Circulation

AHA SCIENTIFIC STATEMENT

Cardiovascular Considerations in Caring for Pregnant Patients

A Scientific Statement From the American Heart Association

ABSTRACT: Cardio-obstetrics has emerged as an important multidisciplinary field that requires a team approach to the management of cardiovascular disease during pregnancy. Cardiac conditions during pregnancy include hypertensive disorders, hypercholesterolemia, myocardial infarction, cardiomyopathies, arrhythmias, valvular disease, thromboembolic disease, aortic disease, and cerebrovascular diseases. Cardiovascular disease is the primary cause of pregnancy-related mortality in the United States. Advancing maternal age and preexisting comorbid conditions have contributed to the increased rates of maternal mortality. Preconception counseling by the multidisciplinary cardio-obstetrics team is essential for women with preexistent cardiac conditions or history of preeclampsia. Early involvement of the cardio-obstetrics team is critical to prevent maternal morbidity and mortality during the length of the pregnancy and 1 year postpartum. A general understanding of cardiovascular disease during pregnancy should be a core knowledge area for all cardiovascular and primary care clinicians. This scientific statement provides an overview of the diagnosis and management of cardiovascular disease during pregnancy.

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Cardiovascular disease (CVD) is the leading cause of pregnancy-related mortality in the United States and has gradually increased over time (from 7.2 to 17.2 deaths per 100 000 live births from 1987–2015).[1] The rise in maternal mortality has been attributed to increasing numbers of women at advanced maternal age undertaking pregnancy, comorbid preexisting conditions such as diabetes mellitus and hypertension, and the growing number of women with congenital heart disease surviving to childbearing age.[1,2] Racial and ethnic disparities in pregnancy-related mortality are significant, peaking among black non-Hispanic women followed by American Indian/Alaskan Native non-Hispanic women, Asian/Pacific Islander non-Hispanic women, white non-Hispanic women, and Hispanic women (42.8, 32.5, 14.2, 13.0, and 11.4 deaths per 100 000 live births, respectively).[1]

Early and specialized multidisciplinary care in the antepartum, peripartum, and postpartum time frames is essential to improve cardiovascular outcomes and to reduce maternal mortality up to the first year postpartum (Figure 1). The cardio-obstetrics team (also referred to as the pregnancy heart team)[3,4] should provide a comprehensive review of maternal cardiovascular risk, obstetric risk, and fetal risk and outcomes. This includes expectant management and prepregnancy counseling on cardiac medication safety throughout pregnancy and lactation phases. The cardio-obstetrics team is often made up of obstetricians, cardiologists, anesthesiologists,

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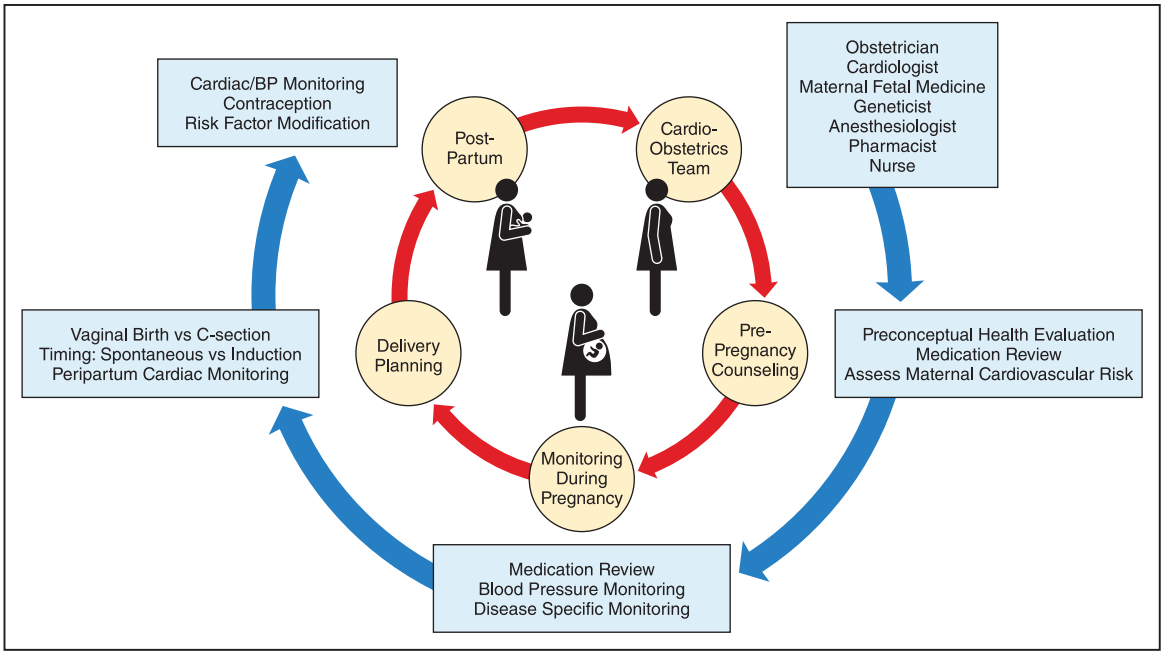

Figure 1. Cardio-obstetrics team in the management of women before pregnancy, during pregnancy, and postpartum.
BP indicates blood pressure.

maternal fetal medicine specialists, geneticists, neurologists, nurses, and pharmacists who jointly develop a comprehensive strategy for management of CVD during pregnancy, delivery, and postpartum.

This scientific statement provides an overview of CVD during pregnancy, exclusive of congenital heart disease and sudden cardiac arrest, which are addressed in recent American Heart Association (AHA) scientific statements on these specific topics.[5,6] In addition, this scientific statement highlights the need for a cardio-obstetrics team for the management of CVD in women during a high-risk pregnancy.

PHYSIOLOGICAL CHANGES DURING PREGNANCY

Predictable and expected hemodynamic and structural changes occur during pregnancy (Data Supplement

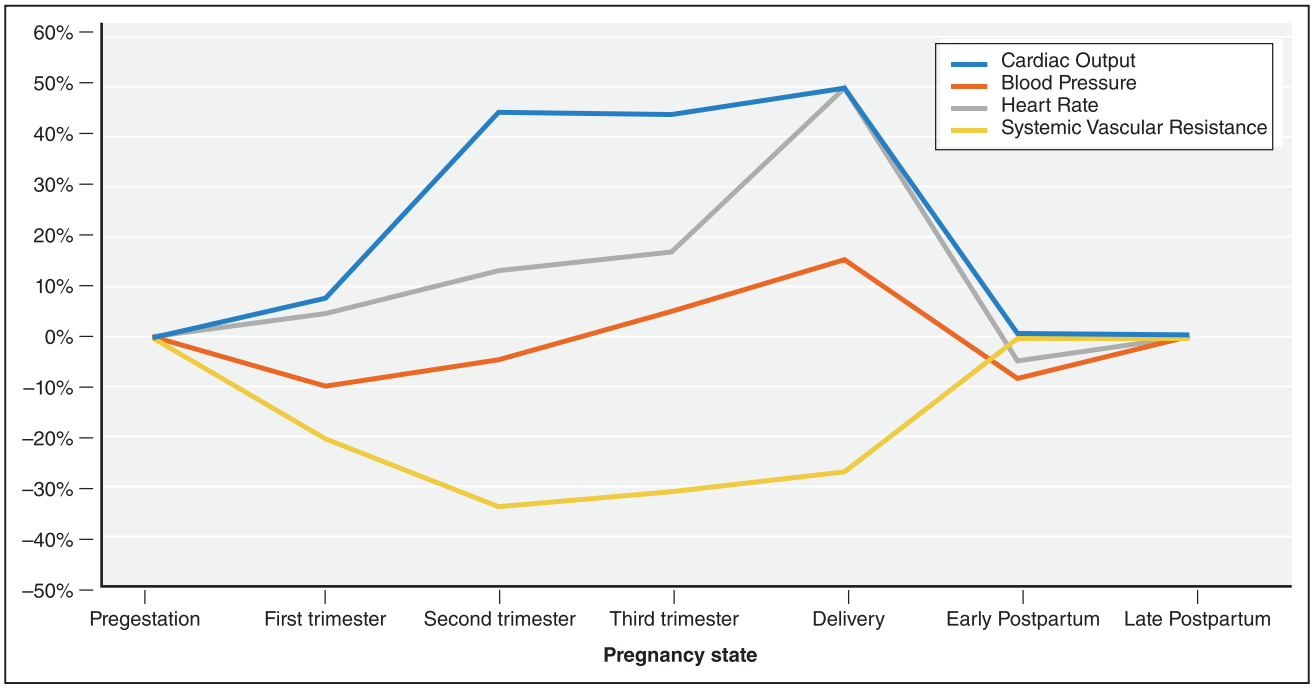

Figure 2. Physiological changes during pregnancy, including variation in cardiac output, blood pressure, and heart rate.[4,7]

