Pregnancy as a possible trigger for heritable pulmonary arterial hypertension

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Abstract: It is unclear whether pregnancy is a trigger or accelerant for idiopathic pulmonary arterial hypertension (PAH). Alternatively, its frequency close to the onset of symptoms and diagnosis in the idiopathic PAH population may represent a coincidence in a disease that predominates in young women. We describe a carrier of a *BMPR2* gene mutation who had an uneventful first pregnancy but had aggressive PAH during her second pregnancy and now has ongoing heritable PAH. The possible role of pregnancy as a trigger in this vulnerable patient is discussed. Databases of patients with heritable PAH should be explored to see whether pregnancy is related to overt manifestation of the disease.

Keywords: pulmonary arterial hypertension, pregnancy, right ventricle, *BMPR2*.

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CASE DESCRIPTION

The proband is a 33-year-old woman of French Canadian origin from Normandy, France, who is living in rural Quebec (Fig. 1). Her paternal grandfather died in 1954, at 31 years of age, due to pulmonary hypertension. Her father presented in 1986 with "primary pulmonary hypertension" at 34 years of age and died 5 years later. A sister died at 28 years of age at another hospital shortly after delivering a healthy child. The proband's 39-year-old brother is asymptomatic at present. A cousin died at 34 years of age. Analysis of the proband's DNA in 2011 revealed a *BMPR2* gene mutation c.741C>A (p.Tyr247X) that causes a premature termination of the *BMPR2* protein and is likely to be pathogenic.

The proband had echocardiograms at 11 and 24 years of age that had normal findings. She remained asymptomatic. At 27 years of age, she had a supine-bicycle stress echocardiogram and reached 100 Watts, stopping because of leg fatigue. There was no evidence of pulmonary hypertension or right ventricular (RV) dysfunction. She disappeared from medical care. She presented again in January 2011 at 28 years of age, declaring that she was pregnant, with her last menstruation 1 month before presentation. She refused to consider termination of the pregnancy. Findings of an echocardiogram obtained at the end of the first trimester estimated her systolic pulmonary arterial pressure (sPAP) at 26 mmHg with normal RV size and function. Her only medications were vitamins and low-dose aspirin. Echocardiogram findings at 38 weeks of gestation estimated the sPAP at 20 mmHg, and the RV size and function were normal. At 40 weeks of gestation, the proband had an induced vaginal delivery that was complicated by mild postpartum hemorrhage. Echocardiogram findings obtained 1 month postpartum were normal. She was in World Health Organization (WHO) functional class I. She refused a cardiac catheterization. She was counseled about her *BMPR2* mutation and was urged to use contraception. Echocardiograms in July 2012 and October 2013 had normal findings.

She reappeared in clinic in April 2014 at 32 years of age and was 5 weeks pregnant (Fig. 2). She again refused termination of the pregnancy. Findings of an echocardiogram obtained at 6 weeks gestation showed normal RV systolic function without sufficient tricuspid regurgitation to estimate the sPAP, but there was a proto-diastolic interventricular septal shift suggestive of increased RV pressure. At 23 weeks of pregnancy, the patient's RV was mildly dilated with a tricuspid annular plane systolic excursion (TAPSE) of 26 mm and an estimated sPAP of 43 mmHg. At 30 weeks of pregnancy, her sPAP was 79 mmHg according to echocardiographic findings with severe RV enlargement but preserved function (TAPSE: 20 mm). By 33 weeks, her echocardiographic sPAP was 111 mmHg with a dilated RV but a TAPSE of 23 mm. Five days before delivery, the patient initiated intravenous epoprostenol at 2 ng/kg/min, and the dosage was increased daily by 2 ng/kg/min up to 8 ng/kg/min. The baby remained in a breech presentation. One day before delivery, the patient initiated a regimen of intravenous norepinephrine at 2.5 μg/kg/min. At 34 weeks and 4 days gestation, the patient underwent elective low transverse cesarean delivery with bilateral tubal ligation under combined spinal-epidural anesthesia and with norepinephrine support at 5 μg/kg/min. Before beginning the surgery,

