

Prenatal hypocalvaria after prolonged intrauterine exposure to angiotensin II receptor antagonists

Journal of the Renin-Angiotensin-Aldosterone System
October-December 2018: 1–5
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1470320318810940
journals.sagepub.com/home/jra



Marine Lallemand¹ , Sarah Prévost¹, François Nobili²,
Didier Riethmuller¹, Rajeev Ramanah¹, Marie-France Seronde³
and Nicolas Mottet¹

Abstract

We report a case of prenatal exposure to angiotensin II receptor antagonists (ARA II) from the beginning of pregnancy in a patient with a hypokinetic dilated cardiomyopathy. This case report emphasizes the fetal renal impact of prolonged intrauterine exposure to renin-angiotensin system (RAS) blockers, and highlights that this exposure can cause severe prenatal hypocalvaria. This delayed ossification can be reversible after birth, but the presence of anhydramnios indicates an early and irreversible block of RAS blockers in the fetus that is responsible for fetal kidney development abnormalities. This association carries a high risk of neonatal death. Prolonged exposure to ARA II or other RAS blockers remains prohibited throughout pregnancy.

Keywords

Renin-angiotensin system blockers, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, hypocalvaria, anhydramnios, fetus

Date received: 7 May 2018; accepted: 24 September 2018

Introduction

Prenatal exposure to angiotensin II receptor antagonists (ARA IIs) cases are rare. Regarding fetal exposure to ARA IIs during the first trimester of pregnancy, the data are rather reassuring. Studies suggest that ARA IIs are not major teratogens when used during the first trimester.^{1–4}

On the other hand, several case reports on renin-angiotensin system inhibitor fetopathies, including those caused by ARA IIs, were reported when they had been used beyond the first trimester of pregnancy.^{2,5–19} Our case highlights hypocalvaria and other fetal complications related to ARA II exposure throughout pregnancy. Current recommendations support a therapeutic class substitution in women treated with ARA IIs if pregnancy is desired.²⁰

The prognosis of children exposed in utero is not confined solely to the risk of neonatal renal failure. Indeed, skull ossification defect is a severe side effect that worsens the neonatal prognosis.^{5,21} This delayed ossification is encountered during prolonged prenatal exposure throughout

pregnancy. It is secondary to chronic hypoxia related to arterial hypotension induced by arterial vasodilatation of the ARA IIs.^{22,23}

Case report

A 34-year-old patient is hospitalized at 23 weeks of gestation (WG) for an evaluation of a severe intrauterine growth restriction associated with anhydramnios. This is the

¹Obstetrics and Gynaecology Department, Besançon University Medical Centre, Franche-Comté University, France

²Paediatric Nephrology Department, Besançon University Medical Centre, Franche-Comté University, France

³Cardiology Department, Besançon University Medical Centre, Franche-Comté University, France

Corresponding author:

Nicolas Mottet, Department of Obstetrics and Gynaecology, Besançon University Medical Centre, Alexander Fleming Boulevard, Besançon, 25000, France.

Email: ncmottet@gmail.fr





Figure 1. Major delayed ossification of the fetal cranial vault visualized in 2D ultrasound. The skull aspect is irregular, deformable under the probe with a punctuated aspect of the parietal ossification.

patient's second pregnancy. She did not encounter any problems during her first pregnancy.

She received an ARA II (candesartan 16 mg/day) and a beta-blocker (bisoprolol 5 mg/day) because of dilated cardiomyopathy caused by two distinct processes: a probable toxic cardiomyopathy secondary to anthracycline chemotherapy in childhood for the treatment of an abdominal neuroblastoma; and peri-partum cardiomyopathy developed after her first pregnancy. Before the first pregnancy, there was no evidence of cardiac impairment. This cardiomyopathy was discovered 8 days postpartum when the patient had cardiogenic shock with a left ventricular ejection fraction of 25%.

Despite our advice following a risk assessment, the patient became pregnant while she was being treated with ARA IIs. At this time, her left ventricular ejection fraction was 45%. Owing to maternal chronic heart failure and poor clinical tolerance of angiotensin-converting enzyme inhibitors, the ARA II treatment could not be suspended or replaced. Although information was given about the risk of maternal cardiac function aggravation throughout pregnancy and the risk of prolonged prenatal ARA II exposure for the fetus, the couple decided to pursue this pregnancy. The first trimester obstetrical ultrasound performed at 11 weeks' of gestation (WG) was unremarkable. An early fetal growth restriction was noted from 18 WG with a normal amniotic fluid volume and no unusual morphological element. The kidneys were seen and had a normal echopattern.

