COVID-19

Management and Perspective of Coronavirus Disease 2019 (COVID-19), Pregnancy, and Hypercoagulability

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Abstract

The modern-day pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread rapidly. There is limited data about the effects of the virus on pregnant women, even in women who were infected by other strains of coronavirus such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). After reviewing numerous articles published in the peer-reviewed journals and other authentic sources, in this mini-review, we evaluated various key clinical and laboratory aspects of coronavirus disease 2019 (COVID-19) in relation to pregnancy. Eligibility criteria included the patient being pregnant upon admission to the hospital, clinically diagnosed, and/or laboratory-confirmed COVID-19. Taking a comprehensive approach by reviewing numerous studies, it is safe to say that there is no concrete evidence of intrauterine transmission. With adequate infection control measures, breastfeeding in neonates of mothers with COVID-19 is safe postpartum. A disruption of Virchow's triad by COVID-19 and the normal physiologic changes of pregnancy put the expectant mothers at great risk of arterial, venous, and placental thrombus formation, which can be managed by antithrombotic and related pharmacologic agents including antiviral and anti-inflammatory drugs.

Keywords Pregnancy · COVID-19 · SARS-CoV-2 · Preterm birth · Fetus · Hypercoagulable state

Introduction

Coronavirus disease 2019 (COVID-19) has been reported to be originated in Wuhan, Hubei Province, China, sometime in December of 2019. It is a novel coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease caused by this virus is therefore named COVID-19. It is believed to have originated via a zoonotic transmission at a seafood wholesale market in Wuhan, China [1]. Eventual human-to-human transmission played a major role in the succeeding outbreak. We have seen cases of coronavirus in the past such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [2]. Looking at the studies from these viruses, this mini-review may help provide insights into our current global situation with SARS-CoV-2 [2–4].

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Diagnostics

Hematologic laboratory findings include thrombocytopenia, lymphopenia, and leukopenia with an initial infection of SARS-CoV-2. The human angiotensin-converting enzyme 2 (hACE2) located in the lower respiratory tract epithelial cells has been confirmed as the receptor for entry of SARS-CoV-2. This in return causes a disruption between angiotensin-converting enzyme (ACE) and hACE2 leading to the activation of the renin-angiotensin system (RAS) [5]. There are several hematologic factors that indicate progression of disease and are seen in severe or critical cases of COVID-19. Neutrophilia, leukocytosis, prolonged prothrombin time, increase in interleukin (IL)-6 and IL-8, and an increase of D-dimers are seen. The neutrophil-to-lymphocyte ratio (NLR) is a predictive factor for critical illness (NLR low risk is < 3.13, and high risk is ≥ 3.13) [5, 6]. Chest computed tomography (CT) is the gold standard for assessing lung involvement, and it is superior to the nasopharyngeal swab for diagnosis involving the lungs [7].

There are benefits of using a point-of-care ultrasound (POCUS) instead of the conventional CT. It may be performed directly at a bedside by a single operator, which decreases the risk of dissemination of the disease among

healthcare professionals. Another major benefit especially in the pregnant population is that in contrast to a CT, a lung ultrasound is radiation-free. Findings in the ultrasound consistent with coronavirus disease–associated pneumonia are "irregular pleural lines and vertical artifacts (B-lines) and patchy areas of white lung" [7]. Chest CT findings may show ground-glass opacities, infiltrate/consolidation, bronchopneumonia, pneumonia, or pleural effusion [8].

Quantitative reverse transcription-polymerase chain reaction (RT-PCR) of samples is taken from the upper and lower respiratory tracts of the mother. Amniotic fluid is checked via direct aspiration at the time of delivery. Cord blood and neonatal throat swabs are collected immediately after delivery in the operation room. Breast milk samples are checked after their first lactation. All of these tests helped with the optimal evaluation of vertical transmission [9]. In a separate study, the placentas were also tested via RT-PCR and were found to be negative [10].

Symptoms

The symptoms of COVID-19 may range from mild to severe and usually appear within 2–14 days after the viral exposure. Symptoms may mimic the common cold in some patients; others may experience new loss of taste or smell and/or gastrointestinal symptoms such as nausea, vomiting, and diarrhea.

