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Successful maternal-foetal outcome using nitric oxide and sildenafil in pulmonary hypertension with atrial septal defect and HIV infection

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ABSTRACT Pulmonary hypertension associated with pregnancy carries a poor prognosis. We describe successful maternal-foetal outcome for a 30-year-old woman who was found to have severe pulmonary hypertension, human immunodeficiency virus (HIV) and an atrial septal defect. Prior to delivery, she was managed with subcutaneous enoxaparine, sildenafil, nitric oxide, careful maintenance of a euvolemic status and antiretroviral therapy. She was planned for an elective Caesarean section to reduce the risk of maternal-foetal HIV transmission, but went into labour in the coronary care unit. During delivery, antibiotic prophylaxis was given, although there was insufficient time for intravenous zidovudine. Peripartum, the patient was continued on nitric oxide and subcutaneous enoxaparine. She was eventually weaned off the nitric oxide and recovered well.

Keywords: atrial septal defect, HIV infection, pregnancy, pulmonary hypertension, sildenafil
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INTRODUCTION

Pulmonary hypertension associated with pregnancy carries a poor prognosis. There has been little data on the impact of vasodilatory therapy on these patients. Sildenafil and nitric oxide have been shown to benefit non-pregnant patients with pulmonary hypertension. We report successful maternal-foetal outcome using sildenafil and nitric oxide.

CASE REPORT

A 30-year-old gravida (G2P1) Malay woman presented at 35 weeks of gestation with increasing exertional breathlessness and orthopnoea for three days. She presented late for obstetric review at 30 weeks and had recently been diagnosed with human immunodeficiency virus (HIV) during her antenatal check-up; however, she had no other medical history. Her first pregnancy ten years ago was uncomplicated, and she denied prior cardiopulmonary disease or drug use.

Her vital signs were stable: blood pressure 103/66 mmHg, heart rate 83 beats/min and respiratory rate 20 breaths/min. Oxygen saturation, as measured by pulse oximetry (SaO_2), was 97% on 100% oxygen, but could drop as low as 92% on room air when the patient exerted herself. There was jugular venous distension and a systolic murmur at the left sternal edge with a loud second heart sound. Lungs were clear on auscultation and there was bipedal oedema. There was no digital clubbing. The patient's cervix was not dilated and she had no symptoms of labour.

An electrocardiogram showed prominent R waves in lead V1. Chest radiography showed cardiomegaly with clear lung fields. Transthoracic echocardiogram showed much dilated right heart chambers, and right ventricular hypertrophy with moderately reduced function. The left ventricular function was normal. A large secundum atrial septal defect (ASD) measuring 29 mm with bidirectional flow was noted. There was moderate tricuspid regurgitation with a central jet, and pulmonary arterial systolic pressure was estimated at 64 mmHg assuming right atrial pressure of 10 mmHg. The patient's full blood count did not show erythrocytosis, with haemoglobin 113 g/L and haematocrit 38.5%. NT-pro brain natriuretic peptide (BNP) level was 12,886 pmol/L. She was admitted to the coronary care unit (CCU) for monitoring.

The patient was initially treated with diuretics, which were then discontinued. She was started on subcutaneous enoxaparine, digoxin and continued on her antiretroviral therapy of zidovudine, lamivudine and nelfinavir. She was also given intramuscular dexamethasone to promote foetal lung maturation. She was planned for an elective Caesarean section to reduce the risk of maternal-foetal HIV transmission within the next two days after medical stabilisation. Soon after admission, her SaO_2 deteriorated to 65% despite being on 100% FiO_2. She was given a single dose of sildenafil, with resultant improvement in SaO_2 to 86% three hours later. She was continued on regular doses of sildenafil 25 mg three times a day, and inhaled nitric oxide 5–20 ppm. The nitric oxide dose was increased hourly to titrate her oxygen saturation to a target of above 90% to reduce right-to-left shunting. Pulmonary artery catheterisation was not used, as there were fears of paradoxical embolism across the ASD. She was also given adequate fluid hydration.

