CASE REPORT

Maternal olmesartan exposure causing neonatal failure

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SUMMARY

Although angiotensin II receptor blockers (ARBs) are contraindicated during pregnancy, new cases are currently being reported.

A 32-week preterm neonate was admitted after C-section due to maternal oligohydramnios. He presented with Potter phenotype, pulmonary hypoplasia with pneumothorax, systemic hypotension and anuria. He required chest drain insertion and continuous positive airway pressure (CPAP), volume expansion plus inotropic support with persistent renal failure. Mother confirmed olmesartan intake during entire pregnancy. Peritoneal dialysis was started with improvement in renal markers and progressive recovery of renal function. He has been followed up until the age of 2 years, observing improved renal function with a glomerular filtration rate (GFR) of 58 mL/min/1.72 m².

Both angiogenesis-converting enzyme inhibitor and ARBs affect nephrogenesis; ARBs being more harmful due to its higher activity. Although some patients may recover normal renal function, its teratogen effect may have fatal consequences. Thus, it is important to emphasise its harmful effects in neonates to avoid new cases.

BACKGROUND

Although ACE inhibitors are contraindicated during pregnancy, new cases are still being reported. If renal replacement therapies are promptly started, good recovery can be expected even in cases of prolonged use.

CASE PRESENTATION

A 32-week preterm neonate was admitted into the neonatal intensive care unit after C-section (C/S) due to maternal oligohydramnios.

Pregnancy was only monitored until week 20. Mother was under antihypertensive treatment due to primary hypertension. Parents were immigrants with low sociocultural level.

On admission, he presented with pulmonary hypoplasia with right pneumothorax, requiring pleural drainage and continuous positive airway pressure (CPAP). On examination, generalised hypotonia, absent reflexes and Potter phenotype were noted (wide nasal bridge, posteriorly rotated low-set ears with cartilaginous hypoplasia, receding small chin, wide and dehiscent anterior and posterior fontanelle, right deviation of head, reducible valgus of hand and feet).

During the first 36 hours, he required fluid volume expansion and dopamine infusion, with

persistent anuria on a furosemide infusion. An abdominal ultrasound showed diffuse echogenicity in both kidneys with reduced size (percentile 10 for his gestational age).

Mother was asked about medication ingestion during pregnancy and daily intake of olmesartan and amlodipine was evidenced (last dose 24 hours before C/S). At 48 hours of life, peritoneal dialysis (PD) was started with good result. He initiated diuresis at fifth day of life, PD was stopped and a furosemide infusion was restarted and slowly weaned off within the following 48 hours. On day 10, he developed a polyuric renal failure phase.

During 2 years of follow-up, renal function has progressively improved as shown in [table 1](#).

INVESTIGATIONS

An abdominal ultrasound showed diffuse echogenicity in both kidneys with reduced size (p10 for his gestational age, see [table 1](#)).

TREATMENT

During the first 36 hours, he required fluid volume expansion and dopamine infusion, with persistent anuria on a furosemide infusion. At 48 hours of life, PD was started with good result. He initiated diuresis at fifth day of life, PD was stopped, and furosemide was restarted and slowly weaned off within the following 48 hours.

Systemic hypertension was initially controlled with nifedipine which was switched to captopril at 1 year of life due to proteinuria. Calcium and sodium oral supplements, VIT D3 and alfacalcidol were required. Treatment of anaemia was achieved with erythropoietin and ferrum sulfate.

OUTCOME AND FOLLOW-UP

During 2 years of follow-up, renal function has progressively improved as shown in [table 1](#).

DISCUSSION

The rennin angiotensin system (RAS) is important for fetal renal development and also for the maintenance of the glomerular filtration and fetal blood pressure. It also stimulates two angiotensin II receptors: type I, located within the glomeruli, tubules and renal vasculature, whose presence increases in the third trimester of fetal life, and type II, which have a more determinant role in the early phases of renal development, in areas of mesenchymal differentiation, acting as a mediator of apoptosis.^{1–3} Thus, angiotensin II receptor blockers (ARBs) deleterious

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Table 1 Two-year follow-up of urea, creatinine and glomerular filtration rate (GFR)

Age	Birth	10 days	25 days	55 days	3 months	22 months
Urea (mmol/L)	10.7	13.3	10.8	6.8	6.6	7.9
Creatinine (μmol/L)	76	362	119	69.8	56.5	60.1
GFR (mL/min/1.72 m ²)	16.5	<5	14	27	37.6	56

effects would be higher in the third half of pregnancy because of the increased number of AT1 receptors.³

The phenotypic features observed in our patient can be explained through the induced renal hypoperfusion, renal failure, oliguria with oligohydramnios causing extremity deformation and pulmonary hypoplasia (Potter sequence), with intrauterine growing delay and hypoplasia of cranial bones.

Amniotic volume is decisive in the development of the fetal lung,^{1,2} as at 20 weeks of gestational age, 90% of the amniotic volume is produced by fetal urine, a reduction in urine output would induce a major lung insult.² Our patient, however, showed a mild degree of pulmonary hypoplasia requiring a short period of CPAP and pleural drainage.

ARBs are more frequently used than angiogenesis-converting enzyme inhibitors because of its major efficacy and less secondary effects in adults,⁴ but its higher blocking effect in RAS and longer half-life makes them more dangerous, increasing risk of renal damage.⁵

First communications of ARBs side effects appeared in mortality series. In 2006, Bass and Faix³ reported 20 cases of fetal ARB exposure, most of them with poor postnatal course. Hünseler *et al*⁴ in 2011 reported seven additional newborn cases. Despite discontinuation of the treatment within the last month of pregnancy, postnatal course was also poor (4/7 died with the rest presenting moderate to severe renal impairment) reinforcing the idea that severity of insult is not entirely related to dose or duration. Our patient, however, showed a good response to therapy with partial recovery of his renal function during his follow-up until 22 months. Although the incidence of cases with good prognosis is uncertain because of publication bias, there are publications of asymptomatic or reversible cases; Hasbún *et al*¹ report a case of late discontinuation of medication in a 30-week neonate with transient renal failure and full recovery of renal function. Conversely, a recent systematic review of long-term follow-up shows that 50% of neonates affected did not have permanent sequelae while the rest of them presented different degrees of renal impairment, growth retardation and neurodevelopmental delay; among them, 10% developed terminal renal illness.⁵

Women receiving ARBs should be informed about potential harmful effects and questioned regarding potential pregnancy at regular intervals. In this case, low sociocultural level with language difficulties and low adherence to obstetric follow-up may have played an important role in fetal prolonged exposure to olmesartan.

Learning points

- Despite the existence of published cases of fetal exposure to angiotensin II receptor blockers (ARBs) with good prognosis, there is enough supported evidence to withdraw these medications in cases of pregnancy or childbearing plans.
- In the scenario of a renal failure in a newborn where other causes have been excluded, antenatal exposure to ACE inhibitors should be investigated.
- If renal replacement therapies are promptly started, a good recovery may be expected even in cases of prolonged antenatal use.
- New cases of ACE inhibitors and ARBs fetopathy are currently being communicated. Minimising the use of these medications, especially in fertile females, and providing adequate education and contraception advice should be emphasised.

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Patient consent Obtained.

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