensina estão entre as drogas mais prescritas para hipertensão. Estas drogas são frequentemente prescritas para mulheres em idade fértil e que pretendem engravidar. Enquanto a toxicidade fetal destas, nos segundo e terceiro trimestres, já é conhecida, seus efeitos durante o primeiro trimestre foi apenas recentemente demostrado. **Conclusão:** A conscientização por parte de médicos e pacientes deve ser realizada de rotina, principalmente no que diz respeito à prescrição e utilização de drogas potencialmente teratogênicas ou fetotóxicas. Este cuidado deve ser redobrado para pacientes que estão em idade reprodutiva e que podem se tornar gestantes em uso rotineiro destas medicações.

Palavras-chave: antagonistas de receptores de angiotensina; complicações na gravidez; hipertensão; toxicidade.

Introduction

Hypertensive disorders represent a leading cause of maternal and perinatal mortality and morbidity worldwide.[1,2] Furthermore, most of the morbidity associated with hypertensive disorders is concentrated among pregnancies complicated by pre-eclampsia and eclampsia, which are the first and second leading causes of maternal death.[3] Moreover, for every woman who dies, approximately 20 others suffer severe morbidity.[4]

Currently, it is widely accepted that sustained, severe hypertension (e.g., blood pressure ≥ 160/110 mmHg) during pregnancy should be treated, since it is considered a risk factor for maternal end-organ complications (such, as stroke), independent of preeclampsia.[5-7] However, insufficient evidence is available to guide the optimal use of antihypertensives for non-severe hypertension (e.g., blood pressure 140-159 mmHg/90-109 mmHg) during pregnancy.[7,8] Therefore, treatment of non-severe hypertension remains controversial due to the lack of clarity regarding benefits and risks for mother and child, as well as concerns about fetal programming effects.[7,8]

Case report

A 37-year-old patient discovered her fifth pregnancy at our hospital after 26 weeks and 4 days of gestation. She reported a history of hypertension over the past five years, and was currently being treated with Losartan (50 mg per day) on a regular basis to maintain adequate blood pressure levels. After admission to the prenatal services of our hospital, routine tests were conducted, and her antihypertensive medication was changed to methyldopa.

When ultrasonography (US) was performed, a single live fetus was observed in pelvic presentation. It had an estimated weight of 1007 g, had a placenta grade of 0 according to Granum classification, an absence of amniotic fluid was detected, and a gestational age of 26 weeks and 4 days was estimated. Elective hospitalization was recommended for the patient and further evaluation of fetal vitality was performed. Corticotherapy was also administered with 12 mg betametasona given in two cycles.

On the fourth day of hospitalization, routine tests were normal, 24 hours proteinuria assay was negative, and the patient's hypertension was adequately controlled. Another US was performed, resulting in a gestational estimate of 27 weeks and 1 day. Pelvic presentation was still observed and the estimated weight of the fetus was 918 g. In addition, severe oligohydramnios was detected. A Doppler examination further revealed fetal centralization with abnormal ductus venosus. Magnesium sulfate was subsequently administered for neuroprotection of the fetus and a cesarean delivery was scheduled.

The delivery was performed with no intercurrence and the birth of a male newborn was achieved. The newborn weighed 1050 g, had an Apgar score of 1 and 5 at the first and fifth minutes, and he required no neonatal resuscitation or orotracheal intubation in the delivery room. However, after 36 hours, the newborn progressed to cardiac arrest and died.

Pathologic evaluation

At autopsy, the fetus weighed 1050 g and manifested the appropriate dimensions for its gestational age. The skullcap had large fontanels and deficient ossification. A slight reduction in lung volume was observed (right, 6.3 g; left, 5.0 g; normal range, 27.0 ± 7.0 g). The kidneys were also slightly enlarged (combined weight, 20.3 g; normal range, 12.0 ± 4.0 g). Following preservation of the kidneys, a microscopic examination further detected underdevelopment of the tubules and the presence of some dilated lumens (Figure 1) compared with normal (Figure 2). Immunohistochemical detection of epithelial membrane antigen (EMA) (typically performed for distal tubules) was positive (Figure 3). Immunoreactivity of CD 15 was also assayed to characterize the proximal tubules, and lumen collapse was observed in some regions (Figure 4). Brain changes secondary to ischemia, including softening of the semi-oval center focus of perivascular hemorrhage in the head of the caudate nucleus and small hemorrhage in the IV ventricle were observed. Foci of hemorrhage were also observed in the lungs. However, the other organs presented no notable changes.

