

Favorable Outcome of Pregnancy with an Elective Use of Epoprostenol and Sildenafil in Women with Severe Pulmonary Hypertension

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Established Facts

- Pulmonary arterial hypertension (PAH) is associated with a high maternal mortality.
- Women with PAH are strongly advised against becoming pregnant.
- New therapies for management of non-pregnant patients with PAH have been shown to improve symptoms and increase life expectancy in this patient population.

Novel Insights

- Better understanding of the pathophysiology and aggressive therapy may improve outcome in pregnant women.
- Planned closed monitoring and combined therapy with pulmonary vasodilators, inotropes and diuretics in preparation for delivery and prior to hemodynamic and clinical deterioration are important.
- Elective approach may help to prevent pregnancy-related mortality in some of the patients.

Key Words

Epoprostenol · Sildenafil · Pregnancy · Pulmonary hypertension

Abstract

Background: Pulmonary hypertension carries significant maternal and fetal risk during pregnancy and the postpartum period. As maternal mortality is high, specific targeted therapy for pulmonary hypertension may be required during pregnancy. **Cases:** We describe 2 pregnant patients who

presented with severe secondary pulmonary arterial hypertension during their last trimester. They were electively treated in the late antepartum and early postpartum periods with sildenafil and intravenous epoprostenol and successfully delivered healthy infants via cesarean section without postpartum complications. **Conclusion:** Although pulmonary hypertension is associated with a risk of maternal mortality and most women are advised against pregnancy, new therapies may improve the outcome of pregnancy in patients with pulmonary hypertension.

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Introduction

Pulmonary arterial hypertension (PAH) due to an idiopathic pulmonary vascular disease or secondary to congenital or acquired disorders is associated with an excessive risk of maternal mortality [1]. Women with PAH are usually advised to avoid or terminate pregnancy but often refuse. Recent advances in the therapy of PAH have resulted in a significant improvement in the morbidity and mortality of non-pregnant women [2]. The potential maternal and fetal benefits and risks of these therapies are not known. We present 2 patients with severe PAH who were treated with epoprostenol and sildenafil during the peripartum period and had a favorable outcome.

Case Reports

Case 1

A 30-year-old Hispanic woman with a 5-year history of systemic lupus erythematosus and antiphospholipid syndrome presented in her 32nd week of pregnancy with a 6-week history of shortness of breath on exertion, paroxysmal nocturnal dyspnea and chest pressure. She was on daily doses of prednisone 15 mg, enoxaparin 40 mg, and aspirin 81 mg. At age 26, the patient had a fetal demise at 12 weeks of gestation and at age 27 she underwent cesarean section at 30 weeks gestation due to preeclampsia and delivered a 2,050 g baby.

Physical examination at presentation showed a gravid female in no acute distress. Her vital signs were as follows: blood pressure 104/70 mm Hg; heart rate 106 beats/min; respiratory rate 20/min; temperature 36.0°C, and O₂ saturation 98% on room air. Cardiac examination demonstrated right ventricular (RV) heave, increased pulmonary components of the 2nd heart sound with no murmurs or abnormal heart sounds. Lungs were clear and there was bilateral mild leg edema. ECG showed sinus tachycardia and rightward axis. Chest X-ray showed cardiac silhouette at the upper limits of normal, with enlarged pulmonary arteries. Echocardiogram showed normal left ventricular function, but a severely dilated RV with decreased systolic function and elevated RV pressures (80 mm Hg). Right heart catheterization demonstrated normal right atrial (RA) pressure (4 mm Hg) elevated RV pressure (85/4 mm Hg), elevated pulmonary artery (PA) pressure (85/35 mm Hg), normal mean pulmonary capillary wedge pressure (5 mm Hg), cardiac output (6.4 liters/min) and markedly elevated pulmonary vascular resistance (PVR) at 583 dynes·s·cm⁻⁵. Prednisone and aspirin were continued; enoxaparin was titrated to achieve a peak anti-Xa factor level of 0.7 units/ml. Furosemide 20 mg every 12 h and digoxin 0.25 mg daily were started, and sildenafil 25 mg three times daily was added and increased to 50 mg three times daily. Epoprostenol was started at 2 ng/kg/min and gradually titrated up over the next 7 days to 9 ng/kg/min, a dose which was continued until the day of delivery. In preparation for delivery, a Swan-Ganz catheter was placed again to monitor RA pressure as well as PVR changes during and after delivery. RA pressure at that time was 5 mm Hg and PVR was decreased to 470 dynes·sec·cm⁻⁵. At 36 weeks and 3 days, cesarean section and bi-

