Clinical Case Report

Medicine®

OPEN

A case report of pulmonary arterial hypertension in pregnancy and complications of anticoagulation therapy

Yangfang Xiang, MD[a], Jun Li, BS[b], Yinxiang Sun, MD[a,*]

Abstract

Rationale: Treprostinil, a potent vasodilator, is the treatment of choice for severe pulmonary arterial hypertension (PAH) during pregnancy. Its inhibition of platelet aggregation increases the risk of hemorrhage. In addition, anticoagulation therapy is widely used in pregnancy with PAH due to the hypercoagulable state. However, very little is known about the complications of anticoagulants' use in pregnancy with PAH.

Patient concerns: A 27-year-old pregnant woman was admitted to the hospital at 32weeks with progressive dyspnea.

Diagnoses: The pregnant was diagnosed with ventricular septal defect 12 years prior to presentation. Combining clinical manifestation with results of right heart catheterization (RHC) and echocardiography, it was consistent with severe World Health Organization (WHO) group I PAH.

Interventions: Supportive treatment included supplemental oxygen, intravenous treprostinil, sildenafil and prophylactic anticoagulation.

Outcomes: Gastrointestinal bleeding is occurred in our patient when dalteparin were used in conjunction with treprostinil. Her care was further complicated refractory to usual conservative measures before delivery.

Lessons: This case report illustrates the complexities that arise when prostacyclin therapies are combined with necessary anticoagulation in patients with PAH during pregnancy. More intention should play to the complications of anticoagulant in pregnancy with PAH during treprostinil therapy.

Abbreviations: ICU = intensive care unit, ITP = immunologic thrombocytopenia, PAH = pulmonary arterial hypertension, PAP = pulmonary arterial pressure, PDE-5 = phosphodiesterase type 5, PPD = postpartum day.

Keywords: anticoagulation, pregnancy, pulmonary arterial hypertension, treprostinil

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance that eventually lead to right ventricular failure and death.[1] Many patients with PAH are of childbearing age; however, pregnancy in the setting of PAH is contraindicated because of the high maternal–fetal morbidity, even with novel medical therapies that have improved outcomes.[2] Efficacy data indicated that treprostinil, a prostacyclin analog, significantly improves the exercise capacity of patients with PAH and may provide survival benefits.[3,4] The primary mechanism of action of treprostinil is reduction of pulmonary artery pressure (PAP) through direct vasodilation of the pulmonary and systemic arterial vascular beds, thereby improving systemic oxygen transport and increasing cardiac output with minimal alterations of the heart rate.[5,6]

Despite the beneficial effects of this drug, complexities arise when prostacyclin therapies are combined with necessary anticoagulation therapy, and we describe the case of a patient with PAH during pregnancy that illustrates these complications.

2. Case report

2.1. Patient information and clinical findings

A 27-year-old woman (gravida 1, para 0; 32 weeks gestation) was diagnosed as having ventricular septal defect 12 years before presentation. Because of exertional dyspnea, she was admitted to the local hospital to undergo echocardiography in 2014.

Echocardiography findings indicated that she had moderate PAH; her PAP was 75 mm Hg. At that time, she was managed with bosentan (62.25 mg twice daily), and her symptoms improved. She discontinued this medication at her own because of preparation for pregnancy in 2016. Because of her diagnosis and New York Heart Association class III functional status in March 2017, she was admitted to the hospital at 32 weeks gestation. The examination showed that her left heart was enlarged (left ventricle diameter: 52 mm).

Editor: N/A.

The authors have no funding and conflicts of interest to disclose.

[a] Pharmacy Department, [b] Cardiovascular Medicine Department, People's Hospital of Zhuhai City, Zhuhai City, China.

[*] Correspondence: Yinxiang Sun, Pharmacy Department, People's Hospital of Zhuhai City, Zhuhai City 519000, China (e-mail: 1725495604@qq.com).

