Chapter 9
Cardiovascular Emergencies of Pregnancy

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Introduction

Cardiovascular emergencies in pregnancy, while rare, can be catastrophic for mother and fetus. The unique physiologic changes of pregnancy are demanding on the cardiovascular system and place pregnant patients at increased risk for potentially lethal complications including venous thromboembolism, aortic dissection, and peripartum cardiomyopathy (PPCM). Diagnosis of these three conditions is difficult as signs and symptoms overlap with each other and can also be experienced in normal pregnancies. Evaluation of the pregnant patient with a cardiovascular emergency comes with unique challenges; ionizing radiation exposure to mother and fetus must be considered when selecting an imaging modality, and certain drugs are contraindicated in pregnancy. Managing a critically ill pregnant patient is stressful for the entire emergency department team as two lives are at stake. Providers must remember that the best chance of fetal survival is maternal survival. A coordinated response by a team that includes obstetricians, surgeons, anesthesiologists, and neonatologists will optimize outcomes for both mother and fetus. It is incumbent on the emergency physician to make an accurate and timely diagnosis, lead resuscitative efforts, and coordinate the interdisciplinary care team.

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Venous Thromboembolism (VTE) in Pregnancy

Venous thromboembolism (VTE) is a disease that includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). Hormonal and physiologic changes that occur in the body during pregnancy including hypercoagulability, venous stasis, decreased venous outflow, mechanical compression of the inferior vena cava (IVC) and pelvic veins by the gravid uterus, and decreased mobility place the pregnant patient at higher risk for VTE [1]. There is up to a tenfold increase risk of a thromboembolic event in pregnancy than in the nonpregnant state, and over one half occur in the third trimester [2]. An increased rate of thrombosis exists until 12 weeks postpartum, but is greatest during the first 3–6 weeks postpartum [3]. When considering risk factors for a thromboembolic event in pregnancy, the most important risk factors are a prior history of DVT/PE and the pre-existing history of a thrombophilia [4, 5]. Thromboembolic events are a leading cause of mortality in pregnancy; PE represented 9.8% of pregnancy-related deaths in 2011 [6].

Deep Vein Thrombosis

DVTs in pregnancy tend to be proximal and large and in the left lower extremity. The left-sided location is thought to be due to the compression of the left common iliac vein by the right common iliac artery and the gravid uterus [4]. Compression ultrasonography is still the first approach in the evaluation of DVT in pregnancy. However, a negative ultrasound doesn't completely exclude a DVT as pelvic DVTs are more common in pregnancy and are often missed on ultrasound. If iliac vein thrombosis is suspected and the ultrasound is negative, the American College of Obstetricians and Gynecologists (ACOG) recommends proceeding to a non-contrast MRI [1]. Serial ultrasounds can be performed in patients with a negative ultrasound, but in whom the clinician has a high clinical concern of DVT. Additionally, ultrasound can be used as a first step even if PE is the primary concern. If a DVT is found, treatment can begin without the need for computed tomography pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scan (Fig. 9.1).

Pulmonary Embolism

The diagnosis of PE is difficult in the pregnant patient as the clinical signs and symptoms of PE (dyspnea, tachycardia, lower extremity edema) occur in normal pregnancy. Clinical decision rules have barely been studied in pregnant patients, and none have been validated in the pregnant population. Standard diagnostic tools such as D-dimer lose accuracy as levels increase physiologically during normal pregnancy. As such, physicians tend to test for PE at lower thresholds in pregnant patients and rely heavily on diagnostic imaging studies. Indeed, the incidence of PE is 5% or less in most studies of pregnant patients with suspected PE, compared to 20–25% in nonpregnant patients [7]. Several diagnostic algorithms have been proposed, but the optimal strategy to diagnose PE in pregnancy remains under debate.

