CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Breathing for Two

Meghan Rudder, M.D., Melissa Russo, M.D., and Corey E. Ventetuolo, M.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

From Women and Infants' Hospital (M. Rudder, M. Russo) and Rhode Island Hospital (C.E.V.), Warren Alpert Medical School of Brown University, Providence. Address reprint requests to Dr. Rudder at the Department of Medicine, Women and Infants' Hospital, 101 Dudley St., Suite 3352, Providence, RI 02905, or at mrudder@wihri.org.

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A 29-year-old pregnant woman (gravida 5, para 3) with undifferentiated connective tissue disease presented at 26 weeks 3 days of gestation with cough and shortness of breath. Two weeks earlier, she had noted gradually increasing exertional dyspnea, 5 days of nonproductive cough, nasal congestion, subjective fevers, and fatigue. She had chest tightness, palpitations, and presyncope after carrying laundry up a flight of stairs. She reported no chills, night sweats, hemoptysis, wheezing, chest pain, orthopnea, headache, visual changes, or abdominal pain.

Dyspnea is common in pregnancy, owing to several physiologic changes. However, dyspnea may also represent new or previously undiagnosed pathologic conditions that are exacerbated by pregnancy. Similarly, although lightheadedness is common during pregnancy because of decreased systemic vascular resistance, dilutional anemia, dehydration from nausea or vomiting, and uterine compression of the inferior vena cava, exertional presyncope arouses concern for a pathologic process. In this patient, pregnancy-specific and nonspecific causes of dyspnea must be considered. Causes to consider include pulmonary (respiratory infection given cough and subjective fevers, interstitial lung disease or pleural disease given the underlying connective tissue disease, and preeclampsia with pulmonary edema given the week of gestation), cardiac (heart failure [including peripartum cardiomyopathy], pericardial or valvular disease given the underlying connective tissue disease, and arrhythmia given presyncope), vascular (pulmonary embolism given hypercoagulability of pregnancy, and vasculitis or pulmonary hypertension given the underlying connective tissue disease), and severe anemia.

The patient's medical history was notable for undifferentiated connective tissue disease (diagnosed approximately 10 months before the current presentation but with isolated manifestations dating back to her most recent pregnancy 5 years earlier) with diffuse lymphadenopathy, biopsy-proven leukocytoclastic vasculitis of the feet and legs, and intermittent cytopenias. Serologic tests were positive for antinuclear antibody titers, anti-Ro (SSA) and anti-La (SSB) antibodies, and low complement levels. Tests for anti–double-stranded DNA (anti-dsDNA) antibodies, anti-Smith antibodies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, anticentromere antibodies, anti–Scl-70 antibodies, and anti-RNP antibodies were negative. She had initially noted shortness of breath at 10 weeks of gestation, with one syncopal episode. Workup at that time revealed a hemoglobin level of 6.2 g per deciliter, a platelet count of 40,000 cells per cubic millimeter, positive results on a direct antiglobulin test, and a low reticulocyte count. Given these findings and an

exposure at her daughter's day-care center, a polymerase-chain-reaction assay for parvovirus B19 was performed, and the virus was detected. Her dyspnea and syncope were attributed to symptomatic anemia from hypoplasia and autoimmune hemolysis related to parvovirus B19 infection and underlying undifferentiated connective tissue disease.

During the following month, she received two red-cell transfusions and a prednisone taper, with abatement of her cytopenias and dyspnea. She was counseled regarding parvovirus-related risks of fetal loss, anemia, and hydrops. Anatomical testing with the use of ultrasonography at 18 weeks showed no anomalies. She was treated with hydroxychloroquine at a dose of 200 mg twice daily and continued prednisone at a dose of 30 mg daily, because recurrent cytopenias prevented tapering. Her hemoglobin level was 10.0 g per deciliter 2 weeks before the current presentation. Other medications included prenatal vitamins and aspirin (81 mg daily) to reduce preeclampsia risk given features of her connective tissue disease similar to those found in lupus. She had a smoking history of 2 pack-years and had quit 8 years previously. She reported no alcohol or drug use. She reported no recent travel. The family history was negative for autoimmune disease, thromboembolic disease, pulmonary hypertension, cardiomyopathy, and sudden death.

