Renin-angiotensin system (RAS) has a significant role in the regulation of blood pressure. The use of RAS blocker (angiotensin converting enzyme inhibitor or angiotensin II receptor blocker [ARB]) for hypertension is common, but this medication during pregnancy may lead to dysgenesis of renal tubule, hypoperfusion and hypoplastic growth of skull and pulmonary vascular hypoplasia in fetus. We report a female baby born to a mother who took ARB up to gestational age 35 weeks, and then did not take ARB for 10 days until delivery on IUP 36 weeks. The baby suffered from hypotension and anuria for few days but suffered severe respiratory difficulty and pulmonary hypertension requiring mechanical ventilation with inhalation of nitric oxide. The baby had also limb contracture, defects of skull ossification, and thrombocytosis. After weaning of mechanical ventilation, the baby had a polyuria and was diagnosed with transient partial nephrogenic diabetes insipidus. The baby showed polycythemia with normal kidney function at 20 months of age. The baby showed normal growth and development based on the results of the Korean Development Screening Test with 20 months of corrected ages.

**Key Words:** Angiotensin receptor antagonist, Diabetes insipidus, Nephrogenic, Maternal exposure, Persistent fetal circulation, Cranial sutures

**Introduction**

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), which are renin-angiotensin system (RAS) blockers, are most widely used as first-line medications for hypertension owing to their effectiveness in preventing long-term renal complications and reducing blood pressure. The National Institute for Health and Care Excellence guidelines recommend calcium channel blockers over RAS blockers as first-line medication for women of childbearing age. RAS blockers indirectly affect the fetus by reducing placenta perfusion in the pregnant mother or directly affect the fetus by crossing the placenta and causing ARB-induced fetopathies such as oligohydramnios, anuria, secondary renal tubular dysplasia, limb contractures, cranial ossification defects, prolonged patent ductus arteriosus, and death in utero.

We report a case of ARB fetopathy or secondary renal tubular dysgenesis (RTD) in an infant born to a mother who took ARBs throughout her pregnancy, and then did not take ARB for 10 days until delivery on IUP 36 weeks. The infant showed severe dyspnea and pulmonary arterial hypertension without severe renal tubular dysgenesis symptoms followed by nephrogenic diabetes insipidus, hypocalvaria, pseudohypoaldosteronism and polycythemia.
Case

1. Maternal history

The mother was a 36-year-old, G2P1L0D1A0 with intrauterine fetal death history. She had polycystic ovarian syndrome and had been taking Pritor 40 (an angiotensin receptor blocker [Telmisartan] and Atorvastatin [Lipitor®; Pfizer Pharmaceuticals, New York, USA]) for chronic hypertension and hyperlipidemia since 3 years before. She was incidentally diagnosed as having 35-week pregnancy during a gynecologic examination for dysuria. The patient stopped taking these medications after being diagnosed with 35 weeks pregnancy. She had a preterm premature rupture of membranes for 2 days at IUP 36+3 weeks, 10 days after stopping the medication. The patient delivered the infant vaginally after one-time administration of antenatal corticosteroids. Fetal ultrasonographic evaluation just before delivery revealed no oligohydramnios and fetal structural abnormalities.

2. Patient history

The female infant had an Apgar score of 5 points at 1 minute and of 9 points at 5 minutes. The infant exhibited nasal flaring with oxygen saturation 90% at 2 hours after birth and was admitted to the neonatal intensive care unit. At the time of admission, the infant had a body temperature of 36.4℃, blood pressure of 56/36 mmHg, HR of 167 bpm, RR of 37 breaths, body weight of 2.72 kg (60th percentile), height of 47 cm (60th percentile), and head circumference of 30.5 cm (20th percentile). On physical examination, the infant was observed to have a large anterior fontanelle measuring 5 cm and arthrogryposis of both wrists and ankles (Fig. 1). At the time of birth, the infant had a white blood cell count of 13.26/L, hemoglobin level of 14.8 g/dL, and platelet count of 402×10^3/L. The C-reactive protein test result was negative. Serum electrolytes Na, K, Cl, tCO2 contents were 138, 4.8, 108, 14.8 mEq/L, respectively. Blood Urea Nitrogen (BUN)/Creatinine (Cr) were 6.2/0.42 mEq/L. Good urination showed at the 1st day. The oxygen saturation level was maintained at 90% until 2 hours after birth. Nasal flaring and chest wall elevation developed 7 hours after birth. A blood gas analysis showed a pH of 7.209 and pCO2 of 53.4 mmHg. Left pneumothorax was observed on the chest radiograph (Fig. 2). High-frequency oscillatory ventilator (HFOV) care was begun after intubation. The infant exhibited differential cyanosis of >10% at 2 days after birth and had tricuspid regurgitation (TR) and a pressure gradient of 60 mmHg on echocardiography. Accordingly, inhaled nitric oxide (iNO) treatment was begun (Fig. 3). After 5 days of the HFOV and iNO care, tricuspid valve regurgitation...
was relieved with a TR velocity of 0.8 m/s. The iNO care was terminated and mechanical ventilation was withdrawn at 8 days after birth.

