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STATE-OF-THE-ART REVIEW

CARDIO-OBSTETRICS

Cardiovascular Complications of Pregnancy-Associated COVID-19 Infections

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ABSTRACT

Cardiovascular complications are frequently present in coronavirus-2019 (COVID-19) infection. These include microvascular and macrovascular thrombotic complications such as arterial and venous thromboembolism, myocardial injury or inflammation resulting in infarction, heart failure, and arrhythmias. Data suggest increased risk of adverse outcomes in pregnant compared with nonpregnant women of reproductive age with COVID-19 infection, including need for intensive care unit admission, mechanical ventilation, and extracorporeal membrane oxygenation utilization. Current statements addressing COVID-19-associated cardiac complications do not include pregnancy complications that may mimic COVID-19 complications such as peripartum cardiomyopathy, spontaneous coronary artery dissection, and preeclampsia. Unique to pregnancy, COVID-19 complications can result in preterm delivery and modify management of the pregnancy. Moreover, pregnancy has often been an exclusion criterion for enrollment in research studies. In this review, we summarize what is known about pregnancy-associated COVID-19 cardiovascular complications.
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As coronavirus disease-2019 (COVID-19) has reached pandemic proportions, attention has turned to cardiovascular complications. These include microvascular and macrovascular thrombotic complications such as arterial and venous thromboembolism, myocardial injury, or inflammation resulting in myocardial injury and infarction (MI), heart failure, and arrhythmias. MI is estimated to occur in up to 12% of infected patients.[1,2] Moreover, adverse outcomes are more common in individuals with cardiac complications.[1,2] Centers for Disease Control (CDC) data suggest increased risk of adverse outcomes in pregnant women compared with nonpregnant women of reproductive age

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ABBREVIATIONS AND ACRONYMS

CDC = Centers for Disease Control

COVID-19 = coronavirus-2019

ECG = electrocardiogram

ECMO = extracorporeal membrane oxygenation

LV = left ventricular

MI = myocardial injury

PASC = postacute sequelae of SARS-CoV-2 infection

PPCM = peripartum cardiomyopathy

SCAD = spontaneous coronary artery dissection

Tn = cardiac troponin

including need for intensive care unit (ICU) admission, mechanical ventilation, and use of extracorporeal membrane oxygenation (ECMO) hemodynamic support. Case series of pregnancy-associated COVID-19 infection have reported MI, ventricular dysfunction, arrhythmias, thrombotic complications, and an increased risk of preeclampsia. Pregnant women also report "long haul" symptoms. The potential for cardiovascular complications may continue to remain high during pregnancy as the prevalence of women receiving vaccine has lagged behind other population groups.[3] The purpose of this review is to address cardiovascular complications and approaches to diagnosis in women with pregnancy-associated COVID-19 infection. The spectrum of cardiovascular complications is presented in the **Central Illustration**.

HIGHLIGHTS

- Pregnant women are at increased risk of severe complications from COVID-19 infection including need for intensive care unit admission, mechanical ventilation, and need for extracorporeal membrane oxygenation support in comparison with nonpregnant women of reproductive age.
- Cardiovascular complications including myocardial injury, arrhythmias, and heart failure have been reported but are not well studied and may require change in pregnancy management.
- Unique pregnancy complications such as preeclampsia, peripartum cardiomyopathy, and spontaneous coronary dissections need to be distinguished from other COVID-19-associated cardiac complications.

