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The clinical course of COVID in pregnancy

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ARTICLE INFO

ABSTRACT

The 2019 novel coronavirus disease (COVID-19) pandemic poses unique challenges to the medical community as the optimal treatment has not been determined and is often at the discretion of institutional guidelines. Pregnancy has previously been described as a high-risk state in the context of infectious diseases, given a particular susceptibility to pathogens and adverse outcomes. Although ongoing studies have provided insight on the course of this disease in the adult population, the implications of COVID-19 on pregnancy remains an understudied area. The objective of this study is to review the literature and describe clinical presentations among pregnant women afflicted with COVID-19.

Introduction

The 2019 novel coronavirus disease (COVID-19) was first reported in the Hubei Province of Wuhan, China in December 2019.[1] Epidemiologic studies in early cases confirmed that the causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is highly contagious and transmissible between humans.[2] Over the ensuing months, rapid increases in case numbers were observed worldwide, prompting the World Health Organization (WHO) to declare a pandemic on March 11, 2020.[3,4] With over 4 million cases confirmed and nearly 280,000 deaths globally, the COVID-19 pandemic continues to pose unique challenges to the medical community.[5] Importantly, because COVID-19 is an emerging infectious disease, the optimal treatment has not been determined and management is often based on individual institutional guidelines.[6]

Pregnancy is generally regarded as a high-risk state in the context of infectious conditions, as the immunologic changes of pregnancy may increase susceptibility to pathogens and their associated complications.[7] Drawing from the experience of prior disease entities involving respiratory illnesses, there was an anticipation that pregnant women may not only experienced higher rates of complications but also could be at increased risk of mortality.[7–9] Although similar outcomes have not been confirmed in COVID-19, these historical lessons call for an immediate understanding of this disease in pregnancy, including clinical presentations, maternal and neonatal outcomes, and possible therapeutic interventions. Herein, we aim to review the published literature with a specific focus on clinical presentations among pregnant women afflicted with COVID-19.

Screening and testing for COVID-19

Disease surveillance, inclusive of both screening and diagnostic testing of various pathologic entities, is a fundamental public health tool required to mitigate disease dissemination.[10] While screening tools may help identify those at risk for a certain disease, diagnostic testing is often required for

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https://doi.org/10.1016/j.semperi.2020.151284
0146-0005/

confirmation. Multiple strategies have been proposed for the screening and testing of COVID-19, as the understanding of the at-risk population evolved from recent travelers to asymptomatic community spread. As a result, the American College of Obstetricians and Gynecologists (ACOG) and Centers for Disease Control and Prevention (CDC) have developed guidelines to assist in triaging patients with suspected COVID-19. These statements encourage clinicians to prioritize testing in high risk populations while considering epidemiologic factors that may increase a patient's a priori risk for the disease.[11] Furthermore, ACOG recognizes the potential for asymptomatic patients presenting to labor and delivery units and implores clinicians to consider additional strategies as appropriate.[12]

Consistent with the guidance put forth by the CDC and ACOG, certain institutions based in geographic regions with higher COVID-19 disease prevalence have opted for universal testing of patients admitted to labor and delivery by via SARS-CoV-2 nasopharyngeal PCR.[13] At many New York City institutions, which are considered to be within an epicenter of the COVID-19 pandemic due to high case burden, implementation of universal testing via SARS-CoV-2 nasopharyngeal PCR has helped to provide a fuller understanding of the variable COVID-19 patient presentations that are possible among pregnant women.[14,15]

Clinical presentations and considerations

The various clinical characteristics of the COVID-19 infection have been documented in the literature as information continues to emerge. In large retrospective studies, common symptoms include the presence of fever, cough, myalgias, fatigue, and dyspnea.[16,17] Less frequently, gastrointestinal symptoms such as nausea/vomiting and diarrhea may be exhibited. Neurological manifestations including anosmia, hypogeusia, and impaired consciousness have also been described. While this COVID-19 symptomatology may be similar in pregnant women, less is known about their clinical presentations, particularly as dyspnea, fatigue, nausea and vomiting are common pregnancy complaints. Therefore, we will review what is known for COVID-19 in the context of maternal adaptations to pregnancy and the physiologic changes that occur, in order to describe both the pulmonary and extrapulmonary manifestations of this disease entity.