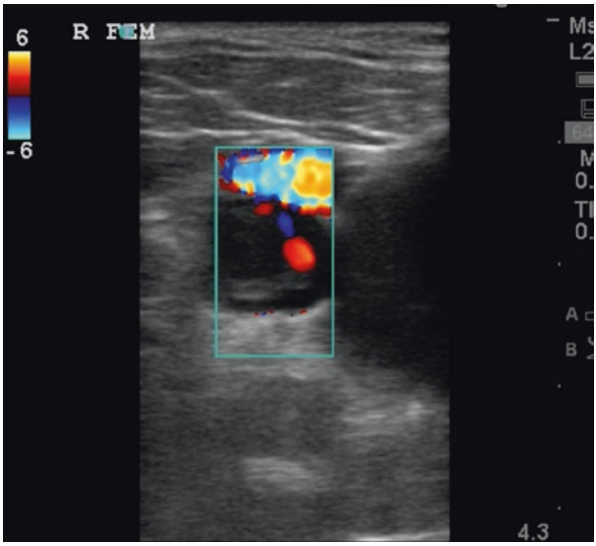

Fig. 9.1 Ultrasound image of decreased blood flow through right femoral vein DVT in transverse view. Reprinted with permission of the MedStar Georgetown University Hospital & MedStar Washington Hospital Center Emergency Ultrasound Group

The D-dimer represents a breakdown product of cross-linked fibrin and is a useful screening tool for DVT/PE in the nonpregnant population. In pregnancy, however, the D-dimer level increases steadily with each trimester, making the test less useful to rule out VTE. Multiple studies have evaluated trimester-adjusted thresholds for normal D-dimer levels in pregnancy, but results are inconsistent [8–12]. Even if "normal range" pregnancy values are firmly established, the threshold to safely exclude VTE would need to be identified. Some authors and guidelines state that a negative D-dimer is still reliably negative in a pregnant patient with low pretest probability [13, 14]. Other guidelines are contradictory and conclude that the D-dimer cannot currently be used to exclude suspected PE in pregnancy [15].

The diagnostic work-up of patients with suspected PE often begins assessment of pretest probability using a validated clinical decision rule. The modified Wells score (MWS) is a validated clinical tool (in nonpregnant patients) used to risk stratify patients in whom there is clinical concern for PE (Table 9.1). It is often used in conjunction with a D-dimer to guide the work-up.

Several studies have evaluated the MWS in pregnancy. A retrospective review by O'Connor et al. [17] applied the MWS to 81 pregnant and 22 postpartum patients referred for CTPA over a 5-year period. The authors found that an MWS of 6 or greater was 100% sensitive and 90% specific with a positive predictive value of 36% for PE on CTPA. This study is small and retrospective and lacked follow-up data, but shows a promising application of the MWS in pregnant patients.

A second study by Parilla et al. [12] evaluated trimester-specific D-dimer levels combined with the MWS as useful risk stratification tools in pregnant women in a prospective and retrospective cohort study. While the number of patients included in the study was low, the results were promising. Using both trimester-specific D-dimers and an MWS was 100% sensitive and 81.4% specific in detecting PE if either of the results were abnormal. In this study, all of the patients with PE would have received a CTPA, and the total number of CTPAs performed would have been decreased by 52.5%.

Currently, imaging tests are the mainstay of diagnostic management of suspected PE in pregnancy. When choosing an imaging modality, risks to the fetus and mother must be considered. The two most commonly used studies for suspected PE are CTPA and V/Q scan. VQ scan confers a higher dose of radiation to the fetus, while CTPA delivers more radiation to the mother, particularly to breast tissue. Breast tissue of pregnant women has a high rate of cell turnover and thus more susceptible to ionizing radiation. However, CTPA can identify alternate pathology. Both forms of imaging confer radiation doses much lower than the exposure associated with fetal harm (Table 9.2).

Multiple diagnostic algorithms for suspected PE in pregnancy have been proposed. The American Thoracic Society and the Society of Thoracic Radiology published one such clinical practice guideline in 2011 [15]. A multidisciplinary panel including members of ACOG was convened to develop evidence-based recommen-

Table 9.1 Modified Wells score[a]—prediction rule for diagnosing PE

Clinical symptoms of DVT	3
Other diagnosis less likely than PE	3
Pulse >100	1.5
Immobilization ≥3 days or surgery in previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1
Malignancy	1
Low probability	0–1
Intermediate probability	2–6
High probability	>6