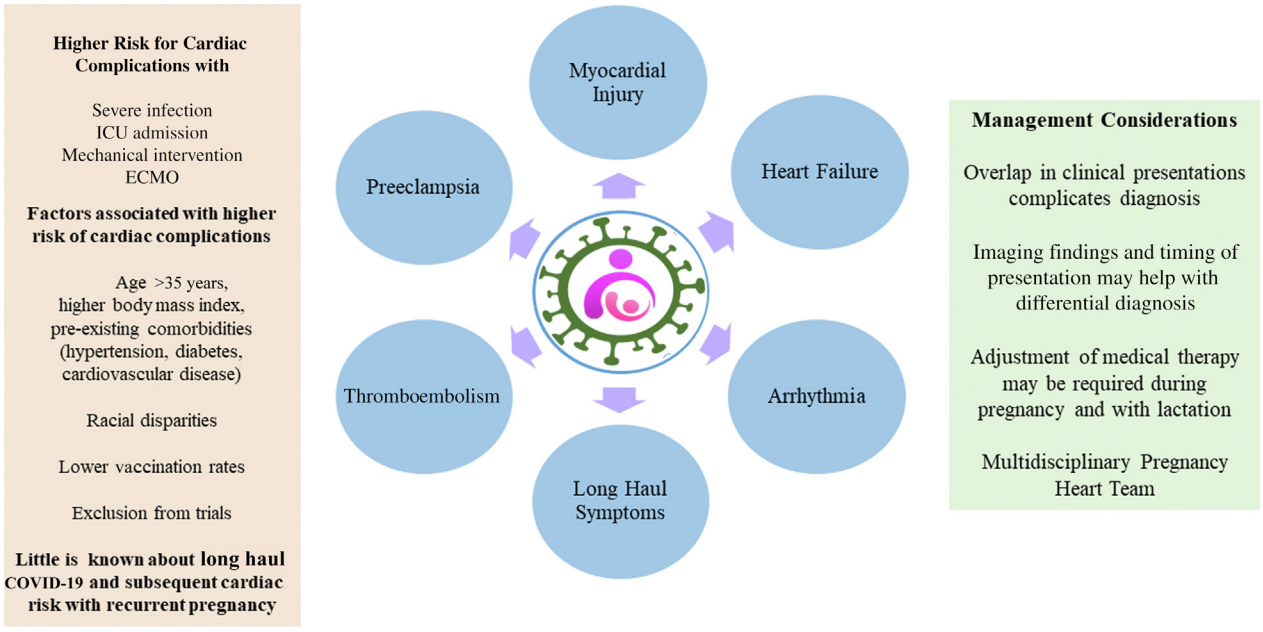
EPIDEMIOLOGY AND ADVERSE OUTCOMES IN ASSOCIATION WITH PREGNANCY-ASSOCIATED INFECTION

The majority of studies of COVID-19 infection in pregnancy have not addressed adverse cardiac outcomes. A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) analysis of 149 studies found adverse outcomes to be more common in case reports and series suggesting reporting bias and raised concerns of patient overlap in registry studies.[4] The most recent update of a live global systematic review of COVID-19 infections in pregnancy included over 60,000 pregnant or recently pregnant women from 192 studies. Reported prevalence of pregnancy-associated infections ranging from 7% with universal sampling to 28% in symptomatic women.[5] Pregnant women were less likely to have fever and myalgias than nonpregnant women. However, pregnancy was associated with severe infection in 10%, ICU admission in 4%, mechanical ventilation in 3%, and ECMO utilization in 0.2%.[5] Risk factors for severe infection included increasing maternal age, high body mass index, and pre-existing comorbidities such as chronic hypertension, preeclampsia, and pre-existing diabetes.[5,6] Compared to pregnant/recently pregnant women without infection, those with infection were at higher risk for preterm birth (odds ratio: 1.47; 95% confidence interval [CI]: 1.14-1.91) and stillbirth (2.84; 95% CI: 1.25-6.45). Overall, 25% (95% CI: 14%-37%) of neonates born to women with COVID-19 were admitted to the neonatal ICU. No differences were observed for other perinatal outcomes.[6]

The Centers for Disease Control (CDC) reports similar findings in a U.S.-specific cohort of 1.3 million symptomatic women of reproductive age (pregnancy status was available for 35.5%). Even after adjusting for race, comorbidities, and age, pregnant women were more likely to be admitted to the ICU (10.5 vs 3.9/1,000 cases; adjusted risk ratio [aRR]: 3.0; 95% CI: 2.6-3.4), receive mechanical ventilation (2.9 vs 1.1/1,000 cases; aRR: 2.9; 95% CI: 2.2-3.8), receive ECMO (0.7 vs 0.3/1,000 cases; aRR: 2.4; 95% CI: 1.5-4.0), and die (1.5 vs 1.2 per 1,000 cases; aRR: 1.7; 95% CI: 1.2-2.4) than their nonpregnant counterparts.[7] Women with pre-existing cardiovascular disease were at a 1.5 to 2.2 increased odd ratio of ICU admission, mechanical ventilation, or death to those with no comorbidities.[7] There were substantial racial disparities: Non-Hispanic Black women represented 14.1% of overall sample but 26.5% of pregnancy-associated deaths. Among Hispanic women, pregnancy was associated with 2.4 times the risk of death.[7] Pregnant Asian and Native Hawaiian/Pacific Islanders are among those at the highest risks of ICU admission.

