CASE REPORT

Pulmonary arterial hypertension and pregnancy

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This is the case report of a pregnant woman who refused pregnancy termination when diagnosed with pulmonary arterial hypertension (PAH) functional class 2–3 at the 24th week of gestation and of her newborn. A pregnant woman with PAH functional class 2–3 was treated with inhaled prostacyclin analog (iloprost), oral sildenafil, oxygen, and low molecular weight heparin. She delivered at 32nd week by Cesarean section. The infant required oxygen up to 36th week postconceptional age and had a short steroid treatment. The mother needed close cardiovascular monitorization, intensive oxygen and pulmonary vasodilator therapy for 2 months and was discharged with oxygen and oral iloprost treatment. A multidisciplinary approach together with pulmonary vasodilator therapy may be succesful in such a high-risk pregnant woman.

Key words: Iloprost, newborn, pregnancy, pulmonary hypertension, sildenafil, survival, therapy

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive dyspnea, exercise intolerance, and right heart failure, leading eventually to death. Median survival was reported to be 2.8 years;[1] but since the introduction of epoprostenol, a prostaglandin analog, important improvements have been gained in the treatment.[2] However, mortality in the first year is still given as 15%.[3]

The pathophysiology of PAH comprises a complex endothelial functional disorder leading to remodeling of pulmonary arterial wall, which causes increased vasoconstriction and disturbed vasodilation. Vascular damage may be idiopathic or related to other diseases. Normal mean pulmonary arterial pressure is 15–20 mm Hg, pulmonary artery wedge pressure is 8–12 mm Hg, and pulmonary vascular resistance is less than 240 dynes-sec/cm^5(3 Wood units). Patients with PAH have a mean pulmonary artery pressure higher than 25 mm Hg, pulmonary capillary wedge pressure of less than 15 mm Hg, and pulmonary vascular resistance of ≥240 dynes-sec/cm^5 (≥3 Wood units).[1,2] Clark *et al*.[4] studied 10 pregnant women by pulmonary artery catheterization between 36 and 38 weeks and repeated the catheterization 11 and 13 weeks postpartum. There was no significant change in pulmonary capillary wedge pressure and central venous pressure.

Patients with idiopathic PAH do not have secondary causes for elevated pulmonary arterial pressure, such as cardiac disorders concerning left heart, lung disease, and thromboembolic disorders.[5]

PAH may not be diagnosed at early stages because the clinical signs are few and not specific. Most patients have dyspnea on exertion, weakness, chest pain, syncope, and lower extremity edema.[2] A complete work-up including pulmonary function tests, diagnostic tests for connective tissue disorders and thromboembolic disorders, echocardiography, and right heart catheterization is required for the differential diagnosis.[2,5] Catheterization is the reference method for the diagnosis and grading of PAH.[5] Pregnancy and delivery is very risky and may be fatal in these patients.[1] This report discusses the successful management of a case of PAH diagnosed at pregnancy.

CASE REPORT

A previously healthy, 30-year-old primiparous pregnant woman with progressive respiratory distress and oxygen need was diagnosed to have PAH in her country of origin at her 24th week of gestation. She was counseled to terminate the pregnancy due to her grave disease, but refused the termination. She applied to our center and was hospitalized in cardiac intensive care unit (Ege University Hospital, Izmir, Turkey, 2011) as a 24 weeks pregnant woman with PAH. Echocardiographic examination showed the findings of severe pulmonary hypertension: enlarged right ventricle (45 mm) and D-shaped left ventricle due to increased pressure of the right side. Right

