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Case Conference

Pulmonary Hypertension in Pregnancy: A Positive Outcome with a Multidisciplinary Team and Individualized Treatment Plan

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PULMONARY HYPERTENSION (PH) is a challenging disease to treat and is associated with a great degree of morbidity and mortality. When a right ventricle, which is accustomed to operating at low pressure, faces the increased afterload that is conferred with PH, especially in the acute setting, it is prone to failure and ultimately can result in hemodynamic collapse. The normal physiologic changes of pregnancy, particularly increased blood volume, lower systemic vascular resistance and systemic blood pressure, and increased cardiac output, are particularly deleterious in the patient with PH. Here, the authors describe a case of a woman who was diagnosed with severe PH during pregnancy and was safely navigated through a cesarean section and the subsequent postpartum period.

Case Report

A 21-year-old woman, G_1P_0, with no known significant past medical history, presented to a community hospital at gestational age 26 weeks and 5 days, with a chief complaint of blood in her sputum. Further questioning revealed a 2-week history of low-volume hemoptysis. Her family history also was notable for the death of her mother while giving birth to her younger sibling due to heart failure. A limited workup was performed, and the patient eventually was discharged home with the working diagnosis of a Mallory-Weiss tear.

At a gestational age of 28 weeks, she presented to the same community hospital with dyspnea on exertion, persistent coughing, and ongoing hemoptysis. A transthoracic echocardiogram (TTE) was obtained, which was notable for a left ventricular ejection fraction of 55%, right atrial and ventricular enlargement, and moderate-to-severe tricuspid regurgitation (TR). Importantly, McConnell's sign was present, and the estimated pulmonary artery systolic pressure (PASP) was greater than 100 mmHg. Given the increased risk for thrombotic

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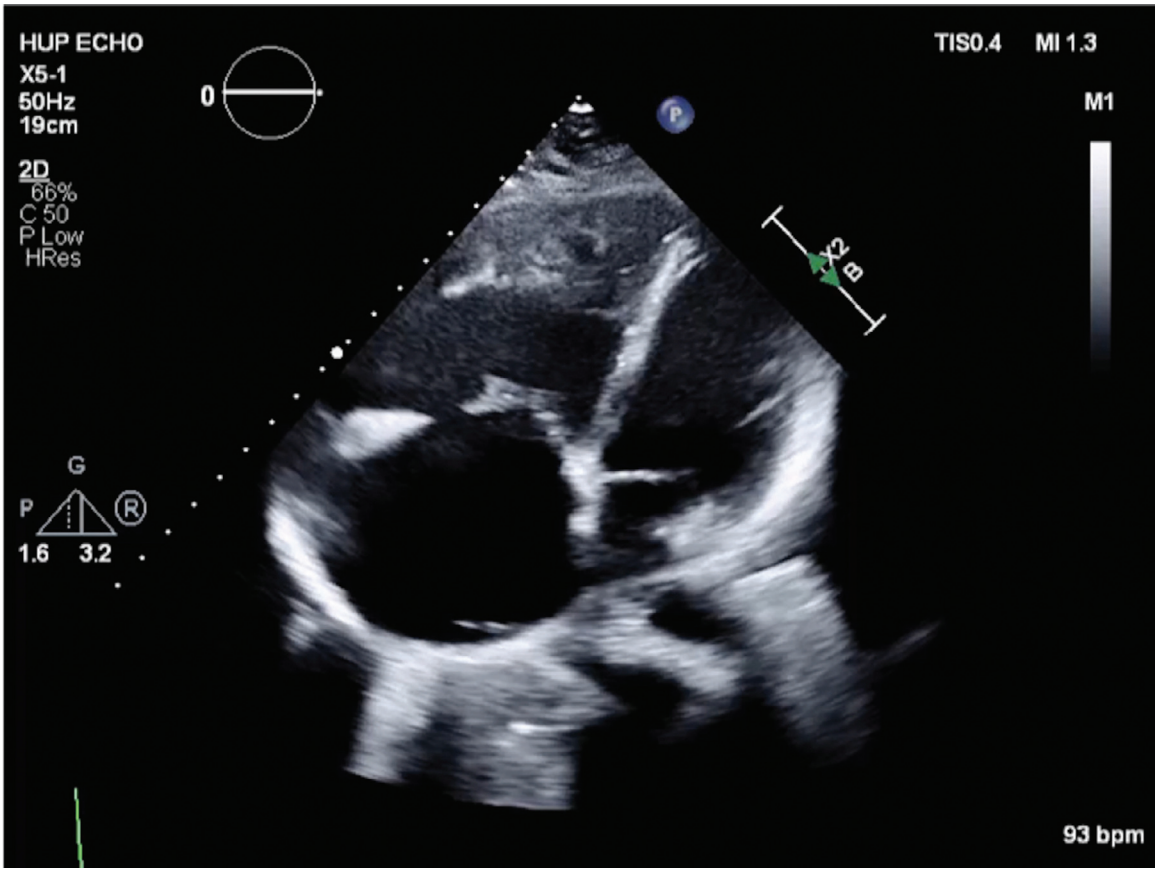

Fig 1. Transthoracic echocardiography apical 4-chamber view showing right ventricular dilation.

complications during pregnancy, a pulmonary embolism was suspected to be the cause of these findings. An unfractionated heparin infusion was started, and a computed tomography scan of the chest was performed. The scan was abnormal, showing multifocal opacities throughout the bilateral lung fields; however, there was no evidence of pulmonary embolism. The patient then was transferred to the authors' tertiary care center for further workup and management.

Upon arrival to the authors' institution, inhaled epoprostenol was initiated at 50 ng/kg/min via a high-flow nasal cannula. Daily diuresis also was commenced. A right-heart catheterization was performed, which showed a right atrial pressure of 15 mmHg, a pulmonary artery pressure (PAP) of 88/41 mmHg (mean 61 mmHg), a pulmonary capillary wedge pressure of 14 mmHg, a cardiac output/index of 8.2/4 L/min, a pulmonary vascular resistance of 5.7 Wood units, and a systemic vascular resistance of 5 Wood units. The inhaled epoprostenol was discontinued, and intravenous treprostinil was initiated at 2 ng/kg/min, with plans to increase the dose by 1 ng/kg/min every 12 hours. The treprostinil eventually would be titrated up to 22 ng/kg/min at the time of delivery, and daily diuresis continued.