Moreover, a recent prospective cohort analysis of over 130,000 pregnant people in Scotland found that 77.4% of those requiring hospital admission, the vast majority (98%) of patients requiring critical care, and all fetal deaths occurred in unvaccinated compared with vaccinated women. Full vaccination rate was

CENTRAL ILLUSTRATION **Spectrum of Cardiovascular Complications in Pregnancy-Associated COVID-19 Infection**



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COVID-19 = coronavirus-2019; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

only 32.3% in pregnancy compared with 77.4% in all women. In this analysis, hospital admission and requirement for critical care were increasingly frequent as pregnancy progressed, peaking in the third trimester.[8]

GENERAL APPROACH TO MANAGEMENT OF COVID-19 INFECTION IN PREGNANCY

The American College of Obstetrics and Gynecology and Society of Maternal Fetal Medicine have published resources to help define the approach to obstetric management, which provide algorithms for the general approach to COVID-19 infection during pregnancy.[9,10] Management of cardiac complications during pregnancy requires assembly of a "Pregnancy Heart Team" to optimize patient care, which may include providers comfortable with high-risk pregnancy, obstetric anesthesia, cardiology, critical care, and neonatal care, depending on the nature of the complication, stage of pregnancy, and severity of disease.

MANAGEMENT OF SEVERE COVID-19 INFECTION

Management of severe respiratory disease in pregnancy is complex and outside of the scope of this review. However, prone positioning can be safely performed during pregnancy, reducing both diaphragmatic compression from the abdomen and aortocaval compression by the gravid uterus.[11] Mechanical circulatory support has been successfully utilized in pregnancy as salvage therapy for patients who cannot be stabilized by medical therapy alone.[12,13] Temporary mechanical support can be provided with extracorporeal membrane oxygenation, intra-aortic balloon pump, or percutaneous ventricular assist devices.

PRESENCE OF MYOCARDIAL INJURY

Acute MI is common in COVID-19 patients, and its incidence is proportional to disease severity.[14-17] Systemic inflammatory stress has been proposed as the major mechanism for MI. Injury is felt to represent a type II process with demand ischemia rather than inflammation leading to plaque destabilization and rupture.[18] A review of MI in COVID-19 infection has estimated an 8% to 12% occurrence of MI and identified that cardiac troponin (Tn) elevations >2.2 times the upper reference limit correlated with adverse outcomes.[18] Another study demonstrated that 33% of patients with COVID-19 admitted to ICU developed MI.[18]

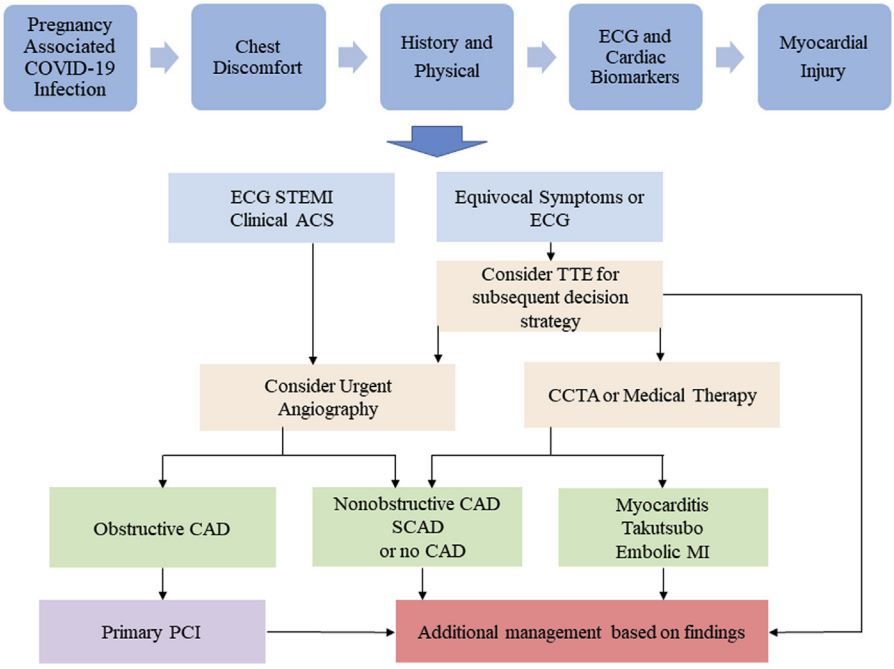
Some of the prothrombotic changes of pregnancy such as complement activation, release of proinflammatory cytokines, antigen-antibody abnormal responses, prothrombotic phenomena, or endothelial-vascular dysregulation are similar to the immune-mediated severe forms of COVID-19 felt to be responsible for MI with infection. Mercedes et al[16] in a case series of 154 pregnant women admitted with COVID-19 infection checked cardiac biomarkers in all finding Tn elevations in 9.7%. All had severe disease, and 86.6% required intubation. Median Tn levels were 34.6 ng/mL (IQR: 14.4-55.5 ng/mL). Most had ventricular dysfunction (mean ejection fraction of 37.67% $\pm$ 6.4%) and elevated pro-B-type natriuretic peptide concentrations (209 pg/mL [IQR: 184-246 pg/mL]). Mortality rate was 13.3%. Since most institutions do not routinely check cardiac biomarkers in all COVID-19 patients, the true prevalence of myocardial injury with pregnancy-associated infection is unknown.

