Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication

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We report the case histories of two HIV-1 positive women in the third trimester of pregnancy who presented with acute lactic acidosis and acute pancreatitis, respectively. One case was fatal for mother and baby. Both women had been stable on regimens containing stavudine and didanosine for at least 2 years before their acute presentations. We speculate on the differential diagnosis, discuss possible reasons for an increased risk of these presentations in pregnant women taking antiretrovirals, and advocate increased vigilance of these women, particularly in the last trimester.

It has been postulated that nucleoside analogue medication may be responsible for a wide spectrum of clinical presentations related to mitochondrial toxicity caused by inhibition of DNA gamma polymerase. Despite widespread use of these drugs in the management of HIV, the risk factors, precipitating factors, and management of these syndromes remain unclear.

We report two cases of suspected nucleoside analogue induced mitochondrial toxicity causing severe complications in two women in the third trimester of pregnancy taking stavudine and didanosine.

CASE 1
A 30 year old Ugandan woman, in the 37th week of pregnancy, presented with acute onset of abdominal pain, shortness of breath, and vomiting. She had been closely followed up in the last trimester of pregnancy and had reported no symptoms.

She was diagnosed with HIV in 1996 when she presented with pulmonary tuberculosis. Subsequently, she was commenced on zidovudine, lamivudine, and nelfinavir with a baseline CD4 count of 188 ×10^6/l. One year later she was switched to didanosine, stavudine, and nevirapine as although she had an undetectable viral load (<400 copies per ml) her CD4 count had fallen from 391 to 221 ×10^6/l.

She tolerated the regimen well and at the time of her pregnancy had a CD4 count of 450 ×10^6/l and undetectable viral load (<50 copies per ml).

She had been on this regimen for 2 years before her acute presentation. Her pregnancy had been unremarkable apart from pregnancy associated hypertension between 34 and 36 weeks’ gestation, at which time a mildly elevated aspartate transaminase (AST) of 51 IU/l was noted on two occasions.

Examination revealed a respiratory rate of 40/minute, pulse 125/minute, and saturations of 100% on room air. She was afebrile with no focal signs of pancreatitis or obstetric complications.

Cardiotocography revealed a normal fetal heart rate. Investigations revealed haemoglobin 13.0 g/dl, neutrophilia of 12 ×10^9/l, platelets 241, international normalised ratio (INR) 1.5, activated partial thromboplastin time (APTT) 78 seconds. Renal function was normal and glucose was 6.5 mmol/l. Liver function revealed bilirubin 15, AST 101 IU/l, alkaline phosphatase 217 IU/l, albumin 17, amylase 78 IU/l. She had a metabolic acidosis (pH 6.938), low bicarbonate (1.38 mmol/l), and an arterial lactate of 22.6 mmol/l (normal range <2 mmol/l). Septic screen was negative and there was no evidence of placental abruption or amniotic fluid embolism.

A diagnosis of severe lactic acidosis was made although the cause was unclear. An emergency caesarean section was performed but despite this resuscitation attempts on the fetus were unsuccessful.

The patient was managed with intermittent positive pressure ventilation on intensive care, haemofiltered with lactate free fluid and a bicarbonate infusion to reverse her acidosis.

She was given infusions of Pabrinex (Link) 20 ml intravenously every 8 hours, containing ascorbic acid 500 mg, anhydrous glucose 1 g, nicotinamide 160 mg, riboflavin 4 mg, and thiamine hydrochloride 250 mg. Prophylactic antibiotics were given and her antiretrovirals were stopped. After 24 hours her lactate level had reduced to 4.0 mmol/l and her pH had risen to 7.30. Her liver function improved with AST falling back to the normal range within 48 hours.

Over the next 14 days she suffered several complications including intra-abdominal bleeding which necessitated further surgery and multiple transfusions of blood products. Her INR and APTT remained high and her platelets fell to a stable level of 90. Her fibrinogen and E-dimers remained within normal limits. Ten days after admission she developed bilateral infiltrates on her chest x-ray suggestive of adult respiratory distress syndrome. She died 14 days after her initial presentation.