A multidisciplinary meeting was held with clinicians from the PH/heart failure cardiology service, cardiac surgery, cardiac anesthesia, maternal-fetal-medicine, and high-risk obstetrics teams. A plan was formulated to deliver the fetus via cesarean section at gestational age 32 weeks and 6 days, utilizing slowly titrated epidural anesthesia and prophylactic femoral arterial and venous cannulation for the prospect of peripartum extracorporeal membrane oxygenation (ECMO). A repeat TTE was performed, which showed a severely dilated right ventricle (Fig. 1 and 2) with mildly decreased function, severe TR, an estimated PASP of 98 mmHg (Fig 3), and a left ventricular ejection fraction of 65%.

On the day of delivery, the patient was brought to the operating room, and a right radial arterial catheter was placed. She then was placed into the seated position for the insertion of a lumbar epidural catheter without sedation. After placement of the epidural, inhaled epoprostenol was initiated at 50 ng/kg/min via a high-flow nasal cannula. The epidural slowly was dosed with 0.5% bupivacaine, which was given in 5- mL aliquots to prevent any abrupt hemodynamically significant changes. She then was placed in a semisupine with a slight reverse Trendelenburg position because she could not tolerate lying flat due to dyspnea. The cardiac surgical team then inserted a femoral arterial catheter and femoral venous sheath in the event that a swift initiation of venoarterial ECMO (VA ECMO) was necessary. A 9-French introducer was placed in the right internal jugular vein to serve as large-bore access and to facilitate central venous pressure monitoring. Two mg of midazolam were given during the placement of the femoral and internal jugular lines for anxiolysis, and 100 μg of fentanyl also were given during the procedure.

An epinephrine infusion was initiated prior to incision to support right ventricular contractility. Phenylephrine and

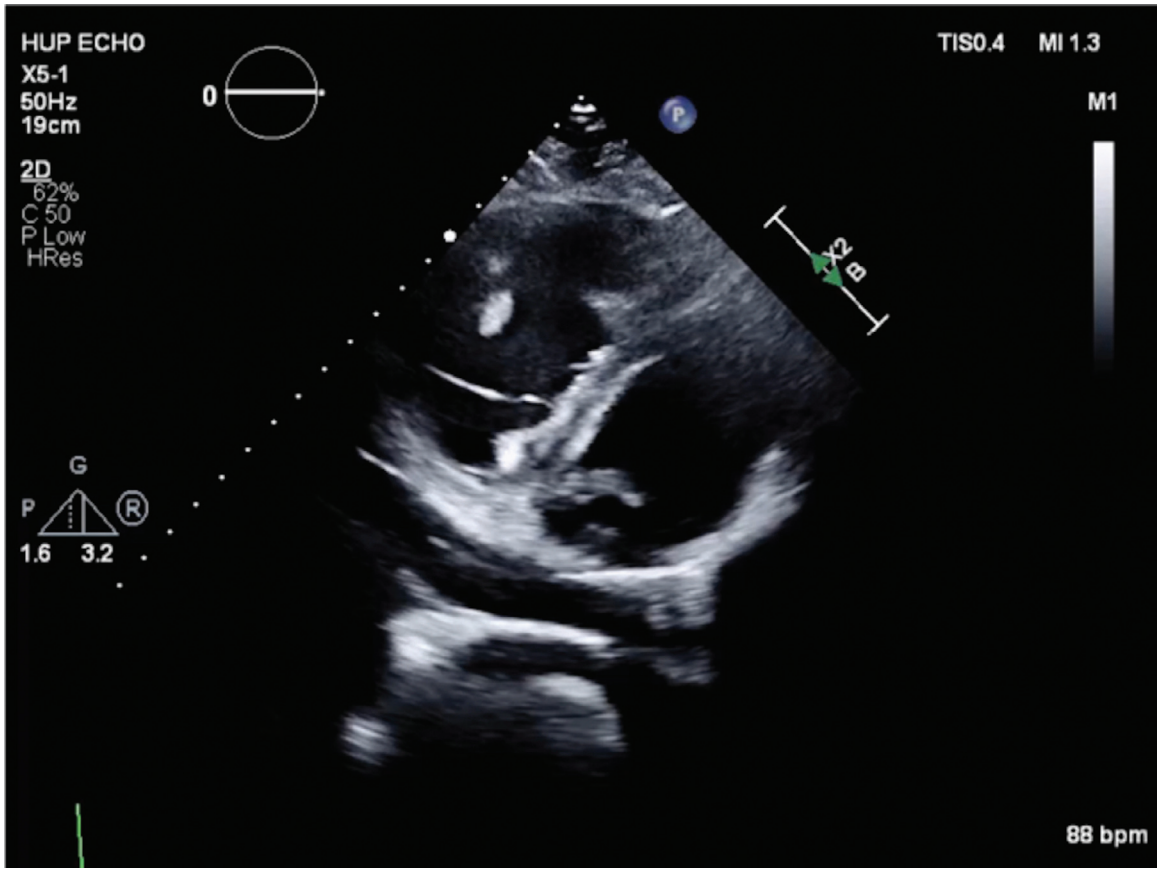

Fig 2. Transthoracic echocardiography parasternal short-axis view showing right ventricular dilation.

vasopressin infusions were used to treat reductions in afterload. Numerous intravenous boluses of these medications also were required throughout the procedure. Overall, the procedure was tolerated well, with an estimated blood loss of 800 mL.

After the procedure, the patient was brought to the intensive care unit for further monitoring, with the femoral arterial and venous lines in place. Inhaled epoprostenol and intravenous treprostinil were continued, with a plan to transition to oral tadalafil. Additionally, intravenous infusions of epinephrine and vasopressin were required. On postoperative day 1, her epidural was removed, and a TTE showed a severely dilated right ventricle with moderately decreased function, moderate TR, and an estimated PASP of 117 mmHg. The TTE on postoperative day 2 was largely unchanged, with an estimated PASP of 125 mmHg. On postoperative day 4, her femoral lines were removed. Vasopressors were weaned completely by postoperative day 6. On postoperative day 15, the right atrium and ventricle still were severely dilated, with moderately decreased right ventricular function, and an estimated PASP of 91 mmHg. Tadalafil, bumetanide, and treprostinil were continued throughout the hospital stay.

