A 26-year-old woman presented to the emergency department with shortness of breath and chest pain worsened with inspiration. She had delivered a newborn by cesarean section 3 days before presentation, and symptoms began early in the postpartum period. Other medical history was notable only for nicotine dependence, and the patient was taking no prescribed medications aside from a prenatal multivitamin.

Her pregnancy course was uncomplicated up to her most recent prenatal appointment, at which mild hypertension and breech presentation of the fetus were noted. Vital signs otherwise were within normal limits at that evaluation, with physical examination identifying a gravid uterus with breech presentation and trace bilateral lower extremity edema. Attempts to manipulate the fetus into proper orientation were unsuccessful. The decision was made to pursue cesarean section for obstetric purposes, and the procedure was performed without complication.

In the immediate postpartum period, the patient noted worsening fatigue and difficulty with speech, including the inability to complete sentences. She reported shortness of breath, particularly with ambulation, and orthopnea. She had no headaches, fever, vision changes, palpitations, abdominal discomfort, or changes in bowel/bladder habits. The dyspnea worsened over the postpartum period 3 days before presentation.

At presentation, vital signs were notable for tachycardia (heart rate to 120 beats/min) and hypertension (blood pressure, 160/118 mm Hg). Peripheral oxygen saturations were 96% while she breathed room air, with respirations at 16 per minute. Auscultation of the heart elicited tachycardia without murmur and an audible \( S_3 \) most prominent in the left lower sternal border; auscultation of the posterior lung fields revealed faint bibasilar crackles. Physical examination of the lower extremities identified symmetric trace pitting edema.

1. In view of the patient’s symptoms and presentation, which one of the following is the most likely underlying diagnosis?
   a. Pulmonary embolus
   b. Acute heart failure with or without associated peripartum cardiomyopathy (PPCM)
   c. Community-acquired pneumonia
   d. Panic attack
   e. Asthma exacerbation

All of these conditions are potential etiologies for shortness of breath in the peripartum and postpartum period. Pregnancy is associated with hypercoagulability, and thus pulmonary embolus should be considered.\(^1\) With the patient breathing room air at a normal rate, this diagnosis would seem less likely given more prominent presenting symptoms and signs consistent with volume overload. With a history of dyspnea on exertion as well as orthopnea and physical examination findings consistent with left-sided heart failure, the most likely underlying diagnosis is acute heart failure. However, without further testing, the diagnosis of PPCM cannot be made. Because the pregnant and nonpregnant population have similar rates of community-acquired pneumonia,\(^2\) an infectious etiology is a potential cause of shortness of breath in the antepartum period, but in the absence of infectious systemic symptoms, this diagnosis is less likely. Panic attack is a common cause of shortness of breath and can occur at any time in pregnancy or in the...
postpartum period. It is a diagnosis of exclusion, however, and should not be considered in the early evaluative process. Finally, asthma exacerbation is unlikely because the patient has no history of asthma. Moreover, historical research with pregnant patients with asthma has found a trend toward decreased exacerbations of asthma during weeks 37 to 40 of gestation. 

Further work-up to determine the etiology of the patient’s shortness of breath revealed the following (reference ranges provided parenthetically): mild anemia with a hemoglobin level of 11.3 g/dL (11.6 to 15.0 g/dL) and mild neutrophil-predominant leukocytosis with a white blood cell count of 13.7 × 10⁹/L (3.4 to 9.6 × 10⁹/L). There were elevations in inflammatory markers including erythrocyte sedimentation rate (78 mm/h [0 to 29 mm/h]) and C-reactive protein (76.3 mg/L (<8 mg/L). The patient had mild transaminitis with aspartate aminotransferase slightly elevated at 46 U/L (8 to 43 U/L) and alkaline phosphatase at 132 U/L (35 to 104 U/L). Thyrotropin and magnesium levels were within normal limits. Creatinine was at her baseline level of 1.0 mg/dL.