The patient later went into spontaneous labour in the CCU within 24 hours of admission. Her cervix was fully dilated and effaced on arrival of the obstetrician. A baby girl was delivered

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vaginally with minimal blood loss. The baby was healthy with an Apgar score of 9. There was insufficient time for intravenous (IV) zidovudine administration, but antibiotic prophylaxis of IV crystalline penicillin and IV gentamicin was given post delivery. Post delivery, the patient was haemodynamically stable. Nitric oxide was initially decreased from 20 ppm to 10 ppm to reduce uterine relaxation, but it was later increased.

The patient's SaO_2 improved post delivery to above 90%. Nitric oxide was weaned off but sildenafil was continued. The NT-pro-BNP level also decreased to 6,553 pg/ml. The patient spent a total of six days in the CCU, as the nitric oxide was slowly down-titrated over two days and was monitored for events. She was discharged to the general ward and subcutaneous enoxaparine was replaced by warfarin. Her course of stay was further complicated by retention of products of conception with resultant menorrhagia and further anticoagulation was withheld. She was given oxytocin and IV antibiotics with improvement, and was mobilised early. She was discharged with a SaO_2 of 95% on room air on sildenafil 25 mg three times a day after 13 days in hospital. She has since resumed an active lifestyle.

DISCUSSION

This patient had pulmonary arterial hypertension (PAH) with congenital ASD and HIV infection. To the authors' knowledge, there have been no reports of management of both of these problems in pregnancy. The patient's recent hypoxia was likely precipitated by right-to-left shunting caused by her pregnancy and excessive diuresis.

Pregnancy and PAH has been associated with a high mortality rate. In a meta-analysis of the outcome of pulmonary vascular disease and pregnancy from 1978 through 1996, Weiss et al[1] reported a maternal mortality rate of 36% in Eisenmenger syndrome, 30% in idiopathic PAH and 56% in secondary PAH. As a result of this high mortality rate, guidelines from the American Heart Association and The American College of Cardiology recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, PAH and Eisenmenger syndrome.

The high mortality rate is due to the increased haemodynamic demands of pregnancy and delivery. During pregnancy, there is a 30%–50% increase in blood volume and cardiac output, a 10–20 beats/min increase in heart rate, an increase in stroke volume, and decreases in both systemic vascular resistance and blood pressure. These changes begin in the first trimester and peak at 20–24 weeks of gestation. During labour, there are further increases in cardiac output and blood pressure. Postpartum, marked volume shifts occur with the return of uterine blood into the systemic circulation,[2] which may sometimes worsen right-to-left shunting. In addition, there is a risk of paradoxical embolism and development of venous thrombosis.

Patients with known pulmonary hypertension must be carefully counselled about the risks of pregnancy on diagnosis. Active advice with regard to contraception must be sought in the presence of significant pulmonary hypertension and when the option of termination of pregnancy is broached. Drugs used for treatment of pulmonary hypertension like bosentan and warfarin are known teratogens and must be discontinued if pregnancy is to continue. The patient should be assessed regularly for functional status, symptoms of right heart failure, oxygen saturations, exercise capacity on six-minute walk tests and biomarkers (e.g. BNP). Echocardiography should be performed at least in the first trimester as baseline and at 28 weeks when cardiac output is maximal.

The principles for management in such cases would include the avoidance of increase in pulmonary vascular resistance, maintenance of right ventricular preload, left ventricular after-load and right ventricular contractility.[2] A euvolemic state is ideal. Diuretic use was therefore limited in our case in order to avoid a decrease in cardiac output, resulting in systemic hypotension and worsening right-to-left shunting. Intra-arterial monitoring of the blood pressure prior to delivery may be considered.