Discussion

PH in pregnancy confers high morbidity and mortality. Historically, the incidence of maternal mortality reached as high as 30%-to-56%.[1] More recent studies reported improved outcomes, which may represent improvements in medicine, such as the availability of epoprostenol in 1996; however, this also could represent a publication bias by which the cases with favorable outcomes were being reported. Even if outcomes have improved, morbidity and mortality remain high enough that groups like the Pulmonary Vascular Institute recommend that women with PH avoid pregnancy. In this case conference, the patient was not known to have PH until she was more than halfway through pregnancy with a viable fetus. The management of this patient required input and coordination of care from a multidisciplinary team, which ultimately resulted in a successful outcome.

Historically, PH was defined as a resting mean PAP of ≥25 mmHg.[2] In 2019, however, the sixth World Symposium on Pulmonary Hypertension recommended that the cut-off be lowered to ≥20 mmHg. PH also can be divided into 5 groups based on etiology. Group 1 refers to pulmonary arterial hypertension, which has many possible causes, including idiopathic. Group 2 is PH due to left-heart disease, such as left ventricular failure or valvular heart disease. Groups 3, 4, and 5 represent patients who have PH due to lung disease, pulmonary arterial obstructive processes, such as pulmonary embolism, or unclear mechanisms, respectively.[2] The term “precapillary PH” encompasses all groups except group 2. Postcapillary PH, however, only includes either group 2 or group 5. Interestingly, it is possible for a patient to exhibit signs of both

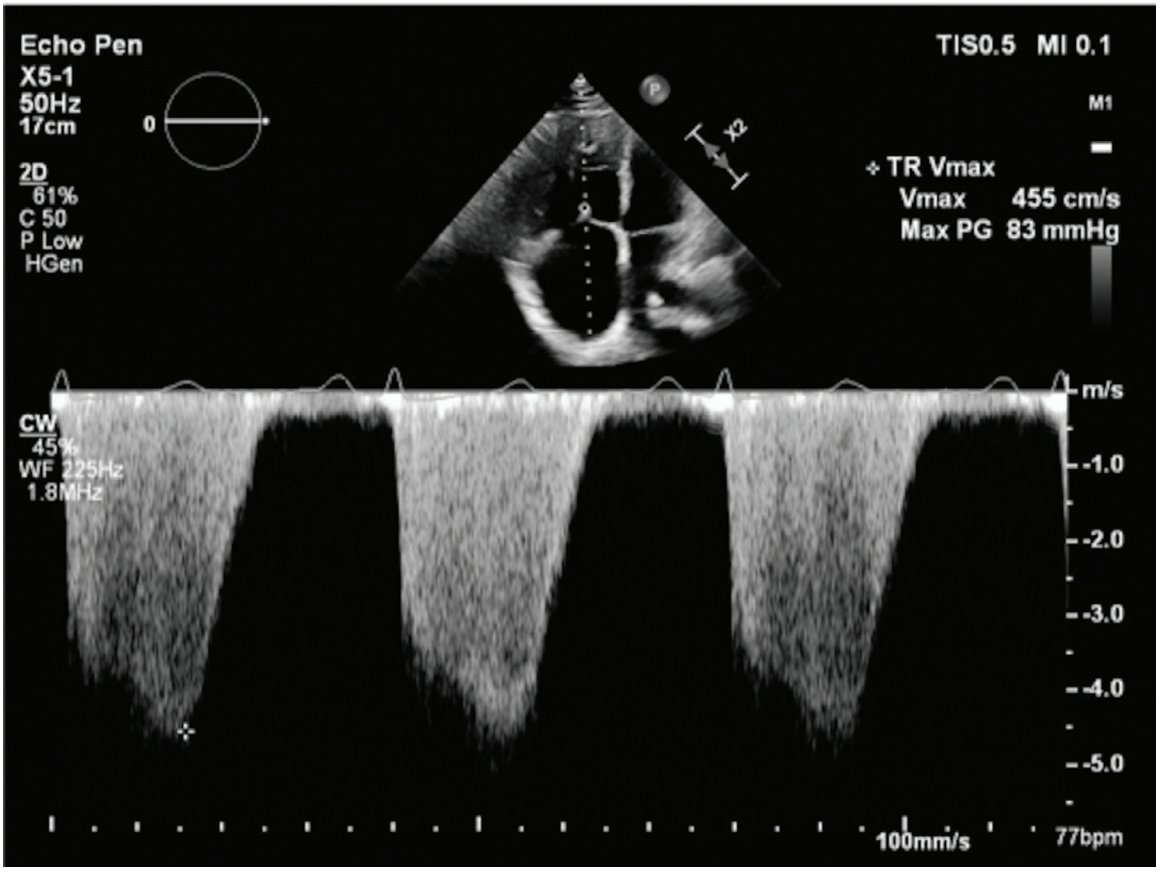

Fig 3. Continuous-wave Doppler tracing obtained from a transthoracic echocardiography apical 4-chamber view showing a peak tricuspid regurgitation pressure gradient of 83 mmHg. The right atrial pressure was estimated to be 15 mmHg, which suggested that the estimated right ventricular systolic pressure was 98 mmHg.

precapillary and postcapillary PH; these patients typically are from either group 2 or group 5.

While echocardiography initially raised suspicion for severe pulmonary hypertension, right-heart catherization is the gold standard for diagnosis.[3] In addition to measuring the pulmonary arterial pressure, the pulmonary capillary wedge pressure should be obtained, and the pulmonary vascular resistance should be calculated. Precapillary pulmonary hypertension typically is characterized by a mean pulmonary arterial pressure $\geq$20 mmHg, a pulmonary capillary wedge pressure $\leq$15 mmHg, and a pulmonary vascular resistance $\geq$3 Wood units. In contrast, patients with postcapillary pulmonary hypertension demonstrate a mean pulmonary arterial pressure $\geq$20 mmHg, a pulmonary capillary wedge pressure $>$15 mmHg, and a pulmonary vascular resistance $<$3 Wood units.[2] If a patient has combined precapillary and postcapillary pulmonary hypertension, however, they may exhibit a mean pulmonary arterial pressure $\geq$20 mmHg, a pulmonary capillary wedge pressure $>$15 mmHg, and a pulmonary vascular resistance $\geq$3 Wood units. The patient in this case exhibited a pulmonary capillary wedge pressure of 14 mmHg and a pulmonary vascular resistance of 5.7 Wood units, consistent with precapillary pulmonary hypertension.