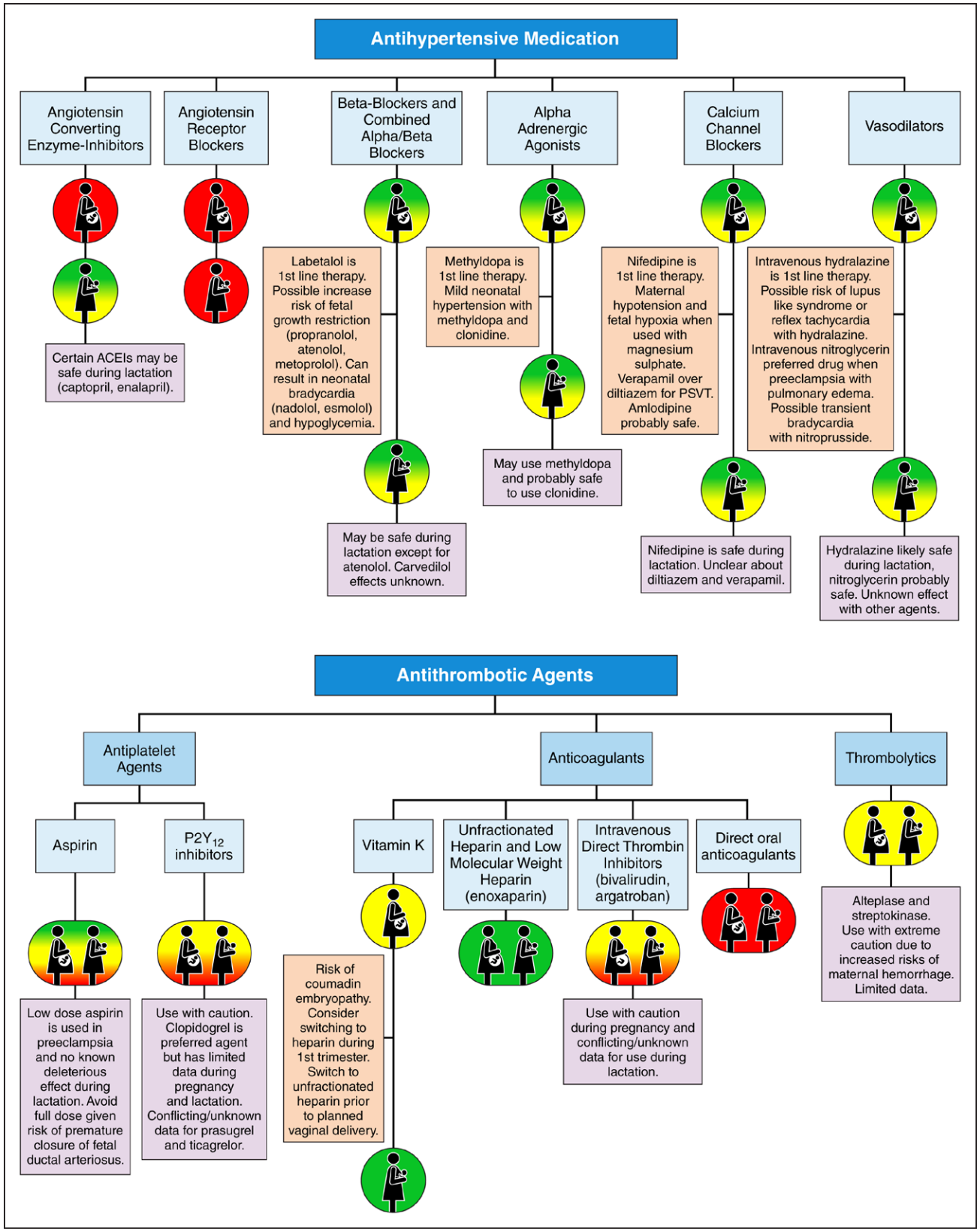

Figure 3. Antihypertensive medications and anticoagulants used during pregnancy.[3,5,9–12]
Boxes with various shades: Red shows contraindicated medications; yellow, use-with-caution medications; and green, relatively safe medications. ACEI indicates angiotensin-converting enzyme inhibitor; and PSVT, paroxysmal supraventricular tachycardia.

Table 1 and Data Supplement Figure 2).[4,7] Along with structural changes of the left ventricle (LV) in pregnancy, activation of the renin-angiotensin-aldosterone system and hormonal fluctuations contribute to the increase in plasma volume, rise in cardiac output, and decline in systemic vascular resistance. Significant fluid shifts at delivery lead to labile peripartum blood pressure, often rising before delivery and then falling within week.[4,7]

PREPREGNANCY COUNSELING

CVD is the leading cause of indirect maternal mortality, and women with CVD should receive counseling on both maternal and fetal risks before conceiving. These women should be cared for by a specialized cardio-obstetrics team (Figure 1) with experience in managing high-risk women with CVD during pregnancy.[8] Preconception counseling is important to ensure that estimates of individual risk are considered when women begin family planning. This counseling permits the high-risk cardio-obstetrics team to include the patient in shared decision-making and to outline anticipated or potential events during pregnancy and management strategies at every stage of the process. In preconception planning, all medications should be reviewed to ensure safety during pregnancy (Figure 3).[3,5,9–12] For example, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are teratogenic and should be replaced with medications known to have a better safety profile in pregnancy. A comprehensive clinical review of a woman's overall health before conception should include reviewing the need for supplemental folic acid and monitoring nutritional status.[13]

The modified World Health Organization (WHO) classification is often the preferred method to estimate individual maternal cardiovascular risk in women with CVD who are contemplating pregnancy (Data Supplement Table 2).[14] Several risk models that estimate maternal cardiovascular risk have been evaluated, but the WHO classification remains the only prospectively validated method for risk assessment. Nonetheless, most models have included several factors known to increase maternal cardiovascular risk, including prior CVD event, history of arrhythmia, prior heart failure, poor functional class, resting cyanosis, use of anticoagulant therapy, and presence of a mechanical valve. In most models of maternal cardiovascular risk estimation, several conditions are felt to be of high/prohibitive risk to continue with pregnancy, including pulmonary arterial hypertension, severe ventricular dysfunction, severe left-sided heart obstruction, and significant aortic dilatation with underlying connective tissue disease.[3] Women with these conditions are often advised to avoid pregnancy. However, it is not uncommon for women to present pregnant, and at that point, the high-risk cardio-obstetrics team must work together to come up with the best way to mitigate maternal cardiovascular and obstetric risk and fetal risk moving forward.