Classifying severity of disease

Included in the initial assessment and management of pregnant women with suspected or confirmed COVID-19 is the determination of illness severity.[12] In the largest cohort of over 44,000 confirmed adult cases of COVID-19 from China, illness severity included mild, severe, and critical disease.[18–20] Mild disease, characterized by mild symptoms and stable vital signs, comprised 81% of the cohort. Severe disease, characterized by significant dyspnea, hypoxia, greater than 50% lung involvement on imaging, comprised 14% of the cohort. Lastly, critical disease, characterized by respiratory failure, shock, or multiorgan system dysfunction, comprised 5% of the cohort. In a series of 43 confirmed COVID-positive patients diagnosed over a two-week period in a New York City hospital, pregnant patients experienced similar rates of clinical severity categorization as non-pregnant adults.[14]

The Society for Maternal and Fetal Medicine (SMFM) has additionally put forth a similar severity scale for the assessment of pregnant patients with COVID-19 including 5 categories, asymptomatic, mild, moderate, severe, and critical disease.[21] Based on these classifications, patients can meet criteria for outpatient or inpatient observation with specific recommendations on their respective management goals. Interestingly, in the summary of 44,000 confirmed COVID-19 cases from China including non-pregnant and pregnant adults, only 889 (1%) patients were categorized as asymptomatic. This study recognizes the insufficient testing capacity that may limit detection of asymptomatic carriers of COVID-19. However, pregnancy may offer a unique opportunity to estimate the true prevalence of asymptomatic carriers in the population, given that certain institutions have opted for universal screening of all patients admitted to Labor and Delivery. In a recent study of 215 pregnant women admitted to a New York hospital between March and April 2020, 211 patients were asymptomatic. Of these 211 patients, 29 (13.7%) were positive for SARS-CoV-2, which may demonstrate that the true prevalence of disease is underreported in the general population, and underscores the true risk of infection in obstetric patients.[22]

Pulmonary manifestations

Among pregnant patients with significant symptoms, ACOG recommends prompt clinical evaluation for respiratory compromise with physical examination, blood gas analysis, pulse oximetry, and radiologic assessment as indicated. However, each of these objective measures may have varying results in the pregnant versus non-pregnant state. Understanding these differences is essential in order to identify patients at risk for worsening disease.

Blood gas analyses and pulse oximetry

Perhaps the most striking change in respiratory physiology during pregnancy is an increase in resting minute ventilation, which is driven primarily by an increase in tidal volume while maternal respiratory rate remains nearly unchanged.[23] In comparison to non-pregnant adults, this relative hyperventilation causes arterial pCO2 to decline with a compensatory decrease in serum bicarbonate. There is additionally a rise in arterial pO2. This compensated respiratory alkalosis defines the normal acid-base status of pregnancy and is integral in the evaluation of critical patients.

In pregnant patients with COVID-19 infections, defining indications for oxygen supplementation requires attention to both maternal and fetal status. In addition to standard criteria for oxygen supplementation, the WHO recommends a higher oxygenation goal in pregnancy, for fetal benefit. In a stable patient undergoing resuscitation, target SpO_2 goal is >90% in a non-pregnant adult, while this goal increases to ≥92–95% in pregnant women.[24] Furthermore, while permissive hypercapnia in acute respiratory failure may allow for protective ventilation, maternal hypercapnia may cause fetal

respiratory acidosis and is thus may not be a desirable option in the management of pregnant women.[25]

While identification of patients requiring supplemental oxygenation is easily achievable in the inpatient setting, a recent report of patients with 'silent hypoxia' has been described, wherein patients without respiratory distress have low SpO_2 levels. Though clinically well appearing, these patients have the propensity to deteriorate quickly.[26,27] Given that these patients are frequently deemed appropriate for outpatient management, SMFM urges obstetrics clinicians to continue close monitoring of COVID-19 patients in the outpatient setting. For patients with remote monitoring available, such as pulse oximetry, an SpO_2 less than 95% should prompt evaluation by a clinician.[21]

