A 20-year-old Gravida 1 Para 0 (G1P0) woman 38 weeks pregnant was admitted for delivery. She had no known comorbidities and was taking no medications. The pregnancy was uncomplicated. Laboratory results revealed a hemoglobin level of 15.0 g/dL (normal range, 11.6-15.0 g/dL), a hematocrit level of 45.0% (35.5%-44.9%), leukocytosis with a white blood cell count of 12.2 × 10^9/L (3.4-10.6) × 10^9/L, and erythrocytosis with a red blood cell count of 5.51 × 10^12/L (3.92-5.13) × 10^12/L. She had an uncomplicated spontaneous vaginal birth with the use of local anesthesia as well as an estimated blood loss of 75 mL.

Four hours after giving birth, she desaturated to 85%. Her heart rate was 113 to 120 beats/min, and she was normotensive. The respiratory rate was 25 breaths/min, and her chest was clear to auscultation bilaterally. She had a 4/6 holosystolic murmur at the left sternal border with a palpable thrill, but no cyanosis or clubbing. She did not have any neurologic changes, skin findings, or lower extremity swelling. The uterus was firm on palpation. A second-degree vaginal tear that had already been sutured several hours before was intact.

Computed tomography (CT) chest angiography ruled out pulmonary embolism but revealed marked dilation of the pulmonary trunk and right pulmonary artery (unable to rule out amniotic fluid embolism). Transthoracic echocardiography (TTE) revealed a sub-pulmonary ventricular septal defect measuring 1.2 cm. She required around 6 L nasal cannula to maintain oxygen saturation in the low 90s.

1. Which one of the following is the most likely cause of this patient’s hypoxemia?
   a. Group I pulmonary arterial hypertension (PAH)/Eisenmenger syndrome (ES)
   b. Amniotic fluid embolism
   c. Hemorrhage
   d. Obstetric related hypertensive disease
   e. Anesthetic complications

Eisenmenger syndrome is elevated pulmonary vascular resistance (PVR) driving right to left intracardiac shunting leading to systemic arterial desaturation. Patients with ES most often have group I PAH—pulmonary hypertension as a result of pulmonary arterial disease itself. The diagnostic criterion is a mean pulmonary artery pressure of 25 mm Hg or greater at rest. Communication between systemic and pulmonary systems result in increased blood flow through the pulmonary vasculature. The increase in pulmonary arterial pressure results in increased right ventricular pressure. Flow from the systemic to the pulmonary system reverses as pulmonary resistance rises above systemic resistance, resulting in cyanosis from shunt reversal. This patient had a large ventricular septal defect on TTE, suggesting ES as the most likely cause of her hypoxemia.

Amniotic fluid embolism is a rare cause of acute hypoxemia in a pregnant patient. There are proposed criteria used for research reporting of amniotic fluid embolism, though it can have a clinical application with a sensitivity of 79.4% and a specificity of 100%. Criteria include sudden cardiopulmonary arrest or both hypotension and respiratory compromise with an oxygen saturation of less than 90%, documentation of overt disseminated intravascular coagulation, clinical onset during labor or within 30 minutes of delivery, and no fever (>38°C) during labor. This patient was hemodynamically stable without signs of disseminated intravascular coagulation.
Two common causes of delivery-related intensive cardiac unit (ICU) admissions are obstetric related hypertensive disease (38%) and hemorrhage (33.2%). Respiratory failure, liver failure, and coagulopathies are the most common end-organ injuries in patients in the obstetric ICU. These diagnoses need to be considered in a decompensating postpartum patient, though in this case the patient was hemodynamically stable.

Anesthetic complications account for 0.4% of obstetric ICU admissions. This patient was also given only local anesthesia, making an anesthetic complication much less likely. Other common causes of postpartum decompensation include sepsis, genitourinary tract infections, cerebrovascular disease, pulmonary embolism, and aspiration.