This patient's history arouses suspicion for recurrent anemia or cardiopulmonary involvement of her connective tissue disease (serositis with pericardial or pleural effusions, cardiomyopathy, interstitial lung disease, pneumonitis, vasculitis, or pulmonary hypertension). She had been taking more than 20 mg of prednisone for more than 8 weeks, which — although unlikely — may increase the risk of opportunistic infections such as *Pneumocystis jirovecii*. Thromboembolism provoked by hypercoagulability of pregnancy as well as preeclampsia should also be considered.

On physical examination, the temperature was 38°C, blood pressure 106/54 mm Hg, heart rate 122 beats per minute, respiratory rate 22 breaths per minute, and oxygen saturation 94% while the patient was breathing ambient air. The mucous membranes were without pallor or ulceration. The jugular venous pressure was elevated, with a prominent *v* wave. Cardiac examination revealed tachycardia with regular rhythm, splitting of the second heart sound, holosystolic murmur at the right sternal border, and a left parasternal heave. Tachypnea, increased work of breathing, and scattered crackles were noted without rhonchi or wheeze. The abdomen was gravid and nontender. There was reticular hyperpigmentation and trace pitting edema over both lower legs. Neurologic and musculoskeletal examinations were normal.

Although the heart rate may increase by 10 to 20% in the second and third trimesters to accommodate increased cardiac output in normal pregnancy, a resting heart rate above 120 beats per minute is worrisome and, combined with the tachypnea and hypoxemia, arouses concern for pulmonary infection, heart failure, or pulmonary embolism. The crackles on examination suggest involvement of pulmonary parenchyma and may indicate pulmonary edema, infection, or interstitial lung disease related to the patient's connective tissue disease. A prominent *v* wave reflects a passive increase in right atrial pressure and volume during late systole and early diastole; this and other cardiac examination findings suggest elevated right heart pressures.

A complete metabolic panel was within normal range. A complete blood count revealed a white-cell count of 13,700 cells per cubic millimeter (60.2% lymphocytes 33.2% neutrophils, 5.6% monocytes, 0.3% eosinophils, and 0.3% basophils), a hemoglobin level of 11.2 g per deciliter, and a platelet count of 203,000 cells per cubic millimeter. A respiratory pathogen panel was positive for respiratory syncytial virus (RSV). A chest radiograph (Fig. 1) was initially read as normal. Symptoms were initially attributed to RSV infection. However, this was reconsidered when an electrocardiogram showed sinus tachycardia with right-axis deviation and T-wave inversion in leads II, III, aVF, and V_3 to V_5 (Fig. 2) and rereading of the chest radiograph revealed prominence of the right descending pulmonary artery, a large left central pulmonary artery with obliteration of the aortopulmonary window, and a reduction in the retrosternal clear space. The B-type natriuretic peptide (BNP) level was 362 pg per milliliter (normal value, ≤100), and the troponin level was less than 0.029 ng per milliliter, which was normal. Tests for anti-Smith and anti-dsDNA antibodies were negative, and complement levels were normal.