At 23 WG, the fetus had a growth restriction below the third percentile, anhydramnios, echogenic bowel and a disorder of the renal corticomedullary differentiation with a hyperechogenic renal parenchyma. The skull aspect was unusual and deformable under the probe with a major delayed ossification of the parietal bones and the occipital vault (Figures 1–3; Video 1). Cerebral

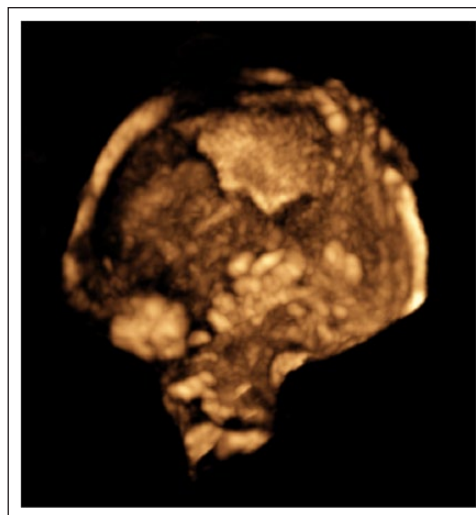


Figure 2. Volume reconstruction of the fetal skull confirming the absence of ossification of the occipital scale with enlarged fontanelles.



Figure 3. Echogenic bowel visualized in 2D ultrasound secondary to a probable ischaemic injury.

morphology was normal for the age of the pregnancy. The dosage level of candesartan was lowered to 8 mg per day but it had no effect on the resumption of the fetal diuresis. A caesarean section was recommended at 26 weeks and 4 days of gestation due to maternal heart function deterioration with a left ventricular ejection fraction of about 15%. The couple was informed about the risk of a difficult resuscitation at this very early term associated with the risk of pulmonary hypoplasia and an impaired renal function. The patient gave birth to a male infant weighing 700 g who died at 3 minutes of life due to inefficient ventilation resulting from the expected major pulmonary hypoplasia. He presented a Potter sequence secondary to the prolonged anhydramnios, as well as an absence of occipital scale. X-rays and an autopsy were refused by the couple.

Discussion

In cases of prolonged exposure to ARA II, the association of a delayed ossification of the skull with anhydramnios gives a poor prognosis. All the prenatal malformations described are secondary to prolonged block of the renin-angiotensin system (RAS) in the fetus.²¹ They are also described in some forms of tubular dysgenesis associated with well-known genetic mutations of RAS components.²⁴ The consequences of this exposure are not systematic and obstetrical ultrasounds can be normal throughout pregnancy.⁶ Human studies regarding the fetotoxicity of a maternal exposure to ARA II are rare. No studies have examined the prenatal semiology according to the type of ARA II or the duration of the exposure. It is reported that candesartan has a higher affinity for angiotensin compared to other ARA IIs with a greater risk of fetal toxicity.^{12,25}

This delayed ossification is mainly found when the fetus is exposed to ARA IIs from the second trimester of pregnancy. The chronic hypoxia secondary to the arterial hypotension induced by the ARA IIs can explain this delayed ossification. Indeed, the prolonged hypoxia limits the angiogenesis and growth of the membranous bones. These hypoxic consequences can also manifest as growth restriction or diffuse ischaemic phenomena, in particular in the digestive system, which is sensitive to variations in oxygenation. The inhibition of some osteoblast growth factors could be another physiopathological hypothesis to explain the delayed ossification.^{22,23} This same theory is also encountered in cases of hereditary proximal tubulorenal dysgenesis.²⁶ This ossification defect of the skull bones can be detected by ultrasound and predominates on the occiput without any repercussions for brain development.²⁷ Bones usually retain a normal shape and position but become hypoplastic. The sutures and fontanelles are symmetrically enlarged.²²