In a meta-analysis review of 19 studies including 79 hospitalized women, it was found that > 90% of the cases had a diagnosis of pneumonia [11]. High fever was the most common symptom, followed by cough and dyspnea, respectively. Preterm birth (< 37 weeks) was the most common adverse pregnancy outcome. Preeclampsia and fetal growth restriction were reported but only in women affected by SARS [11].

In another study, 596 of the patients had known pregnancy trimesters [8]. There were 14 (2.3%) cases in the first trimester, 61 (10.2%) cases in the second trimester, and 521 (87.4%) cases in the third trimester. It was observed that the most common cause for admission in the first two trimesters was COVID-19–related illness. The most common symptoms reported were fever and chills (59.6%) and cough (59.2%) cases. In the third trimester, the most common cause for admission was obstetric indications including labor and delivery. It is also important to note that in this study, 123/596 (20.6%) of the patients had underlying conditions at the time of admission. Of these, the most common were asthma (8.2%), hypertension (4.3%), and diabetes mellitus (3.8%) [8].

Hematologic Considerations

Due to the natural physiologic changes during pregnancy, it causes a hypercoagulable state. This is due to several factors, including an increase in the levels of clotting factors (such as factors VII, VIII, and X; von Willebrand factor (vWF); D-dimer; C-reactive protein (CRP); and fibrinogen). Concurrently, there is an increase in the number of inhibitors of the fibrinolytic pathway. Mild prolongation of prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) is also observed. There is also a decrease in protein S and a resistance to activated protein C (APC), which increases in the second and third trimesters, which are therefore unable to inhibit coagulation. Anatomical changes also play important role(s) by compressing the pelvic veins from a gravid uterus, which leads to a decrease in blood circulation in the lower extremities. This leads to stasis, which may contribute to clot formation [12]. For hospitalized patients with COVID-19–associated coagulopathy, monitoring platelet count, PT and/or aPTT, D-dimer, and fibrinogen levels are highly recommended.

COVID-19 influences many components of Virchow's triad, which is consisted of hemodynamic changes (stasis, turbulence), endothelial injury/dysfunction, and hypercoagulability [13, 14]. Endothelial cell invasion by SARS-CoV-2 leads to endothelial cell injury. This leads to a loss of fibrinolytic function resulting in thrombus formation and a large release of vWF. The loss of protective endothelium and resultant inhibition of clot-lysing system leads to a hypercoagulable state. COVID-19 has also been linked to an increase in intravascular fibrin deposition, which leads to hyper-viscosity. This disruption of Virchow's triad coupled with the normal physiologic changes of pregnancy leads to the increased formation of arterial, venous, and placental blood clot formation. All these data support the fact that COVID-19 is a risk factor for thromboembolism [13, 15].

Management of a hypercoagulable state in pregnant patients with or without COVID-19 is both treated medically with unfractionated heparin (UFH) or low-molecular-weight heparins (LMWH) [13, 15]. A study was conducted to evaluate if LMWH can be transferred via the placenta to the fetus or through breast milk [16]. There was no evidence to support either of these, and no LMWH was found in the placenta. The concentration of LMWH in breast milk was 10 times lower than in the maternal serum, therefore having no clinical significance/impact. Mothers can safely breastfeed while on LMWH or with an appropriate dosage of UFH [16]. It is well known that UFH and LMWH have multiple pharmacologic properties including the release of tissue factor pathway inhibitor (TFPI) from the endothelium and are capable of downregulating inflammatory cytokines. Thromboprophylaxis with LMWH is recommended for hospitalized patients with COVID-19 in the absence of bleeding. Mechanical thromboprophylaxis may be used when pharmacological thromboprophylaxis is contraindicated.

Pharmacologic Considerations

Management of patients diagnosed with COVID-19 is mostly symptomatic. These include, but are not limited to, early

isolation, oxygen therapy, avoidance of fluid overload, empiric antibiotic therapy, laboratory testing for the virus and co-infection, and fetal and uterine contraction monitoring. In patients presenting with progressive respiratory failure, early mechanical ventilation is very important [4].