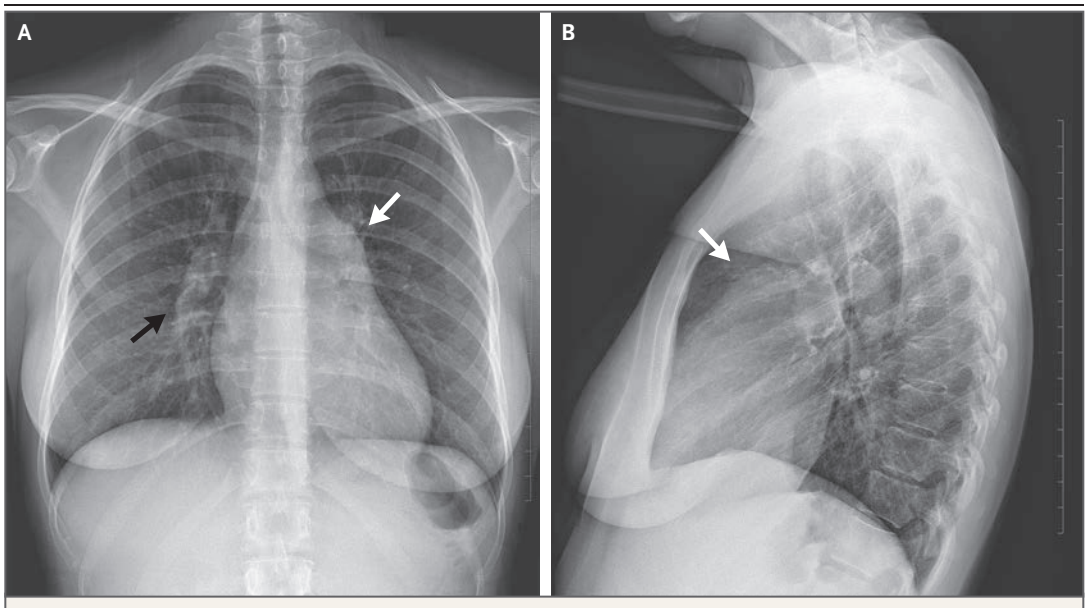

Figure 1. Plain-Film Radiography of the Chest.
Although the radiographs were initially read as normal, further review revealed prominence of the right descending pulmonary artery (black arrow in Panel A), a large left central pulmonary artery with obliteration of the aortopulmonary window (white arrow in Panel A), and a diminished retrosternal clear space (arrow in Panel B). Panel A is a posteroanterior view, and Panel B a lateral view.

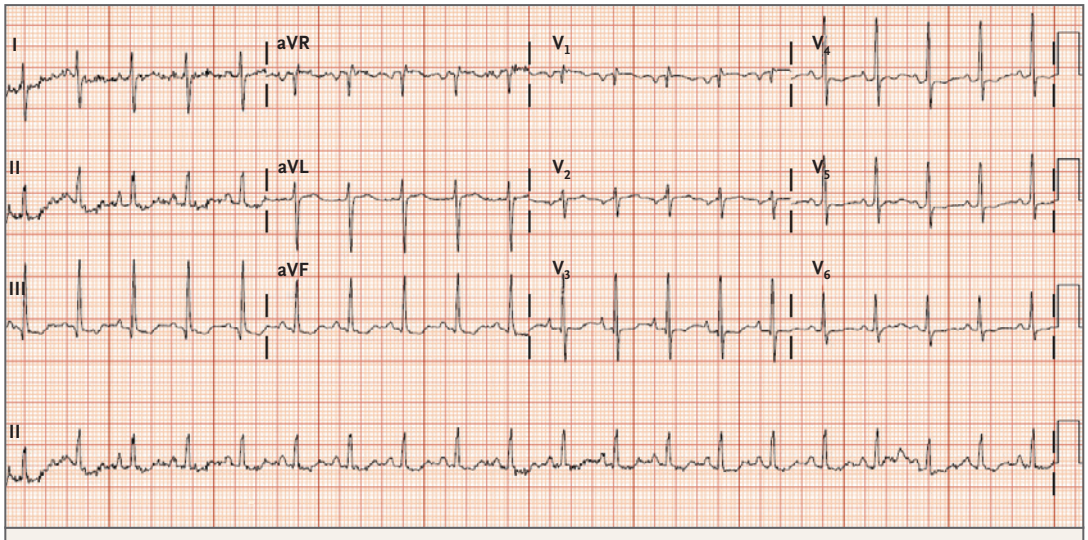

Figure 2. Electrocardiography.
An electrocardiogram showed sinus tachycardia and evidence of right heart strain, including right-axis deviation as well as downsloping ST segments and T-wave inversion in leads II, III, aVF, and V_3 to V_5.