Typically, nonpregnant patients with PH commonly present with fatigue and dyspnea on exertion due to reduced cardiac output and, consequently, decreased oxygen exchange. Because fatigue and exertional dyspnea are common complaints for healthy pregnant women as well, the diagnosis can be delayed in pregnant patients.[4] Pregnancy-related changes eventually can exacerbate symptoms, such as dyspnea on exertion, progressing to dyspnea at rest. In contrast to healthy pregnant women who can accommodate the increased cardiac output with a decreased pulmonary vascular resistance, those with diseased pulmonary vasculature will develop increased pulmonary vascular pressures. Unfortunately, the increased pulmonary vascular resistance in these patients ultimately may prevent the necessary increase in cardiac output for pregnancy. As the disease progresses, right- heart failure may develop due to acute volume and pressure overload. At this stage, patients may begin to complain of right-heart failure symptoms, such as hepatomegaly, swollen ankles, ascites, or chest pain from right-heart ischemia. Heart failure symptoms typically are late-stage signs of disease progression.[5] It was fortunate that the patient in this case sought treatment for her symptoms. Initially, however, pulmonary embolism was thought to be the main pathology.

It was necessary to consider pulmonary embolism in the differential diagnosis because pregnancy induces a prothrombotic state to help prevent significant postpartum hemorrhage. A hypercoagulable state is maintained by increasing clotting

factors V, VII, VIII, IX, XII, fibrinogen, and increased platelet aggregation. Additionally, due to the increased levels of plasminogen activator inhibitor, fibrinolysis also is reduced, ultimately contributing to the prothrombotic state.[6] Simultaneously, due to hormonal influence and the rapidly growing uterus, lower extremity veins increase in diameter and decrease in flow. These expected physiologic changes that accompany pregnancy greatly increase the risk for deep vein thrombosis.[7]

Venous thromboembolism is a feared and major complication during pregnancy and occurs at a frequency of 0.5-to-2.2 per 1000 pregnancies.[8] The increased risk is present during all trimesters of pregnancy, but is highest in the last. Thrombosis risk also extends into the postpartum period for about 3 weeks before it declines.[9] Deep vein thrombosis is more common during pregnancy than pulmonary embolism. Pulmonary embolism risk, however, is higher during the postpartum period and continues to be one of the leading causes of maternal death in pregnancy.[10]

Given this increased risk for thromboembolic complications, an acute pulmonary embolus initially was suspected to be the cause of this patient's symptoms. This diagnosis also was consistent with echocardiogram findings, such as McConnell's sign. Because there was a concern for pulmonary embolism, the patient was immediately anticoagulated. However, the computed tomography scan ruled out a pulmonary embolus. With no active thrombosis or occlusive disease process, PH group 4 was ruled out. The patient did not have any prior history of left ventricular or valvular failure (group 2), and she also did not have any chronic respiratory diseases (group 3). Overall, the preponderance of information, including the right-heart cardiac catheterization data, suggested that group 1 PH was most likely.

Once the diagnosis of PH was made, it became imperative to closely monitor the patient's hemodynamic status as pregnancy progressed. While morbidity and mortality related to PH in pregnancy have improved according to recent literature, thet nevertheless remain a concern. In the registry of pregnancy and cardiac disease, 151 patients with PH were identified between 2008 and 2014.[11] Of these patients, 112 (74.2%) had group-2 PH, whereas 39 (25.8%) had group 1. The diagnosis of PH was known in 88 patients prior to pregnancy. Right ventricular systolic pressures were 30-to-50 mmHg in 90 patients, 50-to-70 mmHg in 43 patients, 70-to-90 mmHg in 8 patients, and >90 mmHg in 10 patients. While no deaths occurred during pregnancy, there were 7 known deaths in the 6 months after delivery. Three of the 7 deaths were in patients with idiopathic pulmonary arterial hypertension. Fetal complications included premature delivery in 21.7% of patients, low birth weight in 19.0%, and fetal mortality in 2%. While this study had limitations, such as unknown timing of PH in 25% of patients, the maternal mortality was considerably less than previously reported.[11]

In a smaller series, Meng et al. analyzed 49 pregnant women with PH between 2001 and 2015.[12] Severe PH was present in 27 patients, whereas mild PH was present in the other 22. Twenty-six women required advanced therapy (vasoactive medications, extracorporeal membrane oxygenation), which was more common in the group with severe PH. The documentation of delivery was present in 41 patients, with 54% of patients undergoing cesarean section. The majority of patients received neuraxial anesthesia for either cesarean section or vaginal delivery, without any anesthetic complications. Overall, the mortality was 16% (8 of 49), with the majority of the deaths occurring in patients with group-1 PH. Notably, all deaths occurred after delivery, including all 6 patients in whom ECMO was used.[12] While there were no neonatal deaths, 26 of 41 deliveries were preterm, and 23.5% of neonates with a documented birth weight were small for gestational age.

A recent study with surprisingly low mortality was published by Thomas et al.[13] The National Inpatient Sample was analyzed, and 1,519 pregnant women with PH were identified between 2003 and 2012. Despite including patients with congenital heart disease, valvular heart disease, and cardiomyopathy, mortality was only 0.8% (12 of 1,519). However, major adverse cardiac events still occurred in 24.8%, which predominantly were driven by heart failure and arrhythmias. Nevertheless, the low rate of mortality was in stark contrast to prior data, such as a systematic review by Bedard et al. demonstrating mortality rates of 38% in a historic cohort and 25% in a more recent cohort, and an older study by Weiss et al., reporting a mortality of 30% in primary PH and 56% in secondary vascular PH (1978-1996).[14,15] Overall, it seems that maternal mortality is lower in the more recent literature, although maternal morbidity remains a concern.