lateral tubal ligation were performed and a viable, 2,410 g female baby with an Apgar score of 5 at 1 min and 9 at 5 min was delivered. After delivery intravenous furosemide and dobutamine were added to prevent an increase in RA pressure and RV failure due to increased venous return. Nitric oxide was available in case of increased PVR and worsened RV function but was not needed. The patient's postpartum course was uneventful and epoprostenol was titrated off over 2 days starting 1 week after the delivery. She was discharged on coumadin, prednisone, sildenafil, and digoxin.

Case 2

A 21-year-old Hispanic female with a history of ventricular septal defect and Eisenmenger's syndrome presented with shortness of breath on exertion and paroxysmal nocturnal dyspnea at 36 weeks of her first pregnancy. The patient was not receiving any cardiac medications prior to her pregnancy and reported dyspnea on moderate exertion and occasional dizziness. The patient became more symptomatic during the 3rd trimester with decreased exercise tolerance and increasing shortness of breath on milder exertion. Physical examination at the time of presentation revealed a gravid female in mild respiratory distress with facial flushing and the following vital signs: blood pressure 127/69 mm Hg; heart rate 82 beats/min; respiratory rate 20/min, temperature 36.2°C, O₂ saturation 85% on 10-liter O₂ face mask. There was no jugular venous distention. Cardiac exam demonstrated a normal regular rhythm, RV heave, widely split 2nd heart sound and prominent pulmonary component with no murmurs and no third or fourth heart sound. Lungs were clear to auscultation and percussion. Her extremities showed marked clubbing and cyanosis. ECG showed a normal sinus rhythm and rightward axis. Chest X-ray showed cardiac silhouette at the upper limits of normal, with enlarged pulmonary arteries. Echocardiogram showed moderate unrestrictive membranous ventricular septal defect, normal left ventricular function, with mildly dilated left and right ventricles and markedly elevated RV pressure (117 mm Hg). The patient was started on an infusion of epoprostenol (2 up to 8 ng/kg/min) and oral sildenafil (25 up to 50 mg 3 times/day). Heparin was infused to maintain a partial thromboplastin time of 65–85 s. Her condition improved and stabilized and she delivered a healthy baby at 37 weeks via cesarean section. Epoprostenol was gradually titrated off and the patient was discharged home on warfarin and sildenafil.

Discussion

PAH secondary to pulmonary vascular disease of unknown etiology, congenital heart disease, or acquired vascular disease has been one of the few cardiovascular conditions associated with a high maternal mortality, estimated as 30–50% and usually occurring a few hours to several days after delivery [1]. Clinical experience [3] suggests a number of potential mechanisms including: (1) a marked increase in PVR and pulmonary pressure due to vasoconstriction after delivery which can cause RV failure and circulatory collapse; (2) an increased venous re-

turn to the heart following delivery (secondary to removal of fetal compression of the inferior vena cava as well as shift of excess fluid from the interstitial space into the intravascular systemic circulation), which may lead to volume overload and RV failure, and (3) pulmonary embolism.

Considering the potential mechanisms for clinical deterioration and death after delivery, our therapeutic plan included the following: (1) use of epoprostenol and sildenafil to lower PVR prior to delivery and prevent a postpartum increase in PVR; (2) close monitoring (hemodynamic and/or echocardiographic) prior to and during delivery and several days postpartum for early detection of significant increase in PVR and of RV enlargement and systolic failure; (3) having nitric oxide available during and after delivery as an additional potent pulmonary vasodilator to offset an increase in PVR if needed; (4) use of dobutamine to improve RV function; (5) effective anticoagulation interrupted only around the time of delivery, in order to prevent pulmonary embolism, and (6) the use of diuretics to prevent RV volume overload after the delivery.