The hemoglobin level of 11.2 g per deciliter and RSV infection may contribute to the patient's symptoms, but neither fully explains her presentation. The electrocardiographic findings, the results of the cardiovascular examination, and the BNP level arouse concern for right ventricular dysfunction. Possible causes of right ventricular dysfunction include pulmonary embolism

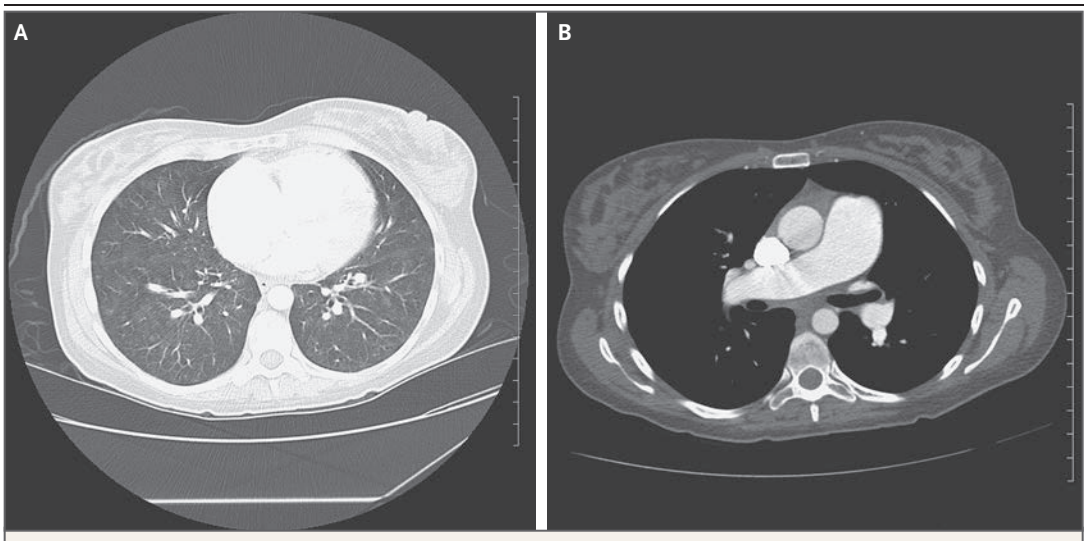

Figure 3. Computed Tomography of the Chest.
Computed tomography showed evidence of diffuse ground-glass opacities and tree-in-bud nodularity as well as enlargement of the pulmonary artery. Both panels are axial views.

or pulmonary hypertension due to pulmonary arterial hypertension, vasculitis, interstitial lung disease, and cardiomyopathy (related to connective tissue disease or RSV infection). Although autoimmune biomarkers have poor negative predictive value for active flares, these results do not suggest heightened disease activity. Computed tomographic (CT) angiography of the chest should be pursued to assess for pulmonary embolism and parenchymal abnormalities. The patient should be counseled that the fetal radiation dose from chest CT angiography is low and that the risk–benefit profile is favorable.

CT pulmonary angiography revealed diffuse, mild tree-in-bud nodularity, ground-glass opacities, and right ventricular enlargement without evidence of pulmonary embolism (Fig. 3). A transthoracic echocardiogram showed a small, hyperdynamic left ventricle with an ejection fraction of 75% and marked dilatation of the right ventricle with severely reduced systolic function and septal flattening (Fig. 4). The right atrium was severely dilated. There was severe tricuspid regurgitation, without other valvular abnormalities. The estimated right ventricular systolic pressure was 74 mm Hg (normal range, 16 to 39), and the systolic excursion of the tricuspid annular plane was 17 mm (normal value, ≥18). A small pericardial effusion was identified.

