Fetal renin-angiotensin system blockade: two case reports

We present two neonates that died due to renal dysplasia and pulmonary hypoplasia where the pregnancies were either unbooked or booked late. Both mothers were taking candesartan, an angiotensin receptor blocker that is known to be associated with fetal renal side effects and is contraindicated in pregnancy. We review relevant literature and the latest evidence in this area. Finally, we make some suggestions to improve management for both mothers and babies, in order to improve neonatal outcomes.

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Key points

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1. Regular medication reviews should be undertaken for women of childbearing age.
2. Neonatologists should ensure that a detailed maternal medication history is taken for all babies admitted to neonatal units.
3. Fetal renin-angiotensin system blockade is a rare but potentially life-threatening condition. For those babies who do survive, neonatologists should ensure appropriate follow-up is put in place post-discharge.

Case 1: a concealed pregnancy

A 30-year-old primigravida woman presented to the accident and emergency department with abdominal pain and was found to be pregnant. This was a concealed pregnancy and therefore there had been no antenatal care. She had been taking candesartan and bendroflumethiazide for hypertension throughout her pregnancy.

Gestation was estimated at 34 weeks' (note: this was later estimated at 36-40 weeks' at post-mortem). An ultrasound scan showed absent/reduced amniotic fluid volume. Cardiotocography (CTG) showed features of fetal distress. A male baby was delivered by emergency caesarean section, weighing just over 2,800g (this is equivalent to the mean for a 37 weeks' gestation baby). Apgar scores of 6, 7 and 8 were seen at one, five and 10 minutes respectively. No amniotic fluid was seen.

Due to respiratory distress, the baby was intubated at three minutes of life and given Curosurf surfactant (240mg). He was started on synchronised intermittent mandatory ventilation (SIMV), requiring a peak inspiratory pressure of 30cmH_2O and a positive end expiratory pressure of 6cmH_2O, rate of 60 breaths per minute. 100% oxygen was required to maintain saturations above 95%. His chest X-ray showed poor lung volumes with chest expansion to approximately six to seven posterior ribs, despite the significant pressures he was receiving via the ventilator. An echocardiogram showed persistent pulmonary hypertension of the newborn (PPHN). He required inotropes (dopamine, dobutamine, adrenaline and hydrocortisone) and he continued to require significant ventilatory support. A second dose of surfactant (480mg) was given at approximately 10-11 hours of life. He was tried on high frequency oscillatory ventilation from 13 hours of life. He was also treated with benzylpenicillin and gentamicin. His C-reactive protein (CRP) levels were 19mg/L, 24mg/L and 31mg/L, but his blood cultures were negative. Significantly, a raised creatinine was noted and his mother's creatinine level was also high.

Although the infant did have umbilical lines inserted, these were later removed when he developed abdominal distension. A long line was subsequently inserted. He had low blood sugar levels and required a glucose bolus followed by 12.5% dextrose maintenance infusion. He had a low haemoglobin level, a low platelet count and deranged coagulation. He received a packed red cell transfusion, a platelet transfusion and vitamin K.

At 19 hours of life his oxygen saturations were persistently in the 70s. His blood pressure dropped further and, despite intensive resuscitation, he died at <24 hours of life.

A post-mortem showed no significant external congenital malformations and no dysmorphic features. There were some subtle features of oligohydramnios. There were prominent folds in the skin beneath the eyes. In addition, there were fixed flexion deformities present at both elbows, both knees and both ankles. The lungs

were noted to be small, but not excessively so. It was felt possible, however, that there had been some impairment of pulmonary growth. The heart and other organs were grossly normal in appearance. The rest of the examination was unremarkable. Blood, cerebrospinal fluid, lung, myocardium and spleen samples were all taken and were all negative for bacteriology.

A post-mortem skeletal survey found no specific features to suggest metabolic bone disease or skeletal dysplasia.

A thrombus was seen in the inferior vena cava and this was felt likely to be due to disseminated congenital venous thrombosis because there was also extensive thrombosis of the renal veins. Renal histology was also abnormal. There was paucity of tubules and an increase in fibrous tissue. It was felt probable that poor kidney function *in utero* led to a low amniotic fluid volume.

