A Successful Delivery of a Woman with Pulmonary Arterial Hypertension: Under Close Observation and without Medications

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ABSTRACT

Pregnant women with severe pulmonary arterial hypertension (PAH) have a high maternal mortality risk. Regardless of the PAH severity, the possibility of maternal death increases before and after childbirth. In general principle, if pregnancy happens, termination is the recommendation. Several case reports noted successful deliveries of pregnant women with PAH while using the drugs of anticoagulants, calcium channel blockers, prostaglandins, and phosphodiesterase V inhibitors. However, choices of treatment are generally achieved by clinical experiences because of no established guidelines of treatments for PAH in pregnancy. We describe a case of a 31-year-old pregnant woman with mild PAH who successfully delivered a viable newborn under close observation and without any medications. In the state of no consensus of the management for PAH in pregnancy, prior to termination or empirical drug treatments, close observation without medications could be considered in mild PAH.

Key Words: Pulmonary arterial hypertension; Pregnancy; Management
calcium channel blockers, low molecular weight heparin administration and sildenafil, a phosphodiesterase type V inhibitor. However, we handled a pregnant woman of PAH diagnosed by transthoracic echocardiography (TTE) without any specific medications and termination. We report a case of the pregnant woman who had mild form of PAH and successfully delivered without any medications.

**Case report**

A previously healthy 31-year-old, at 35 weeks’ gestational age gravida (G3, P1) patient was consulted from obstetrics department for evaluating repetitive cesarean sectional operation risks about the surgery in the past. She had a history of heart valve surgery at 6 years old and after the surgery there was no follow-up due to good progress. Five years ago, she had first uncomplicated pregnancy and delivered a newborn by cesarean section without significant problems. She denied previous hypertension, diabetes mellitus, drug uses, and family histories about cardiopulmonary diseases. She was not a smoker and drunker. She presented no symptoms with the exception of mild exertional dyspnea (New York Heart Association [NYHA] functional class I or II) without chest pain or palpitation.

On physical examination, vital signs were as follows: blood pressure (BP), 110/70 mm Hg; heart rate, 78 beats/min; respiratory rate, 20 breaths/min; body temperature, 36.5°C and oxygen saturation as measured by pulse oximetry, 98%. The jugular venous distention was absent. Cardiac auscultation revealed no murmur and lung sounds were clear to auscultation bilaterally. On abdominal examination, there was no hepatomegaly and splenomegaly. Extremities had no clubbing or edema.

A 12-lead electrocardiogram showed as representing normal sinus rhythm with ventricular rate of 68 bpm and no right heart strain patterns such as right axis deviation or right ventricular hypertrophy. A chest radiography was unremarkable for parenchymal infiltrates, right heart silhouettes, and pulmonary arteries except for post thoracotomy status (Fig. 1). Laboratory values showed hemoglobin level of 12.7 g/dL, white blood cell count of 9,310/mm³, platelet of 166,000/mm³, blood chemistries of aspartate aminotransferase of 11 IU/L, alanine aminotransferase of 4 IU/L, alkaline phosphatase of 80 IU/L, total protein of 6.7 g/dL, albumin of 3.7 g/dL, blood urea nitrogen of 11.0 mg/dL, creatinine of 0.56 mg/dL, glucose of 100 mg/dL, cholesterol of 243 mg/dL, total bilirubin of 0.4 mg/dL, activated partial thromboplastin time of 29.2 seconds, prothrombin time of 12.2 seconds, international normalized ratio of 1.0 and urinalysis was normal. TTE showed normal left ventricular and atrial sizes, ejection fraction of 69%, moderate tricuspid regurgitation (TR) with peak TR velocity of 2.87 m/sec, maximal pressure gradient of 32.93 mm Hg, mild pulmonary valvular regurgitation and PAH of increased right ventricular systolic pressure (RVSP) of 42.93 mm Hg with

**Fig. 1. Chest X-ray shows post thoracotomy status.**
Fig. 2, Images of transthoracic echocardiography. (A) Moderate tricuspid regurgitation (TR) with peak TR velocity of 2.87 m/sec. (B) Increased right ventricular systolic pressure (RVSP) of 42.93 mm Hg presenting pulmonary arterial hypertension.
no evidence of left to right shunt with negative contrast injection. Left side of the heart was normal (Fig. 2).

