Introduction

Prenatal exposure to angiotensin II receptor antagonists (ARA II) cases are rare. Regarding fetal exposure to ARA II during the first trimester of pregnancy, the data are rather reassuring. Studies suggest that ARA II 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 II, 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 II 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 II.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
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 corticomедullary 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 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.

**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.

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

**Figure 3.** Echogenic bowel visualized in 2D ultrasound secondary to a probable ischaemic injury.
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.26,6,15–17 According to the literature (Table 1), among 12 newborns exposed to ARA IIs during pregnancy and with neonatal hypocalvaria, 5 had neonatal anuria.5,9,12,15–19,28,29 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 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 intraterine 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, oligoanhydramnios 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 exposure (WG) | Birth (WG) | Prenatal ultrasound semiology | Clinical examination/fetopathology | Postnatal evolution                  |
|------------------|--------------------------------------|-----------------------|------------|-----------------------------|-----------------------------------|--------------------------------------|
| Serreau et al.   | Candesartan 16 mg/day + methyldopa 250 mg/day | 0-32                  | 35         | + (32)                      | Oligoamnios (GA at diagnosis)     | Renal hypertrophy, echogenic and undifferentiated kidneys, transitory ARF | At 3 months of life: absence of hypocalvaria, normal psychomotor development, normal renal function |
| Martinovic et al. | Losartan 50 mg/day                  | 0-34                  | 34         | + (34)                      | NE                                | Multi-visceral failure, arterial hypotension, RTD | Death D4 |
| Payen et al.     | Candesartan 8 mg/day                | 0-31                  | 33         | + (31)                      | NE                                | Asymmetric FGR, Potter sequence, transitory ARF | D28: Absence of hypocalvaria supposed, normal renal function |
| Schaef er et al. | Candesartan 16 mg/day + bisoprolol  | 0-33                  | 33         | + (33)                      | NE                                | Normal kidneys (ultrasound)         | Neonatal death |
|                  | Valsartan 80 mg/day + hydrochlorothiazide 12.5 mg/day | 28-36                 | 36         | + (unspecified)             | 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         | + (31)                      | NE                                | Renal hypertrophy and multicystic kidneys | At 2 years old: absence of hypocalvaria, good development, normal renal function |
| Korkes et al.    | Losartan 50 mg/day                  | 0-27                  | 28         | + (27)                      | NE                                | Renal hypertrophy, RTD, Grade IV intraventricular haemorrhage | Neonatal death |
| Cox et al.       | Candesartan                         | 0-32                  | 32         | + (32)                      | NE                                | Arterial hypotension, joint contractures, hypospadias, rocker bottom feet, absent right kidney, large abnormal left kidney, RTD | Neonatal death |
| Nayar et al.     | Losartan 25 mg/day + Furosemide 40 mg/day | 0-35                  | 35         | -                           | NE                                | Normal kidneys (ultrasound), dilated bowel loops | D12: absence of hypocalvaria supposed, normal renal function |
| Yamada et al.    | Olmesartan medoxomil 40 mg/day      | 0-36                  | 36         | + (unspecified)             | NE                                | Renal hypertrophy, echogenic kidneys | At 6 months of life: absence of hypocalvaria, CRF, normal cognitive development |
| Ri et al.        | Valsartan                           | 0-40                  | 40         | NE                         | NE                                | Arterial hypotension, pneumothorax, renal hypertrophy, echogenic kidneys, kidney failure, calcineuvalgus foot, inferior vena cava thrombosis | At 2 months of life: absence of hypocalvaria, normal renal function |
| Wegleiter et al. | Olmesartan medoxomil 5 mg/day       | 0-27                  | 40         | + (26)                      | NE                                | Renal hypertrophy and multicystic kidneys, disorder of the corticomedullary differentiation, atrophic tubular proteinuria | At 24 months of life: growth and overall development 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.
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