Pregnant people with severe COVID-19 infection or with multiple risk factors such as diabetes, hypertension, older age, smoking, obesity, or prior cardiovascular disease should be assumed to be at the highest risk of MI.[19] The majority of patients will have type 2 MI related to hemodynamic and respiratory derangements from the primary infection and without symptoms of CAD. There is currently no standardized recommendation for when biomarkers should be checked. Evaluation with biomarkers should be considered for those with moderate or severe disease. Chest discomfort which appears to be of cardiac origin, whether acute or persistent, warrants evaluation with biomarkers. Levels more than 20% above baseline warrant further evaluation.[18]

The overlap of symptoms from COVID-19 infection, myocardial disease, and pregnancy can be challenging. Nevertheless, the approaches to diagnosis of suspected myocardial injury are similar to those in nonpregnant patients. Initial assessment is based on history and physical exam findings, chest x-ray, electrocardiogram (ECG), cardiac biomarkers, and frequently echocardiography.[20] Most cardiovascular testing can be performed safely in pregnancy.[21] In the setting of chest discomfort with abnormal biomarkers, differential diagnosis includes demand ischemia, myocarditis, stress cardiomyopathy, and acute coronary syndromes. While coronary atherosclerosis is rare in the reproductive age group, spontaneous coronary dissections are the most common cause of acute infarction in pregnancy.[22] Urgent angiography is reasonable if the ECG suggests ST-segment elevation myocardial infarction (STEMI) management following the current recommendations for evaluation in the setting of active COVID-19 infection.[23] Equivocal symptoms or ECG findings can prompt evaluation with a focused or full transthoracic echocardiography.[20,23] Presence of wall motion abnormalities will help guide decision to proceed to additional evaluation with coronary angiography, computed tomographic angiography, or treatment with medical therapy. CT angiography is an option for stable patients or patients with divergent findings.[23] The newest American College of Cardiology/ American Heart Association/Society for cardiovascular angiography and interventions guidelines for coronary artery revascularization in pregnant patients with STEMI not due to spontaneous coronary artery dissection (SCAD) state are that primary percutaneous coronary intervention is the preferred revascularization strategy (Class of Recommendation 2a, Level of Evidence: C-LD) and that an invasive strategy is reasonable in the setting of non-STEMI if medical therapy is ineffective (Class of Recommendation 2a, Level of Evidence: C-LD).[24] In the setting of SCAD, conservative therapy is recommended for most.[24] Fibrinolytic therapy has been recommended outside of pregnancy for COVID-19-associated STEMI when percutaneous revascularization is not feasible.[23] However, efficacy of fibrinolysis in pregnancy is not well studied and carries risk of maternal or fetal hemorrhage, fetal loss or preterm delivery, and worsening intramural hematoma in the setting of SCAD.[25] Radiation exposure to the fetus and patient with coronary angiography is considered low risk for teratogenicity and can be performed safely in most patients. Treatment should not be delayed out of concerns for exposure on this basis.[25] Addressing patient concerns can be an essential part of the decision process.

During pregnancy, medications will need to be adjusted to avoid teratogenicity.[25] When there is myocardial injury, a multidisciplinary heart team should be convened to address maternal stabilization of cardiac status and optimal timing for delivery under controlled conditions. Members of the team could include general and interventional cardiology, obstetrics, maternal fetal medicine, critical care, anesthesia, and cardiac surgery based on the patient's hemodynamic status, gestational age, etiology of the injury, and institutional resources. Issues to address include management of anticoagulation such as dual antiplatelet therapy and benefit of revascularization compared with medical therapy.[25] The authors approach to management strategy is illustrated in **Figure 1**.

FIGURE 1 Suggested Approach to Chest Discomfort in Pregnancy-Associated COVID-19 With Suspected Acute Coronary Syndrome



The cardiovascular differential diagnosis of chest discomfort includes demand ischemia, myocarditis, stress cardiomyopathy, and acute coronary syndromes. Urgent angiography is reasonable if the ECG suggests ST-segment elevation myocardial infarction especially with classic symptoms. Equivocal symptoms or ECG findings can prompt evaluation with a focused or full TTE. Presence of wall motion abnormalities will help guide decision to proceed to coronary angiography, computed tomographic angiography, or medical therapy. CT angiography is an option for stable patients or patients with divergent findings to rule out ACS or point to an alternative diagnosis. See further discussion in text. ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; CT = computed tomography; ECG = electrocardiography; MI = myocardial injury; PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection; STEMI = ST-segment elevation myocardial infarction; TTE = transthoracic echocardiography.