Both maternal and fetal deaths were reported to the coroner and the Confidential Enquiry into Maternal Deaths; however no post mortems were carried out.

CASE 2
A 31 year old Ugandan woman in her 33rd week of her first pregnancy presented with a 12 hour history of acute upper abdominal pain and vomiting. She had been well previously.

She was diagnosed HIV positive in 1996 and had been immunologically and virologically stable (CD4 = 650 ×10^6/l, viral load <50 copies per ml) for 2 years on didanosine, stavudine, and nevirapine.

On examination she appeared unwell, pulse 130/minute, respiratory rate 32/minute. She was afebrile with epigastric tenderness on palpation. Investigations revealed a neutrophilia of 22 ×10^9/l, an amylase of 1990 IU/l, with otherwise normal liver and renal function. She had a metabolic acidosis (arterial pH 7.256), a low bicarbonate (10.4 mmol/l), and arterial lactate 6.8 mmol/l.

A diagnosis of acute pancreatitis and lactic acidosis was made.
A live female infant was delivered by caesarean section with a cord pH of 6.7.

The mother was managed as in the previous case with haemofiltration, Pabrinex, cessation of antiretrovirals, and prophylactic antibiotics. Within 2 days her amylase had fallen to 625 IU/l and her acidaemia had resolved. She was discharged symptom free 2 weeks after admission.

The infant was given nevirapine at delivery (4 mg/kg). She was discharged at 36 weeks of gestational age on no antiretroviral medication and has developed normally to date.

Both cases have been reported to the drug manufacturers and Committee on Safety of Medicines.

DISCUSSION

The diagnosis in case 1 cannot be made with certainty. The differential diagnosis includes acute fatty liver of pregnancy (AFLP), the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP), and nucleoside analogue induced lactic acidosis.

A normal bilirubin, the absence of hypoglycaemia, and absence of disseminated intravascular coagulation makes AFLP less likely. Low platelets and haemolysis were not evident when the patient initially presented, although her platelets fell subsequently. In view of the above, the diagnosis of nucleoside analogue induced lactic acidosis seems most likely.

A previous report has been issued highlighting three fatal cases of lactic acidosis (including case 1) and other non-fatal cases of pancreatitis and hepatic failure in women in the last trimester of pregnancy (including case 2).

Similar to the presented two cases, the women were receiving stavudine and didanosine before and at the time of adverse event occurred.

It is unclear whether pregnancy is a risk factor for the development of these lactic acidosis/hepatic steatosis type syndromes caused by nucleoside analogues, or whether mitochondrial toxicity caused by nucleoside analogues increases the likelihood of the development of AFLP/HELLP syndromes.

Acute late gestation disorders of AFLP and HELLP have been linked to a recessively inherited mitochondrial abnormality in the infant that causes an inability to oxidise fatty acids. There is believed to be an increased risk of liver toxicity in the heterozygous mothers of these infants who may be less able to oxidise accumulating maternal and fetal fatty acids causing a fatty liver and lactic acidosis.

The metabolic effects of pregnancy may also directly affect mitochondrial fatty acid oxidation resulting in an increased risk of AFLP.

It has also been suggested that pregnancy may be associated with low levels of riboflavin and this may potentiate the development of mitochondrial toxicity caused by nucleoside analogues.

Riboflavin is a precursor for the flavoprotein co-factors required for oxidative phosphorylation and the production of ATP. If these co-factors are deficient, anaerobic oxidation may be favoured and pyruvate is converted into lactate instead of acetyl CoA. A study by Vir et al has shown lower levels of riboflavin in pregnant compared to non-pregnant women particularly in the third trimester. Riboflavin has been used as part of the treatment of lactic acidosis in several case reports, although strong evidence for its efficacy is lacking.

Given the possibility that HIV positive women may be at greater risk of mitochondrial toxicity in pregnancy all health professionals involved in their care need to be particularly vigilant for factors which may suggest the development of these complications. These include unexplained non-specific symptoms and mild derangement of liver transaminases which should lead to further investigation.

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REFERENCES


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