[a]Modified from Chagnon I, et al. Comparison of Two Clinical Prediction Rules and Implicit Assessment among Patients with Suspected Pulmonary Embolism. Am J Med. 2002 [16]

Table 9.2 VQ scan vs. CTPA for evaluation of pulmonary embolism

	VQ scan	CTPA
Fetal radiation exposure[a]	0.37 mGy dose Radiation exposure greater to fetus	0.01–0.66 mGy Radiation exposure greater to mother, especially maternal breast tissue
Iodinated contrast exposure	N/A	Contrast exposure with possible induction of neonatal hypothyroidism; FDA classifies iodinated contrast as "B" level recommendation for safety
Diagnostic value	Rate of nondiagnostic study is between 7 and 21%	Can identify pathology other than PE

[a]Fetal exposure varies with gestational age, maternal body habitus. Data from: Dubbs SB, Tewelde SZ. Cardiovascular catastrophes in the obstetric population. Emerg Med Clin North Am. 2015;33:483–500. Winer-Muram HT, et al. Pulmonary embolism in pregnant patients: fetal radiation dose with helical CT. Radiology 2002;224:487–92. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Committee Opinion No. 656: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. *Obstet Gynecol*. 2016. *CTPA* computed tomographic pulmonary angiogram, *V/Q* ventilation perfusion

dations. Overall, the panel found that there was "limited amount of direct evidence pertaining to diagnostic test accuracy and patient-important outcomes in the pregnant population." Nonetheless, recommendations were made and are summarized in Fig. 9.2. If the patient has leg symptoms (swelling, calf pain, or asymmetry), bilateral lower extremity ultrasounds to evaluate for DVT should be the starting point. If a DVT is found, begin treatment without further work-up. If there are no leg symptoms, the first step in the evaluation of a PE should be a chest X-ray (CXR) as it may show other etiologies that explain the patient's symptoms (e.g., pneumonia, pulmonary edema). In the pregnant patient with a normal CXR and no history of pulmonary disease (such as asthma), V/Q scan is recommended. If the patient has an abnormal CXR or a history of pulmonary disease, CTPA is recommended.

Other algorithms have been proposed and clinical practice varies widely. Several authors recommend obtaining bilateral lower extremity ultrasounds as a first step when either DVT or PE is suspected [18, 19]. If chest imaging is necessary, the authors believe both CTPA and V/Q scans are equally justifiable for the pregnant patient. The authors prefer CTPA as it may identify alternate pathology. Additionally, there is a risk that the V/Q scan may be indeterminate, requiring that a CTPA be performed as well (Fig. 9.3).

Once the diagnosis of PE/DVT is made in a pregnant patient, treatment with either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is