On fourth-generation testing, cardiac troponin T was elevated at 0.03 ng/mL (<0.01 ng/mL) at 0, 3, and 6 hours. Cholesterol testing revealed suboptimal total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was elevated at 29,200 pg/mL (10 to 140 pg/mL). Random urinalysis revealed severe proteinuria with an estimated 24-hour protein excretion of 1747 mg. Electrocardiography illustrated sinus tachycardia, a rightward axis, and low anterior forces but otherwise normal findings.

Transesophageal echocardiography is not an ideal first test in patients presenting with heart failure because of its semi-invasive nature, especially since basic functional assessment can be achieved with surface echocardiography. If major clot burden affecting the bilateral lower extremities is suspected, lower extremity ultrasonography would be reasonable. In this patient with volume overload causing bilateral lower extremity edema based on physical signs and elevated NT-proBNP level, such testing has less utility. Chest radiography for determination of consolidation or for volume assessment would contribute little to the work-up in the absence of infectious history as well as with the abundant signs and serologic evidence consistent with volume overload. Transthoracic echocardiography is a straightforward bedside test that provides information on overall heart structure and function. A reduction in ejection fraction (EF) and knowledge of overall heart function regarding regional wall motion helps to narrow the etiology of the patient’s heart failure and provides prognostic stratification when the etiology of the heart failure can be determined. Transvaginal ultrasonography would likely have low yield in this situation because the patient has already delivered and the likelihood of retained placental products causing dyspnea and orthopnea without more systemic signs or symptoms is low.

Echocardiography revealed normal left ventricular (LV) chamber size with generalized depressed function and a calculated EF of 34%.

3. Which one of the following is the most important inclusion criterion for the underlying diagnosis?
   a. Evidence of proteinuria
   b. Low EF
   c. Troponinemia
   d. Anemia
   e. Elevated inflammatory markers

The results of the patient’s urinalysis are suggestive of preeclampsia in view of the presentation and historical context. Based on the investigative findings, the underlying
diagnosis is PPCM. Proteinuria, while indicative of preeclampsia, is not necessarily diagnostic of PPCM. Although it has a strong association with PPCM and may represent an etiologic pathway for development of PPCM, preeclampsia does not always have to be present for diagnostic confirmation. Low EF is a pivotal criterion in the diagnosis of PPCM and must be present. Troponinemia is not part of the diagnostic criteria for PPCM but may be present in cases of myocarditis as an etiology for the disease process. Anemia is not necessarily associated with PPCM, and although elevated inflammatory markers may be present in PPCM, neither of these factors are specific to PPCM and can be elevated in many different pathways of heart failure.

The diagnosis of PPCM is based on the following criteria: signs/symptoms of heart failure developing 1 month antepartum to 5 months postpartum, no evidence of preexisting heart disease, EF reduced to below 45%, and no other cause for heart failure can be identified. Most patients with PPCM present in the week after delivery, with a lower proportion presenting before delivery. Thus, this patient’s low EF is the most important inclusion criterion for diagnosis.

Epidemiologically, the incidence of PPCM ranges from 1 in 4000 to 1 in 1000 live births in the United States, and the incidence appears to be increasing. There is considerable heterogeneity in the incidence of PPCM in differing populations globally, with African Americans having 2.9 times the risk of the average white American population and the highest incidence in the populations of South Africa, Haiti, and Nigeria. Potential risk factors for PPCM include African American descent, advanced maternal age, poor socioeconomic status, preeclampsia/eclampsia, and multiparity. Cholesterol has not been found to have an association as a risk factor for PPCM. However, lower total cholesterol levels have been reported to be a prognostic marker for poor outcomes of PPCM in the South African population.

The patient was admitted to the hospital after stabilization in the emergency department. Vital signs after admission included a heart rate of 102 beats/min, blood pressure of 94/68 mm Hg, peripheral oxygen saturation of 95% while the patient breathed room air, and respirations at 18 per minute. The patient was comfortable appearing and had appropriate mentation.