This delayed ossification may be reversible after birth.^{2,6,15–17} According to the literature (**Table 1**), among 12 newborns exposed to ARA IIs during pregnancy and with neonatal hypocalvaria, 5 had neonatal anuria.^{6,9,12,15–19,28,29} Of these, three died in the immediate postnatal period and the two survivors had chronic renal failure. In the absence of neonatal anuria, all newborns with hypocalvaria are alive ($n = 6$). Therefore, it appears that neonatal anuria is a key element in neonatal prognosis. The prenatal association of anhydramnios and delayed ossification may indicate an early and irreversible block of RAS in the fetus. This association poses a high risk for neonatal death. This interpretation is confirmed by Yamada et al.¹⁷ who suggest that the association of hypocalvaria and acute renal failure in the neonatal period remains a poor prognosis. However, an isolated delayed ossification in the prenatal period without any alteration of fetal diuresis does not appear to aggravate the postnatal prognosis, and parents should be informed

of its reversibility after birth. Regarding birth modalities, all newborns with prenatal hypocalvaria are born by caesarean section in order to limit the crushing forces applied to the skull during vaginal delivery.^{2,6,8,9,12,15–17,28}

The most common fetal complication related to ARA II exposure remains renal toxicity.³⁰ The first ultrasound sign to look for is oligoanhydramnios linked to anuria complicating renal failure.^{6,7,22} Fetal anuria may be responsible for an authentic Potter sequence including pulmonary hypoplasia, facial dysmorphism and deformities of the extremities.^{5–9,21–23,31} The kidneys can be hyperechoic and increased in volume with or without a disorder of the corticomedullary differentiation.^{5–10,21,32} These images can be explained by a diffuse dilatation of the renal distal tubules or the presence of cortical cysts.⁸ Many studies do not find any association with abnormalities of the urinary tract.^{7,9,10,32}

It should be noted that the global fetal toxicity of ARA IIs is clearly demonstrated when they are prescribed during the second and third trimesters of pregnancy. Fifteen studies describing cases of prolonged ARA II fetal exposure are available in the literature.^{2,5–16,18,19} The neonatal mortality rate remains very high. Thus, out of 29 cases of antenatal exposure to ARA IIs, 7 postnatal deaths, 3 intrauterine fetal deaths, 5 medical terminations of pregnancy and 14 live births have been reported. Of these 29 cases, 26 cases of oligoanhydramnios were discovered during obstetrical ultrasound. Neonatal anuria is found in 11 out of 21 born alive newborns. Of these 11 live newborns with anuria, 64% died within a few hours or days ($n=7$). Pulmonary hypoplasia was found in 6 out of 29 cases: two of these died in utero and two were born alive but died within a few hours or days (67%). Finally, hypocalvaria was found following clinical or fetopathological examination in 16 out of 29 cases. Therefore, it appears that neonatal anuria and pulmonary hypoplasia are key elements in neonatal prognosis. In addition, oligohydramnios was shown to be reversible in many cases after discontinuation of ARA II treatment with favourable outcomes, although long-term outcomes have not yet been systematically assessed.

Conclusion

This observation underlines the absolute necessity to offer a preconception counselling appointment to women treated with RAS blockers. Fetal consequences secondary to a prolonged exposure to ARA IIs mimic tubular dysgenesis associated with genetic abnormalities of the RAS. The global fetal impact may be significant if the ARA II is continued beyond the first trimester. The delayed ossification that predominates at the level of the cranial vault can be detected in utero by ultrasound and remains a predictor of a poor prognosis when it is associated with oligoanhydramnios.

Table 1. Neonatal prognosis of newborns with prenatal exposure to ARA IIs and hypocalvaria at birth.

