CASE REPORT

Postnatal acute renal failure after fetal exposure to angiotensin receptor blockers

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SUMMARY

Maternal hypertensive treatment with angiotensin receptor blockers (ARBs) during the second and third trimester of pregnancy is associated with several fetal and neonatal complications, and potential adverse outcomes. We report a neonate presenting with transient renal acute failure during the first days of life after maternal treatment with ARBs. Women who became pregnant while taking one of these drugs must modify antihypertensive therapy with a different class drug as soon as pregnancy is recognised.

BACKGROUND

It is a well-known fact that angiotensin receptor blockers (ARBs) are fetotoxic drugs. However, doctors are increasingly using ARBs for the treatment of hypertension in women of childbearing age and, in some instances, these agents are being prescribed to women who are already pregnant, despite the potential for fetal toxicity in conjunction with their treatment. With this case, we point out the extra effort that should be made to prevent the use of these drugs during the second and third trimester of pregnancy.

CASE PRESENTATION

A 33-year-old woman, gravida 1, para 0, with a history of hypertension, was treated with methyl-dopa 250 mg/day in combination with amlodipine 5 mg/day during pregnancy.

Pregnancy follow-up was normal until 32 weeks' gestation, when fetal ultrasound showed large weight (2400 g; >90% centile) and amniotic fluid in the normal range. At 33 weeks' gestation, however, maternal refractory hypertension was diagnosed and treatment with telmisartan (initially, in monotherapy at 40 mg/day, subsequently in combination with hydrochlorothiazide at 80 mg/day) was undertaken.

An emergency caesarean section was performed at 37^{4/7} weeks' gestation due to preeclampsia, oligohydramnios and meconium-stained fluid.

The infant, a male with intrauterine growth retardation, did not need resuscitative manoeuvres at birth; Apgar scores were 8, 9 and 9, at 1, 5 and 10 min, respectively. Anthropometric data were: weight 2380 g (<10% centile); length 47 cm (<25% centile) and head circumference 31.5 cm (<10% centile).

After normal nursery admission, the neonate presented transient tachypnoea treated with oxygen free flow (maximum fractional inspired oxygen 0.28) for 2 h. Feeding with formula milk was started.

During the first 24 h of life, the infant appeared in good clinical condition with blood pressure (BP) 64/30 mm Hg (43); however, no urine output was noted. For persistent anuria on day 2, normal saline infusion was initiated. An ultrasound showed normal anatomy of the urinary system; the bladder was empty.

At 30 h of life, complete blood tests revealed a creatinine level of 3.8 mg/dL (normal range 0.20–2.00 mg/dL) and a blood urea nitrogen (BUN) level of 27 mg/dL (3–12 mg/dL); electrolytes were in the normal range. BP was 59/33 mm Hg (41).

The patient was transferred to the neonatal intensive care unit (NICU) for anuria and suspected acute renal failure. At NICU admission, laboratory examinations showed a further increase in blood creatinine and BUN levels. Doppler ultrasound revealed a marked renal parenchymal hyperechogenicity and increase of interlobar arterial resistance (resistance index 1.0). Echocardiography was normal. BP was 45/23 mm Hg (27). A bolus of normal saline (15 mL/kg) was given through the umbilical catheter. Subsequently, due to the persistence of the anuria, a bolus of furosemide (4 mg intravenously) and rasburicase (0.1 mg intravenously) was administered, with no improvement in the diuresis. A bladder catheter was positioned, as well.

Due to the persistence of anuria, a further bolus of Furosemide was administered (12 mg intravenously); dopamine (initially, at 8 µg/kg/min, then at 12 µg/kg/min) and infusions (initially, at 0.03 µg/kg/min, then at 0.07 µg/kg/min) were started. At 48 h of life, BP was 63/34 mm Hg (43) and laboratory findings showed a further increase of creatinine (5.72 mg/dL) and BUN (67 mg/dL) levels.

Peritoneal dialysis was initiated at 72 h of life, and lasted 3 days. On day 5, diuresis showed first signs of recovery, with urine output at 1.6 mL/kg/h, and blood creatinine and BUN levels at 7.32 and 74 mg/dL, respectively.

Subsequently, laboratory examinations also recovered: serum creatinine (2.99 mg/dL) and BUN (8 mg/dL) on day 15. Dopamine infusion was discontinued after a gradual reduction on day 10.

Growth, clinical examination and BP were normal at follow-up. Renal function was monitored at 1 month of life (serum creatinine level 0.88 mg/dL, BUN 9 mg/dL), and subsequently at 2, 4, 7 and 12 months after birth, persistently showing values in the normal range. Diuresis, renal ultrasound, serum creatinine (0.59 mg/dL), BUN (12 mg/dL) and electrolytes were completely normalised at 12-month follow-up.