4. Which one of the following is the best first step in management after admission to the hospital?
   a. Aspirin and clopidogrel load
   b. β-Blocker therapy
   c. Dopamine infusion
   d. Magnesium sulfate initiation
   e. Intravenous normal (0.9%) saline infusion

The most appropriate location for admission of the patient is a cardiac-monitored setting or intensive care unit to allow for close observation of clinical status while initiating important disease-modifying medicines. Although aspirin and clopidogrel have extensive evidence for use in acute coronary syndrome or after percutaneous coronary intervention, loading with aspirin and clopidogrel has no benefit in PPCM. β-Blocker therapy is appropriate in long-term management of PPCM and would likely benefit the patient, although in the acute setting, β-blocker therapy could cause further decompensation and should thus be initiated cautiously only when safe to do so. Given the patient’s current vital signs, β-blocker therapy should be withheld. There is limited evidence for dopamine initiation in this setting, as this therapy should be considered in patients with acute heart failure and presentation of shock; at present, the patient still has evidence of end-organ perfusion. The initiation of magnesium in preeclampsia-associated cardiomyopathy is required to ensure that the patient does not decompensate toward eclampsia, making this the most appropriate option. Finally, intravenous fluids have no role in the setting of acute heart failure with signs of volume overload; excessive exposure to intravenous fluids should be avoided.

For further management of severe PPCM in patients with clinical deterioration, typical
supportive heart failure management such as inotropic therapy, intra-aortic balloon pumps, ventricular assist devices, and—in the most severe cases—extracorporeal membrane oxygenation should be considered.4

After clinical stabilization in the cardiac intensive care unit, the patient gradually improved. She was discharged with carvedilol (β-blocker) and enalapril (angiotensin-converting enzyme inhibitor) therapy that were both initiated and titrated carefully on an inpatient basis after initial stabilization.

5. With the patient now stabilized and improving, which one of the following would you counsel her regarding outcomes or recovery of LV function in PPCM?
   a. She should avoid breastfeeding to help with LV function improvement
   b. She should initiate bromocriptine for improvement in LV function
   c. She will require implantable cardioverter-defibrillator placement as prophylaxis for reduced LV dysfunction
   d. She does not require thromboembolic prophylaxis because her thromboembolic risk is low
   e. She has risk of PPCM recurrence with future pregnancies, even with full LV recovery

It has been theorized that inhibition of prolactin either with breastfeeding cessation or initiation of bromocriptine therapy may improve patient outcomes because this hormone has been implicated in the potential pathogenesis of PPCM. Prolactin induces the expression of microRNA 146a in endothelial cells, with antiangiogenic effects impairing effective communication between endothelial cells and cardiomyocytes.4 The ensuing endothelial damage is believed to contribute to PPCM. There is no evidence to fully support breastfeeding cessation in patients with PPCM at this time. Furthermore, avoidance of breastfeeding increases risk of newborn malnourishment, especially for patients in the developing world. Although results of early studies of bromocriptine have been encouraging,9 it is still under investigation and not standard of care in treatment. Because of the increased risk of thromboembolic events with bromocriptine therapy, anticoagulation is generally recommended in patients with PPCM treated with bromocriptine, although data to support this recommendation are generally lacking. It is reassuring that perhaps 70% of patients will have LVEF recovery to more than 50% on optimal medical management over a 6-month period. Adverse events—including death, LV assist device implantation, or persisting cardiomyopathy—do occur in 13% of patients.10

Because of this typical excellent recovery in heart function, only a minority of patients with PPCM require implantable cardioverter-defibrillator placement, which should be considered with failure of LVEF recovery to greater than 30% with medical management at 3 months, although more specific indications have not been established in PPCM. It is furthermore known that lower LVEF (<30%) on primary evaluation does portend worse prognosis in heart function recovery, and thus this information can be used to stratify which patients should undergo ambulatory monitoring. Appropriate cardiac monitoring of patients with PPCM in the proper context should be pursued, with arrhythmia being a feared complication of the disease process.