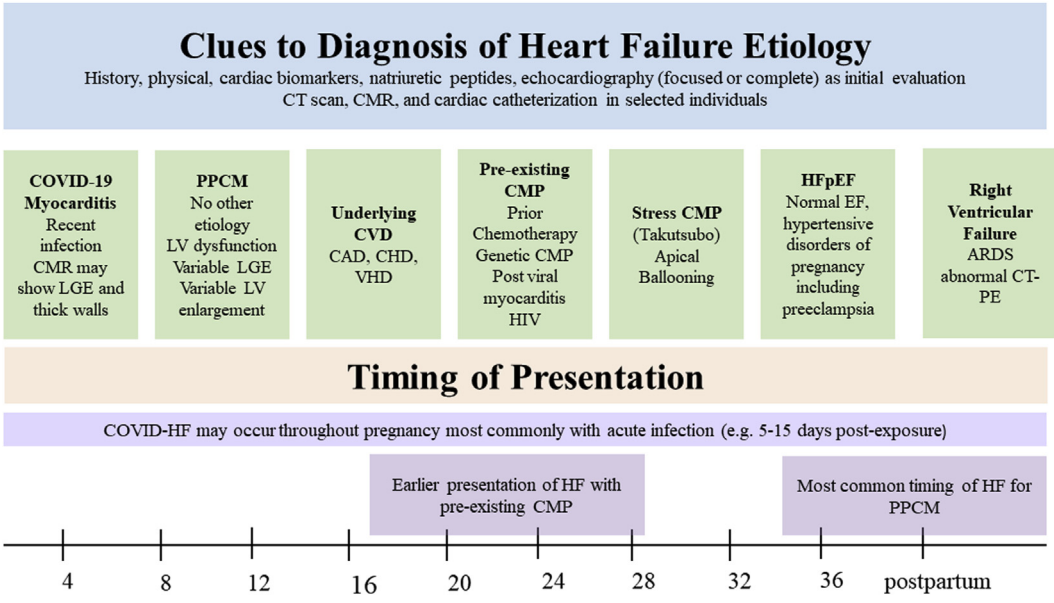
ARRHYTHMIAS

Several factors can predispose to arrhythmias in COVID-19 infection. These include the infection itself and associated electrolyte disturbances, hypoxemia, shock, myocarditis, myocardial injury, and side effects of drug therapy. Reported prevalence varies from 11.7% to 16.7%.[26] Arrhythmias are significantly more common in patients with high Tn and natriuretic peptide levels. In addition, they are more frequent in ICU patients with cardiovascular risk factors, pre-existing cardiac diseases, and history of arrhythmias.[27] The most common rhythm observed was sinus tachycardia, but atrial fibrillation, flutter, and ventricular tachycardia have been reported. Less frequently, bradyarrhythmias and conduction disturbances were noted.[26,27] Also, careful evaluation of the QTc interval is necessary for COVID-19 patients. In a study with 4,250 patients in New York, 6.1% of the patients had a prolonged interval on admission.[28] A QTc interval >500 milliseconds or an increase of >60 milliseconds from baseline was considered a higher risk for developing Torsade de Pointes.[26] In a small series of patients with pregnancy-associated symptomatic COVID-19 infection complicated by myocardial injury from the Dominican Republic, 13.3% had atrial fibrillation, and 2 patients developed Torsade de Pointes; 2 additional patients had supraventricular arrhythmias that responded to metoprolol.[16] The potential for QT prolongation has implications for therapy during pregnancy since drugs may be utilized which can prolong the QT interval.

HEART FAILURE

Heart failure and left ventricular (LV) dysfunction related to COVID-19 infection is recognized, but the true incidence is unknown.[1,14,16,17] During pregnancy, high cardiometabolic demands can precipitate heart failure in previously asymptomatic women with underlying cardiac dysfunction, or de novo peripartum cardiomyopathy (PPCM) may occur in

FIGURE 2 Considerations in Women Symptoms of Heart Failure



Distinguishing the etiology of heart failure in COVID-19 patients without ACS can be challenging as multiple features overlap. Echocardiography, coronary CT angiography, and CMR testing can be considered as diagnostic tools. Timing of presentation is also helpful. COVID-19 infection can occur throughout pregnancy although it may be most severe in the third trimester. Peripartum cardiomyopathy usually presents toward the end of pregnancy or in the months following delivery. See further discussion in the text. ACS = acute coronary syndrome; CAD = coronary atherosclerosis; CHD = congenital heart disease; CMP = cardiomyopathy; CMR = cardiac magnetic resonance imaging; CT = computed tomography; CT-PE = CT pulmonary angiography; CVD = cardiovascular disease; HFpEF = heart failure with preserved ejection fraction; LGE = late gadolinium enhancement; LV = left ventricle; PPCM = peripartum cardiomyopathy; Tn = troponin; VHD = valvular heart disease.

women without pre-existing heart failure. Additionally, symptoms of heart failure can mimic those of normal pregnancy. The signs and symptoms of COVID-19 infection can further obscure the clinical picture. Therefore, when managing pregnant women with COVID-19, particularly those with moderate-severe illness or those with evidence of myocardial injury, care should be taken to evaluate for heart failure and cardiomyopathy.