MEDICAL CONDITIONS DURING PREGNANCY

Hypertensive Disorders in Pregnancy

Hypertensive disorders of pregnancy (HDP) are common in the United States, occurring in 912 per 10 000 delivery hospitalizations.[15] HDP are classified into 4 categories by the American College of Obstetricians and Gynecologists (ACOG): preeclampsia/eclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia[11,12] (Data Supplement Figure 1). Preeclampsia is defined hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg in women after 20 weeks of gestation who were previously normotensive) along with evidence of proteinuria. The salient features of preeclampsia with severe features and associated risk factors are highlighted in Data Supplement Table 3.[16] Preeclampsia is important because women with preeclampsia have a 71% increased risk of CVD mortality, a 2.5-fold increased risk of coronary artery disease, and a 4-fold increased risk of heart failure compared with normal cohorts.[17]

A recent joint presidential advisory from the ACOG and AHA highlighted the need for a multidisciplinary management strategy incorporating lifestyle and behavioral modifications, including diet, exercise, and smoking cessation, as well as electronic medical record–based standardized algorithms targeting cardiovascular risk factors.[18] Several studies have proposed that regular exercise during pregnancy may improve vascular function and prevent preeclampsia.[19,20] Moderate exercise has been studied to evaluate the prevention of preeclampsia. However, large randomized controlled trials evaluating the potential reversal of endothelial dysfunction leading to improved outcomes have still not been done.[21] For women with high-risk conditions (chronic hypertension, previous preterm preeclampsia, preterm birth at <34 weeks of gestation, diabetes mellitus), low-dose aspirin may be considered and should be started in the late first trimester.[3,11,12]

Expeditious triage and treatment within 30 to 60 minutes of confirmed severe hypertension (blood pressure ≥160/110 mm Hg and persistent for 15 minutes) should be initiated to reduce the risk of maternal heart failure, myocardial ischemia, stroke, or renal disease.[11] For severe hypertension, treatment with intravenous labetalol or intravenous hydralazine is typically recommended. However, if intravenous access has not been established, immediate-release oral nifedipine may be administered (Data Supplement Figure 2).[11] Intravenous

nitroglycerin is the preferred drug when preeclampsia is associated with pulmonary edema. For the prevention of eclampsia and treatment of seizures, intravenous magnesium sulfate is recommended. However, there is a potential synergy with calcium channel blockers, which can result in hypotension.[3,11]

Less severe hypertension can be managed with labetalol, nifedipine, and methyldopa, which are commonly used as first-line antihypertensive medications. Hydrochlorothiazide can be used as a second-line agent in patients with developing hypertension.[3,12] In a meta-analysis of 49 trials in pregnant women with mild to moderate hypertension (systolic blood pressure of 140–169 mm Hg and diastolic blood pressure of 90–109 mm Hg), antihypertensive medications reduced the risk of developing severe hypertension, but it was no better than placebo at preventing maternal complications (preeclampsia, death) or neonatal outcomes (preterm birth, babies who were small for gestational age, or neonatal/perinatal death).[22] One large multicenter international trial of women with preexisting or gestational hypertension compared fetal and maternal complications of patients with less tight and those with tight blood pressure control. In this trial, there were no significant differences in adverse perinatal outcomes or overall maternal complications between the blood pressure control groups. However, there was a significantly higher frequency of severe maternal hypertension in the less tight blood pressure control group.[23] Several consensus and guideline statements in this area are published, but there is no clear consensus on the optimal blood pressure threshold to initiate antihypertensive treatment or to target blood pressure in women with nonsevere HDP.[3,11,12,24,25]

Maternal risk stratification is needed to help guide patient care, including timing of delivery, and may help improve cardiovascular outcomes. One such model is the fullPIERS model (Preeclampsia Integrated Estimate of Risk), which was developed to identify predictors of adverse maternal outcomes in women who were admitted with preeclampsia or developed it after admission. Predictors included gestational age, symptoms of chest pain or dyspnea, oxygen saturation levels, platelet count, and serum creatinine and aspartate transaminase concentrations. In this multivariate model, blood pressure did not independently predict adverse maternal outcomes, and it was largely felt to be the only element for which an easy intervention is possible.[26]

For women with HDP requiring antihypertensive therapy, early outpatient blood pressure surveillance during the first 1 to 2 weeks postpartum is encouraged. Antihypertensive therapy should be continued in postpartum patients with persistent hypertension (≥150/100 mm Hg). Blood pressure control continues to be an important consideration in the postpartum period because even those women who are not treated with antihypertensive medications during pregnancy may warrant close surveillance, monitoring, and initiation of medications in the postpartum time frame. An important recognition is that severe hypertension or superimposed preeclampsia also may develop for the first time in the postpartum period; therefore, early ambulatory visits in the first 1 to 2 weeks after delivery or home blood pressure monitoring may be prudent. Medication in the first few weeks postpartum should be adjusted to maintain a systolic blood pressure not higher than 150 mm Hg and a diastolic blood pressure not higher than 100 mm Hg. For those women with persistent hypertension beyond 6 weeks to 3 months postpartum, blood pressure management should be initiated as per the current American College of Cardiology/AHA guidelines and on an individualized basis.[12,24]

Hypercholesterolemia in Pregnancy

Total cholesterol, triglycerides, and low-density lipoproteins levels rise steadily during pregnancy and reach peak levels at the time of delivery. However, neither triglycerides nor total cholesterol exceeds 250 mg/dL in normal pregnancies.[27] After delivery, major lipoprotein levels decline over the next 3 months to near prepregnancy levels (Data Supplement Figure 3). According to the 2018 multisociety guideline on the management of blood cholesterol, estimation of atherosclerotic CVD risk and documentation of baseline low-density lipoproteins with a lipid panel are recommended for adults who are ≥20 years of age and not on lipid-lowering therapy.[28] However given the variation in lipids during pregnancy, it is preferable to screen for dyslipidemia before pregnancy according to the National Lipid Association's recommendations for patient-centered management of dyslipidemia.[29]

The 2 most common conditions in which lipids should be addressed during pregnancy are severe hypertriglyceridemia and familial hypercholesterolemia; however, pharmacological treatment is limited because of fetal risks. Pregnancy-related complications such as preeclampsia and gestational diabetes mellitus are associated with triglyceride levels >250 mg/dL.[27] A heart-healthy lifestyle (diet, exercise, weight management) is recommended for all patients. Those with very high triglyceride levels (>500 mg/dL) are at risk for pancreatitis and may benefit from pharmacological agents (omega-3 fatty acids with or without fenofibrate or gemfibrozil) during the second trimester. The risk for premature atherosclerosis is elevated in patients with familial hypercholesterolemia, and during pregnancy, this risk may be further exacerbated by supernormal atherogenic lipoproteins while the patient is off statin therapy. Statins are contraindicated during pregnancy, and all women who are on any lipid-lowering agents should review with their physician the safety of treatment during pregnancy and whether to discontinue treatment

before pregnancy. Current treatment options for pregnant women with familial hypercholesterolemia include bile acid sequestrants, which lack systemic circulation, and, as last resort, low-density lipoprotein apheresis in severe cases (Data Supplement Figure 4).[28,29]

Ischemic Heart Disease in Pregnancy

Ischemic heart disease during pregnancy constitutes a rare but potentially fatal condition. The risk of acute myocardial infarction (MI) is 3- to 4-fold higher in pregnant women compared with their nonpregnant counterparts. The incidence is between 2.8 and 8.1 cases per 100 000 deliveries, with mortality rates of 4.5% to 7.3%.[30–32] Although atherosclerosis accounts for <50% of patients,[33] pregnancy-related spontaneous coronary artery dissection and MI with nonobstructive coronary arteries are prevalent causes (Data Supplement Figure 5) of acute MI in pregnancy.[34] The third trimester and postpartum are the highest-risk periods.[32,34]

A multidisciplinary team approach should be adopted,[4] and the treatment strategy is guided by the clinical presentation. In patients with atherosclerotic ST-segment– elevation MI, timely coronary reperfusion by percutaneous coronary intervention (PCI) is recommended.[35] Fetal radiation protection with lead shielding and radiation reduction measures should be implemented.[36] If PCI is not readily available, thrombolysis is very rarely used and has been administered with extreme caution because of the risk of maternal hemorrhage.[37,38] An invasive approach is also recommended in patients with non–ST-segment–elevation MI who are unstable or have high atherosclerotic burden. Stable patients at low risk can be managed conservatively.[39]