Thromboembolic risk in the PPCM population is higher than in typical nonischemic cardiomyopathy groups,1 being a complication in upwards of 6% of the PPCM population. Thus, anticoagulation is typically advised in the first 2 months postpartum. Finally, with future pregnancy the probability of PPCM recurrence is high despite recovery of LV function. In those who recover LV function, 27% will have deterioration with future pregnancies. In contrast, patients having incomplete recovery of LV function have a 48% incidence of further deterioration, with up to 16% mortality according to one study.11 No specific recommendations exist regarding counseling patients with PPCM against future pregnancies, but patients should be counseled on the
high recurrence rates regardless of LV function recovery in the postpartum period.

Clinically, the patient continued to do well after discharge. Due to ectopy on monitoring during her hospital course, she was discharged with outpatient heart monitoring and a wearable external defibrillator. Monitoring revealed only rare intermittent accelerated junctional rhythm. Outpatient echocardiography 3 months after hospitalization showed nearly full recovery of LV function with an EF of 52%. Her inflammatory markers had normalized on follow-up testing after 3 months. She was counseled appropriately on both the potential for recurrence with future pregnancies and smoking cessation. Her child is healthy, and the patient was able to return to work.

DISCUSSION
Postpartum cardiomyopathy is a rare but potentially lethal sequela of normal pregnancy and should be considered in any patient presenting with heart failure symptoms in the third trimester of pregnancy up to the first few months in the postpartum period. This diagnosis requires a high index of suspicion with good knowledge of the patient’s history and proper physical examination. The diagnosis of PPCM consists of the following criteria: signs/symptoms of heart failure developing 1 month antepartum to 5 months postpartum, no evidence of preexisting heart disease, EF reduced to less than 45%, and the absence of another recognizable cause for heart failure. Supportive serologic testing such as NT-proBNP may be helpful to initiate pursuit of further imaging such as transthoracic echocardiography to ultimately establish the diagnosis.

Risk factors continue to be identified for this disease process; some identified by the literature include African American descent, advanced maternal age, poor socioeconomic status, preeclampsia/eclampsia, multiparity, and maternal cocaine abuse. Incidence is heterogeneous among populations, and in the United States, African Americans tend to have higher incidence overall compared to whites and Asian Americans. Data from Africa and Asia suggest higher incidence compared to the United States, with an average incidence of 1 in 1000 live births. Due to many factors, much higher incidence has been noted geographically, such as Nigeria with an incidence of 1 in 100 live births. More data are required to fully ascertain the epidemiology around the globe.

Optimization of heart function with the standard of care in pharmacological management of heart failure may help to improve outcomes in these patients. To date, although more disease-specific therapies are being investigated, there is no pharmacological therapy that is unique to treatment of PPCM. Thankfully, with medical optimization most patients with PPCM experience improvement in LV function. The LVEF at presentation is helpful in stratification of recovery, with LV dilatation and more severely abnormal LVEF (<30%) portending a worse chance of LV functional recovery.

It is important to keep in mind the higher thromboembolic risk in the PPCM population because both pregnant patients and patients with cardiomyopathy are at increased risk of thromboembolism. Anticoagulation is typically advised during pregnancy (if the diagnosis is made in the antepartum period) as well as in the first 2 months of the postpartum period. Generally speaking, heparin products are preferred in pregnancy because of concerns about teratogenicity with warfarin and other anticoagulants.

The risk of relapse in future pregnancy for all patients with a history of PPCM remains high, even with adequate recovery of LVEF. Thus, careful counseling is important to ensure that patients with such history are aware of the risk before future pregnancy is considered.

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REFERENCES


CORRECT ANSWERS: 1. b. 2. d. 3. b. 4. d. 5. e