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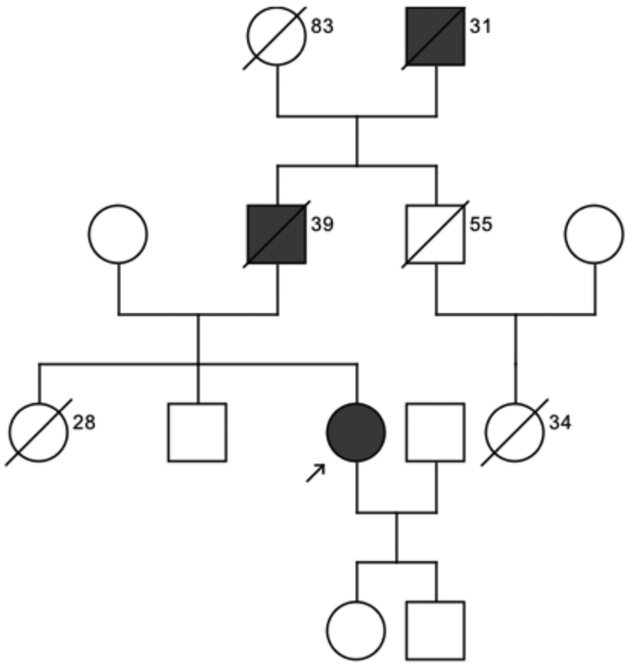

Figure 1. Pedigree of the proband (indicated by an arrow). Filled shapes indicate documented pulmonary arterial hypertension.

her pulmonary artery pressure was 64/31 mmHg (mean: 42 mmHg) with a thermodilution cardiac output of 5.8 L/min. The baby was born healthy. The proband's postpartum course was uneventful. The norepinephrine was tapered and stopped 1 day postpartum. Four days postpartum, the patient's epoprostenol dosage was decreased to 6 ng/kg/min; two days later, it was decreased to 4 ng/kg/min. The patient initiated treatment with tadalafil 40 mg orally daily and macitentan 10 mg orally daily. Three days later, her epoprostenol dosage was reduced to 2 ng/kg/min, and it was stopped 1 day after that. An echocardiogram obtained in December 2014 showed improved RV size and function (TAPSE: 24 mm) with an estimated sPAP of 48 mmHg. The patient remained in WHO functional class II, but findings of an echocardiogram obtained in June 2015 estimated the sPAP at 76 mmHg. A normal radioisotopic ventilation/perfusion lung scan excluded the diagnosis of pulmonary embolism. A cardiac catheterization in November 2015 revealed a mean right atrial pressure of 7 mmHg, pulmonary artery wedge pressure of 14 mmHg, pulmonary artery pressure of 75/31 mmHg (mean: 46 mmHg), cardiac output of 6.27 L/min, and cardiac index 3.23 L/min/m^2. As of January 2016, the patient remained clinically stable in WHO functional class II but with significant pulmonary hypertension and an N-terminal pro-brain natriuretic peptide level that was in the upper range of normal for her age (Fig. 2).

Genetic counseling was offered to the patient and her family. Options included genetic testing of her children or periodic clinical and echocardiographic assessments as they grow up. At present, she is considering the options and has not decided.

DISCUSSION

In women, the years of fertility coincide with the years of highest risk of developing idiopathic pulmonary arterial hypertension (PAH).