Radiologic findings

Chest imaging findings in the context of COVID-19 are variable. In the non-pregnant adult population, chest CT images typically demonstrate multifocal bilateral peripheral ground glass opacities, which is a non-specific marker of COVID-19. In a retrospective study of 59 patients with laboratory-confirmed or clinically-diagnosed COVID, pregnant women were more likely to have mixed or complete consolidations on chest imaging.[28] Given these variable and non-specific findings, the CDC and American College of Radiology (ACR) do not recommend chest imaging for the diagnosis of COVID-19. Instead, CT chest or chest x-ray may be used as an adjunct in the diagnosis and treatment of other clinical entities, such as bacterial pneumonia or pulmonary embolism.[11,29]

Hematologic and immunologic manifestations

Many studies have cited the role of laboratory investigations in the identification of patients at risk for severe or critical disease.[17,30,31] Importantly, the pathophysiology of COVID-19 infection appears to involve a pro-inflammatory and pro-thrombotic state.[32] Interpretation of common markers of inflammation and thrombosis, however, may be limited in pregnancy given a known baseline elevation in serum reactants during this time. An understanding of the normal hematologic and immunologic parameters in pregnancy is necessary in the interpretation of COVID-19 severity.

Immunologic response

A commonly cited laboratory finding among patients with COVID-19 is a normal white blood cell count accompanied by a depressed total lymphocyte count, or lymphopenia. Pregnancy, on the other hand, is characterized by a physiologic mild leukocytosis with neutrophilia.[33] In a retrospective review of 55 pregnant women, a lower lymphocyte count was noted in patients with confirmed COVID-19 in comparison to controls, which may indicate that lymphopenia is a reliable marker for disease progression in this population.[34]

In addition to lymphopenia, elevations in several acute phase reactants have been cited in the literature as potential markers of COVID-19 infection, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and ferritin.[11] Though large studies reviewing these analytes in COVID-19 positive pregnant patients have not been published, it is important to recognize the dynamic changes in each of these markers in the normal progression of pregnancy.[35] Given the known elevation of these markers during pregnancy, the absolute value of each of these indices may be non-specific. However, further studies determining their clinical utility when trended over time may provide insight as to potential roles as markers for severe COVID-19 infection.

Coagulation pathways

The complex interplay between the immune response to infection and the activation of coagulation pathways results in a procoagulant state in patients afflicted by COVID-19.[32] Patients are at risk for both arterial and venous thrombi, leading the WHO to release interim guidance for the use of prophylactic heparin among these patients.[11,36] Pregnancy also poses an increased risk of hypercoagulability.[37] As a result, use of venous thromboembolism prophylaxis among pregnant and postpartum patients with COVID-19 is also recommended.[21]

Cardiovascular manifestations

Increased maternal and fetal metabolic demands throughout pregnancy give rise to hemodynamic changes during this time.[38] Knowledge of these physiologic responses, including an increased cardiac output, expanded plasma volume, and reduced vascular resistance, are required to interpret cardiovascular tests in pregnancy and guide treatment.[39]

With regards to COVID-19 in the general adult population, the cardiovascular complications include direct myocardial injury/myocarditis, cardiomyopathy, myocardial infarction, and arrhythmia.[40] Select case reports have documented cardiovascular findings in the obstetric population, including COVID-19 related cardiomyopathy.[41] Additionally, several studies in the non-pregnant population have shown that pre-existing cardiovascular disease or development of cardiac injury may predispose patients to significantly worse outcome.[40,42] Although no specific studies have assessed this association in pregnancy, pregnant women with underlying cardiovascular or metabolic disease may be at elevated risk for complications related to COVID-19 and should therefore be monitored closely for development of severe or critical disease.