Given the possibility of hemodynamic compromise during delivery, consideration was given to ECMO as a rescue strategy. Before cesarean section, the patient's severely elevated PAP and increased plasma volume secondary to the pregnancy already were placing a significant amount of strain on the right ventricle. Intraoperatively, volume shifts, along with potential increases in pulmonary vascular resistance due to hypoxia, hypercarbia, acidemia, or pain, could place the right ventricle at high risk for acute failure. Therefore, the perioperative care team elected to place predelivery femoral vein and artery catheters. These catheters would be utilized for the institution of VA ECMO if acute hemodynamic instability occurred during delivery. The catheters were to remain in place for several days postpartum as well. An important consideration when deliberating on ECMO as a rescue device is determining whether the underlying condition is treatable and if the condition is recoverable. As previously discussed, patients with PH have difficulty tolerating the physiologic changes associated with pregnancy. Because pregnancy is of limited duration, and this patient population typically is younger and often without significant comorbidities, the right ventricle should be recoverable.

Unfortunately, there is a lack of supportive evidence for the use of ECMO in the obstetric population. Data supporting ECMO use in the pregnant population primarily are focused on venovenous ECMO (VV ECMO) for respiratory support rather than VA ECMO. Moore et al. searched outcomes for pregnant patients who were supported with ECMO during their

pregnancy. The study looked at 45 patients, but only 4 were on VA ECMO, while the rest were supported with VV ECMO. The overall maternal survival rate was 77.8%, while the fetal survival rate was 65%.[16] In another study, Agerstrand et al. similarly examined 18 patients who were placed on either VV or VA ECMO, but only 4 were supported during pregnancy (VA ECMO or VAV ECMO), and the remaining patients were supported postpartum.[17] Indications for ECMO included PH (n = 1), pulmonary embolism (n = 2), and amniotic fluid embolus (n = 2), but the majority were acute respiratory distress syndrome on VV ECMO support. Overall, maternal survival was 88.9% (16 of 18), and fetal survival was 77.8% (14 of 18). Of the 4 patients who were placed on ECMO support during pregnancy, 2 delivered while on ECMO support. Fetal complications were not attributed to ECMO support. Complications during the study included bleeding in 6 patients, and 14 patients required blood transfusions. One patient required a lower extremity amputation secondary to cannulation site-associated limb ischemia. One patient with PH was supported on VA ECMO during pregnancy and successfully delivered. However, after delivery, disseminated intravascular coagulation ensued, along with abdominal compartment syndrome, which required an exploratory laparotomy. Despite serious complications, she eventually was weaned off support and successfully discharged from the hospital.[17]

Overall, this case conference emphasizes the significance of PH in pregnancy. PH is a contraindication to pregnancy because of its associated high morbidity and mortality. Patients with a diagnosis of PH are counseled appropriately to help prevent harm to themselves. Nevertheless, some patients will knowingly take the risk of pregnancy. Others, however, may not yet know they have PH and may be asymptomatic due to compensatory mechanisms. The patient in this case conference was otherwise healthy and did not carry a diagnosis of PH until the changes of pregnancy ensued, and she was unable to compensate anymore. While ECMO was not needed to rescue this patient, the evidence supporting its use for this population is minimal. Patients who might require such support should be transferred to centers with experience, resources, and dedicated teams to initiate ECMO, if necessary. The decision to proceed with ECMO requires careful consideration, and it should be considered only in patients with recoverable conditions. The risks of ECMO must be weighed against the benefits it will provide for the patient.

Expert Commentary (Dr. Kiers, Dr. Younger, and Dr. Sanders)

Providing anesthesia to patients who have PH is a medical challenge, especially when treating pregnant women who have PH. In parturients, PH confers an increased risk of morbidity and mortality to both the mother and the fetus.[18-22] Historically, mortality rates for pregnant women with PH have ranged from 30%-to-50%.[1,14,19,23,24] However, more current studies suggest that maternal mortality rates for women with PH have decreased in recent years to 12%-to-30%, in part due to advancements in modern medicine, an increased focus on early treatment with close monitoring, and the use of multidisciplinary medical teams for these at-risk patients.[11,12,14,20,22,24] However, even with these improvements in outcomes, some experts continue to recommend against pregnancy for women with PH and may suggest that elective termination be offered.[12,18,19,25] Considering the high risk of decompensation and death for pregnant women with PH, it is essential that each patient be provided an individualized, tailored anesthetic approach. The case presentation highlighted here considered a successful cesarean delivery with epidural anesthesia in a woman with severe PH. This case demonstrated how the use of a specialized multidisciplinary team and individualized planning can lead to favorable outcomes for these at-risk patients.

Historically, PH has been defined as a mean PAP $\geq$25 mmHg at rest as measured via right-heart catheterization. Newer guidelines from the sixth World Symposium on Pulmonary Hypertension recommend a revised PAP cut-off of 20 mmHg.[2,25,26] PH has many causes, which are grouped by shared clinical features and pathophysiology. The current group classifications of PH are as follows: Group-1 PH is caused by idiopathic and familial causes or specific drugs and toxins; Group-2 PH is due to left-sided heart disease; Group-3 PH occurs as a consequence of lung disease or hypoxia; Group-4 PH is caused by thromboembolism; and Group-5 PH is due to multifactorial or unknown causes.[2,25,26] When possible, the underlying cause of PH should be identified because it has significant implications for treatment approaches, including anesthetic plans. Recent studies suggest that the causes of PH also may affect mortality rates.[11,22] Although the presented case did not specify the patient's PH classification, she likely had Group-1 PH, given that no alternative cause was identified.

The physiologic changes that occur during pregnancy have been well-described. These changes affect nearly all organ systems and have significant effects on women with PH.[1,23,24,27] Hemodynamic changes occur early in pregnancy, with significant increases in cardiac output and plasma volume starting in the first trimester.[25,27] This highlights how quickly systemic changes occur in pregnancy and helps clarify how pregnancy in undiagnosed patients may lead to the development of symptoms and an ultimate diagnosis of PH.[25,27] The patient presented in this case conference fit this picture, as she had no symptoms of PH before pregnancy. Patients presenting with new symptoms suggestive of PH should be evaluated with echocardiography and, when applicable, right-heart catheterization.[18,25,28]

