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CASE REPORTS

Primary pulmonary hypertension in pregnancy; a role for novel vasodilators

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We describe the case of a 28-week pregnant woman presenting with severe primary pulmonary hypertension (PPH). She had an elective Caesarean section under general anaesthesia at 32 weeks gestation. Pulmonary artery pressures (PAP) measured from a pulmonary artery catheter before anaesthesia were in excess of 100 mm Hg. Intraoperative nitric oxide was used to reduce PAP. After the delivery of a healthy infant PAP was controlled with nebulized iloprost and a prostacyclin infusion. Seven days later she was discharged from intensive care taking an oral calcium antagonist and warfarin. She developed intractable right heart failure and died 14 days after delivery. Despite increasing experience in the use of drugs to reduce PAP, the clinical course of pregnancy complicated by severe PPH is usually fatal.

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The mortality for primary pulmonary hypertension (PPH) complicating pregnancy is very high,[1 2] and the only long-term 'cure' is a heart-lung transplant. Increased pulmonary vascular resistance combined with the normal physiological changes of pregnancy and delivery is difficult to manage. A series from Canada[3] described the successful use of epidurals to manage the delivery of women with pulmonary hypertension from a variety of causes. A successful outcome has also been described following general anaesthesia for Caesarean section in a woman with PPH and coarctation of the aorta.[4] We describe our experience of delivery by Caesarean section under general anaesthetic in a woman with severe PPH.

Case report

A 26-yr-old multiparous woman presented with increasing dyspnoea at 28 weeks of pregnancy. There was no significant past medical history. A pregnancy 3 yr previously had ended in induction of labour at 35 weeks gestation for hypertension and the birth of a healthy daughter.

On examination she had a sinus tachycardia, arterial pressure was 130/80 mm Hg, the jugular venous pressure was 10 cm above the clavicle and there was a parasternal heave. On auscultation she had an accentuated pulmonary component of the second heart sound and a systolic murmur of tricuspid regurgitation. ECG showed right heart strain, and a chest radiograph showed a dilated right heart and prominent pulmonary arteries. An echocardiogram showed normal intra-cardiac anatomy, but a dilated right heart, impaired right ventricular systolic function, tricuspid regurgitation and a right ventricular end systolic pressure of 100 mm Hg. The left heart was normal. A mild microcytic anaemia was present and a ventilation/perfusion scan excluded pulmonary embolic disease.

A clinical diagnosis of PPH was made and she was given heparin, aspirin, ferrous sulphate and intra-muscular dexamethasone to promote foetal lung maturation.

An elective Caesarean section was planned for the 32nd week of pregnancy under general anaesthetic. She was premedicated with temazepam 20 mg, ranitidine 150 mg and metoclopramide 10 mg. In the anaesthetic room she received 0.3 M sodium citrate 30 ml orally, then midazolam 1.5 mg i.v. after which an arterial cannula and pulmonary

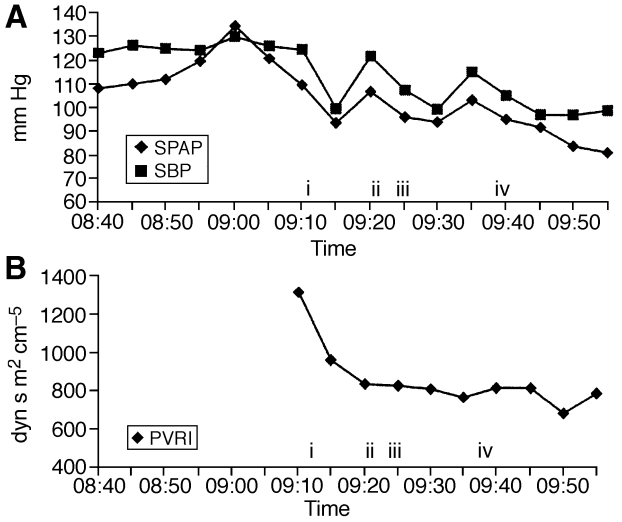

Fig 1 Intra-operative haemodynamic variables showing trends in: (A) systolic pulmonary artery pressures (SPAP) in relation to systemic blood pressure (SBP); and (B) pulmonary vascular resistance index (PVRI) at times (i) induction of anaesthesia, (ii) delivery, (iii) start of nitric oxide, (ii–iv) duration of syntocinon infusion.