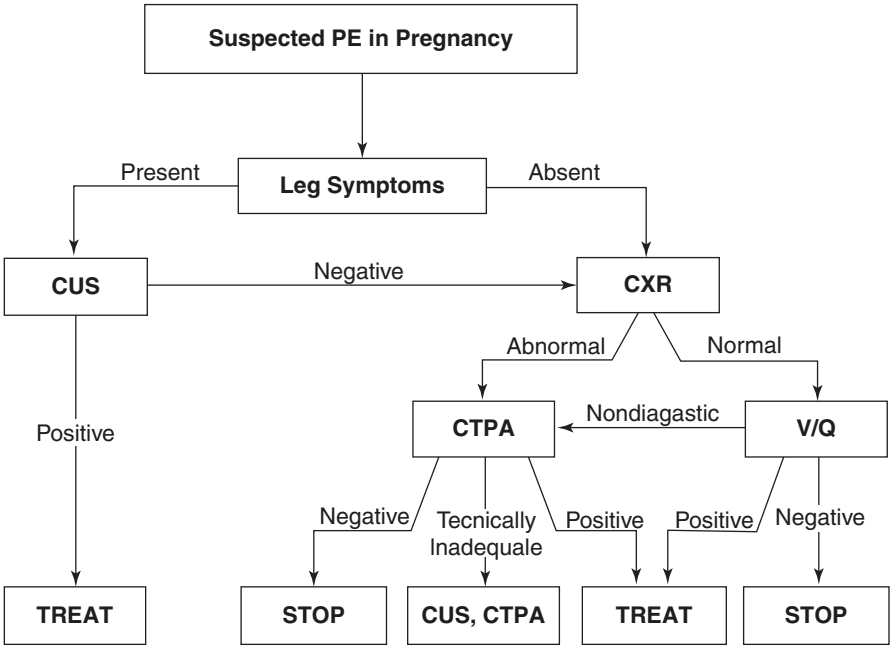

Fig. 9.2 Diagnostic algorithm for suspected PE in pregnancy. (Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Leung AN, et al. [15]. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. *CUS* compression ultrasonography, *CXR* chest X-ray, *CTPA* computed tomographic pulmonary angiogram, *V/Q* ventilation perfusion)

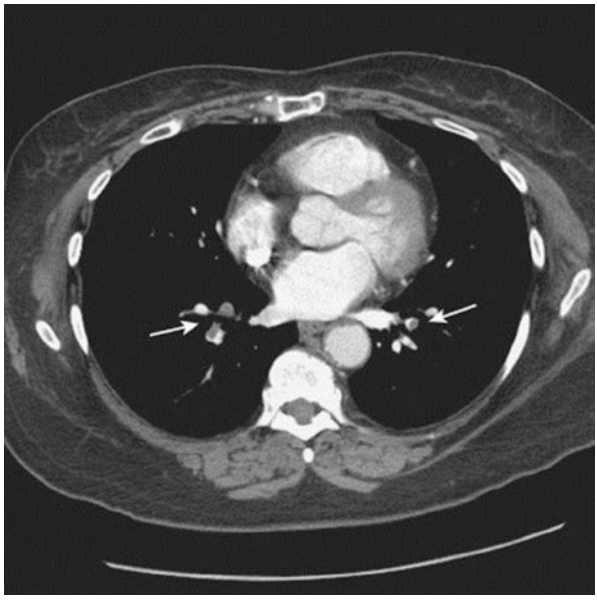

Fig. 9.3 CTPA revealing intraluminal filling defects (*arrows*) in the pulmonary vascular tree. From Sibai BM, eds. *Management of Acute Obstetric Emergencies*. Philadelphia: Saunders, 2011; With permission

indicated. Neither drug crosses the placenta and both are considered safe in pregnancy. UFH is recommended instead of LMWH in patients with GFR less than 30 mL/min or in situations where delivery, surgery, or thrombolysis is imminent. Thrombolytic therapy should be considered for pregnant women with life- or limb-threatening VTE [20]. Warfarin is contraindicated in pregnancy because it is associated with teratogenic fetal effects. To the authors' knowledge, there is no controlled human data regarding novel anticoagulants and pregnancy.

Disposition of pregnant patients with newly diagnosed VTE is similar to non-pregnant patients, but decisions should be made in close consultation with the patient's obstetrician. In general, patients who are clinically stable with no major risk factors for bleeding and easy access to medical care may be treated as outpatients. Hospitalization is indicated in patients who are hemodynamically unstable and have extensive VTE or maternal comorbidities that increase their risk of major bleeding or in patients that require treatment with UFH.

Aortic Dissection

A rare but devastating cardiovascular emergency of pregnancy is a major vessel arterial dissection. While an overall uncommon event, the majority of aortic dissections in women of childbearing age occur during pregnancy. Indeed, for women younger than 40, pregnancy is associated with a markedly increased risk of aortic dissection (odds ratio of 25) [21]. The role of the emergency physician includes early recognition, resuscitation, early activation of institutional massive transfusion protocols, immediate surgical and obstetrical consultation, and overall coordination of care.

The well-described physiologic and hemodynamic changes of pregnancy in concert with accompanying hormonal changes create significant new stresses on the circulatory systems. The gravid uterus compresses the abdominal aorta and iliac arteries, leading to increased vascular resistance at the point of compression and increased stress on the intimal layers of the more proximal aorta. It is suspected that these stresses, in combination with increased effective circulating volume, heart rate, cardiac output, and other hemodynamic changes of pregnancy, create new strains on the vasculature of even previously healthy pregnant patients. The role of elevated progesterone and, more importantly, estrogen augments these hemodynamic stresses. As early as the first trimester, maternal arterial vessels begin to demonstrate increased compliance [22]. Postmortem histopathologic examination from fatal aortic dissections in pregnant patients demonstrates severe degeneration of elastin fibers and other markers of "arterial degeneration" [23]. Patients with known connective tissue disorders or conditions (Ehlers-Danlos, Marfan's, and Turner's syndromes) are also at increased risk for acute aortic dissection.