While the series from the Dominican Republic is small (154 patients in total) and must be interpreted in that context, 9.7% of pregnant patients admitted with symptomatic COVID-19 infection had elevated cardiac Tn. All demonstrated LV dysfunction by transthoracic echocardiography with concomitant elevation in natriuretic peptides.[16] Thirteen percent had LV dilatation.[16] Notably, LV dilatation can be a finding in normal pregnancy, but a reduction in LV ejection fraction is not.[21] Most patients in this series presented with dyspnea (67%), but some presented with palpitations (16%), both of which are also common symptoms during pregnancy. Two of the 15 women (13%) died from malignant arrhythmias. In a smaller case series, 2 of 7 pregnant women with severe COVID-19 infections developed reduced LV ejection fractions (40%-45%).[29] An additional case of heart failure with preserved ejection fraction has been reported.[30]

The differential diagnosis of heart failure in the setting of pregnancy and COVID-19 infection includes myocarditis, stress-induced cardiomyopathy, heart failure with preserved ejection fraction, and PPCM. Specific mechanisms by which COVID-19 may induce cardiomyopathy have been postulated, including oxygen supply-demand mismatch, inflammation, coronary plaque rupture, microvascular thrombosis, and adrenergic stress.[31] COVID-related cardiomyopathy needs to be differentiated from PPCM due to implications for long-term follow-up and counseling regarding risks with future pregnancies. Timing of heart failure presentation can aid in distinguishing PPCM from pregnancy-associated COVID-related cardiomyopathy since COVID-19 infection occurs throughout pregnancy. Patients with PPCM are typically symptomatic toward the end of pregnancy or in the months following delivery, with the most common time of diagnosis being the first month postpartum.[21] In contrast, patients with COVID-related

cardiomyopathy will develop symptoms close to the time of infection, typically in the setting of severe features of COVID, with improvement in myocardial function and symptoms of heart failure as the acute infection improves. However, the 2 conditions may be more challenging to differentiate in patients infected with COVID during the third trimester or the early postpartum period and among patients with risk factors common to both conditions, such as those with chronic hypertension, diabetes, and/or older maternal age. Hypertensive disorders of pregnancy (especially preeclampsia) are seen in both disorders.

Imaging can also help to differentiate the cause of heart failure. The echocardiogram in COVID-19 can be normal (32%) or may show right ventricular dilatation and dysfunction (39%), LV diastolic dysfunction (16%), or LV systolic dysfunction (10%).[32] Cardiac magnetic resonance imaging may reveal myocardial edema, fibrosis, and impaired right ventricle function in patients with prior COVID-19 infection,[33] whereas persistent LV dysfunction would be more common with PPCM, and the presence of late gadolinium enhancement is variable with PPCM.[34] While cardiac magnetic resonance imaging is considered safe in pregnancy, the use of gadolinium is problematic as it accumulates in amniotic fluid.[21] A history of prior chemotherapy, family history of cardiomyopathy, or other diseases associated with LV dysfunction suggest prior cardiomyopathy as the diagnosis. Computerized tomography findings may point to pulmonary embolism or acute respiratory distress syndrome as the etiology. An approach to diagnosis of LV dysfunction is illustrated in **Figure 2**.

If LV systolic dysfunction is diagnosed during pregnancy, modification of medical therapy to avoid teratogenicity will need to be instituted, and a decision plan made regarding optimal timing and delivery plan based on maternal and fetal status.

VACCINE-ASSOCIATED MYOCARDITIS AND PERICARDITIS

Rare reports of acute myocarditis and pericarditis are reported following administration of messenger RNA vaccines most commonly in younger males within a few days of the second vaccination.[35] These complications have not yet been reported in pregnancy but should be suspected in women with new heart failure in the absence of acute COVID-19 infection or another heart failure etiology in proximity to receiving vaccines. While long-term outcomes remain unknown, data suggest improvement with guideline-directed medical therapy.[36]

PREECLAMPSIA IN COVID-19

Preeclampsia is a hypertensive disorder of pregnancy complicating 2% to 8% of pregnancies.[37] It is defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure and presence of proteinuria or thrombocytopenia, renal insufficiency, impaired liver function, or pulmonary edema. Known risk factors include nulliparity, multifetal pregnancy, prior preeclampsia, chronic hypertension, diabetes, thrombophilia, immune disorders, obesity, age >35 years, kidney disease, assisted reproductive technology, and obstructive sleep apnea.[37]