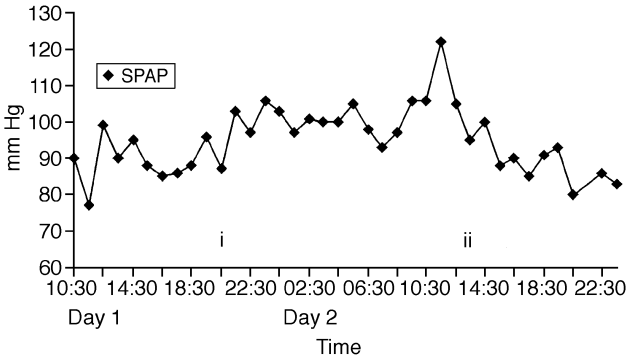

Fig 2 Trends in systolic pulmonary artery pressures (SPAP) during the first 36 h post operation: (i) extubated, nitric oxide stopped, iloprost started; (ii) i.v. prostacyclin started.

artery catheter were inserted. Systolic pulmonary artery pressure (PAP) was equal to systemic pressure at 130 mm Hg. After pre-oxygenation, anaesthesia was induced with propofol 40 mg, fentanyl 1 mg and suxamethonium 100 mg. Cricoid pressure was applied. The trachea was intubated and the lungs ventilated with oxygen and isoflurane. Vecuronium was used for muscle relaxation.

Nitric oxide 1.5 p.p.m. was given after induction of anaesthesia but had to be stopped because of multiple premature ventricular complexes. A live baby boy was delivered 10 min after induction of anaesthesia. He was heavily narcotized but responded rapidly to naloxone. Augmentin 1.2 g i.v. was given after delivery and syntocinon 10 units i.v. as an infusion over 20 min to contract the uterus, which caused only a slight increase in pulmonary artery pressures. Nitric oxide was recommenced after delivery and was well tolerated. The dose was gradually increased to 16 p.p.m. PAP decreased progressively to systolic PA pressures 15 mm Hg below systemic pressures by the end of the procedure (Fig. 1). She was subsequently transferred to intensive care.

Postoperative echocardiography was unchanged. Intravenous heparin was recommenced 4 h post-Caesarean section to maintain an activated partial thromboplastin ratio of 2–2.5. Two hourly nebulized iloprost was introduced. This enabled the nitric oxide and pressure support ventilation to be weaned without any rebound increase in PAP. She was extubated 11 h after surgery. PAP remained at or slightly below systemic pressures (Fig. 2). In an attempt to reduce PAP, the following day an i.v. infusion of prostaglandin I_2 (PgI_2) was started at 2 ng kg^{-1} min^{-1}. The maximum dose of i.v. PGI_2 tolerated was 7.5 ng kg^{-1} min^{-1}, limited by the side effects of headache, flushing, nausea and abdominal cramps. Although cardiac index remained fairly stable (1.9 –3.1) the mixed venous oxygen saturation (Sv_{O_2}) decreased as low as 40% over the subsequent days. Contact with the regional transplant centre had been made preoperatively to discuss timing of a heart-lung transplant. Persistent cardiovascular instability made her unsuitable for early transplantation.

Oral nifedipine 20 mg was given on the 5th postoperative day and increased to 40 mg bd and allowed the i.v. PGI_2 to be reduced. Iloprost nebulizers were given 3–4 hourly and ferrous sulphate was restarted for anaemia (Hb 8.8 g dl^{-1}). On the 8th postoperative day oral anticoagulation with warfarin was commenced and the patient discharged to the ward.

Her course was complicated by recurrent syncope, increasing signs of right ventricular failure with gross peripheral fluid retention. A temporary improvement was achieved with the re-introduction of i.v. PGI_2 and i.v. furosemide but a further syncopal episode resulted in readmission to intensive care. The nifedipine was discontinued and heparin substituted for warfarin. Subclavian central line insertion was complicated by a pneumothorax. The initial chest drain failed to completely re-expand the lung and a second drain was inserted which drained both air and blood. Her condition deteriorated throughout the day. She became progressively more hypoxic and acidotic and died on the 14th postoperative day. Post-mortem examination confirmed right heart failure and unexplained pulmonary hypertension as the cause of death.

Discussion

PPH is defined as a sustained elevation of pulmonary artery pressure (mean greater than 25 mm Hg at rest) in the absence of a demonstrable cause. Pulmonary vasoconstriction, medial hypertrophy, thrombosis in situ and dysfunctional pulmonary vascular endothelium are believed to contribute.[5]

Pulmonary hypertension is tolerated poorly in the parturient. Deterioration typically occurs in the second trimester with symptoms of fatigue, dyspnoea, syncope and chest pain. This corresponds to the physiological increase in cardiac output and blood volume of 40%. During labour, uterine contractions effectively add 500 ml of blood to the circulation. The pain and expulsive effort of labour increase right atrial pressure, blood pressure and cardiac output.[6]

Women with PPH are advised against pregnancy. In early pregnancy a termination is considered. Where PPH is not diagnosed until late in pregnancy an elective delivery is preferred. This facilitates cooperation between specialities, permits monitoring to be started in advance, the pain and haemodynamic consequences of labour to be minimized and an intensive care bed arranged. Premature spontaneous labour is common[2 3] therefore delivery is usually planned for 32–34 weeks gestation. In our patient the cardiovascular physiological changes of pregnancy had already occurred by the time of presentation and some clinical improvement had occurred with oxygen and heparin therapy, so the pregnancy was allowed to continue.