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ventricular ejection fraction was calculated as 45% and severe tricuspid failure with a tricuspid regurgitant flow velocity of 4.4 m/ sec (normal range: 2.8 m/sec) was detected. Pulmonary artery systolic pressure was calculated as 80 mm Hg (normal range: 25–30 mm Hg). Cardiac catheterization showed a mean pulmonary arterial pressure of 50 mm Hg (normal range: 15–20 mm Hg), pulmonary wedge pressure of 9 mm Hg (normal range: 8–12 mm Hg), pulmonary vascular resistance of 880 dynes-sec/cm^5 (11 Wood Units) (normal range: 100–250 dynes-sec/cm^5), and cardiac output of 3.7 L/ min (normal range: 5–7 L/ min). Additional laboratory work-up for the differential diagnosis excluded the causes other than idiopathic pulmonary hypertension, including cardiac disorders, lung disease, thyroid disease, human immunodeficiency virus, thromboembolic disorders, connective tissue diseases, and deep venous thrombosis, as described in 2009 guidelines for PAH.[6] The patient was in functional class 3 according to New York Heart Association classification, which may correspond to 2.5 years of median survival expectation. [4] She was once again counseled about the severity of her illness and the poor prognosis, but she refused the termination of the pregnancy. The treatment of the patient was then programmed in a multidisciplinary approach by a team of cardiologists, obstetricians, pulmonologists, and neonatologists. Treatment with inhaled iloprost (10–20 mcg 7–9 times daily) and oral sildenafil (10–20 mg three times a day) was simultaneously started in lowest doses and gradually increased to target the maximum tolerated dose carefully because of the risk of lowering the cardiac output. Patient was kept in bed rest in left lateral decubitus position. Anticoagulant therapy with low molecular weight heparin was started for thromboprophylaxis. Arterial oxygen saturation was around 80% despite oxygen treatment via nasal cannula. Delivery was planned for the 31st–32nd week because the patient was decompensating. Fetal well-being was pregnancy evaluated with biophysic scoring and sonographic fetal biometry. Inhaled iloprost was replaced with intravenous iloprost infusion (2 ng/kg/min) 5 days before delivery because of increased oxygen needs and as a prophylaxis for the very high risk peripartum period. Antenatal betamethasone therapy was given for the lung development of the infant.

At 31 weeks + 6th day of pregnancy, she delivered a male infant with good Apgar scores of 8 in the first minute and 9 in the 5th minute by Cesarean section under epidural anesthesia. Birth weight was 1700 g (75–90P), birth height was 41 cm (25–50P), and head circumference was 30 cm (75–90P). Clinical findings were normal and he had a sinusal tachycardia and mild respiratory distress syndrome with oxygen need. Echocardiography, cranial and abdominal ultrasounds were normal. Formula feeding was initiated because of the mother's poor health conditions and the ongoing treatment agents with unknown effects on breastfed infant. At 18th day of life, the infant was having full feeds enterally.

Oxygen needs of the infant around 30% of fractional inspired concentration continued up to 36th week despite negative X-ray findings. Anemia and infectious findings which might explain this oxygen need were negative clinically and on blood tests. The infant was then diagnosed of having mild bronchopulmonary dysplasia (BPD) and a short duration of dexamethasone therapy helped to resolve the oxygen requirement and the infant was weaned to room air. The infant was discharged home at the 36th day of life with a weight of 2360 g. The mother was followed in cardiac intensive care unit and required oxygen of 4 L/min and pulmonary vasodilator therapy with the same dose of inhaled iloprost and oral sildenafil as in pregnancy. She was discharged home at 2 months of delivery with oxygen and inhaled iloprost treatment. She was advised regarding contraception; however, no sterilization procedure was performed during the Cesarean operation due to her refusal. At the time of writing the manuscript, she was alive for 10 months after delivery with the same echocardiographic findings under the same vasodilator treatment and oral anticoagulation with warfarine sodium.