Three-dimensional brain computer tomography (CT) was performed to identify the cause of the large anterior fontanelle measuring >5 cm and the widened suture line of the skull bones. Hypocalvaria was observed on CT (Fig. 4). Renal ultrasound showed an increase in cortical echogenicity in both kidneys. The size of the kidneys was 4.4 cm in the left and 4.5 cm in the right. Around 20 days of life the infant showed stable systemic vital signs. BUN/creatinine ratio were 22/0.42 mg/dL. Serum electrolytes Na, K, Cl, CO$_2$ content were 145, 5.5, 116, 13.6 mEq/L, respectively. There were no clinically dehydrated or over hydrated signs. But the amount of urine inexplicably increased progressively above 5 mL/kg/hour. Plasma ADH level was high at 26.14 pg/mL. Water deprivation test was done (Fig. 5). Under the diagnosis of partial nephrogenic diabetes insipidus, vasopressin administration was begun at 21 days after birth and stopped at 36 days after birth, when symptom relief was observed. After that, mild metabolic acidosis and hyperkalemia tended to persist as follows: the levels of serum electrolytes Na, K, Cl, total CO$_2$ contents and BUN/creatinine were 137, 6.0, 99, 10 mEq/L, and 11.8/0.40 mg/dl, respectively. The plasma renin activity and aldosterone levels were 262.6 ng/(mL×hr) and 1,115.62 ng/dL, respectively at 38 days of age. On the basis of these results, the infant was diagnosed as having pseudohypoaldosteronism. Electrolyte abnormalities, renin, and aldosterone levels gradually normalized over 1 month.

At the most recent outpatient visit at 20 months of age, the laboratory tests and physical examination findings were as
follows. BUN/cr were 11.1/0.25 mg/dL. Serum electrolytes were Na, K, Cl, tCO₂ contents were 139, 4.2, 103, 22 mEq/L. The hemoglobin, hematocrit, and red blood cell levels were 16.1 g/dL, 48.7%, and 5.86/μL, respectively, indicating mild polycythemia. The erythropoietin level was normal at 10.7 mIU/mL. The height, body weight, and head circumference were all within their normal ranges (height 60th percentile, body weight 50th percentile, head circumference 30th percentile). The infant showed normal development based on the results of the Korean Development Screening Test (K-DST).

Discussion

Exposure to ARB during pregnancy has an evident impact on infant renal function. In a case series analysis by Nadeem et al., renal involvement in ARB fetopathy was observed in most infants, and 8 mothers who took ARBs during pregnancy required renal replacement therapy. Three mothers who took ARB during early pregnancy had nephrogenic diabetes insipidus. The infants of who were exposed to ARBs during the second or third trimester had significantly lower estimated glomerular filtration rates and more severe irreversible renal injuries than those exposed to ARBs during the first trimester. This

![Fig. 5. Water deprivation test. After administration of desmopressin, urine osmolality increased.](image)

| Table 1. comparison of the characteristics in ARB fetopathy cases |
|---------------------------------------------------------------|
| Case 1 | Case 2⁷ | Case 3⁸ | Case 4⁷ |
| Medication drug | ARB (Telmisartan®) | ARB (Candesartan®) | ARB (Valsartan®) | ARB (Olmesartan®) |
| Medication period | 10 days just before delivery | 10 days just before delivery | Throughout pregnancy | Throughout pregnancy |
| Gestational age | 36¹ weeks | 36¹ weeks | 40⁰ weeks | 40⁰ weeks |
| Oligohydramnios | (-) | (-) | (-) | (+) |
| Organ involvement |
| Lung | Pneumothorax | Severe respiratory distress | Pneumothorax | Pneumothorax |
| | PPHN required iNO | | PPHN required iNO | |
| Heart | Hypotension | - | - | - |
| Kidney | Nephrogenic diabetes | Anuria | Oliguria | Renal failure required CRRT |
| | Polycythemia | CAH | IVC thrombosis | SIP |
| Others | Arthrogryposis | Hypocalvaria | Arthrogryposis | Hypocalvaria |
| Skeletal systems | | | | |
| Prognosis | Live | Live | Live | Death due to ESRD |

Abbreviations: ARB, angiotensin II receptor blocker; PPHN, persistent pulmonary hypertension; iNO, inhaled nitric oxide; CRRT, continuous renal replacement therapy; CAH, congenital adrenal hyperplasia; SIP, spontaneous intestinal perforation; ESRD, end stage renal disease.
observation was attributed to the fact that renal development is crucial during middle to late pregnancy.