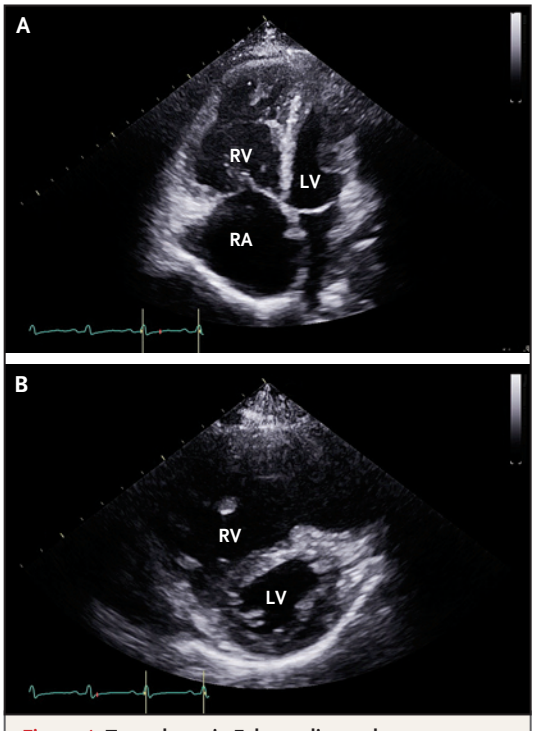

Figure 4. Transthoracic Echocardiography.
Echocardiograms showed an enlarged right ventricular (RV) cavity, dilated right atrial (RA) cavity, and small left ventricular (LV) cavity with flattening of the interventricular septum. A trace pericardial effusion is also seen. Panel A is an apical four-chamber view, and Panel B a parasternal short-axis view.

Diffuse tree-in-bud nodularity and ground-glass opacification are nonspecific and may represent infectious or inflammatory causes but here are most consistent with known RSV infection. Evidence of right ventricular enlargement on CT rightfully prompted an echocardiogram. Marked right ventricular dilation and systolic compromise with elevated right ventricular systolic pressure, low systolic excursion of the tricuspid annular plane, the absence of left-sided valvular disease, and a hyperdynamic left ventricle suggest precapillary pulmonary hypertension with right ventricular failure. Although the absence of filling defects on CT angiography rules out large pulmonary embolism, ventilation–perfusion scanning is more sensitive for chronic thromboembolic pulmonary hypertension. Right heart catheterization is indicated to confirm pulmonary hypertension. The patient should be counseled on procedural risks; however, in this case, accurate hemodynamic assessment is critical to diagnosis and management.

Right heart catheterization showed a right atrial pressure of 19 mm Hg (normal range, 2 to 6), systolic pulmonary arterial pressure of 82 mm Hg (normal range, 15 to 25), diastolic pulmonary arterial pressure of 45 mm Hg (normal range, 8 to 15), mean pulmonary arterial pressure of 57 mm Hg (normal range, 10 to 20), pulmonary-capillary wedge pressure of 5 mm Hg (normal range, 4 to 12), thermodilution cardiac output of 2.7 liters per minute (normal range, 5.8 to 6.2 during pregnancy), and pulmonary vascular resistance of 19.2 Woods units (normal value, ≤1.6). There was no response to inhaled nitric oxide. A subsequent ventilation–perfusion scan showed normal perfusion.

Elevation of the mean pulmonary arterial pressure above 20 mm Hg with a normal pulmonary-capillary wedge pressure and a pulmonary vascular resistance above 3 Wood units is consistent with precapillary pulmonary hypertension. A cardiac output of 2.7 liters per minute is lower than expected for nonpregnant patients and substantially lower than expected for 26 weeks of gestation (normal range, 5.8 to 6.2 liters per minute). A normal ventilation–perfusion scan rules out chronic thromboembolic pulmonary hypertension. The patient's clinical picture suggests severe connective tissue disease–associated pulmonary arterial hypertension (Group 1.4.1 in the World Symposium on Pulmonary Hypertension [WSPH] classification) (Table 1) with right ventricular failure, precipitated by hemodynamic changes of pregnancy with possible contribution from RSV infection.