Discussion

The potential risks related to drug exposure during pregnancy represent a vast chapter in modern obstetrics. For patients with hypertension who qualify for medication, there are several antihypertensive alternatives available for clinical application, and these do not appear to have a risk of teratogenicity or fetotoxicity.[9-11] However, data regarding the safety of antihypertensive drugs during pregnancy are relatively

Figure 1. Staining of paraffin-embedded kidney sections by haematoxylin and eosin showed normal development of glomerular structures with a disarray of cortical zone, decreased numbers of tubules, abundant mesenchimal tissue, abnormal, irregular size and enlarge tubules, and proximal and distal convoluted tubules could not be distinguished. The tubular structures were lined by hypoplatic epithelial cells (cuboidal cells) with prominent lumena. Magnification x100.

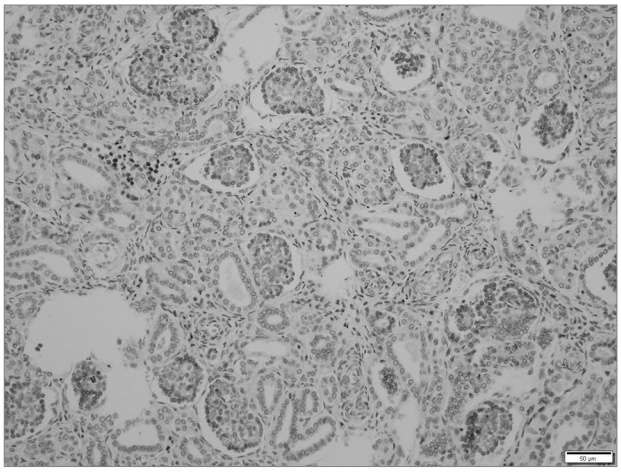
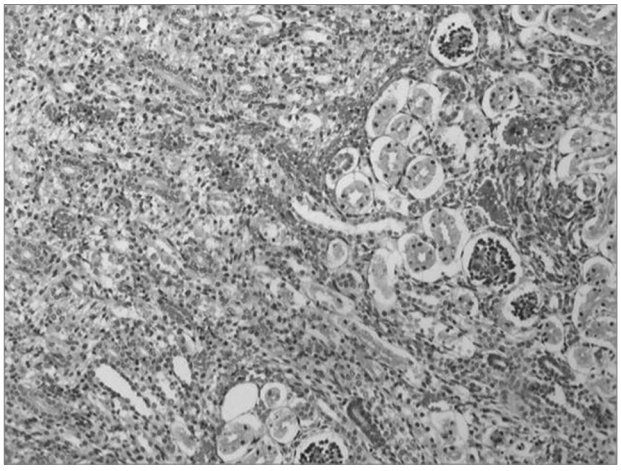


Figure 2. Staining of paraffin-embedded kidney sections by haematoxylin and eosin show normal renal development in a liveborn fetus at 39 weeks gestation. Distal tubules well developed and stained acidofilic by eosin. Magnifications: x100.



scarce.[9,12] There is evidence from animal studies that administration of angiotensin-converting enzyme inhibitors (ACEIs) during pregnancy is associated with fetal toxicity and an increased rate of stillbirths.[13] Treatment with angiotensin receptor antagonists (ARAs) has similar risks, and is also associated with oligohydramnios, fetal growth retardation, pulmonary hypoplasia, neonatal hypotension, renal failure with oliguria/anuria, renal tubular abnormalities, and calvarial hypoplasia.[14-17]

The most widely used ARAs include losartan, candesartan, valsartan, and tasosartan,[14] and these medications modulate the renin-angiotensin-aldosterone system by selectively blocking type 1 angiotensin II receptors.[18]

Figure 3. Positive immunolabeling of distal tubules using monoclonal antibodies raised against anti-epithelial (EMA) showed decreased numbers of these structures and poor differentiation. Magnification: x100.