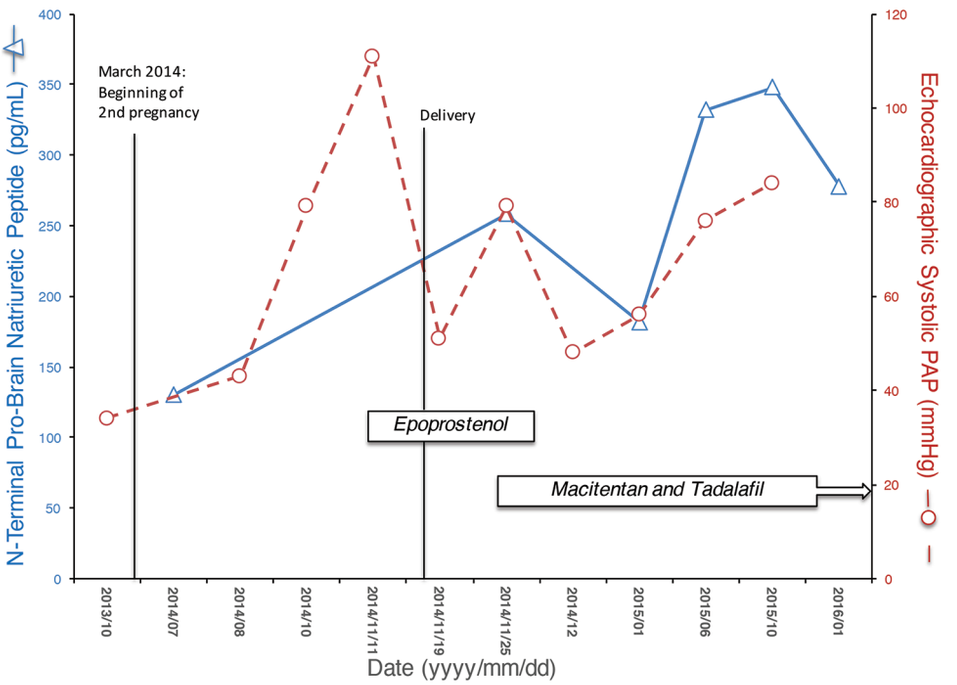

Figure 2. Clinical course of the proband as assessed by levels of N-terminal pro-brain natriuretic peptide (solid blue line, triangles) and echocardiographically estimated systolic pulmonary arterial pressure (PAP; dashed red line, circles). The time line on the abscissa is not linear and highlights the peripartum period. Boxes indicate durations of pulmonary arterial hypertension–specific therapy.

Indeed, it has long been noted that idiopathic PAH may first be noticed during pregnancy or postpartum.[1,2] However, neither the National Institutes of Health primary pulmonary hypertension registry nor the Fifth World Symposium on Pulmonary Hypertension identified pregnancy as a risk factor for development of idiopathic PAH.[3,4] Whether that is true for a population with a clear substrate for PAH (i.e., those carrying gene mutations for *BMPR2*) is unknown. *BMPR2* gene mutation carriers who do not have overt heritable PAH may demonstrate a pulmonary hypertensive phenotype when their circulation is stressed, such as during exercise echocardiography.[5] Pregnancy should represent an even greater stress in an at-risk population. Our patient could have had subclinical PAH for many years, but we have no indication of that. Indeed, she had normal exercise echocardiogram findings 1 year before her first pregnancy, and she tolerated that pregnancy without any echocardiographic evidence of pulmonary hypertension. However, we do not have cardiac catheterization data from after the first pregnancy, nor did the patient have a repeat exercise echocardiogram to see whether she was developing exercise-induced pulmonary hypertension. Certainly, once pulmonary hypertension is established, the hemodynamic abnormalities worsen during pregnancy.[6] Her second pregnancy was typical of patients with PAH, with worsening right heart strain and dysfunction, and current data suggest that her mortality risk during that pregnancy was high.[7] She has now developed overt heritable PAH and is being treated with PAH-specific therapy.

Given that the PAH that appeared in this patient occurred at an age similar to that of her other affected family members, it might be coincidental to the pregnancy. However, it is intriguing to postulate that the high volume and cardiac-output vascular shear stress, hormonal influences, and metabolic changes associated with her repeated pregnancies might have initiated clinically occult vascular remodeling or accelerated it to a clinically overt threshold.[8-10] Indeed, a recent report has described recurrent PAH in a patient that resolved after each pregnancy.[11] Patients with well-characterized gene mutations that cause heritable PAH, such as those of *BMPR2*, represent a unique and valuable at-risk cohort for the study of trigger factors.[12] Registries of asymptomatic *BMPR2* gene mutation carriers should be followed up longitudinally to see whether pregnancy can truly provoke PAH in a population at risk.

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