Although she was diagnosed as PAH during pregnancy, considering the patient’s World Health Organization (WHO) functional classes I or II and TTE results, we decided to follow-up without any drug treatments. We educated her that she should have enough rests and low salt diets to reduce the cardiac demands and lie in the lateral position to avoid caval vein compression. Thereafter, additional two TTE were carried out once a week to check the changes of RVSP. The RVSP showed continuous mild PAH. On physical examination during follow-up periods, she invariably had no unusual symptoms but for prior mild dyspnea (below NYHA functional class II) and vital signs were stable. The WHO functional class for PAH was consistently I or II. To check the condition of the fetus we monitored the non-stress test with amniotic fluid volume and fetal biometry at 36 and 37 weeks of pregnancy. The test results of the fetus were satisfactory compared to the gestational age. Therefore we planned to maintain no drug treatments and observations.

At 38 weeks + 3th day of pregnancy, under the supervision of cardiovascular conditions, she successfully delivered a viable male infant by elective cesarean section under spinal anesthesia, because general anesthesia can worsen the hemodynamic status of some afflicted patients. The newborn had good Apgar scores of 8 in the first minute and 9 in the 5th minute. The baby’s birth weight was 2,565 g (range, 5th to 10th percentile), birth height was 46 cm (range, 3rd to 5th percentile), head circumference was 33.7 cm (range, 10th to 25th percentile) and chest circumference was 29 cm. The newborn’s physical examination and clinical findings were normal. The patient and baby did not reveal the specific cardiovascular symptoms during admissions and have been on outpatient observation for twenty months.

Discussion

Severe PAH in pregnancy is considered to a very serious condition due to high maternal mortality risks (30% to 50% in older series and 17% to 33% in more recent papers). The disease is characterized by increased vasoconstriction and poor vasodilation due to remodeling of the walls of the pulmonary arteries. Smooth muscle proliferation decreases the size of vessel lumen with an associated increased resistance to blood flow. Over expression of endothelin-1 plays an important role in inflammation and vasoconstriction, and a decrease in the production of vasoactive substances (such as prostacyclin and nitric oxide) contributes to the underlying pathophysiology of endothelial dysfunction. Traditionally, pregnancy is contraindicated in patients with PAH because of the high mortality rates. During pregnancy, 30% to 50% increase in blood volume, and 50% increase in cardiac output due to a reduction in systemic vascular resistance is observed. In pregnant patients with PAH, increased blood volume and cardiac output cannot be accommodated and may be fatal due to right heart failure. Other physiologic changes include an increase in cardiac output during labor in patients receiving local anesthesia (pudendal block) and postpartum intravascular volume shifts resulting from blood loss or diuresis. These physiologic events place a great demand on the cardiovascular system, with the greatest incidence of mortality occurring during the first several postoperative days. Therefore, maternal death may occur at the labor, delivery, and in postpartum period. It is reported to be as high as 30% to 50% due to these circulatory and hematologic changes. Maternal deaths mostly occur during the first 10 days after delivery. Preterm delivery rate is about 50%. Recognition of the elevated maternal-fetal mortality rate has led physicians to recommend effective contraception
and, in the event of a pregnancy, early fetal termination.\textsuperscript{12)}

The TTE and Swan-Ganz catheter through the right side of the heart provides pressure measurements for diagnosis of PAH. A mean pulmonary arterial pressure $\geq 25$ mm Hg at rest or $> 30$ mm Hg during exercise is indicative of PAH.\textsuperscript{3)} The PAH was also considered present if the Doppler echocardiography-estimated RVSP exceeded 35 mm Hg in at least one echocardiogram. The grade of PAH was then categorized as mild (range, 36 to 45 mm Hg), moderate (range, 46 to 55 mm Hg), or severe ($\geq 56$ mm Hg).\textsuperscript{13)} However, hemodynamic monitoring by Swan-Ganz catheter may be associated with serious complications such as pulmonary artery rupture, while its utility has not been demonstrated; therefore, it is rarely if ever indicated.\textsuperscript{3)} In addition, its use has not been associated with improved survival,\textsuperscript{14)} and there is an increased risk of thrombosis in these conditions.\textsuperscript{15)} In this context, our patient was diagnosed as mild PAH by TTE presenting increased RVSP of 42.93 mm Hg.