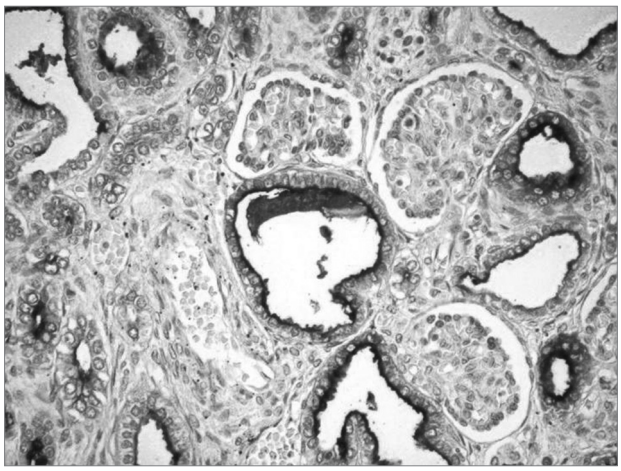
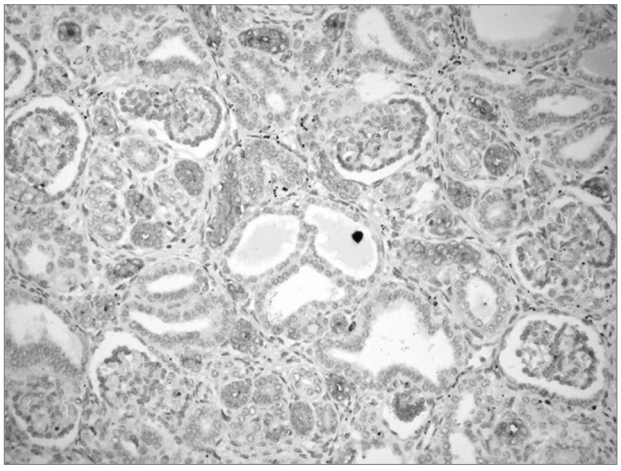


Figure 4. Immunoperoxidase staining with an anti-CD15 antibody. Decreased numbers of proximal tubules and poor differentiation were observed. Magnifications: x100.



ACEIs and ARAs are among the most widely prescribed drugs for hypertension. While their fetal toxicity in the second or third trimesters has been documented,[15,19] their teratogenic effect during the first trimester has only recently been demonstrated.[20,21]

In a recent meta-analysis of five observational cohorts, including 786 exposed infants and over one million controls, first trimester exposure to ACEIs or ARAs did not lead to a higher risk of major congenital malformations compared to other antihypertensive drugs.[18] Inadvertent exposure to these drugs in the first trimester of pregnancy has also not been found to present significant risks for malformations in live births, however, higher rates of spontaneous abortion have been reported for patients prescribed.[10] In addition, an increased risk for cardiovascular and

central nervous system malformations in infants whose mothers were prescribed an ACEI during their first trimester was recently reported.[22]

Given the conflicting data regarding the adverse effects of ACEIs and ARAs during pregnancy, the authors believe that as a preventive policy, physicians should not routinely prescribe these drugs for pregnant women, or for women who are considering becoming pregnant. Information regarding possible adverse events associated with these drugs should also be provided to patients, with informed consent required for women of childbearing age who elect to receive such drugs.

Conclusion

It is known that drugs with possible harmful fetal effects are included in the therapeutic armamentarium for many diseases, and that it is possible women will become pregnant when using these medications. Thus, constant awareness by physicians and patients should be encouraged, particularly in regard to the prescription of antihypertensive drugs in women of childbearing age who are or intend to become pregnant.

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