Increased rates of preeclampsia are noted in women with COVID-19 infection. INTERCOVID, a large multinational study, reported data on 2,184 pregnant women, 672 of whom were confirmed COVID-19 positive, to determine if the associated high rate of preeclampsia was due to the shared common risk factors or if COVID-19 infection independently increased the risk of preeclampsia.[38] After adjustment for the conventional risk factors for preeclampsia, the relative risk for preeclampsia was 1.89 (95% CI: 1.17-3.05), independent of the confounding variables. The COVID-19 virus creates a similar pathophysiologic state as that of preeclampsia, ie, direct endothelial damage, inflammation, immune dysregulation, and effects the renin-angiotensin-aldosterone system, which may be driving the higher rate of preeclampsia in these women.[39]

While it may be challenging to parse out the contribution of baseline underlying risk factors from that of COVID-19 infection, it is safe to say that COVID-19 is independently associated with higher risk of developing preeclampsia. Current recommendations are to treat similarly.

VENOUS THROMBOEMBOLIC (VTE) DISEASE IN PREGNANCY-ASSOCIATED COVID-19

Pregnancy is a hypercoagulable state characterized by increased prothrombotic factors—including factors VII, VIII, X, XII, von Willebrand factor, and fibrinogen, as well as decreased protein S—and altered fibrinolysis.[40-42] The risk of VTE in pregnant and postpartum women is 7 to 10 and 15 to 35 times higher than that in age-matched controls, respectively.[43]

Patients with COVID-19 are at increased risk of VTE in the setting of excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[44]

Several pathophysiologic mechanisms have been highlighted, including hospital-associated VTE and immunothrombosis.[42,44] Since pregnancy is a risk factor for severe COVID-19,[6] and pregnancy is a hypercoagulable state, pregnant and postpartum patients with COVID-19 may be at higher risk of VTE. This theoretical concern, however, has not yet been demonstrated in cohort studies of hospitalized patients. In a cohort of 64 hospitalized pregnant people with COVID-19 in the United States, 58% and 16% were anticoagulated with prophylactic and therapeutic dose of heparin, respectively, and none developed VTE.[45] Moreover, no cases of VTE were reported in a cohort of 427 hospitalized pregnant participants with COVID-19 across the United Kingdom (UK).[46] However, clinicians must remain vigilant, as cases of VTE and VTE-related mortality in pregnant patients with COVID-19 are reported in the literature.[47,48]

VACCINE-INDUCED IMMUNE THROMBOCYTOPENIA AND THROMBOSIS AND PREGNANCY

A widely administered vaccine, ChAdOx1 nCoV-19 (Oxford; AstraZeneca), which figured prominently in the UK vaccine rollout, uses a nonreplicating adenovirus to deliver the spike antigen to the recipient. In March 2021, reports emerged of a rare complication named vaccine-induced immune thrombocytopenia and thrombosis (VITT), more commonly among people aged 50 years and younger, with mortality ranging between 30% and 50%.[49] Pathogenically, VITT has similarities with heparin-induced thrombocytopenia (sera demonstrate high titers of antibodies to platelet factor 4) although VITT occurs in the absence of heparin.[50] The pathophysiology underlying VITT is distinct from the occurrence of VTE, and there is no reason to suspect that pregnancy increases the risk of VITT. However, in view of published retrospective safety data with messenger RNA vaccines in pregnancy, these are generally the preferred recommended vaccine choice.[51] The degree of virus exposure, comorbidities, or other risk factors for developing severe disease and vaccine availability should be factored into vaccination decision, recognizing that pregnancy is a risk factor for severe diseases. Vaccination is now routinely recommended in this population.[52-54]

In the absence of pregnancy-specific data from clinical trials, decision-making surrounding anticoagulation in pregnant patients with COVID-19 must be made on a case-by-case basis. Even though pregnancy was not an exclusion criterion for some countries in the ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) trial, very few or no pregnant women were randomized. In critically ill patients, the ATTACC trial found that therapeutic anticoagulation resulted in increased harm in people requiring mechanical ventilation,[55] and so preemptive anticoagulation during pregnancy with COVID-19 requiring this level of support should likely, similarly, be avoided in the absence of another indication for full anticoagulation.