Table 1. World Symposium on Pulmonary Hypertension Updated Clinical Classification of Pulmonary Hypertension.*

1: PAH
1.1: Idiopathic PAH
1.2: Heritable PAH
1.3: Drug- and toxin-induced PAH
1.4: PAH associated with:
1.4.1: Connective tissue disease
1.4.2: HIV infection
1.4.3: Portal hypertension
1.4.4: Congenital heart disease
1.4.5: Schistosomiasis
1.5: PAH in patients with long-term response to calcium-channel blockers
1.6: PAH with overt features of venous or capillary involvement (PVOD or PCH)
1.7: Persistent PH of the newborn
2: PH due to left heart disease
2.1: PH due to heart failure with preserved LVEF
2.2: PH due to heart failure with reduced LVEF
2.3: Valvular heart disease
2.4: Congenital or acquired cardiovascular conditions leading to post-capillary PH
3: PH due to lung diseases, hypoxia, or both
3.1: Obstructive lung disease
3.2: Restrictive lung disease
3.3: Other lung disease with mixed restrictive and obstructive pattern
3.4: Hypoxia without lung disease
3.5: Developmental lung disorders
4: PH due to pulmonary-artery obstructions
4.1: Chronic thromboembolic PH
4.2: Other pulmonary-artery obstructions
5: PH with unclear or multifactorial mechanisms
5.1: Hematologic disorders
5.2: Systemic and metabolic disorders
5.3: Others
5.4: Complex congenital heart disease

* Adapted from Simonneau et al.[1] HIV denotes human immunodeficiency virus, LVEF left ventricular ejection fraction, PAH pulmonary arterial hypertension, PCH pulmonary capillary hemangiomatosis, PH pulmonary hypertension, and PVOD pulmonary veno-occlusive disease.

The patient was admitted to the intensive care unit (ICU) and began receiving intravenous epoprostenol and sildenafil. Intractable headaches necessitated a transition to tadalafil. Estimated right ventricular systolic pressure and function improved as seen on echocardiography, and she was discharged with a plan for weekly assessments and increases in the dose of epoprostenol to the maximum tolerated dose. Before planned cesarean delivery, she was admitted for hemodynamic reassessment and management. At 33 weeks 4 days of gestation, venoarterial sheaths were placed for possible extracorporeal membrane oxygenation (ECMO), and she underwent an operatively uncomplicated cesarean section under epidural anesthesia. She delivered a male infant with Apgar scores of 8 (at 1 minute) and 9 (at 5 minutes). She received intravenous furosemide (targeting a central venous pressure of <10 mm Hg) and supplemental oxygen and was observed in the ICU for 7 days postoperatively. At most recent follow-up 7 months post partum, the patient had World Health Organization functional class I symptoms. Her 6-minute walk distance, echocardiographic findings, BNP level, and hemodynamic variables have improved since delivery.

COMMENTARY

As many as 70% of women have dyspnea during normal pregnancy.[2] Although the mechanism is incompletely understood, contributing factors include increased blood volume and cardiac output (which peak between 24 to 32 weeks of gestation at 130 to 150% of the prepregnancy baseline value[3]), elevation of the diaphragm, decreased functional residual capacity, and progesterone-mediated increase in respiratory drive and minute ventilation.[2] Nevertheless, dyspnea in pregnancy may signal new or previously undiagnosed cardiovascular or pulmonary disease, and the presence of associated symptoms or an underlying diagnosis that confers a predisposition to these conditions, such as our patient's history of undifferentiated connective tissue disease, should prompt evaluation beyond typical dyspnea of pregnancy.