Examination of the placenta also revealed evidence of thrombosis within an area of fetal circulation, suggesting a fetal thrombotic vasculopathy. Placental histology also showed fetal thrombotic vasculopathy. After a post-mortem case review involving obstetrics, neonatology and pathology teams, the described findings were felt to be a result of fetal renin-angiotensin system (RAS) blockade, secondary to maternal use of candesartan.

Case 2: a late booker

A 40-year-old woman booked late at just over 29 weeks as she had been unaware of her pregnancy. This was her second pregnancy. She had a history of essential hypertension and she was taking candesartan (32mg) for this. This medication was stopped by her GP at booking, once the pregnancy was known.

At approximately 30 weeks' gestation, there was premature rupture of the membranes and a few days later the mother went into labour. A female baby was born via emergency caesarean section due to pathological CTG. She weighed 2,200g at birth.

The baby was born in a 'fair' condition. Apgar scores were 7, 9 and 9 at one, five and 10 minutes, respectively. She required five inflation breaths, followed by ventilation breaths. She then required positive end-expiratory pressure (PEEP) and briefly received 100% fraction of inspired oxygen (FiO_2) in theatre. This was weaned to 40% by 20 minutes of life. She was transferred to the neonatal intensive care unit and started on continuous positive airway pressure (CPAP; 5cmH_20), requiring approximately 50% FiO_2. This was later escalated to bilevel positive airway pressure (BiPAP), however her respiratory distress syndrome symptoms appeared to quickly improve and this was switched back to CPAP.

A high vaginal swab taken from her mother grew group B streptococcus. An umbilical swab taken from the baby also grew group B streptococcus. Toxoplasma, cytomegalovirus, rubella and parvovirus were all negative. The baby was commenced on intravenous benzylpenicillin and gentamicin. Her maximum CRP was 11.4mg/L and her blood cultures were negative.

She was noted to have some non-pitting oedema over the left side of her chest and left shoulder, extending to the left upper arm and elbow, with contracture of the elbow. No hypoglycaemic episodes were recorded during the stay. She had a worsening metabolic acidosis which commenced on day one. She had deranged renal function from birth with an initial creatinine of 115µmol/L, which increased to 146µmol/L after 12 hours. Her urine output was initially approximately 1.5mL/kg/hr but by 24 hours of life it was less than 1mL/kg/hr.

An echocardiogram showed a structurally normal heart with poor biventricular function, significant tricuspid regurgitation and PPHN. In view of these findings, dobutamine was started on day two of life.

At 31 hours of life, she had an acute deterioration with an increase in FiO_2 requirements to 100%. She was intubated to secure the airway. She continued to desaturate despite maximum FiO_2 support. Cold light transillumination was suggestive of a right sided pneumothorax; however, attempts at needle thoracocentesis were negative. Full resuscitation was started but this was unsuccessful and she died shortly thereafter.

Initially it was felt that the infant had died as a result of sepsis and prematurity. However, a post-mortem showed no evidence of bacterial or viral infections. It did reveal a degree of pulmonary hypoplasia. A skeletal survey showed poor ossification of the central portion of the skull vault, with only small specks of ossification seen, hypocalvaria (incomplete formation of the skull bones) with an otherwise normal skull shape. Bone mineralisation of the rest of the skeleton was normal. Mild contractures of the knees, hips, shoulders and elbows were noted.

The post-mortem also revealed renal tubular dysplasia and a significant paucity of differentiated proximal tubules, with those proximal tubules that were present being abnormally developed. There was also an increase in interstitial parenchyma, patchy subcapsular cystic changes and interstitial haemorrhage. A microarray analysis showed a normal genetic profile with no pathogenic variants.

The combination of these findings was felt by the pathologist to be a result of RAS blockade fetopathy, secondary to the mother's use of candesartan.