The patient underwent electrocardiography (ECG) before TTE. Other findings of echocardiography included increased right ventricular wall thickness, an estimated right ventricular systolic pressure of 98 mm Hg, an estimated right atrial pressure of 10 mm Hg, and a calculated left ventricular ejection fraction of 56%; no regional wall motion abnormalities and normal left ventricular wall thickness; mild to moderate tricuspid valve regurgitation; and moderate pulmonary valve regurgitation.

2. Given the additional findings of echocardiography, which one of the following would be most likely seen on the ECG?
   a. Increased amplitude of the “P” wave in leads II and III
   b. Increased “P”-wave duration in leads II and III
   c. Abnormally increased P-wave amplitude and duration
   d. Left axis deviation
   e. Left bundle branch block

The echocardiographic findings describe mild to moderate tricuspid valve regurgitation, which can have evidence of right atrial abnormality on the ECG. This is typically seen with an increased amplitude of the P wave defined as over 2.5 mm, most notably in leads II and III. If a right atrial abnormality is present, the signal from the right atrial component is enhanced. The tall upright P wave is the combination of the enhanced right atrial signal and the simultaneous left atrial component. Patients with ES and resultant group I PAH can have tricuspid regurgitation.

Left atrial abnormalities are evidenced on the ECG with an increased P-wave duration (>120 ms). A left atrial abnormality results from left atrial activation beginning and ending later than the right atria. Normally, right and left atrial peaks are nearly simultaneous and are represented as a single peak. When left atrial abnormalities are present, the delay in left atrial activation may cause a double-peaked or notched P wave.

An increase in both the amplitude and the duration of the P wave can suggest biventricular enlargement. The additional echocardiographic findings indicate tricuspid regurgitation, but do not mention left atrial abnormalities.

Left axis deviation can be associated with left ventricular hypertrophy (LVH). Many different criteria exist to diagnose LVH, the most common being the Solokow-Lyons criteria (sum of the S wave in V1 and the R wave in V5 or V6 >35 mm). Generally, the sensitivity for various criteria for LVH is low (<50%) but specificity ranges from 85% to 90%. The findings of echocardiography indicate right ventricular hypertrophy (RVH). This would be evidenced by right axis deviation rather than left axis deviation.

Findings indicative of RVH on the ECG are incomplete right bundle branch block as well as tall R waves in leads V1 and V2. Left bundle branch block can be an anatomic variant or, when pathologic, may be suggestive of LVH in the right context. This patient has RVH on the echocardiogram and a normal left ventricular wall thickness.

The patient was transferred to the cardiac ICU from labor and delivery and still required oxygen for appropriate saturation. Her pressures remained stable.

3. Which one of the following is the best next step in evaluating this patient’s pulmonary hypertension?
a. Ventilation-perfusion (V/Q) scan
b. Pulmonary function testing
c. Right and left cardiac catheterization
d. Lung biopsy
e. Six-minute walk test

A V/Q scan is helpful when evaluating for group IV pulmonary hypertension—chronic thromboembolic pulmonary hypertension. A V/Q scan is the study of choice as this has a sensitivity of 96% and a specificity of 90% to 95%. Computed tomography of the pulmonary arteries has a sensitivity of 51% and a specificity of 99%. A negative CT result cannot rule out chronic thromboembolic pulmonary hypertension. In this case, she already has an identifiable cause for her PAH.

Pulmonary function testing can be helpful in clarifying the etiology of pulmonary hypertension, especially in World Health Organization group III pulmonary hypertension. Patients with PAH can have normal lung diffusion capacity for carbon monoxide, although most are decreased. If, for example, chronic obstructive pulmonary disease causes hypoxia and resultant pulmonary hypertension, the diagnosis is made with irreversible airflow obstruction with increased residual volumes and reduced diffusion capacity for carbon monoxide.