Study	Molecule and dosage	Time of exposition (WG)	Birth (WG)	Prenatal ultrasound semiology			Clinical examination/fetopathology			Postnatal evolution	
				Oligoamnios (GA at diagnosis)	Hypo calvaria	Other signs	Birth weight (g) (percentiles)	Neonatal anuria	Pulmonary hypoplasia		Other abnormalities
Serreau et al. ⁶	Candesartan 16 mg/day + methyldopa 250 mg/day	0-32	35	+	+	Echogenic and enlarged kidneys, retrognathism	3240 (97)	-	-	Renal hypertrophy, echogenic and undifferentiated kidneys, transitory AFR	At 3 months of life: absence of hypocalvaria, normal psychomotor development, normal renal function Death D4
Martinovic et al. ⁹	Losartan 50 mg/day	0-34	34	+	NE	-	NE	+	-	Multi-visceral failure, arterial hypotension, RTD	
Payen et al. ¹⁶	Candesartan 8 mg/day	0-31	33	+	-	-	1660 (18)	-	+	Asymmetric FGR, Potter sequence, transitory ARF	D28: Absence of hypocalvaria supposed, normal renal function Neonatal death
Schaefer et al. ²⁹	Candesartan 16 mg/day + bisoprolol	0-33	33	+	NE	-	2250 (84)	+	+	Normal kidneys (ultrasound)	
	Valsartan 80 mg/day + hydrochlorothiazide 12.5 mg/day	28-36	36	+	NE	-	2240 (19)	+	NE	Renal hypertrophy, echogenic kidneys, joint contractures	At 8 months of life: absence of hypocalvaria supposed, CRF, good development
	Losartan 50 mg/day	0-31	31	+	NE	-	1590 (66)	-	-	Renal hypertrophy and multicystic kidneys	At 2 years old: absence of hypocalvaria, good development, normal renal function Neonatal death
Korkes et al. ²⁸	Losartan 50 mg/day	0-27	28	+	NE	-	1007 (37)	NE	+	Renal hypertrophy, RTD, Grade IV intraventricular haemorrhage	Neonatal death
Cox et al. ¹²	Candesartan	0-32	32	+	NE	FGR	1120 (1)	+	-	Arterial hypotension, joint contractures, hypospadias, rocker bottom feet, absent right kidney, large abnormal left kidney, RTD	Neonatal death
Nayar et al. ¹⁵	Losartan 25 mg/day + Furosemide 40 mg/day	0-35	35	-	NE	-	1740 (2)	-	-	Normal kidneys (ultrasound), dilated bowel loops	D12: absence of hypocalvaria supposed, normal renal function
Yamada et al. ¹⁷	Oimesartan medoxomil 40 mg/day	0-36	36	+	NE	FGR	1878 (2)	+	+	Renal hypertrophy, echogenic kidneys	At 6 months of life: absence of hypocalvaria, CRF, normal cognitive development
Ri et al. ¹⁸	Valsartan	0-40	40	NE	NE	NE	3160 (30)	-	-	Arterial hypotension, pneumothorax, renal hypertrophy, echogenic kidneys, kidney failure, calcaneovalgus foot, inferior vena cava thrombosis	At 2 months of life: absence of hypocalvaria, normal renal function At 24 months of life: growth and overall development delay
Wegleiter et al. ¹⁹	Oimesartan medoxomil 5 mg/day	0-27	40	+	NE	Echogenic kidneys	2940 (16)	-	-	Renal hypertrophy and multicystic kidneys, disorder of the corticomedullary differentiation, asymptomatic tubular proteinuria	At 6 months of life: resolution of the proteinuria At 9 months of life: microcephaly, muscular hypotonia, motor delay

WG : weeks of gestation; GA: gestational age; g: grams; FGR : fetal growth restriction; RTD: renal tubular dysgenesis; Supposed[†]: pulmonary hypoplasia is supposed in front of respiratory distress at birth; ARF : acute renal failure; CRF : chronic renal failure; D: day; M: month; + : presence; - : absence; NE : non-evaluated.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