A recent nationwide study from the Netherlands [24] examined vascular dissections causing death in 23 pregnant patients (incidence 0.74 per 100,000 live births). The authors observed the most frequent location of dissection to be the aorta, with coronary and splenic artery dissections less common. The clinical presentation for a thoracic aortic dissection was variable, but the majority of patients had classic complaints of severe, sharp chest pain described as "ripping" and/or "tearing" and radiating to the back, sometimes accompanied by nausea and vomiting. However, making the diagnosis is challenging. Undoubtedly, the clinical presentation of dissections often significantly overlaps with other cardiovascular emergencies in the pregnant patient such as PE, acute coronary disease, amniotic fluid embolism, or preeclampsia. As described previously in the VTE section, D-dimer is not a useful screening tool as levels rise steadily throughout normal pregnancy.

To definitively diagnose aortic dissection, imaging is required. Similar to nonpregnant patients, CT or transesophageal electrocardiography (TEE) may be used. TEE is ideal in pregnancy as it confers no ionizing radiation and can be performed in the ED, but is not always available. CT does confer ionizing radiation and requires intravenous contrast; however, these risks must be weighed against the risks of missing a potentially lethal vascular catastrophe. Importantly, a necessary diagnostic test should not be withheld from a pregnant patient out of concern for possible risk to the fetus. Bedside ultrasonography may also be useful. Findings such as intimal flaps within the abdominal aorta, grossly dilated vascular size, a false lumen, or hemopericardium warrant emergent angiography or other more immediate action depending on the patient's hemodynamic status (Fig. 9.4).

For thoracic aortic dissections, management depends on its location. Type A (proximal/ascending) dissections require emergent surgical intervention with fetal monitoring. If the fetus has reached viability (>23 weeks), delivery via caesarian should be considered prior to vascular surgical repair as cardiac surgery is associated with increased fetal loss. Medical management is preferred for uncomplicated type B dissections. Endovascular procedures are being used now in complicated type B dissections [25].

In the patient without aortic rupture but confirmed dissection, ED management includes lowering the heart rate then blood pressure while maintaining clinical indicators

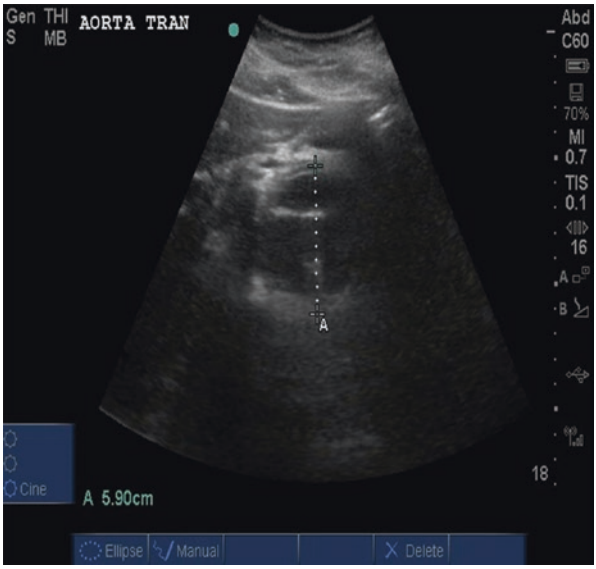

Fig. 9.4 Transverse view of aortic dissection with flap and false lumen in a patient with Marfan's. Reprinted with permission of the MedStar Georgetown University Hospital & MedStar Washington Hospital Center Emergency Ultrasound Group

of adequate perfusion. Vasodilation without beta-blockade can cause reflex tachycardia, increase sheer stress on the damaged intima, and potentially paradoxically worsen extension of the false lumen. Labetalol, nitroprusside, nitroglycerin, and nicardipine all available as infusions are the agents of choice (Table 9.3). Higher doses than usual may be required due to the higher baseline sympathetic drive of pregnancy. All patients with acute aortic dissections required hospital admission, usually to an intensive care unit.