Right and left heart catheterization is the best next test for this patient. Cardiac catheterization establishes the diagnosis of group I PAH and assesses the degree of PAH. Patients also undergo nitric oxide vasodilator testing during catheterization to evaluate for a response to potential therapy. This patient’s PVR index (PVRi) was severely elevated at 34.5 WU·m⁻² (WU stands for Wood units), and PVR was 12.5 WU. The main pulmonary artery in this patient had a pressure of 97/43 mm Hg at baseline with a mean pulmonary arterial pressure of 67 mm Hg. With 80 ppm nitric oxide, the main pulmonary artery had a pressure of 93/37 mm Hg, the mean pulmonary arterial pressure was 60 mm Hg, and the fraction of inspired oxygen was 92%. There was a considerable change in shunt with the addition of nitric oxide.

The Qp/Qs ratio quantifies the net shunt. A normal Qp/Qs ratio is 1:1, indicating no shunt or that the flow is even. A Qp/Qs ratio greater than 1 indicates that flow is greater in the pulmonary system, indicating a left to right shunt. If the Qp/Qs ratio is less than 1, this suggests a right to left shunt. In this patient, the Qp/Qs ratio was 0.41 at baseline and 2.3 after 80 ppm nitric oxide and 92% fraction of inspired oxygen, indicating therapy would be beneficial.

Lung biopsy is not routinely used to assess pulmonary hypertension. This procedure, either open or thoracoscopic, carries a risk of morbidity and mortality and is unlikely to change treatment or diagnosis.

A 6-minute walk test is a submaximal exercise test that is widely used, easy to perform, inexpensive, and familiar to patients. One function of this test is assessing response to therapy once it has been initiated. This may be useful for this patient in the outpatient setting, but cardiac catheterization is necessary first to establish the diagnosis.

She remained hemodynamically stable and was transferred to the floor with systolic pressures in the 90s and mean arterial pressures in the 60s.

4. Which one of the following treatments are most likely to benefit the patient? (Mean corpuscular volume [MCV] at the time of discharge is 83.8 fl [normal range, 81.6-98.3 fl].)
   a. Diltiazem
   b. Shunt closure
   c. Bosentan and sildenafil
   d. Apixaban
   e. Iron supplementation

For patients with congenital heart disease and PAH, therapy is mostly based on expert opinion, as evidence-based studies are few. In patients with group I PAH who do not have ES, diltiazem is used if a response is seen with vasodilator testing. There are no clear data to support calcium channel blocker use in patients with ES. There is concern that the negative inotropic effects of calcium channel blockers and
systemic vasodilation can predispose the patient to serious adverse effects. Empirical use of calcium channel blockers should be avoided.

Shunt closure is considered correctable on the basis of PVR or PVRi. PVR less than 2.3 WU or PVRi less than 4 WU·m$^{-2}$ is considered correctable. PVR greater than 4.6 WU or PVRi greater than 8 is not considered correctable. PVR between 2.3 and 4.6 WU or PVRi between 4 and 8 WU·m$^{-2}$ is decided on a case-by-case basis. This patient's baseline PVRi was 34.6 WU·m$^{-2}$.

A combination of bosentan and sildenafil can be used if symptomatic improvement does not occur with either medication alone. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 was a multicenter, randomized, double-blinded, placebo controlled study that reported bosentan (a dual endothelin receptor antagonist) improved exercise capacity and hemodynamics in patients with ES. In a retrospective study, sildenafil (a phosphodiesterase-5 inhibitor) was found to be independently associated with survival in a multivariate analysis. Note that breastfeeding while taking these medications is not well studied. This patient was initiated on sildenafil and ambrisentan in the inpatient setting and gradually up-titrated with close monitoring.

Apixaban and anticoagulation in patients with ES remain controversial. Anticoagulation can be considered if the patient has pulmonary artery thrombosis, signs of heart failure, and absent or minimal hemoptysis. The Registry to Evaluate Early and Long-term PAH Disease Management prospectively collected data from patients with newly diagnosed group I PAH to develop and validate a predictive algorithm for 1-year survival. Once the predictive power of this calculator has been validated, it could guide when to implement anticoagulation.