M. Lallemant  <https://orcid.org/0000-0002-3341-5267>

References

- Diav-Citrin O, Shechtman S, Halberstadt Y, et al. Pregnancy outcome after in utero exposure to angiotensin converting enzyme inhibitors or angiotensin receptor blockers. *Reprod Toxicol* 2011; 31(4): 540–545.
- Schaefer C. Angiotensin II-receptor-antagonists: further evidence of fetotoxicity but not teratogenicity. *Birth Defects Res A* 2003; 67:591–594.
- Biswas PN, Wilton LV and Shakir SW. The safety of Valsartan: results of a postmarketing surveillance study on 12881 patients in England. *J Hum Hypertens* 2002; 16(11): 795–803.
- Walfish A, Al-Maawali A, Moretti ME, et al. Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers. *J Obstet Gynaecol* 2011; 31(6): 465–472.
- Alwan S, Polifka JE and Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. *Birth Defects Res A* 2005; 73(2): 123–130.
- Serreau R, Luton D, Macher MA, et al. Developmental toxicity of the angiotensin II type I receptor antagonists during human pregnancy: a report of 10 cases. *BJOG* 2005; 112(6): 710–712.
- Saji H, Yamanaka M, Hagiwara A, et al. Losartan and fetal toxic effects. *Lancet* 2001; 357(9253): 363.
- Plazanet C, Arrondel C, Chavant F, et al. Fetal renin-angiotensin-system blockade syndrome: renal lesions. *Pediatr Nephrol* 2014; 29(7): 1221–1230.
- Martinovic J, Benachi A, Laurent N, et al. Fetal toxic effects and angiotensin-II-receptor antagonists. *Lancet* 2001; 358: 241–242.
- Hinsberger A, Wingen AM and Hoyer PF. Angiotensin II receptor inhibitors in pregnancy. *Lancet* 2001; 357(9268): 1620.
- Lambot MA, Vermeylen D and Noel JC. Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001 May;357(9268):1619–20.
- Cox RM, Anderson JM and Cos P. Defective embryogenesis with angiotensin II receptor antagonists in pregnancy. *BJOG* 2003; 110(11): 1038.
- Briggs GG and Nagoette MP. Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacother* 2001; 35: 859–861.
- Pietrement C, Malot L, Santerne B, et al. Neonatal acute renal failure secondary to maternal exposure to telmisartan, angiotensin II receptor antagonist. *J Perinatol* 2003; 23: 254–255.
- Nayar B, Singhal A, Aggarwal R, et al. Losartan induced fetal toxicity. *Indian J Pediatr* 2003; 70(11): 923–924.
- Payen V, Chemin A, Jonville-Béra AP, et al. Fetal toxicity of angiotensin-II receptor antagonists. *J Gynecol Obstet Biol Reprod (Paris)* 2006; 35(7): 729–731.
- Yamada A, Tsuji Y, Kato Y, et al. Renal tubular dysgenesis and reversible hypocalvaria after intrauterine exposure to an angiotensin receptor blocker. *NDT Plus* 2011; 4(2): 141–142.
- Ri S, Shin J, Je B-K and Choi BM. Hypocalvaria of newborn infant: intrauterine exposure to an angiotensin receptor blocker. *Perinatology* 2017; 28(3): 103.
- Wegleiter K, Waltner-Romen M, Trawoeger R, et al. Long-term consequences of fetal angiotensin II receptor antagonist exposure. *Case Rep Pediatr* 2018; 2018: 5412138.
- French National Agency for the Safety of Medicines: Information point: ACE / ARA II and pregnancy: never use during the 2nd and 3rd trimesters of pregnancy, not recommended in the 1st trimester of pregnancy. 2017
- Bullo M, Tschumi S, Bucher BS, et al. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. *Hypertension* 2012; 60(2): 444–450.
- Barr M. Teratogen update: angiotensin-converting enzyme inhibitors. *Teratology* 1994; 50: 399–409.
- Barr M and Cohen M. ACE inhibitor fetopathy and hypocalvaria: the kidney–skull connection. *Teratology* 1991; 44: 485–495.
- Gubler MC, Gribouval O, Antignac C, et al. Renal tubular dysgenesis and mutations in the renin-angiotensin system genes. *Bull Acad Natl Med* 2014; 198(2): 339–348; discussion 348–349.
- Lumbers ER, Burrell JH, Menzies RI, et al. The effects of a converting enzyme inhibitor (captopril) and angiotensin II on fetal renal function. *Br J Pharmacol* 1993; 110(2): 821–827.
- Kumar D, Moss G, Primhak R, et al. Congenital renal tubular dysplasia and skull ossification defects similar to teratogenic effects of angiotensin converting enzyme (ACE) inhibitors. *J Med Genet* 1997; 34(7): 541–545.
- Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. *Early Hum Dev* 2006; 82(1): 23–28.
- Korkes HA, de Oliveira LG, Berlinck L, et al. Human fetal malformations associated with the use of an angiotensin II receptor antagonist: case report. *J Bras Nefrol* 2014; 36(3): 410–413.
- Schaefer C. Drugs during pregnancy and lactation. In *Handbook of prescription drugs and comparative risk assessment*. Amsterdam: Elsevier, 2001.
- Nadeem S, Hashmat S, Defreitas M, et al. Renin angiotensin system blocker fetopathy: a Midwest Pediatric Nephrology Consortium Report. *J Pediatr* 2015; 4: 881–885.
- Gersak K, Cvijic M and Cerar LK. Angiotensin II receptor blockers in pregnancy: a report of five cases. *Reprod Toxicol* 2009; 28(1): 109–112.
- Bass J and Faix RG. Gestational therapy with an angiotensin II receptor antagonist and transient renal failure in a premature infant. *Am J Perinatol* 2006; 23(5): 313–317.