In a substantial percentage (33 to 76%) of women with pulmonary hypertension in pregnancy, the condition is newly diagnosed during pregnancy or post partum, in part because women with known pulmonary arterial hypertension are typically counseled to avoid pregnancy.[4-10] Delay in diagnosis, and presumably in the initiation of therapy, has been independently associated with a higher risk of death.[10] Therefore, recognition of pathologic dyspnea and consideration of pulmonary vascular disease in pregnancy are paramount.

Diagnosing pulmonary arterial hypertension in pregnancy is challenging because signs and symptoms overlap with those of normal pregnancy. Typically, patients with pulmonary arterial hypertension present with progressive fatigue and exertional dyspnea[11] and may also have weight gain (from edema), anorexia, or abdominal pain and swelling. As the disease advances — or, in pregnancy, as gestational age advances — exertional chest pain, presyncope, and syncope may develop, indicating right ventricular ischemia or failure. These manifestations should always prompt further investigation. During pregnancy, decompensation most frequently occurs between 20 and 24 weeks of gestation (when blood volume and cardiac output are reaching their peak), in the third trimester, and post partum.[12]

Physical examination may reveal increased intensity of the pulmonic component of the second heart sound or signs of right ventricular failure such as increased jugular venous pressure with an initially prominent *a* wave, subsequent *v* wave, parasternal heave or subxiphoid thrust, widely split second heart sound, tricuspid regurgitation or pulmonary systolic ejection murmurs, hepatomegaly, peripheral edema, or ascites. A radiograph of the chest may show central pulmonary arterial enlargement, diminished retrosternal clear space, or cardiomegaly. Electrocardiogram may show signs of right ventricular hypertrophy or strain.

Echocardiographic findings commonly suggest pulmonary hypertension, but the diagnostic standard is right heart catheterization. The traditional diagnostic criterion has been a mean pulmonary arterial pressure of at least 25 mm Hg while the patient is supine and at rest, although 20 mm Hg was recently proposed as a new diagnostic threshold.[1] The diagnosis of pulmonary arterial hypertension is classified clinically (i.e., idiopathic or associated with a systemic condition, such as connective tissue disease) and additionally requires normal left heart filling pressures (pulmonary-

capillary wedge pressure, <15 mm Hg) and a pulmonary vascular resistance of at least 3 Wood units.[1]

Although the reported pregnancy-associated mortality among women with pulmonary hypertension has decreased with the availability of targeted therapies and specialized pulmonary hypertension centers, morbidity and mortality remain high. Mortality of 17 to 33% was described in case series between 1997 and 2007,[4] and a series of 49 pregnant women with pulmonary hypertension of various subtypes showed a mortality of 16%, deterioration in 80%, and use of advanced therapies (inotropic support, pulmonary vasodilators, or ECMO) in more than 50%.[13] Given the high risk, multiple professional societies recommend avoidance of pregnancy or consideration of pregnancy termination in women with pulmonary hypertension.[5,12]