There were 4 domestic cases up to this case (Table 1).\textsuperscript{5-7} Case 2\textsuperscript{5} is interesting to compare because the dosing period of the drug is opposite to that of our case (case 1). In our case, the drug was discontinued 10 days before birth, and Case 2 was the case of using the drug only 10 days before birth. But in our case of long-term drug use, there was no anuria or hypotension, and in case 2 of short-term use for just 10 days, there was anuria for 10 days and hypotension. In other words, it can be seen that these two patients may be evidence that 34–36 weeks gestation is a critical period of renal injury. Similarly, there was other report that even though the mother took the drug in the second or third trimester of pregnancy, the amniotic fluid volume was normalized after the drug was discontinued before 34–36 weeks of gestation when nephrogenesis is terminated and the baby did not show renal impairment.\textsuperscript{8} In our case, there was no oligohydramnios just before delivery after disrupting of ACEI medication. In case 36 and case 4,\textsuperscript{4,7} it is shown that the presence or absence of amniotic fluid can be an important factor in predicting severe symptoms such as anuria and hypotension. In 2017, case 3\textsuperscript{5} was reported mild hyponatremia, mild elevation of BUN level, and increased renal parenchymal echogenicity in infants with hypocalvaria and ARB fetopathy. On the contrary, partial nephrogenic DI was observed in this case rather than any other renal dysfunction. The ARBs taken by the mother during the second trimester in the present case may have affected the formation and affinity of the vasopressin receptors for ADH, consequently inducing partial nephrogenic DI and pseudohypaldosteronism in the infant.\textsuperscript{9} The vasopressin administration was discontinued at 6 months after observing symptom relief. This improvement may be attributed to the tubule development and growth that occur during infancy.

Renal involvement of ARBs reduces infants’ ability to produce amniotic fluid, causing oligohydramnios, which affects their lung maturation. Pulmonary hypoplasia caused by oligohydramnios can lead to severe respiratory distress in the early period after birth. Alwan et al.\textsuperscript{10} reported pulmonary hypoplasia in 3 of 15 infants exposed to ARBs. Reduced production of amniotic fluid can lead to limb contractures due to mechanical reasons. Pryde et al.\textsuperscript{11} reported that pregnant women who took ARBs had oligohydramnios that led to severe respiratory distress and limb contracture in their infants.\textsuperscript{12} The infant in the present case study also had severe respiratory distress, pneumothorax, and arthrogryposis immediately after birth, exhibiting the symptoms experienced by infants exposed to ARBs in previous studies. The infant was later subjected to iNO inhalation due to persistent pulmonary hypertension. However, as the infant recovered from these symptoms, the infant was deemed to have no pulmonary hypoplasia. This patient had no lack of amniotic fluid but had deformity of limbs. It is estimated that the child may have suffered from amniotic fluid deficiency for a long time, so even if there are few symptoms of pulmonary insufficiency after birth, if there is a history of suspected ACEI fetopathy and hand deformity, close observation of the heart and lung symptoms is necessary.

Lennestål et al.\textsuperscript{13} reported that antihypertensive medications taken during pregnancy can cause heart anomalies in infants and explained that ARBs can cause pulmonary valve stenosis and Ebstein’s anomaly in infants. However, the infant in the present case did not exhibit any congenital anomalies. This observation was consistent with the case series report by Nadeem et al.\textsuperscript{4} in which no heart defects were found in infants. ARB fetopathy can still compromise the cardiac function of an infant by causing pulmonary hypertension.

Hypoplastic and poorly ossified skull bone is commonly observed in infants with ARB fetopathy. Alwan et al.\textsuperscript{10} reported hypoplastic and poorly ossified skull bones in 9 of the 15 infants in their case review. In 1991, Barr and Cohen\textsuperscript{14} reported hypoplasia of the membranous bones of the skull (hypocalvaria) in the infants of mothers who took ARBs or ACEIs in the second or third trimester. Although the mechanism by which ARBs or ACEIs cause hypocalvaria is unclear, Barr and Cohen\textsuperscript{14} conjectured that it is caused by poor peripheral perfusion of superficial tissues due to oligohydramnios and fetal hypotension. Fetal membranous bones require highly vascular perfusion and high oxygen tension. Thus, inhibition of mineralization by fetal RAS may cause hypocalvaria. The infant in this case study showed an abnormally large anterior fontanelle and a widened suture line of skull bones. Hypocalvaria was observed on three-dimensional skull bone CT.

In 2006, Cooper et al.\textsuperscript{15} suggested the possibility of central nervous system malformation as symptoms of ARB fetopathy. However, Quan\textsuperscript{16} explained that the likelihood of brain involve-
ment in ARB fetopathy is low. In various case studies, long-term neurodevelopment was not reported in infants with ARB fetopathy. However, Ri et al. reported delayed growth based on K-DST results in 24-month-old infants with ARB fetopathy in 2017. Further research on the association between brain development and ARB fetopathy is needed. The infant in this case study showed normal neurodevelopment based on the K-DST test result at 24 months after birth, supporting the claim of Quan that brain involvement in ARB pathogenesis is unlikely.

Laube et al. studied three patients whose infants had ACEi fetopathy for 6–18 years. All three patients had polycythemia with normal level of erythropoietin, of whom two had reduced GFRs associated with the severity of polycythemia. These patients were also observed to have small kidneys. One of these patients, an 18-year-old infant, was receiving quadruple antihypertensive combination therapy and may thus have a poor long-term prognosis due to RAS blocker fetopathy. The infant in this case report exhibited polycythemia at 20 months after birth, requiring close monitoring of renal function and blood pressure.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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