Peripartum Cardiomyopathy

The pregnant or postpartum patient presenting with progressive dyspnea and/or chest discomfort may be manifesting the development of peripartum cardiomyopathy (PPCM), also referred to as pregnancy-associated cardiomyopathy or pregnancy-associated heart failure. Though several working definitions of PPCM exist, one of the most inclusive was defined in 2010 by the European Society of Cardiology (ESC) as an "idiopathic cardiomyopathy presenting with heart failure secondary to left-ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found" [26]. The incidence of PPCM in the USA is relatively low (estimates range from 1:2500–4000 to 0.1%) but carries considerable morbidity and mortality, ranging from 5 to 32% [27]. Cardiology and obstetric consultation should be sought early in the ED course of a patient with PPCM.

Risk factors for the development of PPCM include those classically associated with the development of cardiovascular disease (hypertension, diabetes, tobacco use) as well as pregnancy-specific factors (e.g., advanced maternal age, multiparity, multiple pregnancies, use of tocolytics, nutritional status). The exact cause of PPCM is not clear. Proposed mechanisms of the pathophysiology of PPCM include viral

Table 9.3 Profiles of common cardiovascular medications available during pregnancy

Action	Medication	Considerations
Afterload reduction	Hydralazine	Safe and well studied in pregnancy. Often chosen first
	Nitrates (isosorbide mononitrate, nitroglycerin, nitroprusside)	Commonly used and considered safe, but pose a theoretic risk of cyanide toxicity (nitroprusside)
	Calcium channel blocker	Not first-line/preferred therapy, only nifedipine has been shown to be safe in pregnancy
	ACE inhibitors ARBs	*Contraindicated* in pregnancy, but first choice in postpartum patients
Preload reduction	Loop diuretics	Most likely necessary; can cause decreased placental blood flow
	Nitrates (isosorbide mononitrate, nitroglycerin, nitroprusside)	Commonly used and considered safe, but pose a theoretic risk of cyanide toxicity (nitroprusside)
	Spironolactone (aldosterone antagonist)	Avoid during pregnancy—believed to have androgenic effects in the first trimester
β-Blockers	Metoprolol, labetolol	Considered safe; some evidence of IUGR; β-1 selective preferred because β-2 receptor blockade can theoretically have an anti-tocolytic action
Anticoagulants	Coumadin	Contraindicated in pregnancy; potential for teratogenicity as well as pregnancy loss
	Low molecular weight heparin	Preferred anticoagulant in pregnant women with acute VTE
	Unfractionated heparin	Use if patient's GFR < 30 mL/min; use if anticipate thrombolysis, urgent surgery or delivery

Adapted from: Sommerkamp SK, Gibson A. Cardiovascular disasters in pregnancy. Emerg Med Clin North Am. 2012;30:952. Sahni G. Chest Pain Syndromes in Pregnancy. Cardiol Clin 30 (2012) 343–367
ACE angiotensin-converting enzyme, *ARB* angiotensin-receptor blockers, *VTE* venous thromboembolism, *GFR* glomerular filtration rate, *IUGR* intrauterine growth restriction

myocarditis, abnormal immune response to pregnancy, abnormal response to the hemodynamic stress of pregnancy, and possibly genetic factors [28].

The majority of patients develop symptoms in the first 4 months after delivery, with 75% of cases diagnosed in the first month postpartum [29]. Symptoms of PPCM are the same for typical heart failure, including pedal edema, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, persistent cough, abdominal pain from hepatic congestion, dizziness, chest pain, and palpitations. PPCM can be difficult to diagnose because, like PE and dissection, many of the symptoms overlap with the normal physiologic changes of pregnancy. Normal pregnancy, with increased blood volume, increased metabolic demands, mild anemia, changes in vascular resistance associated with mild ventricular dilatation, and increased cardiac output, can mimic the early signs and symptoms of PPCM. Some patients may present with acutely decompensated heart failure, with New York Heart Association class III or IV symptoms (symptoms with minimal exertion or at rest) [30].