Angiography is the gold standard for the diagnosis of ischemic heart disease in pregnancy (Data Supplement Figure 6). In the case of atherosclerotic plaque rupture or coronary thrombosis, PCI with stent implantation is recommended.[35,40] Because pregnant women were generally excluded from stent trials, scarce evidence is available for this population. Post-PCI low-dose aspirin is considered safe throughout pregnancy, and clopidogrel may be used with caution for the shortest duration possible. Other antiplatelet agents should be avoided.[9]

Pregnancy-related spontaneous coronary artery dissection is a challenging diagnosis in clinical practice (Data Supplement Table 4).[41] Similar to the general population, conservative management with inpatient monitoring is recommended for most patients,[42] with a high rate of lesion recovery within months of its occurrence.[43,44] Radial forces generated by balloon inflation or stent expansion may broaden the dissection, resulting in procedural failure.[43–45] PCI should be performed only in a patient presenting with left main coronary artery dissection, hemodynamic instability, recurrent chest pain, or ongoing ischemia.[42,43] Although pharmacotherapy in this clinical scenario is not well established, antiplatelet agents combined with β-blockers (ie, labetalol) represent the most accepted regimen.[3,45,46] MI with nonobstructive coronary arteries should be considered a working diagnosis warranting further investigation. The recent AHA scientific statement on MI with nonobstructive coronary arteries offers a comprehensive diagnostic algorithm.[47] Treatment should be tailored to the underlying pathophysiology.

Pregnancy in women with preexisting coronary artery disease is considered to be very high risk. The probability of developing ischemic complications is ≈10%, and only 21% of women have a completely uncomplicated pregnancy.[48] In those patients with prior spontaneous coronary artery dissection, LV dysfunction, and signs of residual ischemia, consultation and shared decision-making with the cardio-obstetrics team are essential when these women are counseled about the increased cardiovascular risks with future pregnancy.[39] Women with a history of these conditions who become pregnant should be monitored very closely.

Cardiomyopathies in Pregnancy

The diagnosis and management of cardiomyopathy during pregnancy are challenging because both dilated cardiomyopathy and peripartum cardiomyopathy (PPCM) may represent a condition within a spectrum of similar pathophysiology. Therefore, it is important to exclude reversible causes of left ventricular dysfunction (eg, myocarditis, hypertension, underlying valve disease, toxin-induced, ischemia).[49] PPCM is defined as new-onset cardiomyopathy with systolic dysfunction (LV ejection fraction <45%) without a reversible cause presenting near the end of pregnancy or in the postpartum period in a woman without known heart disease and is a significant cause of maternal morbidity and mortality.[50] The prognosis for women with PPCM is strongly linked to LV ejection fraction at presentation. The IPAC study (Investigations of Pregnancy Associated Cardiomyopathy) followed up 100 women with PPCM with echocardiography during the first postpartum year and determined that recovery of LV function occurred almost exclusively within the first 6 months postpartum, with little subsequent change. In addition, major cardiovascular events (heart transplantation, LV assist device, or death) occurred almost exclusively in women with an ejection fraction of <30%.[51] Treatment of heart failure during pregnancy is directed at controlling volume status (eg, diuretics), afterload reduction (eg, nitrates, hydralazine), rhythm control (eg, β-blockers, digoxin), and anticoagulation if necessary (Data Supplement Figure 7). Many causes of PPCM have been proposed, and animal models of suppression of prolactin production have been shown to prevent the development of PPCM. Bromocriptine, which

suppresses prolactin production, has been shown to be associated with improvement in LV function[52] and may be considered as adjunctive treatment in women with PPCM according to the 2018 European Society of Cardiology guidelines for the management of CVD during pregnancy.[3] Appropriate contraception choices and risk in future pregnancies of recurrent PPCM must be discussed early in the management of these women.[53]

The management of pregnant women with other forms of cardiomyopathies is often determined by the individual's physiology and the severity of the condition. For example, some women with hypertrophic cardiomyopathy tolerate pregnancy well. However, up to 23% of women experience heart failure or arrhythmia-related complications during pregnancy, most commonly in the third trimester or postpartum.[54] Treatment should be tailored for specific indications (eg, β-blockers for LV outflow tract obstruction or arrhythmias). Diuretics must be used cautiously for volume overload because many of these women need to maintain preload in the setting of LV outflow tract obstruction.[55] Particular attention must be paid in the early postpartum period, when dramatic fluid shifts and changes in afterload may worsen underlying hemodynamics.

Arrhythmias in Pregnancy

Data gathered between 2000 and 2012 in 57 million pregnancies have shown a rise in the number of pregnancy-related hospitalizations for arrhythmias, a finding that has been felt to be related to increasing numbers of women pursuing pregnancy at advanced maternal age, particularly in women 41 to 50 years of age.[56] Pregnant black women have an increased frequency of any arrhythmia compared with women in other ethnic groups.[57] Palpitations caused by sinus tachycardia and atrial and ventricular ectopy are usually self-limited and benign and require no pharmacological treatment.[58] More complex arrhythmias require a cardio-obstetrics team approach, and management strategies may include initiation or titration of antiarrhythmic therapy or consideration of an electrophysiological study and radiofrequency ablation.

Sustained arrhythmias are more frequent in patients with underlying structural heart disease or thyroid or electrolyte disturbances. Stable supraventricular tachycardia treatment should be no different in pregnant patients, and if vagal maneuvers fail, then intravenous adenosine may be used.[59] Wolff-Parkinson-White syndrome can worsen during pregnancy[60]; intravenous procainamide can be used for wide-complex tachyarrhythmia.[61] Catheter ablation for atrial arrhythmias may be needed if medical therapy fails, ideally with minimal radiation exposure.[62,63]

New-onset atrial fibrillation in pregnancy usually indicates underlying heart disease and should be treated on an inpatient basis by a cardiologist.[64] If the patient is unstable, direct cardioversion is recommended over chemical cardioversion because it is highly safe and effective. Digoxin, β-blockers, and calcium channel blockers can be used for rate control; however, amiodarone should be avoided. If necessary, catheter ablation can be used for atrial flutter refractory to medication, avoiding/limiting fluoroscopy if possible and preferably delaying the ablation until the second trimester. For stroke prevention in patients with valvular heart disease or high stroke risk, vitamin K antagonists can be used after the first trimester, whereas low-molecular-weight heparin (LMWH) should be accompanied by periodic evaluation of anti–factor Xa.[64]

Prepregnancy counseling in women with congenital long-QT syndrome is advised to discuss the significantly increased risk of malignant tachyarrhythmias, and these women require β-blockade throughout pregnancy.[65] Recent American and European practice guidelines for the management of patients with ventricular arrhythmias outline nuances of management of this condition (Data Supplement Table 5).[66,67] Because there are no trials, registry data, or systematic analyses, data on the safety of antiarrhythmic drugs are limited. In patients with severely symptomatic bradycardia, a pacemaker is indicated regardless of pregnancy status.

Synchronized cardioversion is used if there is hemodynamically significant supraventricular tachycardia, atrial fibrillation, and ventricular tachyarrhythmia, similar to nonpregnant patients.[68] In the event of hemodynamic compromise, treatment is similar to that in a nonpregnant patient with direct unsynchronized cardioversion.[69] There are limited human reports on pharmacological therapy for the treatment of sustained ventricular tachycardia in hemodynamically stable patients; in general, intravenous procainamide and lidocaine are considered safe.[70] Data Supplement Table 6 summarizes antiarrhythmic treatment options for pregnant patients according to underlying arrhythmia.