Discussion

Maternal hypertension

Chronic hypertension has been reported in 7.7% of women of childbearing age, with 4.2% of women of childbearing age using antihypertensive medication.[1] Hypertension rates in pregnancy have been reported at between 10% and 15%.[2] Current National Institute for Health and Care Excellence (NICE) guidelines on management of hypertension in adults[3] recommend (after lifestyle measures) that an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) should be the first line of treatment offered to all non-black people under 55 years of age and all people of any ethnicity with type 2 diabetes (recommendation 1.4.30). The guideline states that this includes women of 'childbearing potential'. However, it is recommended that women who are considering pregnancy should have their hypertension managed in line with NICE's specific guidelines on hypertension in pregnancy (recommendation 1.4.28). NICE's guideline on management of chronic hypertension in pregnancy[4] notes the increased risk of congenital abnormalities if ACE-I or ARB are taken during pregnancy (recommendation 1.3.2). It recommends stopping these medications 'preferably within two working days of notification of pregnancy'. A recent audit in three inner-city London Clinical Commissioning Groups found that pre-conception and contraception advice was recorded in the past 12 months in only 1.3% and 8.7% of the 2,651 female patients of childbearing age identified to be on an ACE-I or an ARB.[5]

ACE-I and ARB

ACE-I is a group of compounds used in managing hypertension and diabetic nephropathy.[6] They competitively inhibit the activity of angiotensin converting enzyme to prevent formation of angiotensin II from angiotensin I. Angiotensin II is a potent vasoconstrictor that promotes aldosterone release and facilitates sympathetic activity.[7] By preventing the formation of angiotensin II, ACE-I promote vasodilation and therefore reduce blood pressure. It is known that ACE-I cross the human placenta.[8]

An ARB is used as an alternative where ACE-I are not tolerated. An ARB works by selectively antagonising the action of angiotensin II at the angiotensin II type 1 (AT1) receptor.[9]

Effects on the fetus/neonate

Fetal anomalies reported with maternal use of ACE-I and ARB include:[2,10,11]

- oligohydramnios
- hypocalvaria
- craniofacial dysmorphia
- renal tubular dysplasia
- limb contractures
- pulmonary hypoplasia
- intrauterine growth restrictions.

It is thought that the effects on the fetus are due to fetal hypotension resulting in renal impairment and anuria. ACE-I and ARB appear to be safe in the first trimester, with the effects on the fetus only occurring during exposure in the second and third trimesters.[12] This explains why NICE still recommends their use in women of childbearing age, unless they are known to be pregnant or actively considering pregnancy. However, there remains a risk of *in utero* exposure to ACE-I or ARB in unplanned, unbooked and concealed pregnancies. It should also be noted that at least one other study has suggested ACE-I are also not safe in the first trimester.[12] The methodology of this study has been questioned,[13] however it is generally accepted that ACE-I and ARB should be stopped as soon as possible after pregnancy has been confirmed, regardless of the trimester. This is in keeping with current NICE guidelines.

The case reports

The cases presented in this report both describe early neonatal death as a consequence of maternal use of antihypertensive medication during pregnancy based on findings at post-mortems. The cases highlight the importance of full medication reviews for pregnant women or for women of childbearing age. In one of the cases, the mother presented in active labour and so there was no time for medication to be reviewed and stopped prior to delivery. In the other case, the ARB was appropriately stopped as soon as the GP was aware of the pregnancy, however, it was well into the third trimester at this point and the baby delivered within days.

It is not possible to tell from the case notes if the mothers had previously been made aware of the potential risks should they become pregnant while taking these medications. It is not clear whether they had been offered contraception advice or alternative antihypertensive medications. The cases highlight the importance of health professionals, including GPs, midwives, obstetricians and neonatologists, making women of childbearing age aware of these risks.

Although neither of the babies survived, this is not the outcome for all babies exposed to these medications *in utero*. A 2012 systematic review[14] of published case reports of babies with *in utero* exposure to ACE-I or ARB over a 30-year period, found 72 relevant reports documenting 168 cases in total. Statistical analysis in the review was limited by heterogeneity in the case reports analysed, however, it did find that prenatal exposure to ARB appeared to be associated with a greater risk of fetal RAS blockade syndrome in preterm infants when compared to prenatal exposure to ACE-I. Neonates in the review were more likely to survive if the exposure to ACE-I or ARB was in the first trimester only. These babies were also more likely to have normal renal function at the six-month follow-up examination. However, at least one baby with only first trimester exposure demonstrated mild renal insufficiency and developmental delay at the six-month follow-up, although it is important to note that other factors could have been responsible for these findings in this particular case. In the review, of 22 surviving babies exposed either at the end of, or during the entire pregnancy, the outcome was described as:

- 'good' in 10 cases
- 'mild' in 10 cases (ie mild renal insufficiency, arterial hypertension, proteinuria or developmental delay)
- 'bad' in two cases (ie the need for dialysis or transplantation).