DISCUSSION

Traditionally, pregnancy is contraindicated in patients with PAH because of the high mortality rates.[7] During pregnancy, 30–50% increase in blood volume, and 50% increase in cardiac output due to a reduction in systemic vascular resistance is observed.[8] In pregnant patients with PAH, increased blood volume and cardiac output cannot be accommodated and may be fatal due to right heart failure.[9] Every contraction during labor increases the blood volume by 300–500 ml and causes a 50% increase in cardiac output. Maternal blood volume further increases by 500 ml right after the delivery. Cardiac output remains high for the first 48 h following delivery and then gradually decreases to the values prior to pregnancy. It may take up to 6 months for these changes to return to pre-pregnancy level.[10]

Even in normal pregnancy, there is a stage of hypercoagulability that further aggravates postpartum period due to relative resistance to activated protein C, decreased protein S levels, and increased levels of factors I, II, V, VII, VIII, X, and XII. PAH and hypoxia also increase the risk of hypercoagulability via hemoconcentration and hyperviscosity, and cause new thrombus formation or pulmonary embolism in an already compromised pulmonary circulation, which may not be tolerated.[11]

Maternal death may occur at the labor, delivery, and in postpartum period. It is reported to be as high as 30–50%

due to these circulatory and hematologic changes.[11] Maternal deaths mostly occur during the first 10 days after delivery. Preterm delivery rate is about 50%.[12]

The close follow-up of pregnant women with PAH must be performed in a multidisciplinary manner. A team approach of obstetrician, anesthesiologist, cardiologist, hematologist, and neonatologist is necessary for the management of patient. Hospitalization at the second trimester is appropriate because of the high risk of hemodynamic complications and preterm delivery. These patients are monitored with echocardiography and the compression of inferior vena cava must be prevented. Oxygen treatment is given to keep the PaO_2 higher than 70 mm Hg. Pulmonary arterial hypoxemia is a potent vasoconstrictor which has important hemodynamic results and must be avoided. Loop diuretics such as furosemide and torsemide may be used under close observation if right heart failure occurs. Etachrynic acid and spiranolactone cannot be given because of the ototoxicity and anti-androgenic effects. Low molecular weight heparin prophylaxis is given against the high risk of thromboembolism.[13] Anticoagulant therapy is discontinued during delivery and the surgical procedures, and postnatally it is continued with warfarin.

Endothelin receptor antagonists such as bosentan and sitaxsentan play an important role in the treatment of PAH; however, they cannot be used during pregnancy because of their teratogenicity.[14] A small group of PAH patients respond to oral sildenafil treatment and its use in pregnancy is safe.[15] Prostacyclin is a potent vasodilator and its deficiency plays an important role in the pathogenesis of PAH. Prostaglandin analogs, therefore, are preferred in pregnant patients.[16] Continuous intravenous infusion of prostaglandin is suggested[17] and iloprost was safely administered in our patient. In patients with severe disease, administration of prostaglandin is often advocated as the first-line therapy.[18]

Programming the timing and type of delivery is also important. The optimum mode of delivery form women with PAH is controversial. Vaginal delivery may be preferred to avoid the risk of anesthesia. If the vaginal route is selected for delivery, it should be performed under intensive care. Delivery in the lateral position prevents fetal compression of the inferior vena cava and so maintains venous return. However, prolonged second phase of delivery, uncontrolled vaginal hemorrhage risk, and the hemodynamic disturbances caused by contractions and pushing down are prevented by Cesarean section. Myocardial depression, sudden changes in cardiac filling pressure and systemic blood pressure must be prevented during regional or general anesthesia.[14] Epidural anesthesia must be accomplished carefully to minimize peripheral vasodilatation and deterioration of the hemodynamics. Our patient delivered safely by a planned Cesarean section under epidural anesthesia.

Patients should be kept in hospital for 2 weeks postpartum for monitoring.[19] Pulmonary vasodilators are prescribed under careful supervision. Some of the pulmonary vasodilators may be excreted in breast milk and breast feeding is usually avoided.[20] In our patient, breast feeding was avoided because of iloprost medication. At the time of writing the manuscript, the patient was alive after 10 months of delivery.

Both mother and the infant survived with the help of meticulous medical care from this fatal disease which is aggravated with pregnancy. So far, there are only a few reports on successful management of pregnant patients with PAH and they are mostly reports of several isolated pulmonary vasodilator treatments. Combination of oral sildenafil and inhaled/intravenous iloprost under a close surveillance may be a life-saving treatment option for mother and baby, as in our case. The effective and safe doses and durations of these medications are not known and need further evaluation in larger case series.

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