Valvular Heart Disease in Pregnancy

Valvular heart disease pathologies in women of childbearing age are most commonly congenital but may include rheumatic, acquired, and native degenerative causes. Many young women have undergone preconception valvular repair or replacement. Regardless of pathogenesis and prior treatment, women with a history of valvular heart disease should undergo preconception evaluation by the cardio-obstetrics team. Safety and potential risks should be discussed before pregnancy, including in those with mechanical prosthetic valves or moderate to severe native regurgitant or left-sided stenotic valvular lesions and those with associated ventricular dysfunction or pulmonary hypertension. Frequency of monitoring, composition of the care team,

delivery planning, and management during pregnancy are determined on the basis of patient risk.[2,5,71–76] The recently published ACOG guidelines recommend the estimation of risk and subsequent management with the modified WHO classification (Data Supplement Table 2).[4,77] Ideally, severe valvular heart disease should be treated before conception. Clinical judgment prevails in each case; however, consideration should be given to performing valvular repair/replacement with a bioprosthesis to minimize the need for therapeutic anticoagulation during pregnancy.[4,78]

Left-sided stenotic valvular lesions are associated with the highest-risk valve lesion in pregnancy. A summary of the clinical features is presented in Data Supplement Table 7. Symptoms may develop in previously asymptomatic patients because increased blood volume, higher heart rate, and diminished cardiac output exaggerate stenotic physiology. Pregnancy-related hemodynamic changes lead to expected physiological augmenting of derived velocity, and imaging specialists must be aware of these normal changes when interpreting studies performed throughout pregnancy. Mitral stenosis, most commonly from rheumatic heart disease, is associated with increased maternal and fetal morbidity and mortality. Untreated mitral stenosis can lead to heart failure with pulmonary edema, atrial arrhythmias, cerebrovascular events, and death.[77,79,80] Although the cardiovascular risk profile of mitral stenosis in pregnancy has changed over time, the risks escalate with increasing severity of stenosis.[81] β-1–Selective β-blockers along with activity restriction are the primary treatment recommendations for patients with mitral stenosis who either are symptomatic or have significant pulmonary hypertension. Percutaneous mitral commissurotomy can be performed in pregnant (preferably after 20 weeks of gestation) patients with mitral stenosis with severe symptomatic heart failure or significant pulmonary artery hypertension despite optimal medical management.[3] While typically associated with better outcomes than mitral stenosis, severe aortic stenosis can also be associated with increased maternal cardiovascular risk during pregnancy, including heart failure, arrhythmias, and rarely death.[82] Adverse fetal outcomes include prematurity and fetal growth restriction, with the highest risk again occurring in those with more severe aortic stenosis. The management of women who are contemplating pregnancy or who are already pregnant is guided largely by the severity of aortic stenosis and whether symptoms are present.[83]

Valvular regurgitant lesions are generally well tolerated in pregnancy. These lesions are less likely to cause complications because diminished afterload is present as a result of low-resistance placental circulation and an expected decrease in systemic vascular resistance. However, the presence of ongoing symptoms despite optimal medical therapy before pregnancy should lead to consideration of valvular repair or replacement before conception.[84,85] Even if stable throughout pregnancy, women with valvular regurgitant lesions may be at risk for developing pulmonary edema postpartum when systemic vascular resistance abruptly increases in the setting of high total body volume.[86]

Pregnancy in women with mechanical prosthetic heart valves is associated with increased risk of fetal and maternal morbidity and mortality.[4,75,76,78] Maternal risks include increased mortality, valve thrombosis–associated valvular dysfunction, heart failure, stroke, and maternal hemorrhage. Risks to the fetus include increased mortality, teratogenicity, and hemorrhage.[75,78,87] The optimal strategy for maintenance of anticoagulation during pregnancy in women with prosthetic heart valves remains controversial. Given the known dose-dependent teratogenicity, the 2014 AHA/American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease and the 2018 European Society of Cardiology Guideline for the Management of CVD During Pregnancy recommend continuing warfarin if therapeutic anticoagulation can be maintained at a dose ≤5 mg/d.[3,85] If the dose of warfarin required to maintain therapeutic anticoagulation exceeds 5 mg/d or the patient prefers to avoid warfarin, suggested alternatives include dose-adjusted LMWH (guided by weekly peak and consideration of trough anti–factor Xa levels, targeting a range of 0.8–1.2 U/mL) or dose-adjusted continuous unfractionated heparin (UFH). Warfarin can be resumed safely in the second trimester and then transitioned to dose-adjusted continuous UFH in anticipation of delivery. Brief cessation of anticoagulation is required before delivery. With regard to labor and delivery, the use of epidural anesthesia is contraindicated in the anticoagulated patient. The American Society of Regional Anesthesia and the Society for Obstetric Anesthesia and Perinatology recommend holding intravenous UFH for 4 to 6 hours and LMWH for 24 hours before the administration of epidural anesthesia.[88,89] The 2018 European Society of Cardiology guidelines for the management of CVD during pregnancy recommend planned delivery in women with mechanical valves. These women should be hospitalized and placed on intravenous UFH or LMWH with close monitoring at 36 weeks, and at ≈36 hours before planned delivery, they should be on intravenous UFH, which is recommended to be discontinued 4 to 6 hours before delivery. Intravenous UFH can be restarted as early as 4 to 6 hours after delivery, depending on the type of delivery and whether there were bleeding complications.[3] Cesarean section should be performed in women who go into labor while therapeutically anticoagulated with warfarin because of the risk of fetal hemorrhage associated with vaginal delivery.[3,5]

Aortic Disease and Pregnancy

Aortopathy in the pregnant woman carries substantial cardiovascular risk (modified WHO pregnancy risk category of III–IV, Data Supplement Table 2) because of the combination of hemodynamic changes and hormonally driven structural effects on the integrity of vascular/connective tissue.[90,91] Heritable fibrillinopathies, bicuspid valve–associated aortopathy, and Turner syndrome are a few of the many causes of aortopathy, which results in aneurysms and dissection in women of childbearing age. The heritability and syndromic features of genetic aortopathies are heterogeneous, as is the risk of pregnancy-associated maternal cardiovascular morbidity and mortality (Data Supplement Figure 8). Unfortunately, this contributes to the challenging nature of caring for these women in pregnancy.

Several published guidelines address prophylactic aortic root replacement to avoid spontaneous dissection.[84,85,92–95] However, data in pregnancy are less clear and may include consideration of absolute diameter and the ratio of cross section to height (Data Supplement Table 8). In general, a multipronged approach to women with aortopathy is required during the antepartum, peripartum, and postpartum periods with clinical