Mangano[7] outlined the principles for management of delivery in these patients as avoidance of increases in pulmonary vascular resistance (PVR) and maintenance of right ventricular preload, left ventricular after-load and right ventricular contractility.

Most reported cases have recommended vaginal delivery under epidural analgesia.[3 8] Pain, oxygen consumption and the haemodynamic consequences of labour can be reduced with epidural analgesia. Epidural diamorphine with low dose bupivacaine gives minimal risk of vasodilatation. However, most describe the management of patients with Eisenmenger's syndrome in whom changes in PVR are better tolerated because the intra-cardiac defect allows the pressure increases to be transmitted to the left side of the heart.

Smedstad has described use of oxytocin both for induction of labour and to increase uterine tone after delivery without apparent haemodynamic consequence.[3] However, oxytocin can cause systemic vasodilatation and low dose infusion has been associated with an acute rise in PVR and fall in cardiac output.[9] Prostaglandin $F_2\alpha$ causes pulmonary vasoconstriction[10] and must be avoided.

An opioid-based general anaesthetic was considered appropriate for a failing right ventricle, not least because the patient refused a regional technique. It facilitated the control of PAP and the use of nitric oxide. Nitric oxide can be administered by facemask but is poorly tolerated, difficult to monitor and cannot be scavenged. A narcotic-based technique minimizes increased pulmonary pressures during laryngoscopy and avoids the excessive negative intropic effect of inhalational agents. Nitrous oxide increases PVR and was omitted. Care was taken to avoid reducing venous return during positive pressure ventilation. Narcotic-related neonatal depression is usually easily managed. O'Hare *et al.*[4] reported a successful outcome following an emergency Caesarean section under general anaesthetic for a woman with PPH and coarctation of the aorta. They employed glyceryl trinitrate intraoperatively and intravenous and aerosolized prostacyclin postoperatively.

Vasoconstriction is a prominent feature, leading to the rationale for using pulmonary vasodilators such as oxygen, nitric oxide, epoprostenol and iloprost in the short term and calcium antagonists in the long term. Nitric oxide has been used in the pre- and post-delivery management of PPH in pregnancy, with clear reductions in PAP as evidenced by cardiac catheterization data,[11] but not during Caesarean section.

Epoprostenol is a naturally occurring prostaglandin and potent vasodilator. It affects vascular remodelling and inhibits platelet aggregation. Iloprost is a synthetic analogue of epoprostenol with improved metabolic and chemical stability, which decreases PAP and PVR, increases cardiac output, and has minimal effect on systemic arterial pressure.[12] The pulmonary vasodilator effect lasts 60–120 min. In comparison, intravenous prostacyclin (epoprostenol) reduces PVR with similar efficacy but reduces systemic arterial pressure to a greater degree[13] with no clinically significant reduction in PAP. Neither iloprost nor prostacyclin is recommended in pregnancy because of concerns over the effect on uterine blood flow. Iloprost is associated with toe deformities in rats.[14]

Patients with PPH are at risk of thrombosis and thromboembolism. The Mayo Clinic group has reported that anticoagulation may improve the outcome in severe pulmonary hypertension.[15]

Pulmonary artery catheterisation provided early warning of rising PAP, deteriorations in right ventricular function and the effects of therapeutic interventions. Its use has not been associated with improved survival[1] and there is an increased risk of pulmonary artery rupture and thrombosis in these conditions.[16]

Excessive systemic dilatation resulting from the nifedipine may have contributed to syncope in our patient. Syncope can also result from ventricular tachyarrhythmias secondary to an ischaemic ventricle, but no such arrhythmias were documented.

Roberts[1] found that the only survivors since 1982 had a cardiac index (CI) >4 litres min^{-1}, right atrial pressure (RAP) <10 cm H_2O and PVR <1000 dyn s^{-1} cm^5. This put our patient into a very high-risk category with CI <4, RAP $\geqslant$10 and PVR as high as 1142 dyn s^{-1} cm^5. Higgenbottam *et al.*[17] suggest mixed venous oxygen saturation (Sv_{O_2}) as the best prognostic indicator in PPH with a 5 yr survival rate of 17% with Sv_{O_2}<63% or 55% with an Sv_{O_2}>63%. Sv_{O_2} as low as 40% were recorded in our patient.

PPH complicating pregnancy remains a fatal condition with deaths reported to occur between 2 and 9 days post-delivery,[1] usually from right heart failure. Iloprost and nitric oxide therapies may have a role in controlling PAP in this condition but there is no evidence of improved survival.

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