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DISCUSSION

We report a case of transient renal failure during the first days of life. Due to refractory hypertension not controlled by methyldopa and amlodipine, the mother was treated with Telmisartan from 33 to 37 weeks' gestation, when an emergency caesarean section was performed.

Telmisartan is an antihypertensive drug of the class of angiotensin II type 1 receptor antagonists, also known as ARBs, a group of pharmaceuticals that modulate the renin-angiotensin-aldosterone system.¹⁻³

In 2001, the first case report of fetal toxic effects related to maternal treatment with ARBs was published.⁴ Since then, more than 50 new cases of fetus/neonates born of pregnant women treated with ARBs during the second and third trimester of pregnancy have been reported.⁵⁻⁶ A wide range of clinical conditions has been described including oligohydramnios/anhydramnios,⁷ neonatal renal failure,⁸⁻⁹ pulmonary hypoplasia,⁴⁻⁷⁻⁸ joint contractures,⁴⁻¹⁰ skull hypoplasia,⁷ fetal death⁷⁻¹¹ and neonatal death.⁹⁻¹² Three cases with inferior vena cava thrombosis have also been reported.¹¹

The critical period for the development of oligohydramnios seems to start around 18–20 weeks' gestation. During the human embryogenesis, the first glomeruli appear at about 9 weeks of gestation. The tubular function begins by 13 weeks and nephrogenesis continues until 34–36 weeks.⁶ The kidney begins to function producing urine and contributing to the formation of amniotic fluid from 9 weeks of gestation.¹³ From 20 weeks' gestation, 90% of the amniotic fluid is generated by the urine of the fetus. Renin-angiotensin system activity in the fetus is crucial for the maintenance of arteriolar constriction. This would lead to an adequate glomerular filtration rate.¹⁴ The inhibition of this system with the use of ARBs is responsible for reducing renal filtration with diuresis contraction that causes oligohydramnios/anhydramnios resulting in pulmonary hypoplasia, joint contracture and, in more severe situations, the death of the fetus or newborn. The risk of fetopathy increases with exposure to treatment with ARBs.

Our patient showed diuresis improvement after cessation of treatment and, at 1 year of life, we found complete structural and functional recovery, suggesting that fetal renal damage is reversible.¹⁵

Previous cases of ARB fetopathy in humans have been described, but there are limited data on long-term consequences of ARB fetopathy that include decreased glomerular filtration rate,¹⁶ salt-losing nephrogenic diabetes insipidus,¹⁶ arterial hypertension¹⁷ and loss of corticomedullary differentiation.¹⁷

It should be emphasised that fetopathy is determined by exposure to the hypotensive effects of this class of drugs and not to any direct effect of the drugs on embryogenesis. This explains why ARB fetopathy would not be expected to occur in the infants of women who discontinue treatment before the 10th week of pregnancy. Indeed, an increased incidence of fetopathy in patients treated with ARBs during the first trimester of pregnancy has not been reported in the literature.¹⁰

Despite the cases reported in the literature, some doctors are still prescribing ARBs during pregnancy. Physicians should be more aware of the risk of fetopathy and intrauterine or neonatal death if these drugs are used in the second and third trimesters of pregnancy. It is to be noted that international guidelines on hypertensive disorders are available and may help in the management of these patients.¹⁸⁻²⁰

Meanwhile, it is important to remember that, despite these drugs not being associated with an increased risk of birth defects due to their use during the first semester of pregnancy,¹⁰

the treatment should be discontinued as soon as possible in order to avoid the risk of severe fetal hypotension and renal failure if exposure continues. If BP remains uncontrolled despite antihypertensive treatment, preterm delivery of the fetus should be considered.

Infants exposed to these drugs during the second and third trimesters of pregnancy are at risk for chronic kidney disease and developmental delay. For this reason, a corresponding long-term follow-up is always warranted.

In future studies, it would be interesting to also evaluate if any of the poor long-term outcomes reported¹⁶⁻¹⁷ are specifically related to precise clinical conditions that occur following exposure to the drugs (ie, severity of oligohydramnios, severity of maternal hypertension).

Learning points

- ▶ Angiotensin receptor blockers (ARBs) are widely used antihypertensives with well-recognised renoprotective and cardioprotective effects.
- ▶ ARB treatment during the second and third trimesters of pregnancy has been associated with several fetal and neonatal complications, and potential negative outcomes (oligohydramnios/anhydramnios, renal failure, joint contractures, etc).
- ▶ Although the use of ARBs in the first trimester of pregnancy is not associated with an increased risk of birth defects in the infant, treatment with these drugs should be stopped by the 10th week of pregnancy in order to avoid the risk of fetopathy.
- ▶ An alternative regimen of hypertensive therapy should be considered, even if ARBs are thought to be the most effective drugs.

Competing interests None declared.

Patient consent Obtained.

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