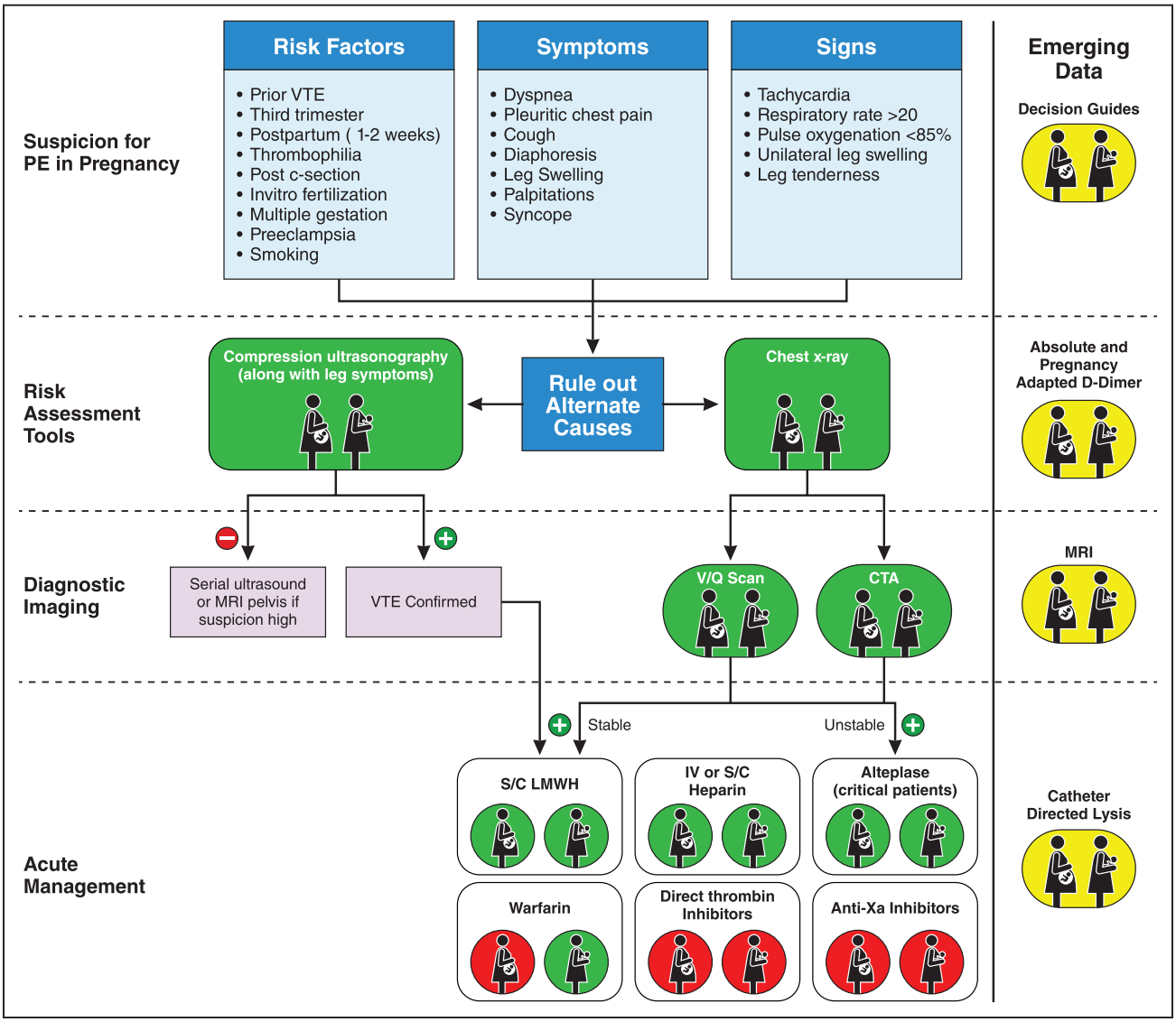

Figure 4. Proposed algorithm for the diagnosis of pulmonary embolism (PE) during pregnancy.[3,99–116]
Guidelines for diagnosing PE during pregnancy are limited and based on low-level evidence derived primarily from data from small observational trials. Acquired or inherited thrombophilia include lupus anticoagulant, shortened activated partial thromboplastin time, factor V Leiden, prothrombin variations, familial proteins C and S, and antithrombin deficiency. Other population-based risk factors include age; presence of autoimmune conditions, sickle cell disease, or obesity; history of cancer; or bed rest for >72 hours. Absolute cutoff for D-dimer is typically <500 μg for most commercial assays, and the adjusted cutoff may be <500 or <1000 μg or dependent on gestation.[101–103,108] Given the high risk of hemorrhage with systemic thrombolytics, particularly in the postpartum period, catheter-based thrombolysis may be considered as an alternative.[112] In stable patients, low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin given the longer half-life, similar efficacy and safety, and lower risk of thrombocytopenia and osteoporosis.[97] CTA indicates computed tomographic angiography; IV, intravenous; MRI, magnetic resonance imaging; S/C, subcutaneous; V/Q, ventilation/perfusion; and VTE, venous thromboembolism.

evaluation of blood pressure and echocardiographic assessment of aortic dimensions. Consideration of pharmacological therapy with β-blockers for strict blood pressure control is recommended. Echocardiographic evaluation of the aorta should be performed during pregnancy (may be reasonable every 12 weeks in low-risk women with mildly dilated aorta and warranted every month in women with severely dilated aorta or at high risk of dissection) and at 6 months after delivery.[3] The cardio-obstetrics team approach would also include consideration of intervention if appropriate, multidisciplinary delivery planning, and postpartum follow-up (Data Supplement Figure 9), including when surgical replacement of the aorta is recommended (Data Supplement Table 8). During pregnancy, Stanford type A dissection is a surgical emergency that would necessitate cardiothoracic surgical intervention to rapidly deliver the fetus and repair the dissection. Conservative medical management, including strict blood pressure control, is recommended for stable type B aortic dissections.[3]

Deep Venous Thrombosis and Pulmonary Embolism in Pregnancy

Venous thromboembolism (VTE), referring to deep venous thrombosis (DVT) and pulmonary embolism (PE), is 4 to 5 times more common during pregnancy. However, the absolute risk of VTE during pregnancy remains low at 0.3% for PE and 1.2% for DVT, with the majority (70%) occurring in the postpartum period.[96,97] Accordingly, low rates of pregnancy-related PE have been reported in emergency department evaluations.[98]

DVT commonly presents with extremity pain or swelling and is diagnosed with compression ultrasonography. However, DVT in pregnancy is often proximal (iliac or iliofemoral) and predominantly left-sided.[96] Therefore, if ultrasonography is negative and clinical suspicion remains high, serial ultrasonography measurements in 3 to 7 days or magnetic resonance imaging of the pelvis should be considered.[3,99]

The diagnosis of PE is challenging because the presentation often overlaps with symptoms common during normal pregnancy (Figure 4). It therefore requires a high index of suspicion, particularly in the presence of risk factors such as a history of VTE or thrombophilia. One-third of patients with PE do not have any symptoms.[100] The initial evaluation for PE should include ECG, chest x-ray, and blood tests to rule out alternative causes such as ischemia, anemia, or infection. A clinician may weigh risk factors and presentation (Figure 4) to estimate pretest probability in order to guide the need for testing or early up-front therapy before obtaining imaging results.[3,99–116] However, there is no consensus on this approach. Recently, pregnancy-adapted decision algorithms have been proposed with promising early data, but they require validation in larger studies.[102–104]

D-dimer testing to rule out PE during pregnancy has remained controversial (Data Supplement Table 9). D-dimer physiologically increases with each trimester, leading to low specificity[101,105,117] and even, in rare cases, false negatives.[118,119] Emerging data support a negative predictive value of ≈100% for high-sensitivity D-dimer assay in low-risk patients, especially during the first and early second trimesters.[103,106,107,120] Further work is needed to determine normal levels for each week of gestation.[105,108]

A definitive diagnosis of PE requires imaging such as lung scintigraphy (ventilation/perfusion scan) or coronary tomographic angiography. The choice of diagnostic test should be based on institutional protocols, availability, and shared decision-making that involves a discussion of maternal and fetal risks with the patient (Data Supplement Table 10).[121] Coronary tomography and ventilation/perfusion scans have similar sensitivity, yet coronary tomographic angiography is often more readily available and more efficient with lower interobserver variability than the ventilation/perfusion scan in an emergency department setting. However, selection of the most appropriate test is often guided by local expertise and the level of radiation exposure.[108,122,123]

Once diagnosed, all VTE should be treated with antithrombotic therapy (Table 1). Intravenous UFH is recommended for acute PE and for DVT with large clot burden, for hemodynamic instability, and when surgery or delivery is anticipated. In stable patients, LMWH is preferred over UFH. Approximately 4% of pregnant patients with VTE experience cardiac arrest. Thrombolysis is recommended for patients with hemodynamic instability or massive PE.[37] Inferior vena cava filters may be considered only in cases in which anticoagulation is contraindicated or has failed.[124]

Cerebrovascular Disease in Pregnancy

Pregnancy introduces specific cerebrovascular risk factors uncommon in an otherwise healthy young-adult female population. Cerebrovascular risk is highest in the third trimester and within 6 weeks postpartum (puerperium) and includes ischemic stroke, cerebral venous thrombosis (CVT), intracerebral hemorrhage, reversible cerebral vasoconstriction syndrome (RCVS), and posterior reversible encephalopathy syndrome (PRES). In the United States, combined ischemic and hemorrhagic stroke risk is estimated to occur in 30 per 100 000 pregnancies.[125]

In a recent meta-analysis, the arterial ischemic stroke rate in pregnancy was 12.2 per 100 000 (separating arterial and venous thrombosis).[125] There are multiple risk factors for ischemic stroke in pregnancy, including hypertension, sickle cell disease, systemic lupus erythematosus, and migraines. Pathogenetic factors for stroke in