After the introduction of epoprostenol in 1996, with a multidisciplinary and aggressive approach to treatment, mortality rates have improved. Bedard et al.\textsuperscript{1)} compared maternal mortality rates for the recent decade (1997 to 2007) to 1978 to 1996 data reported by Weiss et al.,\textsuperscript{2)} demonstrating the maternal mortality rate of 17% in primary pulmonary hypertension, 28% for patients with Eisenmenger syndrome, and 33% for those with secondary pulmonary hypertension.\textsuperscript{3)} Nowadays, among the available drugs for treatment of PAH, bosentan, a non-selective endothelin receptor A and B antagonist, can be generally used. The renin-angiotensin system is associated with PAH and bosentan makes effects to renin-angiotensin system in PAH.\textsuperscript{16)} In addition, Kim et al.\textsuperscript{17)} reported that bosentan can be an effective therapeutic option for PAH related to HIV infection. But this drug is contraindicated in pregnancy because of concerns for increased rates of congenital malformations in animal studies. Calcium channel blockers are considered safe for use in pregnancy; however, only about 10% of patients with pulmonary hypertension respond to this type of therapy with a sustained effect.\textsuperscript{18)} Several case reports in the literature describe the use of prostacyclins in pregnant patients.\textsuperscript{11,19,20)} The short half-life of these compounds require frequent administration, either by inhalation or continuous intravenous infusion. Nitric oxide and sildenafil, a phosphodiesterase type V inhibitor which is a degrading enzyme of the second nitric oxide messenger, have also been used successfully either as sole agents or as adjuncts to other medications during the intra-partum course. A small group of PAH patients respond to oral sildenafil treatment and its use in pregnancy is safe.\textsuperscript{21)} In Korea, some case reports described successful deliveries of women with PAH while using calcium channel blockers, low molecular weight heparin administration and sildenafil.\textsuperscript{5,6)} A management guideline of PAH, not specified for pregnant women, suggests starting oral treatment for patients in the WHO functional classes II and III, and considering parenteral prostanoids in suitable patients in the class IV or those with poor prognostic markers in the class III. If response to treatment is suboptimal, switching or adding further drugs is suggested.\textsuperscript{22)}

The mortality probably increases with more elevated PAH. However, even moderate forms of PAH can worsen during pregnancy and no safe cut-off value is known.\textsuperscript{3)} There is a substantial need for long-term observational studies evaluating the various treatments in terms of survival, side effects, quality of life, and costs. Since no data are available from head-to-head comparisons of approved therapies, the choice of treatment will be dictated by clinical experience and the availability of drugs, as well as by patients’ preferences.\textsuperscript{18)} Most of primary pulmonary hypertension patients are also young.
women of child bearing age. Therefore, the established management guideline for PAH during pregnancy is necessary. The close follow-up with no drug treatments used for our patient may also be included in the management guideline.

Programming the timing and type of delivery is also important. The optimum mode of delivery form of 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 BP must be prevented during regional or general anesthesia. Epidural anesthesia must be accomplished carefully to minimize peripheral vasodilatation and deterioration of the hemodynamics. The patients are recommended keeping in hospital for two weeks postpartum for monitoring. Although the mode of delivery for patients with pulmonary hypertension is controversial, cesarean delivery was planned for our patient due to previous cesarean delivery. Our patient safely delivered a newborn with the planned cesarean section under spinal anesthesia. Regional anesthesia to control pain and to avoid pain-related tachycardia was needed, but very close observation and care were required during dosing of the epidural to avoid sudden maternal hypotension and decrease in cardiac output due to systemic vasodilation. The review of literature by Weiss et al. and Bedard et al., on the other hand, showed neonatal survival rate of nearly 90% regardless of the subgroup of pulmonary hypertension, with fetal growth restriction reported in 3% to 33% of pregnancies. In this case, the newborn’s Apgar scores and physical examination outcomes were favorable.

In summary, the PAH is a rare disease which affects young women of child bearing age. And the disease is associated with high maternal mortality and morbidity risks. Despite significant progress on comprehending the pathophysiology of PAH, no practical management guidelines for PAH in pregnancy are available to date. Although women with severe PAH seem to be at higher risks, a safe cut-off value is not known. Anticoagulants, calcium channel blockers, prostaglandins, and phosphodiesterase V inhibitors as well as termination used to be empirically selected for PAH in pregnancy. We report a pregnant woman who was diagnosed as PAH by TTE at 35 weeks’ gestational age and during close observations without any medications successfully delivered a viable newborn at 38 weeks + 3th day by elective cesarean section through spinal anesthesia. In conjunction with uses of the drugs for PAH managements, the observation without any medications could be considered for mild PAH in pregnancy on the basis of comprehensive understanding about patient’s symptoms, conditions and test results. After childbirth she and the newborn did not reveal the specific symptoms during admissions and are on outpatient observation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References