When pregnancy nonetheless occurs in women with known pulmonary hypertension, or pulmonary hypertension is newly diagnosed in pregnancy, therapy is guided by observational studies and extrapolation from nonpregnant populations. Conventional therapies include supplemental oxygen to maintain oxygen saturations above 95% during pregnancy, diuretics to maintain euvolemia, and anticoagulation in certain patients with pulmonary arterial hypertension. Patients who were using anticoagulation before pregnancy should be switched to low-molecular-weight or unfractionated heparin (because warfarin is a known teratogen and new oral anticoagulants are pregnancy category C, with insufficient data on use in pulmonary arterial hypertension). For patients who were not previously using anticoagulation, prophylactic heparin is recommended in the peripartum period.[12] Targeted therapies that are approved for WSPH Group 1 pulmonary arterial hypertension include prostacyclin analogues, a prostacyclin-receptor agonist, phosphodiesterase-5 inhibitors, endothelin-receptor antagonists, and a soluble guanylate cyclase stimulator. Prostacyclin analogues, which have been shown to improve hemodynamic variables, functional class, exercise capacity, and (in the case of epoprostenol) survival in nonpregnant patients, are listed as pregnancy category B (epoprostenol and treprostinil) or C (iloprost).[12] The Pulmonary Vascular Research Institute recommends continuing prostacyclin analogues started before pregnancy and maintaining a low threshold to initiate them if decompensation occurs during pregnancy.[6,7,12] The phosphodiesterase-5 inhibitors sildenafil and tadalafil have improved outcomes in randomized trials involving nonpregnant patients with WSPH Group 1 pulmonary arterial hypertension[8] and are listed as pregnancy category B. Large case series have described positive outcomes with the use of sildenafil in pregnancy.[6,12,13] Although there are few reports of tadalafil use for pulmonary arterial hypertension in pregnancy, it has been safely used in pregnancy for other indications.[14] Endothelin-receptor antagonists and the soluble guanylate cyclase stimulator riociguat are avoided in pregnancy owing to teratogenicity.[12] The oral prostacyclin-receptor agonist selexipag has not been evaluated in adequate or controlled studies in pregnancy. Some patients with vasoreactivity who have sustained hemodynamic improvement with calcium-channel blockers outside pregnancy have been reported to have a durable response to ongoing treatment with calcium-channel blockers in pregnancy.[9]

The preferred timing and mode of delivery in women with pulmonary arterial hypertension are uncertain and should be individualized. Maternal risks of continuing pregnancy should be weighed against appropriate therapy for pulmonary arterial hypertension, as well as neonatal risks of preterm delivery. In this patient, delivery was delayed until 33 weeks of gestation to allow initiation of targeted therapies with the goal of improving hemodynamic variables and reducing the risk of maternal death during delivery. In women whose condition is stable, planned delivery at approximately 34 to 36 weeks of gestation is recommended, with reassessment and earlier delivery for evidence of symptomatic decline.[12] Although cesarean section poses greater risks of blood loss and infection, it minimizes pain, Valsalva maneuver, and vasovagal response during vaginal delivery, which may result in sympathetic surge and decreased cardiac preload.[12] Assisted vaginal delivery with epidural anesthesia may also minimize these effects. Planned cesarean section also reduces the risk of emergency cesarean delivery, which has been associated with increased mortality among women with pulmonary arterial hypertension.[9,13] General anesthesia poses particular risks among patients

with pulmonary arterial hypertension owing to hemodynamic changes associated with induction, anesthetic-mediated decreased cardiac contractility, and positive-pressure ventilation.[4,12]

Multiple studies have identified delivery and the immediate postpartum period (up to 2 months) as posing the highest risk of cardiovascular collapse and death among pregnant women with pulmonary hypertension.[4,6,7,9,10,12,13] Independent risk factors for death include severe hemodynamic compromise, right heart failure, WSPH Group 1 pulmonary arterial hypertension, and diagnosis during pregnancy or post partum.[5,10,13] Most deaths occur within the first month after delivery, with heart failure, sudden death due to arrhythmia or pulseless electrical activity arrest, and thromboembolism as the main causes of death.[4,10] Intravascular volume shifts, hypoxemia, acidosis, thrombotic complications, and decrease in pregnancy hormones in the peripartum period may negatively affect pulmonary vascular tone and right ventricular function.[12] Therefore, monitoring with continuous electrocardiography, pulse oximetry, central venous pressure, and intraarterial blood pressure is recommended during labor.[12] There is no consensus regarding the use of pulmonary arterial catheters during delivery.[12] ECMO is now more widely available as a bridge through the peripartum period, but data supporting this indication are limited.

This case highlights the complexities of diagnosis and management of pulmonary vascular disease during pregnancy. The favorable outcome in this patient, despite multiple high-risk features, emphasizes the importance of expedient diagnosis and treatment, availability of (or transfer to) an appropriate level of specialized care, and multidisciplinary collaboration to improve maternal and fetal outcomes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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