The decision to use advanced therapies to treat pregnant women who have PH should be case-specific. Current advanced therapies include calcium-channel blockers, prostaglandins, phosphodiesterase-5 inhibitors, and endothelin-receptor antagonists.[1,19,20,29] Advanced therapies should be initiated, continued, or escalated based upon the etiology of PH and the patient's clinical presentation.[18,20] Among therapies for qualifying patients with significant right ventricular dysfunction, intravenous epoprostenol has been widely described.[1,28] For some patients, inhaled prostaglandins may

be suitable, with the acknowledgment that switching to intravenous therapy may be required in cases of clinical worsening.[1,28] The patient in this case was started on inhaled treprostinil therapy, with a subsequent change to intravenous epoprostenol in the antepartum period; however, she eventually had a successful delivery while she was taking inhaled treprostinil. It is critical to note that endothelin-receptor antagonists, such as bosentan, are teratogenic, and, therefore, should be discontinued in pregnant women when possible to avoid potential developmental harm.[1,25] Other pertinent therapies typically used for patients with PH include anticoagulation with heparin, fluid restriction, and diuretics for intravascular fluid management.[1,19,21,24,25]

Given the complexity of treating pregnant women who have PH, one of the most important therapeutic steps involves the formation of a specialized, collaborative multidisciplinary team.[14,18,20,22,23,25,29] Healthcare providers with expertise in PH, advanced obstetrics and maternal-fetal medicine, and neonatology, as well as obstetric and cardiothoracic anesthesia, are key members of these teams.[1,20,23,25,29] In this case report, the patient was transferred to a tertiary-care center, where a multidisciplinary team was assembled, and a detailed plan for delivery was constructed.

For delivery of the fetus within the context of maternal PH, the current professional consensus is that cesarean delivery is the preferred route.[1,29] While vaginal delivery is associated with the benefits of decreased risks of bleeding, infection, and thromboses, there are multiple negative aspects to this delivery route pertinent to women with PH.[1,14,23,29] These include potential worsening of already elevated pulmonary pressures, a decrease in venous return with Valsalva maneuvers, increased risk of significant pain resulting in sympathetic stimulation, and increased risk of acidosis, all of which can place the PH patient at high risk for cardiovascular collapse.[1,14,23,29] For these reasons, early and effective analgesia is of paramount importance for patients with PH who undergo vaginal delivery.[1,23] Assisted vaginal delivery also may be beneficial by reducing maternal effort.[25]

In keeping with the general recommendation for cesarean delivery, recent analyses have reported that most pregnant women with PH undergo cesarean deliveries.[1,11,14,19,20] In these patients, planned cesarean delivery has the benefit of allowing the provider team to determine the timing of delivery during daytime hours, which provides the assurance that adequate staff and resources are available if needed.[19,20,23,29] Furthermore, cesarean delivery avoids the potentially deleterious effects of reduced preload and cardiac output that are associated with the use of the Valsalva maneuver during vaginal delivery.[1,14,23,29]

When cesarean delivery is performed, neuraxial anesthesia is preferred over general anesthesia (GA).[1,23] A review by Bédard et al. found that pregnant women with PH who received GA were 4 times more likely to die than those who underwent neuraxial anesthesia.[14] While this seems to suggest that neuraxial anesthesia is the optimal method of anesthetic management during cesarean delivery, it is important to note that selection bias may have limited the significance of these observed results.[14] For example, it is possible that GA may be required for acutely ill patients, which could explain poorer outcomes.[1,14] GA also may be required for instances in which neuraxial anesthesia is contraindicated or rejected by the patient.[1,23] When GA is used for pregnant women with PH, it is important that the anesthesiologist be aware that potentially harmful effects of GA include cardiac depression from volatile agents and changes in pulmonary pressures during laryngoscopy, intubation, and positive-pressure ventilation.[1,14]

When neuraxial anesthesia is deemed appropriate, epidural anesthesia generally is considered the safest approach, as it allows for a slow, incremental, low-dose administration of a local anesthetic, which reduces the risk of acute hemodynamic changes from sympathectomy.[1,19] As an alternative, combined spinal-epidural anesthesia is also a safe option when low-dose intrathecal opioid or local anesthetic is used, because it provides a denser block along with the option of incremental dosing via the epidural.[1,19,23] Spinal anesthesia, conversely, is generally avoided, given the proclivity for sympathectomy.[1] The patient highlighted in the presented scenario underwent a slowly titrated epidural anesthetic, which likely aided in her overall relative hemodynamic stability throughout the cesarean procedure.

Regardless of the anesthetic approach taken, the period immediately after delivery for women with PH is associated with a significant risk for decompensation and hemodynamic collapse.[1,11,14,19,22,27,29] The physiologic changes that occur in the immediate postpartum state include sudden relief of vena caval compression, which results in increased preload, extravascular fluid volume shifts, and a massive increase in cardiac output to 60%-to-80% of prelabor levels.[1,23,27] These acute hemodynamic changes may lead to right ventricular failure, cardiorespiratory failure, and even sudden cardiac arrest in patients with PH.[1,23] Multiple reviews have reported the postpartum period to be particularly dangerous for women with PH.[11,14,19,22] A review by Sliwa et al. examined the outcomes of 151 pregnant women with PH who were included in the European Registry of Pregnancy and Heart Disease.[11] While those findings indicated that no deaths had occurred during pregnancy, maternal death occurred in 3.3% of patients in the immediate peripartum period up to 1 week postdelivery, and 2.6% of 78 follow-up patients had died within 6 months after delivery.[11] Another more recent study by Low et al. found that while the maternal mortality rates of 12%-to-20% that they observed were lower than those historically reported, depending on the cause of PH, 61% of maternal deaths occurred within 0-to-4 days postpartum, with the cause of death occurring from right ventricular failure, cardiac arrest, PH crisis, pre-eclampsia, and sepsis.[22] Vasopressors, inotropes, and advanced intravenous and inhaled PH treatments should be available for use during delivery.[1,22]

Given the precariousness of delivery and the postpartum state for women with PH, special monitoring and plans for stabilization in the setting of acute decompensation are recommended.[1,23] In general, patients should deliver at a care center with access to intensive care units for both the mother and neonate.[1,12,23,29] Advanced hemodynamic monitoring with an arterial line also is recommended, especially when PH is

deemed severe.[1,23] A central line may be used, especially as an access point for expected vasoactive medication administration or intravenous pulmonary dilator therapy; however, there is no clear consensus regarding the placement of a central line within this context.[1,23]