In general, based on the ATTACC trial, hospitalized patients with COVID-19 may be anticoagulated with therapeutic heparin in noncritical illness,[56] and with prophylactic heparin in critical illness.[55] Some centers may choose to apply these recommendations in pregnant patients based on existing extensive safety data for heparin during pregnancy. When planning for delivery, bleeding risks and time-off anticoagulation may be minimized by using low-molecular-weight heparin in twice-daily dosing, or therapeutic unfractionated heparin. The use of prophylactic anticoagulation in the outpatient setting still needs to be clarified, and usual precautions for optimization of VTE risk in pregnancy should be applied.[42]

POSTACUTE SEQUELAE OF COVID-19 INFECTION

Long-term manifestations of COVID-19 infection can persist weeks to months following acute presentation and be classified by the National Institute of Health as postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC).[57-59] The COVID Symptom Study showed that PASC is more commonly reported by women.[60] Specific data on PASC in pregnancy are limited. One study found that up to 25% of pregnant patients had lingering symptoms more than 8 weeks after acute COVID infection.[61]

The pathophysiology of PASC remains uncertain; however, current findings suggest a persistent proinflammatory state mediated by endothelial dysfunction or increased levels of angiotensin-II in the renin-angiotensin-aldosterone system. This is attributed to the virally mediated downregulation of ACE2 receptor, which regulates angiotensin-II levels.[62] The most commonly reported symptoms include fatigue, chest pain, dyspnea, palpitations, joint pain, and neuropsychiatric sequelae such as mood changes and memory loss.[63] Cardiovascular presentations of PASC include myocarditis, post-COVID-19 tachycardia syndrome, postural orthostatic tachycardia syndrome, and dysautonomia.[64-67] Evidence of myocarditis, persistent myocardial

inflammation, or subclinical myocardial injury can be seen months following acute COVID infection.[33,67,68]

A GUIDE FOR FUTURE PREGNANCIES

Preconception evaluation for patients with underlying cardiac conditions is essential to risk-stratify, identify mitigating strategies, discontinue teratogenic medications, and modify existing therapy prior to conception.[69] In patients who have recovered from COVID-19 infection or have PASC, potential for cardiac complications must be addressed. Ongoing symptoms should be reviewed with an assessment of functional class, and further investigations based on this clinical assessment should be conducted. Specific assessment of LV systolic function is a critical component of this process, particularly for patients with cardiac involvement related to COVID-19 disease. It may also be appropriate for those with severe disease requiring ICU admission or with long-haul symptoms. Cardiac medications should be reviewed to replace teratogenic medications with acceptable substitutes.

Risk-stratification tools, such as CARPREG (Cardiac Disease in Pregnancy Study) II or modified World Health Organization classification system, can be utilized for risk-stratification and informing the patients of their risks of pregnancy from cardiac disease.[70,71] While these tools have not been validated in COVID-19 infection or PASC, they may serve as a guide for risk stratification until further evidence is available. In patients with identified cardiac disease following COVID-19 infection, a multidisciplinary cardio-obstetrics team should be involved for preconception planning and pregnancy management to avoid cardiac complications during pregnancy and delivery.[72]

KNOWLEDGE GAPS: FAILURE TO INCLUDE WOMEN IN CLINICAL TRIALS

Recognition of cardiovascular complications and interventions during pregnancy has been hampered by failure to include women in clinical trials. The Institute of Medicine recommends that pregnant women be presumed eligible for participation in clinical studies. The vast majority of COVID-19 trials testing new or repurposed medications have excluded pregnant participants despite several calls for their inclusion.[73-76] Consequently, pregnant women with COVID-19 may continue to be undertreated or inadequately treated due to a lack of trial data having examined safe and effective therapeutic options or conversely may be exposed to therapies that are non-evidence-based.

It is important to note that failure of inclusion of lactating or pregnant people in vaccine trials may contribute to vaccine hesitancy despite increased risk of adverse outcomes in pregnancy. Nevertheless, available data are supportive of vaccination in pregnancy with good safety and immunogenicity profiles during pregnancy and protective transfer of immunoglobulins to neonates. Guidelines published by the CDC, Advisory Community on Immune practices, American College of Obstetrics and Gynecology, and the Society of Maternal Fetal Medicine recommend vaccination in pregnancy.[52-54] Cardiology providers should support these recommendations.

CONCLUSIONS

COVID-19 infection in pregnant women is associated with worse outcomes than that in women who are not pregnant. Mechanisms for adverse outcomes in pregnant people may reflect more serious outcomes of viral infection in pregnancy, changes in the immune system, increased clotting risk, older age, and underlying comorbidities such as diabetes, hypertension, obesity, and racial and social disparities. Most cardiac complications described outside of pregnancy such as arrhythmias, myocardial injury, thromboembolic complications, and long-haul symptoms are reported in women during pregnancy. Additional concerns include increased risk of preterm labor and delivery and development of preeclampsia. Cardiologists should be vigilant in assessing women with COVID-19 for cardiac complications.

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