Evaluation of potential PPCM is multimodal in an attempt to delineate heart failure from PE, acute coronary syndrome, thoracic aortic dissection, or preeclampsia. Electrocardiography is often abnormal, with 66% of patients with PPCM showing left ventricular hypertrophy and nearly all demonstrating some degree of ST-T wave abnormality [31]. CXR can confirm pulmonary congestion or reveal another etiology of shortness of breath such as pneumonia or pleural effusions. Echocardiography is the most important study and should be performed in all patients suspected of having PPCM. The ejection fraction (EF) is nearly always reduced below 45%, though there may not be left ventricular dilation [26]. Laboratory tests such as brain natriuretic peptide (BNP) may be helpful in ruling in or out heart failure. Additional labs such as complete blood count, complete metabolic profile, and urinalysis may help distinguish PPCM from preeclampsia.

Management of heart failure in the pregnant patient depends on severity of the disease and is similar to the treatment of nonpregnant patients. An important exception is the choice of pharmacologic agents. While diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), hydralazine plus nitrates, and aldosterone antagonists have all demonstrated prolonged survival in nonpregnant patients, ACE inhibitors, ARBs, and aldosterone antagonists are associated with harmful fetal effects and are contraindicated in pregnant patients. Also, atenolol has been linked to fetal growth restriction [32]. In general, agents that preferentially act as beta-1 receptors vs. beta-2 are preferable so as to not inhibit beta-2-mediated uterine relaxation and peripheral vasodilation. Diuretics may be necessary, but should be used with caution in pregnant patients as maternal volume depletion can lead to uteroplacental hypoperfusion. Critically ill patients may require noninvasive ventilation support or intubation. Patients that experience refractory or a devastating initial presentation of heart failure during pregnancy with a suspected reversible cause can be candidates for specific advanced therapy, including an intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) to provide maximal circulatory support. Additionally, these patients can be candidates for mechanical support devices like left ventricular assist devices (LVADs) as either a bridge to cardiac transplant or permanent therapy. Bromocriptine, a dopamine 2 agonist that blocks the release of prolactin and aims to combat prolactin split product cardiotoxicity, has prevented onset of PPCM in several animal models and is being studied with ongoing prospective randomized control trials. A small “proof-of-concept” study adding bromocriptine to the standard heart failure therapy showed promising results of improved left ventricular ejection fraction and composite clinical outcome [33].

Summary

The consequences of cardiovascular emergencies in the pregnant patient can be catastrophic and require decisive evaluation, diagnosis, and management in the ED in close consultation with obstetric and surgical colleagues. Initial diagnoses of these life-threatening complications of pregnancy are difficult because symptoms

overlap between disease states and with normal pregnancy. Once VTE, aortic dissection, and peripartum cardiomyopathy have been identified, prompt intervention and coordinated interdisciplinary care can make the difference between life and death for both mother and fetus.

Key Points

- Cardiovascular emergencies in pregnancy require prompt recognition, resuscitation, appropriate surgical and obstetrical consultation, and overall coordination of complex interdisciplinary care.
- Signs and symptoms of cardiovascular emergencies significantly overlap with normal physiologic changes and symptoms associated with pregnancy.
- Ionizing radiation exposure to mother and fetus must be considered when selecting an imaging modality; however, a necessary diagnostic test should not be withheld from a pregnant patient out of concern for the fetus.
- Several medications classically used in the treatment of venous thromboembolism, dissection, and cardiomyopathy carry adverse safety profiles in pregnancy and should be avoided.
- Obstetric consultation should be obtained early in the ED course of all pregnant patients with a cardiovascular emergency.