Adults with cyanotic congenital heart disease can develop erythrocytosis, iron deficiency, and bleeding diathesis because of chronic hypoxemia. Iron-depleted red cells (microspherocytes with an MCV of <82 fl) have decreased oxygen carrying capacity and increased risk of deformity and intravascular sludging. The risk of a cerebrovascular event is considerably increased with microcytosis in these patients, even with a normal hemoglobin level. Thus, iron replacement is recommended in patients with MCV less than 82 fl. This patient had an MCV of 83.8 fl at discharge, so iron supplementation was not indicated.

The patient was stable for discharge on 2 L nasal cannula, and appropriate follow-up was arranged.

5. Which one of the following is most likely included in appropriate counseling and outpatient management for this patient?
   a. Prescribing indefinite daily antibiotic prophylaxis
   b. Combination birth control pill
   c. Mirena intrauterine device (IUD)
   d. Therapeutic phlebotomy
   e. Avoidance of vaccinations

Patients with adult congenital heart disease have an increased risk of developing infective endocarditis. The most common pathogens are *Streptococcus viridans*, *Staphylococcus* species, and *Enterococcus* species. Antibiotic prophylaxis against infective endocarditis is not recommended for non-dental procedures in the absence of infection. It is reasonable before dental procedures in high-risk patients including those with uncorrected cyanotic heart disease.

Pregnancy in ES is very high risk and is associated with an increased rate of maternal death (up to 50%) as well as an increased risk of spontaneous abortion (up to 40%). Appropriate birth control is highly recommended in women of childbearing age in this population.

Combination hormone pills are not recommended for patients with peripartum cardiomyopathy as combination oral contraceptives may cause fluid retention and worsen heart failure. Additionally, there is concern for prothrombotic effects with combined oral contraceptives.

Mirena IUD is an effective form of birth control. There is no direct evidence
regarding the safety of IUDs in women with peripartum cardiomyopathy. Limited indirect evidence from noncomparative studies did not report increased arrhythmias or infective endocarditis in women with cardiac disease using IUDs. 

Therapeutic phlebotomy has a limited role. Indications for therapeutic phlebotomy include a hemoglobin level greater than 20 g/dL, and the hematocrit level is greater than 65% with associated symptoms of hyperviscosity (eg, headaches and vision changes) without evidence of dehydration. This patient had a hemoglobin level of 15 g/dL, a hematocrit level of 45%, and no symptoms of hyperviscosity.

Patients with congenital heart disease and PAH are susceptible to pneumonia, which is poorly tolerated in this population. Vaccinations to prevent pneumococcal pneumonia and influenza are strongly recommended. This patient received a medroxyprogesterone acetate injection outpatient for birth control, appropriate vaccinations, and follow-ups regularly.

DISCUSSION

Eisenmenger syndrome is elevated PVR driving right to left intracardiac shunting leading to systemic arterial desaturation and is most often associated with group I PAH. Other etiologies of decompensation in postpartum patients include obstetric related hypertensive disease, hemorrhage, sepsis, genitourinary tract infections, cerebrovascular disease, pulmonary embolism, and aspiration.

Right atrial abnormalities from tricuspid regurgitation can be seen on the ECG with an increase in the amplitude of the P wave. This can be seen in ES and group I PAH. Right ventricular hypertrophy is also seen and is evidenced by right bundle branch block and tall R waves in leads V1 and V2.

Cardiac catheterization confirms the diagnosis of group I PAH and assesses the degree of PAH. A 6-minute walk test is a submaximal exercise test and can assess response to therapy once it has been initiated. A combination of bosentan and a phosphodiesterase-5 inhibitor can be used to medically treat patients with ES if symptomatic improvement does not occur with either medication alone.

Appropriate birth control is highly recommended in women of childbearing age. Combination hormone pills are not recommended for patients with peripartum cardiomyopathy, as combination oral contraceptives may cause fluid retention and worsen heart failure. Levonorgestrel-releasing IUDs are effective forms of birth control and are a reasonable option.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Correspondence: Address to Nandan S. Anavekar, MB, BCh, Department of Cardiovascular Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (anavekar.nandan@mayo.edu).

ORCID

Roberto Herrera: https://orcid.org/0000-0002-3933-3764; Ikram Haq: https://orcid.org/0000-0003-3574-5814

REFERENCES