Medicine (2018) 97:32(e11810)

Received: 13 April 2018 / Accepted: 17 July 2018

http://dx.doi.org/10.1097/MD.0000000000011810

2.2. Diagnostic assessment and therapeutic interventions

Right heart catheterization was performed on the next day, and we confirmed the diagnosis of severe World Health Organization group I PAH. Intravenous treprostinil was initiated at a dose of 2.5 ng/kg/min. She responded quickly to treprostinil. When the target dose of 10.83 ng/kg/min was achieved over the following 4 days, her PAP decreased from 94/52 (70) mm Hg to 70/30 (46) mm Hg. Sildenafil (25 mg thrice daily) and potassium chloride sustained-release tablets (2 g, stat order) were administered. On hospital day 4, she had symptoms such as nausea and nonprojectile vomiting. Her platelet count decreased from 181,000/μL on admission to 151,000/μL. Her nausea was relieved with a vitamin B_6 infusion. After ruling out the typical causes of nausea during pregnancy, we determined it was a side effect of treprostinil. To minimize the risk of vomiting-related complications, the dosage of treprostinil was decreased to 8 ng/kg/min.

Considering that the hypercoagulable state of pregnancy increases the risk of pulmonary thrombus formation, the patient required additional anticoagulation therapy. Prophylactic heparin was chosen given the potential need for rapid delivery. Dalteparin (5000 U every 24 hours) was started on day 5. However, she vomited 50-mL of coffee ground-like material on day 6, which led to a decrease in the platelet count to 117,000/μL. Because she developed gastrointestinal bleeding, supportive treatments including supplemental oxygen, antiemetic drugs, withdrawal of dalteparin, and downregulation of treprostinil were provided. A near-term delivery via cesarean section was planned, along with bilateral tubal ligation after continuous fetal monitoring and a rescue dose of dexamethasone for lung maturity of the fetus.

A low dose of treprostinil was continued throughout the intrapartum period. The cesarean delivery was uncomplicated, and the estimated intraoperative blood loss was 400 mL. Postoperatively, the patient was monitored in the intensive care unit (ICU), and the infusion of treprostinil was changed to a subcutaneous injection. To avoid recurrent gastrointestinal bleeding, anticoagulation therapy was still discontinued 12 hours after epidural removal. The platelet count increased to 196,000/μL on postpartum day (PPD) 3.

2.3. Follow-up and outcome

The patient was transferred to the cardiac ICU until she was discharge home on PPD 7. She was instructed to take sildenafil (0.025 g thrice day). A timeline of her hemoglobin levels according to the medications administered is shown in Figure 1. Treatment time of treprostinil and dalteparin during her hospital stay were shown in Figure 2. The prothrombin time and international normalized ratio were normal over the duration of treatment. At 3 weeks postpartum, the treprostinil was weaned to off and she continued bosentan 125 mg twice daily. The patient is doing well to date, maintained on bosentan and sildenafil, 1 year postpartum.

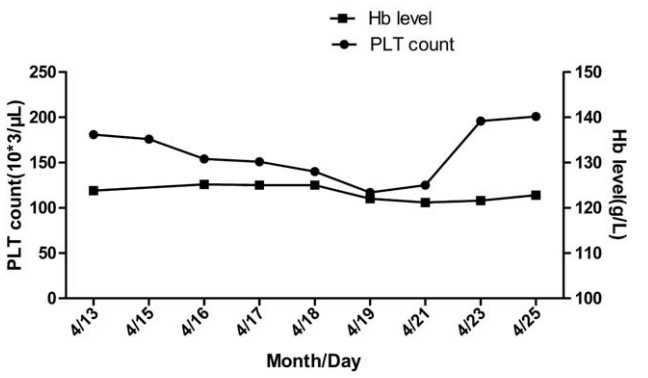

Figure 1. Timeline of the platelet counts and hemoglobin levels according to the medications administered. PLT = platelet; Hb =hemoglobin.

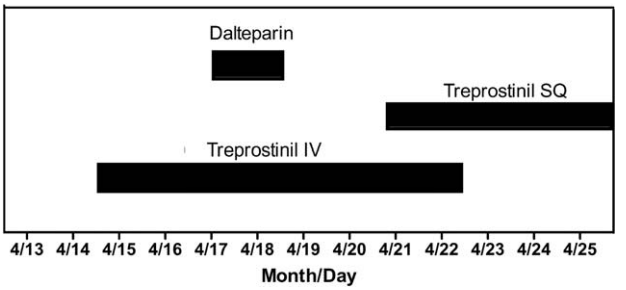

Figure 2. Treatment time of treprostinil intravenously (IV) or subcutaneously (SQ) and dalteparin during the hospital stay.