Medical management is also mostly supportive care; currently, no targeted therapy is available [1]. Certain immunosuppressive medications, which include antivirals, antibiotics, antimalarial drugs, and steroids, have been tested in clinical trials. None of them has been proven to provide a definite therapy yet. Some of these medications include lopinavir-ritonavir, remdesivir, hydroxychloroquine, and azithromycin [17–19]. Notably, on October 22, 2020, the U.S. Food and Drug Administration (FDA) approved remdesivir for use in adult and pediatric patients (12 years or older, weighing at least 40 kg) for the first treatment of COVID-19 requiring hospitalization. It is cautioned that remdesivir should only be administered in a healthcare setting capable of providing acute care comparable to inpatient hospital care. However, clinical trials assessing the safety and efficacy of remdesivir in pregnant patient population are yet to be ascertained.

In a study that looked at a total of 114 mothers who were infected with SARS-CoV-2, a conclusion was drawn that it is safe for the neonate to be breastfed [20]. The mother's milk was analyzed, and antibodies of the coronavirus were detected, therefore being protective against the virus. In the postpartum period, direct breastfeeding is favored as long as the mother and neonate's health allows it. Appropriate respiratory measures should be taken to reduce the risk of transmission of the virus while breastfeeding. If for some reason, the mother cannot directly breastfeed, then her breast milk should be expressed and fed to the neonate [20]. In addition, supplementing with pasteurized donor human milk or infant formula may also be effective if the mother is unable to breastfeed exclusively [21].

Survival/Mortality Outcomes

In a study of 38 pregnant women, there were no maternal, fetal, or neonatal deaths due to COVID-19 [10]. In a separate study involving 12 patients infected with SARS, seven of the 12 patients were in their first trimester and resulted in four spontaneous abortions [22]. Four of the five patients with SARS after 24 weeks of gestation delivered preterm. The fatality rate was 3/12 (25%). In another study involving 13 patients infected with MERS, there were two cases of fetal demise and two preterm births [4]. Two of these 13 patients were asymptomatic and were identified due to a contact investigation. Three of the 13 (23%) patients died [4]. There was a high percentage of deliveries by cesarean, which is mostly due to the physician's preference and is based on a case-to-case scenario [23].

The COVID-NET Surveillance Study gives us further insight into the pregnancy outcomes in women hospitalized with COVID-19 in the USA from March to August of 2020. There were a total of 598 women, and the study was conducted across 13 states. Of those, 326 (54.5%) patients were asymptomatic of any COVID-19 signs or symptoms. The remaining 272 (45.5%) of the patients were symptomatic, of which two (0.7%) patients died, 23 (8.5%) cases were put on mechanical ventilation, and 44 (16.2%) cases were admitted to the ICU [8].

Notably, pregnancy outcomes from the COVID-NET Surveillance Study reported 448 live births with 10 cases of pregnancy loss. Of the 10 cases resulting in pregnancy loss, seven of the patients were symptomatic, and three were asymptomatic upon admission to the hospital [8]. Of the live births, 134/141 of these patients were symptomatic upon being admitted to the hospital. Interestingly, 314/317 cases were asymptomatic at the time of their hospital admission. The symptomatic patients saw a higher rate of preterm births as opposed to the asymptomatic patients. The percentages were 23.1% as opposed to 8%, respectively [8]. The modes of delivery of the 458 births were 65.9% vaginally, 33% via cesarean section, and 1.1% unknown [8].

Conclusion and Future Perspectives

As the burden and scope of COVID-19 continue to grow globally, there is still much to discover about the effects of COVID-19 on pregnancy and the perinatal and neonatal outcomes. Taking a comprehensive approach by reviewing numerous studies, it is safe to say that there is no concrete evidence of intrauterine transmission. Such was the case with SARS and MERS, both of which had a higher rate of maternal death than COVID-19. With adequate infection control measures, breastfeeding in neonates of mothers with COVID-19 is safe postpartum. A disruption of Virchow's triad by COVID-19 and the normal physiologic changes of pregnancy put the expectant mothers at great risk of arterial, venous, and placental thrombus formation, which can medically be managed with the use of pharmacologic agents such as heparin anticoagulants that also have antithrombotic properties. Eventually, along with the ongoing effective/safe vaccination programs, development of COVID-19 coagulopathies is also highly desirable keeping this contagious respiratory disease in perspective. Thankfully, with the latest developments with the FDA emergency use authorization (EUA) of COVID-19 vaccines in December 2020, the future outcomes are expected to improve in this arena.

Declarations

Ethics Approval   Not applicable.

Consent to Participate   Not applicable.

Consent for Publication   All the authors have read and approved the final draft for publication.

Competing Interests   The authors declare no competing interests.

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