Special acute interventions, such as ECMO, may be necessary for women with PH in the peripartum period.[1,12,23,29,30] While many patients will not require ECMO, some risk factors necessitating ECMO use include severe PH, severe right ventricular dysfunction, Eisenmenger syndrome, and World Health Organization group-1 PH.[23,29] Currently, there are no guidelines regarding the use of ECMO in pregnant women with PH. A recent systematic review by Naoum et al. showed that there is a paucity of research regarding ECMO use for pregnant women.[30] One study that assessed 358 pregnant women who had venoarterial, venovenous, or combined support, showed a maternal survival rate of 75.4% at 30 days postdelivery and 74.3% after 1 year.[30] Observed complications were relatively low, with 18.4% of patients developing moderate bleeding, 13.4% developing severe bleeding requiring surgical intervention, and 5.3% developing intracranial neurologic morbidity.[30] In regard to pregnant women with PH specifically, the authors noted a survival rate of 50%, which seems to be a significant improvement compared to 16.7% in previous studies.[30] Further studies regarding ECMO use are needed to guide the best treatment strategies for pregnant women with PH. Although there are no guidelines that recommend prophylactic ECMO cannulation for pregnant women at this time, it can be considered a reasonable approach for patients with severe PH, such as in the presented patient's case. Because ECMO has relatively low complication rates, it is prudent that anesthesiologists discuss this option with patients early in the course of treatment.[30]

Although several recent retrospective studies analyzing PH during pregnancy have been done, several factors may limit the utility of these findings. First, publication bias and minimal reporting of adverse outcomes may limit an understanding of true morbidity and mortality rates.[1,11,14,20,24] Furthermore, small sample sizes limited data collection and analysis.[11] As there are obvious moral implications to performing prospective studies on this vulnerable population, additional retrospective research will be needed to guide future treatment optimization.[11] In the presentation of this case, the authors have demonstrated that, despite having a high risk for decompensation and death, pregnant women with PH can have favorable outcomes when they are treated by a specialized multidisciplinary team and treated with advanced PH therapies. Also, the careful creation of contingency plans, such as prophylactic ECMO cannulation, should be prepared for these at-risk patients to prevent or treat acute hemodynamic collapse.

Expert Commentary (Dr. Knott and Dr. Fernando)

In this case conference, the authors discuss a case in which a young woman was diagnosed with PH during pregnancy. She previously was thought to be healthy until dyspnea, cough, and hemoptysis prompted an investigation into the cause of these symptoms. After severe PH was diagnosed, she required a prolonged hospital stay to ensure close monitoring, administer treatment, and facilitate the delivery of the child, while ensuring the appropriate cardiovascular resources were available for the mother should she experience cardiovascular collapse. In this commentary, the role of echocardiography in this complex case is explored. First, however, it is imperative to understand the altered physiology that occurs during pregnancy.

While it is not known how long this patient had PH, the physiologic changes of pregnancy likely unmasked it. These changes include an approximately 45% increase in blood volume, a 20%-to-25% increase in heart rate, increased stroke volume, and an increase in cardiac output.[27] Patients with preexisting PH may not have the capacity to manage the increased blood volume and cardiac output, which subsequently can overwhelm the right ventricle into failure.[31] The decrease in blood pressure that typically accompanies pregnancy[27] also can be problematic for patients with PH. Normally, the right ventricle receives perfusion during both systole and diastole. Patients with PH, however, have elevated right ventricular systolic pressures, which can result in perfusion that is limited to diastole.[32] Overall, the physiologic changes of pregnancy likely contributed to the manifestation of symptoms in this previously asymptomatic patient.

At 28-weeks' gestation, persistent dyspnea, cough, and hemoptysis prompted an echocardiographic evaluation. It is worth noting that there are several echocardiographic changes that are normally observed during pregnancy. These include increases in left ventricular dimensions, left ventricular diastolic and systolic volumes, as well as left ventricular wall thickness.[33] The left ventricle also develops more of a spherical shape, as indicated by a decrease in the sphericity index. However, in the context of PH, the changes in the morphology of the right ventricle induced by pregnancy are perhaps more concerning. Ducas et al. studied 34 pregnant women who underwent TTE and cardiac magnetic resonance imaging in the third trimester and postpartum.[34] They demonstrated increases in right ventricular end-diastolic diameters during the third trimester by both imaging modalities without changes in right ventricular function. Notably, the postpartum values were used as the "baseline." In another study, Del Prado Diaz et al. compared 43 pregnant women to 19 nonpregnant women. They also demonstrated increases in right ventricular diameters; in contrast to the prior study, they noted decreases in some markers of right ventricular function as the pregnancy progressed.[35] Specifically, the S' velocities obtained by tissue Doppler imaging did not decrease during pregnancy, but the right ventricular fractional area change and tricuspid annular plane systolic excursion (TAPSE) measurements did decrease. Despite this decrease, however, right ventricular markers for systolic function still were within the normal range. A prospective cross-sectional study by Melchiorre et al. yielded similar results.[36] In this study, a group of 50 healthy, nonpregnant women was used as controls. Four similarly sized groups of nulliparous pregnant women, ranging from 95-to-109

participants, were recruited at various stages of pregnancy. Compared to the nonpregnant controls, S' velocities did not significantly differ, and although TAPSE still was within the normal range, it was significantly lower at term.[36] Collectively, these studies demonstrated that in healthy pregnant patients, the right ventricle may dilate and may experience some dysfunction. In the patient with preexisting PH, however, right ventricular dilation and dysfunction already may exist, and the stress of pregnancy may threaten the ability of the right heart to further compensate.

In this patient, the degree of right ventricular enlargement on the echocardiogram at 28 weeks was not specified by the authors. Nevertheless, the development of moderate-to-severe TR was concerning. While the valvular incompetence was unfortunate, it did facilitate the diagnosis of the patient's PH. Traditionally, the velocity of the TR jet (v) is measured using continuous-wave Doppler, and the right ventricular systolic pressure is estimated by using the following equation: $4v^2$ + right atrial pressure.[37] If she did not have sufficient TR to obtain this measurement, it is possible her diagnosis could have been missed or delayed. While some may assume that patients with PH will have a TR velocity that is easily measurable, this is not necessarily the case. In a retrospective study by O'Leary et al., 1,262 patients who had a TTE within 2 days of a right-heart catheterization that diagnosed PH were studied.[38] PH was diagnosed in 47% of patients who did not have a reported TR velocity. This included some patients with mean PAPs approaching 60-to-70 mmHg. Overall, the lack of a reported TR velocity only had a negative predictive value of 53% to exclude the diagnosis of PH. Interestingly, larger left atrial diameters and right ventricular dysfunction were associated with the group, from which TR velocities were not reported, and PH due to left-heart disease was the most prevalent type.[38]

If this patient did not have significant TR but PH was strongly suspected, the pulmonary artery acceleration time also can be used (PAAT). Yared et al. used PAAT by placing the pulsed-wave Doppler sample gate at the level of the pulmonic valve annulus and subsequently measuring the time from the onset of right ventricular ejection to the peak.[37] The PASP then can be estimated based on the equation $\log_{10}(\text{PASP}) = -0.004\ (\text{PAAT}) + 2.1$. This method is not without limitations, as the PAAT may be affected by external factors, including right ventricular function. Abnormal right ventricular function, for example, can result in a higher PAAT.