2.4. Ethical statement

This study was approved by the Ethics Committee of The People's Hospital of Zhuhai City, and written informed consent was obtained from the patient.

3. Discussion

Significant advances in the treatment of PAH have been achieved over the past decades. Its management strategy consists of endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors, and prostacyclin analogs. Given the astoundingly high mortality rate of patients with PAH, pregnancy is not recommended in these patients. If patients do become pregnant and decline fetal termination, they are treated with PDE-5 inhibitors, prostanoids, diuretics, and supplemental oxygen as needed.[2] Other treatments such as endothelin and nitric oxide are contraindicated because they cause fetal malformations. Clinical practice guidelines recommend oral PDE inhibitor therapy for mild to moderate PAH.[7,8] The mainstay of treatment for severe PAH is prostanoids. Prostanoids include epoprostenol, treprostinil, and beraprost. However, epoprostenol was withdrawn from the Chinese market in late 2016 because of external factors, that is, its use was not approved by health insurance.

Treprostinil, a stable prostacyclin analog, can dilate pulmonary vessels through the depolarized membrane potential of promoting cyclic adenosine monophosphate, release and enable the Ca_{2+}-activated K channel by binding with the prostacyclin receptor in pulmonary vascular endothelial cells because of the effect of antiplatelets, dilate blood vessels, and inhibit vascular smooth muscle cell proliferation. Treprostinil shares pharmacologic actions similar to epoprostenol. In contrast to epoprostenol, treprostinil is chemically stable at room temperature, has a neutral pH, and has a longer half-life (approximately 4 hours), thereby permitting continuous subcutaneous infusion rather than continuous intravenous infusion and avoiding the risks of severe infection and thrombosis. Treprostinil is classified as a category B drug during pregnancy.[9] Data regarding the safety of

treprostinil therapy during pregnancy are sparse. Reproductive studies involving treprostinil and pregnant rat and rabbit models[10] have been performed, and they revealed no evidence of fetal harm in the rat model; however, fetal skeletal variations and a reduction in maternal body weight were associated with continuous subcutaneous infusion in the rabbit model during organogenesis. Nevertheless, several recent trials demonstrated that the use of treprostinil therapy is effective for treating PAH.[3,4,11]

Cesarean delivery is not a preferred delivery method because of the increased risk of mortality that is likely related to the increased incidence of thromboembolism or dynamic shifts in postsurgical fluid.[12] Fortunately, the patient underwent elective cesarean delivery successfully with slowly titrated epidural anesthesia.[13] Subcutaneous treprostinil administered after delivery resulted in a significant decrease in systolic PAPs, and her postoperative period was uneventful. The dosing regimens of intravenous and subcutaneous treprostinil were similar to those used for standard pulmonary hypertension treatment.[14,15]

In our case, the episodes of vomiting and slightly decreased platelet count occurred with intravenous treprostinil therapy before parturition. In Zamanian et al study,[16] the discontinuation rate of 22% in the oral treprostinil group was presumably due to a higher incidence of side effects, such as headache, nausea, flushing, and jaw pain. Further, associated reports about thrombocytopenia with treprostinil therapy are rare. Louis et al reported that one patient had a low normal platelet count, a condition in which the platelet levels decreased after continuous intravenous treprostinil administration for approximately 7 months.[17] Wang and Chen also reported a case of treprostinil-induced thrombocytopenia, for which the platelet counts were directly related to the rate of intravenous treprostinil administration.[18] We have not yet seen studies about the pathogenesis of thrombocytopenia caused by treprostinil treatment. The pathogenesis of drug-induced thrombocytopenia mainly includes immunologic thrombocytopenia (ITP), nonimmune thrombocytopenia, and bone-marrow suppression thrombocytopenia. The ITP is not usually dose related[19] and associated with a platelet count $<30\times10^9$/L; however, nonimmune thrombocytopenia always shows a dose-dependent relationship with drugs. In the FREEDOM-C study, most adverse events were dose related and occurred with the first dose and the subsequently increased doses of treprostinil.[20] In our case, the platelet counts were related to the dosage of treprostinil during the first 5 days, and the additionally anticoagulation therapy decreased the platelet count to a low value. Treprostinil naturally occurs in the human body; therefore, low platelet counts may be nonimmunogenic, thereby directly eliminating the effects of platelets. Although platelet counts increased steadily and gradually after the transition from intravenous to subcutaneous treprostinil in our patient, it is unclear whether the rapid infusion or the administration route, or both have an effect on platelets.