Table 1. Anticoagulation for Thromboembolic Events During Pregnancy

Drug	Teratogenic	Crosses Placenta	Compatibility with Breastfeeding	Antepartum Indications	Postpartum indications	Therapeutic Doses
Warfarin	Yes	Yes	Probably compatible	Atrial fibrillation/flutter, after first trimester (bridge with LMWH during first 6–12 wk of gestation)	DVT/PE	Individualized starting dose and adjusted to INR (goal 2.0–3.0 typically but may be higher with certain conditions such as mechanical valves)
Direct thrombin inhibitors (dabigatran)	Insufficient data	Yes	Avoid	Avoid	DVT/PE	150 mg twice a day
Anti–factor Xa inhibitors (rivaroxaban, apixaban, edoxabab, betrixaban)	Insufficient data	Yes	Avoid	Avoid	DVT/PE	Rivaroxaban 15 mg twice a day Apixaban 10 mg twice a day Edoxaban 60 mg once a day Betrixaban 160 mg once a day
UFH	No	No	Probably compatible	DVT/PE	DVT/PE	80 U/kg intravenous bolus followed by 18 $U \cdot kg^{-1} \cdot h^{-1}$ Subcutaneous 10 000 units every 12 h Therapeutic target aPTT is 1.5–2.5 times the control 6 h after injection (aPTT is at least 2 times the laboratory control in mechanical valves)
LMWH	No	No	Probably compatible	Atrial fibrillation/flutter, DVT/PE	Preferred	Enoxaparin 1 mg/kg subcutaneous every 12 h Deltaparin 200 U/kg once a day Tinzaparin 175 U/kg once a day Target is 0.6–1.0 U/mL anti–factor Xa level 4 h after last injection for twice-daily dosing regimen; may be higher for once-daily dosing injections (if mechanical valve present, then target anti–factor Xa level is 0.8–1.2 U/mL 4–6 h after dosing)
Fondaparinux	Insufficient data	Yes	Probably compatible	In cases of heparin allergy DVT/PE	In cases of heparin allergy DVT/PE	5 mg (body weight <55 kg) 7.5 mg (body weight 55–100 kg) 10 mg (body weight >100 kg)
Thrombolysis alteplase	No	No	No information	Massive PE or limb-threatening DVT	Massive PE or limb-threatening DVT	Intravenous 100 mg

aPTT indicates activated partial thromboplastin time; DVT, deep venous thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; and UFH, unfractionated heparin.

Adapted from American College of Obstetricians and Gynecologists and American Society of Hematology guidelines.[109,113]

pregnancy include hypercoagulability, paradoxical embolism via patent foramen ovale, amniotic fluid embolism, arterial dissection, and cardioembolic phenomena resulting from PPCM.[125,126] Hypercoagulability in pregnancy is mediated by increased von Willebrand factor, factor VIII, plasminogen activators 1 and 2, and fibrinogen, as well as protein C resistance, reduced protein S concentration, and platelet aggregation caused by hyperprolactinemia, compressive and hemodynamic venous stasis, and endothelial trauma during delivery.[126] Elevated blood pressures are not the only cause of acute strokes in pregnancy. In fact, rates of cerebral hemorrhage are low in women with preeclampsia, including those with sustained severe hypertension. Another contributory cause of stroke in women with preeclampsia is endothelial dysfunction, which leads to proteinuria and edema and, as a result, injury to the normal blood-brain barrier system.[126,127]

Intravenous thrombolysis in acute ischemic stroke of the pregnant patient is still considered a relative contraindication in the absence of disabling deficits; however, retrospective studies have found it to be safe. In the setting of a disabling ischemic stroke, thrombolysis should be considered.[128] Patients with an indication for anticoagulation or antiplatelet therapy should follow the aforementioned pharmacological recommendations for ischemic stroke prevention during pregnancy and postpartum.[129–131]

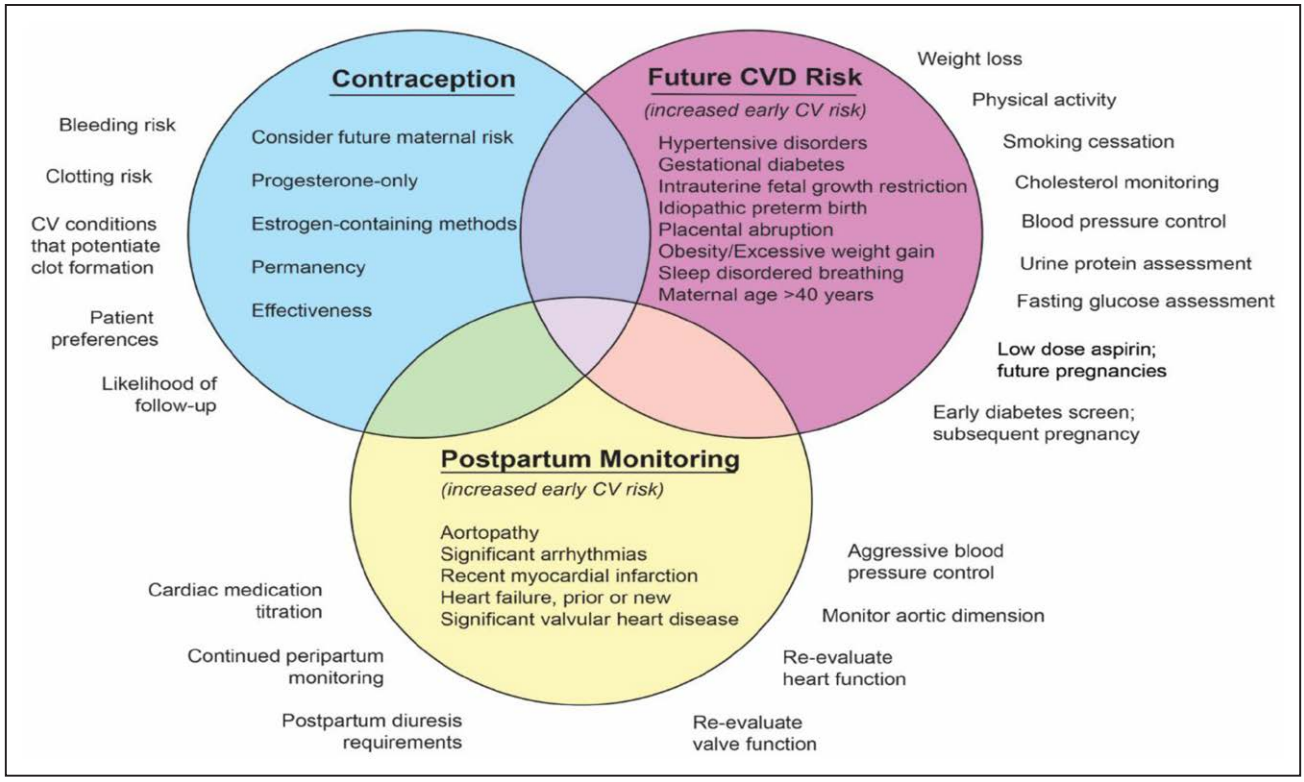

Figure 5. Postdelivery follow-up and late cardiovascular (CV) risk.
CVD indicates cardiovascular disease.

CVT rates pooled in a recent meta-analysis were 9.1 per 100 000 pregnancies, with pregnant and postpartum women making up 20% of adult patients with CVT.[125,132] In a recent retrospective case-control study of 813 cases and 6296 controls, CVT was associated with the puerperium, not with pregnancy.[133] The choice of anticoagulant for CVT should be guided by stage of pregnancy and breastfeeding status.[129]

Intracerebral hemorrhage and nonaneurysmal subarachnoid hemorrhage risk is also increased during pregnancy and puerperium, especially in the setting of preeclampsia and eclampsia. In a meta-analysis, the intracerebral hemorrhage rate was 12.2 per 100 000 pregnancies.[125] Risk factors for puerperium intracerebral hemorrhage include age >35 years, black race, preexisting hypertension, gestational hypertension, preeclampsia and eclampsia, coagulopathy, and tobacco use.[134] Intracerebral aneurysms and vascular malformations pose increased risk during pregnancy.[128,134] Prepregnancy counseling in patients with known vascular malformations should include vascular neurology and neurosurgical evaluation with lesion-specific monitoring.