Hepatic manifestations

Liver injury may be present among COVID-19 patients at nearly all spectrums of the disease.[43] Recent studies in non-obstetric populations have documented the incidence of hepatic involvement ranges from 14.8% to 53%, as demonstrated by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels.[44] In a study assessing non-ICU hospitalized adults, nearly one-third of patients had serologic evidence of liver injury.[43] Although the specific cause for these abnormalities is unclear, elevations in serum biochemistries may ultimately reflect direct virus-induced cytotoxic effect or immune-mediated inflammation.[45] Regardless of etiology, liver injury in mild COVID-19 cases is usually transient and does not require specific treatment.[46] However, the American Association for the Study of Liver

Diseases (AASLD) advises clinicians to consider all potential etiologies for hepatic injury, and pursue further work-up should liver biochemistries worsen.[47]

In the obstetric population, SMFM encourages obstetricians to consider laboratory findings among COVID-19 patients that may overlap with other obstetric conditions, such as HELLP syndrome and preeclampsia with severe features.[48] While the diagnostic criteria for these illnesses remains unchanged, it is reasonable to consider testing for SARS-CoV-2 if a patient presents with transaminitis and has additional risk factors for COVID-19. Moreover, a diagnosis of COVID-19 should not exclude the possibility of co-existing obstetric disease which should therefore always be considered. Management should continue to be dictated by established guidelines for both obstetric and non-obstetric etiologies of hepatic injury.

Neurologic manifestations

The neurologic manifestations of COVID-19 have been described in three different categories: central nervous system manifestations, peripheral nervous system manifestations, and skeletal muscular injury manifestations.[49] Central nervous manifestations include dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures. Peripheral nervous system manifestations include taste impairment, smell impairment, vision impairment, and nerve pain. Lastly, skeletal muscular injury manifestations include skeletal muscle pain with an accompanying elevation in serum creatinine kinase level. In a study of 214 non-obstetric patients with confirmed COVID-19 infection in China, 78 (36.4%) had neurologic manifestations.

With a large percentage of patients in the non-pregnant population presenting with these neurologic symptoms, it is not unreasonable to expect the obstetric population to experience similar manifestations. However, while some neurologic symptoms may be fairly specific to COVID-19, such as taste and smell impairments, other symptomatology may again overlap with obstetric conditions. Headache, acute cerebrovascular disease, and seizures, for example, may prompt an investigation for preeclampsia in the obstetric population.

Renal manifestations

Akin to the hepatic manifestations of this disease, the exact etiology of acute kidney injury (AKI) among patients with COVID-19 is unclear. While some studies have purported AKI is secondary to multi-organ failure and shock, others have suggested the possibility of direct virus-induced cytotoxic effect.[50,51]

With the normal progression of pregnancy, both plasma and interstitial oncotic pressure fall, with the latter decreasing to a greater extent. Therefore, special precaution should be taken with fluid resuscitation among pregnant patients. There is additionally an increase in capillary hydrostatic pressure.[52] The combination of these two forces results in extravasation of fluids into the interstitial space in pregnancy. As a result, pregnant patients with AKI and pulmonary injury secondary to SARS-CoV-2 may be at particular risk for pulmonary edema. Serial volume assessments in the context of the specific clinical scenario must be undertaken to determine the appropriate fluid resuscitation goals for each individual patient.

Management of AKI typically begins with conservative efforts, with close attention to potential electrolyte derangements and fluid status of the patient as the disease progresses. Discontinuation or judicious use of nephrotoxic medications are necessary management strategies in caring for women with COVID-19 infection. Renal replacement therapy is reserved for kidney injury not responsive to supportive management. In the pregnant patient, similar principles are applicable in the management of AKI; however, additional obstetric etiologies of AKI such as severe preeclampsia must be taken into consideration.

Conclusions/future directions

COVID-19 infection results in both pulmonary and extra-pulmonary manifestations. While the multi-organ involvement of this disease entity has been cited extensively in the literature, there is limited data confirming these findings in the obstetric population. Herein, we reviewed the presentation of this disease per organ system, as well as special considerations that must be undertaken among pregnant patients. Future studies assessing specific findings in the obstetric population will allow clinicians to gain a better understanding of the progression of this disease and develop guidelines for system-based treatment as this pandemic continues to unfold.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Grant support

None.

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