References

1. James A, The Committee on Practice Bulletins. Practice bulletin no. 123: thromboembolism in pregnancy. Obstet Gynecol. 2011;118:718–29.
2. Heit JA, Kobbervig CE, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005;143(10):697–706.
3. Kamel H, Navi BB, et al. Risk of thrombotic event after the 6-week postpartum period. N Engl J Med. 2014;370(14):1307–15.
4. Conti E, Zezza L, et al. Pulmonary embolism in pregnancy. J Thromb Thrombolysis. 2014;37:251–70.
5. Regitz-Zagrosek V, Lundqvist CB, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J. 2011;32:3147–97.
6. Neggers YH. Trends in maternal mortality in the United States. Reprod Toxicol. 2016;64:72–6. doi:10.1016/j.reprotox.2016.04.001.
7. Van de Pol LM, Mairuhu ATA, Tromeur C, et al. Use of clinical prediction rules and D-dimer tests in the diagnostic management of pregnant patients with suspected acute pulmonary embolism. Blood Rev. 2016; doi:10.1016/j.blre.2016.09.003.
8. Kline JA, Williams GW, Hernandez-Nino J. D-dimer concentrations in normal pregnancy: new diagnostic thresholds are needed. Clin Chem. 2005;51:825–30.
9. Kovac M, Mikovic Z, Rakicevic L, et al. The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2010;148:27–30.
10. Wang M, Lu SM, Li S, et al. Reference intervals of D-dimer during the pregnancy and puerperium period on the STA-R evolution coagulation analyzer. Clin Chim Acta. 2013;425:176–80.

11. Ercan S, Ozkan S, Yucel N, et al. Establishing reference intervals for D-dimer to trimesters. J Matern Fetal Neonatal Med. 2015;28:938–87.
12. Parilla BV, Fournogerakis R, et al. Diagnosing pulmonary embolism in pregnancy: are biomarkers and clinical predictive models useful? Am J Perinatol Rep. 2016;6:e160–4.
13. Chan WS, Chunilal S, Lee A, et al. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. Ann Intern Med. 2007;147:165–70.
14. Sommerkamp SK, Gibson A. Cardiovascular disasters in pregnancy. Emerg Med Clin North Am. 2012;30:949–59.
15. Leung AN, Bull TM, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184:1200–8.
16. Chagnon I, Bouraneaux H, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med. 2002;113:269–75.
17. O'Connor C, Moriarty J, et al. The application of a clinical risk stratification score may reduce unnecessary investigations for pulmonary embolism in pregnancy. J Matern Fetal Neonatal Med. 2011;24(12):1461–4.
18. Kline JA, Kabrhel C. Emergency evaluation for pulmonary embolism, part 2: diagnostic approach. J Emerg Med. 2015;49:104–17.
19. Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. N Engl J Med. 2008;359(19):2025–33.
20. Bates SM, Middeldorp S, et al. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41:92–128.
21. Rajagopalan S, Nwazota N, Chandrasekhar S. Outcomes in pregnant women with acute aortic dissections: a review of the literature from 2003–2013. International Journal of Obstetric Anesthesia. 2014;23:348–56.
22. Poppas A, Shroff SG, et al. Serial assessment of the cardiovascular system in normal pregnancy: role of arterial compliance and pulsatile arterial load. Circulation. 1997;95:2407–15.
23. Nolte JE, Rutherford RB, et al. Arterial dissections associated with pregnancy. J Vasc Surg. 1995;21:515–20.
24. la Chapelle CF, et al. On behalf of the Dutch Maternal Mortality Committee. Maternal mortality attributable to vascular dissection and rupture in the Netherlands: a nationwide confidential enquiry. BJOG. 2012;119:86–93.
25. Sahni G. Chest pain syndromes in pregnancy. Cardiol Clin. 2012;30:343–67.
26. Sliwa K, Hilfiker-Kleiner D, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail. 2010;12:767–78.
27. Johnson-Coyle L, Jensen L, Sobey A, ACCF AHA. Peripartum cardiomyopathy: review and practice guidelines. Am J Crit Care. 2012;21(2):89–98.
28. Ntusi N, Mayosi B. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. Int J Cardiol. 2009;131(2):168–79.
29. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. Circulation. 2005;111(16):2050–5.
30. Lampert MB, Lang RM. Peripartum cardiomyopathy. Am Heart J. 1995;130:860–70.
31. Diao M, Diop IB, et al. Electrocardiographic recording of long duration (Holter) of 24 hours during idiopathic cardiomyopathy of the peripartum. Arch Mal Coeur Vaiss. 2004;97:25–30.
32. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens. 1999;12:541.
33. Sliwa K, Blauwet L, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy; a proof-of-concept pilot study. Circulation. 2010;121:1465–73.