Both RCVS and PRES are associated with preeclampsia and eclampsia and are considered to be secondary to dysfunctional cerebral autoregulation.[135] RCVS typically presents with a thunderclap headache (reaching peak intensity within ≤1 minute). Compared with nonpregnant populations, PRES tends to present with a higher prevalence of headaches and less encephalopathy in pregnant women. RCVS and PRES can occur at the same time and can manifest with convexity nonaneurysmal subarachnoid hemorrhage. Treatment for RCVS may include calcium channel blockade (nifedipine) and magnesium. PRES is treated with hypertension management.[135]

Neurological emergencies may warrant the use of computed tomography and contrast dye; however, when able/indicated, magnetic resonance imaging and angiography are the preferential modalities to avoid radiation and contrast dye exposure. Given the breadth of cerebrovascular disease that presents during pregnancy and the puerperium, it is important to thoroughly evaluate neurological symptoms in pregnancy and to seek expert consultation (Data Supplement Figure 10).

TIMING AND MODE OF DELIVERY

Contemporary approaches to labor and delivery favor spontaneous labor and vaginal birth for the majority of women with heart disease in pregnancy.[3,5,136] Cesarean delivery is known to carry increased risk of infectious morbidity and thrombotic complications and increased blood loss.[137] In general, cesarean delivery should be reserved for obstetric indications such as breech presentation, failure to progress in labor, elective repeat cesarean delivery, and fetal heart rate abnormalities. Induction of labor may be recommended for care coordination for women planning to deliver at a tertiary care center that may not be close to home. There is evidence that induction of labor may

be protective against cesarean delivery and other obstetric morbidity and therefore should be used to facilitate care planning as needed.[138,139] Induction agents are generally safe in women with CVD. The cardio-obstetrics team will determine delivery plans, including determination of which patients should not deliver vaginally or require assisted second stage of labor.[4] Many hemodynamic changes occur during labor and delivery, particularly in the second stage of labor during Valsalva. For the highest-risk gravidas, it may be appropriate to allow passive descent of the fetal head during the second stage and assist with either forceps or vacuum for delivery when the head reaches the perineum. Cesarean delivery for the indication of cardiac disease should be reserved for the most decompensated women for whom delivery needs to be achieved in the shortest time possible and for women who are fully anticoagulated with vitamin K antagonists in order to protect the fetus from hemorrhagic complications.

The timing of delivery may be a contentious topic because the care team is often weighing maternal, obstetric, and fetal risks, and should include input from the cardio-obstetrics team. The ACOG recommends elective induction of labor for pregnant women with cardiac disease between 39 and 40 weeks of gestation in patients who do not have spontaneous onset of labor or clinical indications for preterm delivery. The timing of delivery for women with active, maternal, or fetal conditions is highly variable according to the underlying medical problem.[4] The ACOG literature does not provide specific information about delivery timing in WHO class IV maternal cardiac conditions; thus, these decisions are frequently made on a case-by-case basis by the high-risk cardio-obstetric team.[140]

POSTPARTUM FOLLOW-UP

The peripartum admission offers an excellent time to discuss the possibility of future pregnancy, contraception, follow-up needs, and the likelihood of late cardiovascular risk. Unique considerations exist prospectively in each of these areas and are often directly related to the specific type of underlying CVD (Figure 5).

Ideally, contraceptive plans have been made in the antepartum period, but if not, contraception should be discussed and offered before discharge. Many long-acting reversible contraceptives such as the intrauterine device or progesterone-only subdermal implants can be used in the immediate postpartum period. Thrombogenic conditions (complex congenital heart disease, cyanotic heart disease, VTE risk), rheumatological conditions, and bleeding risk (women on dual antiplatelet therapy, cyanotic heart disease) need to be carefully considered during the selection of the type of contraception offered. The Centers for Disease Control and Prevention Medical Eligibility Criteria for Contraceptive Use is the trusted resource to consult in the evaluation of contraception safety and appropriateness

Table 2. Approach to Contraceptive Use in Women With CVD

Condition	Subcondition	IUD	Implant	DMPA	POP	CHC
DVT/PE	Remote, not receiving anticoagulation	R	R	R	R	U
	Acute	R	R	R	R	U
	History, receiving ≥3 mo of anticoagulation	R	R	R	R	U
	Family history (first-degree relative)	R	R	R	R	R
High blood pressure in pregnancy	History in prior pregnancy	R	R	R	R	R
Hypertension	Controlled	R	R	R	R	U
	SBP >140–159 mm Hg, DBP >90–99 mm Hg	R	R	R	R	U
	SBP >160 mm Hg, DBP >100 mm Hg	R	R	U	R	U
	Vascular disease	R	R	U	R	U
IHD	Current	Variable depending on whether IHD is present before vs after contraception. Copper IUD safe. For progesterone-IUD, implants, DMPA, and POP, risk likely outweighs benefit. CHC should be avoided.				
Multiple cardiovascular risk factors	Tobacco, diabetes mellitus, hypertension, older age, dyslipidemia	R	R	U	R	U
PPCM	Normal/mild systolic dysfunction	R	R	R	R	U
	Moderate to severe systolic dysfunction	R	R	R	R	U
Valvular heart disease	Uncomplicated	R	R	R	R	R
	Complicated*	R	R	R	R	U

CHC indicates combined hormonal contraception; CVD, cardiovascular disease; DMPA, depot medroxyprogesterone acetate; DBP, diastolic blood pressure; DVT, deep venous thrombosis; IHD, ischemic heart disease; IUD, intrauterine device; PE, pulmonary embolism; POP, progestin-only pill; PPCM, peripartum cardiomyopathy; R, reasonable (benefit outweighs risk); SBP, systolic blood pressure; and U, unreasonable (risk outweighs benefit).

*Defined as a condition that places the woman at an increased risk as a result of pregnancy.

Adapted from Curtis et al.[141]

in the context of general underlying medical conditions, including CVD (Table 2).[141]

In general terms, specific types of maternal CVD affect immediate and postdischarge monitoring requirements. Early after delivery, women with preexisting or new heart failure, significant arrhythmia, severe valve disease, aortopathy, or recent MI will require continued invasive monitoring until postdelivery hemodynamic stability is achieved. In some cases such as patients with aortopathy or the development of new PPCM, risk continues throughout the fourth trimester and beyond. These women require specialized long-term cardiovascular follow-up.

Adverse pregnancy outcomes such as preterm birth and HDP, including gestational hypertension and preeclampsia, gestational diabetes mellitus, and small for gestational age, are a group of interrelated disorders that share common pathways and are thought to be caused by placental dysfunction and oxidative stress.[142] These adverse pregnancy outcomes are associated with increased risk of future CVD (hypertension, ischemic heart disease, stroke)[17,143–146] and are included in the 2018 multisociety guideline on the management of blood cholesterol as cardiovascular risk–enhancing conditions.[28] These patients warrant follow-up in the fourth trimester, at which time aggressive risk factor modification should be undertaken and future risk should be discussed with the patient.[4]

CONCLUSIONS

CVD is the primary causative condition related to the maternal mortality in the United States. Advancing maternal age and preexisting comorbid conditions (including congenital heart disease) have contributed to the increased rates of maternal mortality. Preconception counseling and early involvement of the multidisciplinary cardio-obstetrics team are warranted in order to provide a comprehensive review of maternal and fetal risks associated with pregnancy. In women with a high-risk pregnancy, a cardio-obstetrics team is essential to prevent maternal morbidity and mortality during the length of the pregnancy and postpartum.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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