Anticoagulation therapy has been indicated due to the increased risk for pulmonary thromboembolism resulting from sluggish pulmonary blood flow, dilated right heart chambers and *in situ* microscopic thrombosis in PAH. Warfarin has been shown to improve survival in these patients,[3] but is contraindicated in the peripartum period due to an increased risk of foetal intracranial haemorrhage during normal vaginal delivery. Subcutaneous enoxaparine was therefore used for our patient pre-delivery and postpartum for control of the haemorrhage.

Pulmonary artery catheterisation would be useful with information of rising pulmonary artery pressures, deteriorations in right ventricular function and in monitoring the effects of therapy prior to Caesarean section. However, its use has not been associated with improved survival and there is an increased risk of pulmonary artery rupture and thrombosis in these conditions.[4] Paradoxical embolisation is also possible in the presence of a right-to-left shunt.

A Caesarean section was planned to minimise maternal-foetal transmission of HIV, although the unplanned vaginal delivery may have benefitted our patient. Greater morbidity and mortality has been associated with Caesarean section in patients with PAH,[1] and prior discussion with the patient and her care team is needed to assess the risks and benefits. Normal vaginal delivery with an assisted second stage may be preferable in the absence of concurrent HIV infection. Pain, oxygen consumption and the haemodynamic consequences of labour could have been reduced with low-dose epidural analgesia,[5] but the timing needs to be carefully co-ordinated in a patient on anticoagulation. Nitrous oxide and ergometrine, both of which increase pulmonary vascular resistance, should not be used. Antibiotic prophylaxis is given before delivery in most expert centres.

Known pulmonary vasodilator therapies include nitric oxide, prostacyclin analogues, the endothelin-receptor antagonist and most recently, sildenafil. Nitric oxide has been used in the peripartum patient with idiopathic PAH, with reductions in

pulmonary artery pressures seen on cardiac catheterisation.[6] Nitric oxide activates guanylate cyclase, which catalyses the conversion of guanosine-5-triphosphate to cyclic guanosine monophosphate (cGMP). cGMP mediates vascular smooth muscle relaxation.[7] Nitric oxide can also cause uterine muscle relaxation, which may reduce the onset of premature labour. Rebound pulmonary hypertension could occur following withdrawal of nitric oxide therapy and has to be slowly down-titrated. Addition of sildenafil has been demonstrated to reduce this rebound phenomena. Sildenafil is a selective inhibitor of cGMP-specific phosphodiesterase-5, which normally degrades cGMP. The double-blind, randomised placebo-controlled Sildenafil Use in Pulmonary Hypertension trial demonstrated improvement in six-minute walk distance and haemodynamics in patients receiving sildenafil, with only mild adverse effects.[8]

Our patient was continued on antiretroviral therapy. The role of highly active antiretroviral therapy in managing HIV-associated PAH is still not well established. A beneficial effect on pulmonary haemodynamics has been seen in patients treated with nucleoside reverse transcriptase inhibitors. Uncontrolled studies have suggested that patients with severe HIV-associated PAH may respond to a combination of antiretroviral therapy, epoprostenol or bosentan.[9,10]

There have been concerns over the use of iloprost and prostacyclin in pregnancy due to their effect on uterine blood flow. Iloprost has been associated with toe deformities in rats.[11] There has been limited data on the safety of IV epoprostenol, although there have been case reports recording good maternal as well as foetal outcomes.[12-14] Inhaled iloprost may also be considered in pregnancy as it has localised effects on the pulmonary vasculature and does not have problems of rebound or tachyphylaxis. Bosentan should not be used in pregnancy due to foetal teratogenicity. Sildenafil use in pregnancy has similarly not been well studied, but case reports have recorded its successful use.[15,16] There have been no prior reports of adverse systemic effects in adult patients receiving both nitric oxide and sildenafil therapy for PAH.[17]

In conclusion, PAH can worsen during pregnancy, and is associated with a high maternal mortality rate. Our case shows how a multidisciplinary approach and treatment with appropriate pulmonary vasodilatory therapy could improve outcome.

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