Our patient was at an increased risk for bleeding because of the additional anticoagulation therapy administered for the hypercoagulable state of pregnancy. Unfortunately, gastrointestinal bleeding developed from the treprostinil infusion with the concomitant administration of dalteparin, and our patient required a transfusion of 2 U of packed red blood cells. The following features of our case of gastrointestinal bleeding were peculiar and deserve further discussion: the platelet count decreased progressively but at low values and concomitantly with nausea; prophylactically dosed anticoagulation therapy was administered antepartum; and bleeding resolved after down-regulation of treprostinil and the discontinuation of dalteparin.

Treprostinil may have a dual role of inhibiting platelet aggregation and dilating the blood vessels, thus eventually contributing to diffuse intragastric mucosal hemorrhage from small blood vessels. Mindus et al[21] reported the occurrence of severe intra-abdominal bleeding during treprostinil infusion in a patient with systemic sclerosis-associated PAH who was likely previously described in the literature for gastrointestinal bleeding.[22] In the meantime, the complications of anticoagulation therapy with PAH cannot be ignored. Herrero et al[23] reported 3 patients with severe PAH during pregnancy and mentioned the range of different complications (e.g., thrombocytopenia, wound hematoma, and postpartum hemorrhage) that arose from anticoagulation therapy in the setting of epoprostenol. In Simonneau et al trial,[22] 2 patients in the treprostinil treatment group presented with episodes of gastrointestinal hemorrhage, which were attributed to the concomitant administration of anticoagulant therapy, as indicated in PAH. Herrero et al[23] reported frequent hemorrhagic complications in patients with idiopathic PAH treated with anticoagulation therapy and epoprostenol, suggesting that this combination of treatment may increase the risk of bleeding. A single case of fatal bleeding in a pediatric patient receiving epoprostenol and an increased risk of alveolar hemorrhage were reported when patients received epoprostenol and warfarin together.[24] Therefore, extreme caution and close monitoring must be provided to patients receiving concomitant platelet function inhibitors and anticoagulants. Nonetheless, long-term anticoagulation therapy with warfarin was not associated with a higher incidence of major bleeding complications in patients with PAH or idiopathic PAH treated with subcutaneous treprostinil.[25] The use of anticoagulation therapy as part of the treatment regimen for PAH remains a topic of debate.[26,27] Of course, in women with PAH where the indication for anticoagulation therapy outside pregnancy is established, anticoagulation therapy should also be maintained during pregnancy. No robust randomized trial of PAH has weighed the risks and benefits of including anticoagulation therapy in treatment regimens, thereby leaving clinicians to surmise the value for patients on an individual basis.

4. Conclusion

More studies should be performed to clarify the risks and potential benefits of anticoagulation therapy for patients with PAH, especially during pregnancy. Knowing how to balance the necessary anticoagulation therapy and prostacyclin therapies in patients with PAH is especially important. It is necessary to develop a management protocol for prescribing anticoagulants on a case-by-case basis during pregnancy in women with PAH.

Author contributions

Conceptualization: Yangfang Xiang, Yinxiang Sun.
Data curation: Yangfang Xiang.
Formal analysis: Yangfang Xiang.
Project administration: Yinxiang Sun.
Resources: Jun Li.
Supervision: Yinxiang Sun.
Validation: Yangfang Xiang, Jun Li.
Writing – original draft: Yangfang Xiang.

References

[1] Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351:1655–65.

[2] Matthew Moll , Julie G, Payne , et al. Gestational pulmonary arterial hypertension. Pulm Circ 2015;5:730–3.