In addition to the estimated right ventricular systolic pressure being greater than 100 mmHg, the TTE also was concerning for McConnell's sign. McConnell's sign describes a particular pattern of right ventricular motion in which there is akinesis of the mid-free wall but preserved motion of the right ventricular apex that is associated with acute pulmonary embolism.[39] It is not entirely clear why such a pattern manifests, but several theories exist. These include (1) ischemia, specifically in the free wall; (2) wall stress that results in a change in right ventricular shape; and (3) transmitted movement from a hyperdynamic left ventricle that mimics right ventricular apical contraction.[39] Interestingly, despite the classic teaching of this sign, it may not be very sensitive. In a retrospective study by Kurnicka et al., of 511 patients with acute pulmonary embolism, only 101 (19.8%) demonstrated McConnell's sign.[40] A review that pooled data from 2 other studies found a similar sensitivity of 19% but also demonstrated a high specificity of 98%.[41] Another potential echocardiographic finding is the "60/60" sign. This refers to the presence of both a PAAT <60 ms and a TR jet pressure gradient <60 mmHg.[39] In the previously mentioned study by Kurnicka et al., the 60/60 sign was seen only in 66 of 511 patients (12.9%).[40] These signs performed more favorably in a study that specifically examined patients with submassive or massive acute pulmonary embolus.[42] In this study, the sensitivity and specificity were 52% and 97% for McConnell's sign, respectively, and 51% and 96% for the 60/60 sign, respectively. Notably, both of these signs were outperformed by early systolic notching, a pattern seen on the waveform obtained by placing the pulsed-wave Doppler sample gate in the right ventricular outflow tract, which had a sensitivity and specificity of 92% and 99%, respectively. In contrast, the sensitivities for McConnell's sign, 60/60 sign, and early systolic notching were only 7.1%, 7.0%, and 2.3%, respectively, in patients with subsegmental pulmonary emboli.[42] Overall, both McConnell's and 60/60 signs seem to have poor sensitivity but perform better in patients with more extensive pulmonary emboli. In patients with a submassive or massive pulmonary embolus, however, early systolic notching may be the more sensitive and specific sign.

Echocardiography also can be used to monitor the patient in the perioperative period. During a cesarean section, this patient received a neuraxial anesthetic, which can result in hypotension. In addition, the autotransfusion of blood from the uterus immediately after delivery potentially could result in right ventricular failure. Kumaresan et al. studied 98 pregnant patients who underwent delivery by cesarean section using a spinal anesthetic comprised of 11.25 mg of 0.75% hyperbaric bupivacaine, with 25 μg of fentanyl and 250 μg of morphine.[43] All patients received a preoperative TTE immediately before surgery, as well as within the first 2 hours after surgery. Notably, the right ventricular function was depressed at baseline, as evidenced by a mean fractional area change of 24.0%. While no significant difference was found in the right or left ventricular function before versus after surgery, the right ventricular image quality was only sufficient in 81% of patients prior to surgery and in 67% of patients after surgery. Additionally, because the heart may be in a different position before and after surgery due to the delivery of the baby, it may result in images that are not necessarily comparable.[43]

Presumably, transesophageal echocardiography would have been used intraoperatively if GA were chosen. While transesophageal echocardiography was not possible under a neuraxial anesthetic in this awake patient, a focused TTE examination could have been performed in cases of hemodynamic instability or dyspnea to help narrow the differential.[44] TTE is a noninvasive, relatively low-risk procedure that pregnant women are accustomed to and can be performed on awake patients. The subcostal view may be best reserved for the postpartum

period because the supine position is required and may predispose the patient to aortocaval compression. In contrast, the left lateral position to avoid aortocaval compression may facilitate obtaining parasternal and apical views. However, apical views may be limited due to increased breast size. A focused TTE examination can provide information on the left ventricular ejection fraction, which may be impaired due to peripartum cardiomyopathy. Additionally, the presence of pericardial effusion or aortic dissection also can be evaluated. In the patient with PH, increased attention needs to be dedicated to evaluating the right ventricle. In particular, an assessment of structure, as well as the systolic function with either fractional area change or TAPSE, should be performed.[44]

Overall, echocardiography can play an important role in the pregnant patient with PH. In this patient, echocardiography facilitated the diagnosis of PH and allowed for monitoring before and after the cesarean section. While it certainly can be an asset, anesthesiologists should bear in mind that pregnancy results in a variety of physiologic adaptations, which can be apparent on echocardiography. Knowledge of these changes during pregnancy allows the echocardiographer to interpret unexpected findings within the appropriate context. Ultimately, this can lead to improved decision-making and allow for optimization of the patient's clinical care.

In summary, this case conference highlights the management of a complex patient with a high-risk pregnancy. Because PH can confer significant morbidity and mortality, it generally is recommended that these patients avoid pregnancy due to the additional stress from the physiologic changes that occur. In this patient, however, it was not known that she had PH until the pregnancy was well underway and the fetus already was viable. There were several steps that were integral to ensuring a successful outcome. First, the use of echocardiography to investigate this patient's symptoms ultimately led to the correct diagnosis. Second, the formation of a multidisciplinary team involving the relevant clinicians was critical. This team of providers included high-risk obstetrics, maternal-fetal medicine, heart failure and/or PH cardiology service line, cardiac surgery, cardiac anesthesia, and obstetric anesthesia. The expertise from these teams allowed for optimization of this patient's clinical status based on the known changes of pregnancy, formation of a unique treatment plan taking into account medications that are contraindicated during pregnancy, and ensuring the ability to rapidly institute advanced measures, such as ECMO, if necessary.

Conflict of Interest

None.

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