In the review, of all babies exposed to ACE-I or ARB at some point during pregnancy, 50% were reported as having a normal outcome at six-month follow-up, with the other 50% having a range of issues including renal failure, a need for dialysis/transplantation, growth retardation and developmental delay. This highlights the importance of arranging neonatal follow-up for babies who are known to have had *in utero* exposure to ACE-I or ARB.

Conclusions

The cases reported here highlight the importance of full medication reviews for pregnant women or women considering pregnancy, as well as clearly documented discussions of the risk of ACE-I and ARB in women of childbearing age. Even when adhering to NICE guidelines, there will always be a potential for some cases of fetal RAS blockade to occur, particularly where mothers have limited engagement with medical professionals during pregnancy. Therefore, consideration for this needs to be given when prescribing antihypertensives for women of childbearing age. Fetal RAS blockade presents significant challenges to neonatal management of these rare cases, and unfortunately often has a poor outcome. Neonatal care providers should always ensure that maternal medication history during pregnancy is carefully reviewed for drugs that have a potential to cause harm to the fetus. For those babies who do survive, careful consideration needs to be given to long-term follow-up.

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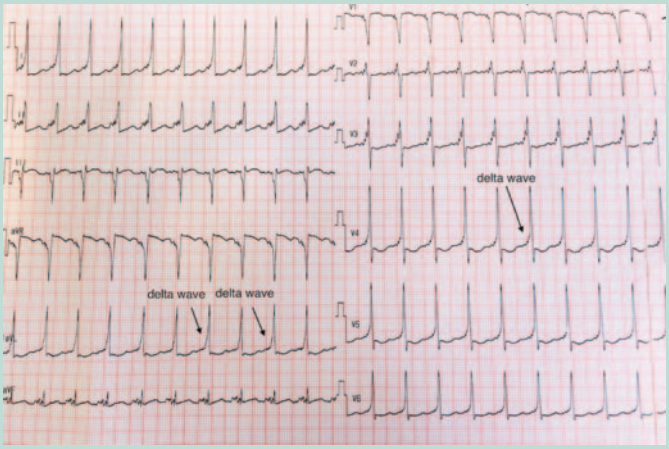
A newborn with arrhythmia – thinking beyond conduction pathways

Answers to the quiz on page 70

1. The correct answer is (c)

The ECG shows features of Wolff-Parkinson-White (WPW) syndrome as there is pre-excitation with a short PR interval and a delta wave (slurring of the upstroke of the QRS complex), as noted in **FIGURE 1.**



2. The correct answer is (a)

The management of narrow complex or supraventricular tachycardia (SVT) includes initial assessment of the infant for cardiovascular stability and the presence of shock, along with measures for terminating the episode.[1] If unstable or shocked, they will need synchronized DC cardioversion. Stable infants will need the termination of the SVT through vagal manoeuvres (ice pack on the face) or pharmacological measures. Intravenous access in a large vein as close as possible to the heart should be attempted. In the newborn, the umbilical vein provides easy access to the inferior vena cava. Intravenous adenosine is the pharmacological mainstay and needs to be followed by a quick flush in view of its very short half-life (<10 sec) and its inactivation by adenosine deaminase in the bloodstream. Subsequent 24-hour ECG recording may be helpful for detection of further episodes and to aid in diagnosis.

3. The correct answer is (b)

Tuberous sclerosis complex (TSC) is a genetic syndrome that presents with cardiac rhabdomyomas and has associations with WPW syndrome.[2] The other conditions mentioned include hereditary cancer syndromes and neurocutaneous syndromes, which do not typically present with these features. About 70-90% of children with rhabdomyomas have TSC. Cardiac rhabdomyomas are often multiple and can cause haemodynamic effects, congestive cardiac failure, and outflow obstruction. They tend to regress spontaneously, although surgical resection may be needed in some cases of haemodynamic compromise. Cardiac arrhythmias are a significant and relatively common problem in TSC and can vary from slow to irregular to fast heart rhythms. They may result from cardiac rhabdomyomas or in isolation. Hence, it is recommended to obtain a baseline ECG in individuals of all ages with TSC and at regular intervals to assess for underlying conduction defects.[3,4]

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