[3] Fallah F. Recent strategies in treatment of pulmonary arterial hypertension: a review. Glob J Health Sci 2015;7:307–22.

[4] Buckley MS, Berry AJ, Kazem NH, et al. Clinical utility of treprostinil in the treatment of pulmonary arterial hypertension: an evidence-based review. Core Evid 2014;9:971–80.

[5] Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension Chest 2006;129:1636–43.

[6] Whittle BJ, Silverstein AM, Mottola DM, et al. Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. Biochem Pharmacol 2012;84:68–75.

[7] Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [in Polish]. Eur Respir J 2015;46:903–75.

[8] Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013;62:D60–72.

[9] Olschewski H, Kovacs G. European Society of Cardiology; European Respiratory SocietyESC guidelines 2015 on pulmonary hypertension. Herz 2015;40:1055–60.

[10] Brucker MC, King TL. The 2015 US Food and Drug Administration Pregnancy and Lactation Labeling Rule. J Midwifery Womens Health 2017;62:308–16.

[11] Treprostinil (Remodulin) for pulmonary arterial hypertension. Med Lett Drugs Ther 2002;44:80–2.

[12] Spitzer Y, Weiner MM, Beilin Y. Cesarean delivery in a parturient with left ventricular noncompaction complicated by acute pulmonary hypertension after methylergonovine administration for postpartum hemorrhage. A A Case Rep 2015;4:166–8.

[13] Aziz AS, Hui D, Chinnappa V, et al. Successful pregnancy, epidural anaesthesia, labour, and delivery in a woman with Sturge-Weber syndrome and previous hemispherectomy. J Obstet Gynaecol Can 2013;35:917–9.

[14] Skoro-Sajer N. Optimal use of treprostinil in pulmonary arterial hypertension: a guide to the correct use of different formulations. Drugs 2012;72:2351–63.

[15] Smith JS, Mueller J, Daniels CJ. Pulmonary arterial hypertension in the setting of pregnancy: a case series and standard treatment approach. Lung 2012;190:155–60.

[16] Zamanian RT, Levine DJ, Bourge RC, et al. An observational study of inhaled-treprostinil respiratory-related safety in patients with pulmonary arterial hypertension. Pulm Circ 2016;6:329–37.

[17] Louis L, Bair N, Banjac S, et al. Subdural hematomas in pulmonary arterial hypertension patients treated with prostacyclin analogs [corrected]. Pulm Circ 2012;2:518–21.

[18] Wang R-R, Chen F. Thrombocytopenia associated with use of treprostinil in a pulmonary arterial hypertension patient. Chin J New Drugs Clin Rem 2015;11:891–2.

[19] Neunert CE. Management of newly diagnosed immune thrombocytopenia: can we change outcomes? Blood Adv 2017;1:2295–301.

[20] Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest 2012; 142:1383–90.

[21] Mindus S, Pawlowski J, Nisell M, et al. Intra-abdominal bleeding during treprostinil infusion in a patient with pulmonary arterial hypertension. BMJ Case Rep 2013;008677.

[22] Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165: 800–4.

[23] Herrero T, Martin E, Poch DS, et al. Anti-coagulation complications in pregnancies with severe pulmonary arterial hypertension. J Matern Fetal Neonatal Med 2018;31:1209–13.

[24] Badalian SS, Silverman RK, Aubry RH, et al. Twin pregnancy in a woman on long-term epoprostenol therapy for primary pulmonary hypertension. J Reprod Med 2000;45:149–52.

[25] Ascha M, Zhou X, Rao Y, et al. Impact on survival of warfarin in patients with pulmonary arterial hypertension receiving subcutaneous treprostinil. Cardiovasc Ther 2017;35:1755–5922.

[26] Roldan T, Landzberg MJ, Deicicchi DJ, et al. Anticoagulation in patients with pulmonary arterial hypertension: An update on current knowledge. J Heart Lung Transplant 2015.

[27] Xiong CM. Controversy over anticoagulation in patients with pulmonary arterial hypertension [in Chinese]. Zhonghua yi xue za zhi 2018;98:81–3.