In the present cases, both epoprostenol and sildenafil were used to lower PVR and prevent an increase in pulmonary pressures after the delivery. Epoprostenol is a naturally occurring prostaglandin and vasodilator that decreases PVR and improves RV function [2]. It is classified as a pregnancy category B drug and has been used in several patients with pregnancy and pulmonary hypertension [3, 4].

Sildenafil citrate is a phosphodiesterase type 5 inhibitor that causes vasodilation of the pulmonary vascular bed and the systemic circulation and has been shown to reduce PA pressures in patients with symptomatic PAH [2]. The safety of sildenafil for the fetus is described as category B, the experience with the use of this drug in pregnant patients with PAH, however, is limited. The use of 150 mg of sildenafil in combination with L-arginine in a 22-year-old woman with Eisenmenger's syndrome at 31 weeks of gestation was not associated with any adverse effect [5]. A second patient with Eisenmenger's syndrome previously on bosentan was started on sildenafil at 28 weeks of gestation [6]. The patient was delivered successfully by cesarean section at 30 weeks due to maternal and fetal deterioration; however, the infant died at 26 weeks from viral infection. Bédard et al. [3] reported the use of sildenafil during pregnancy in 5 additional patients with PAH who survived their pregnancy, but no further information was provided.

The introduction of new therapy for the management of non-pregnant patients with PAH has resulted in improved symptoms and increased life expectancy in this patient population [2]. Can such therapy improve maternal and fetal outcomes in women with PAH undergoing pregnancy? Recent preliminary publication by Zwicke and Buggy [4] reported successful management of 37 consecutive patients with PAH and a mean PA pressure of 61 mm Hg. The etiology of PAH, however, was of various causes and patients were treated with various medications including digitalis, dobutamine, i.v. epoprostenol, i.v./s.q. treprostinol, diuretics, inhaled NO, and oxygen. Although the authors stated that aggressive management of this patient population can result in successful outcome, no information was provided regarding the choice of medication in individual patients as well as the timing and regimen of drug administration. A recent systematic review by Bédard et al. [3] summarized information on 73 cases of pregnancy in women with PAH published between 1997 and 2007. Advanced therapies for PAH which included NO, prostacyclin analogs, bosentan or sildenafil was used in 72% of these patients during pregnancy, labor or delivery. Although mortality seemed lower compared with previously reported historical control group of women with PAH, it was still unacceptably high at about 25%. Since advanced therapy was often administered as a last resort when the patients were already unstable with refractory heart failure, it is possible that such therapy when given electively during pregnancy may be more helpful in the prevention of hemodynamic and symptomatic deterioration and thus improve outcome. The data reported by Zwicke and Buggy [4] and our successful elective use of pulmonary vasodilation with both epoprostenol and sildenafil during the peripartum and early postpartum periods in the 2 patients reported here may support such a hypothesis but needs to be further investigated.

Clinical Implications

Pulmonary hypertension has been a strong predictor of an unfavorable pregnancy outcome with high maternal mortality. Recent reports indicate that with better understanding of the pathophysiology and aggressive therapy, outcome of pregnancy may improve. Our experience of successful pregnancy in 2 patients with PAH receiving therapy with pulmonary vasodilators in preparation for delivery and prior to hemodynamic and clinical deterioration, may suggest that such an elective approach may

help to prevent pregnancy related mortality in some of the patients. At the same time, however, recent reports of maternal mortality [3] suggest that successful outcome of pregnancy cannot be guaranteed and maternal death may still occur in spite of current therapy. For this reason

and until more information on the impact of new therapy on the outcome of pregnancy in women with pulmonary hypertension is available, patients with this condition who seek preconception consultation should be advised against becoming pregnant.

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