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Outcomes and epidemiology of COVID-19 infection in the obstetric population

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ABSTRACT

As of June 19, 2020 there are more than 8.6 million COVID-19 cases worldwide with over 450,000 deaths. Providing obstetrical care in the setting of the pandemic poses challenges to the healthcare system in that, in comparison to many other medical specialties, obstetrical care cannot be deferred. Pregnant patients represent a high risk population for exposure and infection with respiratory pathogens and, as they require multiple points of contact with the healthcare system, are especially vulnerable. The purpose of this review is assess current epidemiology and outcomes research related to COVID-19 with a focus on obstetric patients. This review covers the global spread of the SARS-CoV-2 virus, symptomatology, modes of transmission, and current knowledge gaps related to epidemiology and outcomes for the obstetric population.

Introduction

In December 2019, a cluster of cases of severe viral pneumonia was identified in Wuhan, a city in the Hubei Province of China, that rapidly spread to a global pandemic with over eight million cases of infection globally.[1] Coronavirus disease of 2019, commonly known as COVID-19, is the disease caused by the novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] As of June 17, 2020, there are 2132,321 confirmed cases in the U.S. and 116,862 deaths in the United States.[3] Genomic sequencing of SARS-CoV-2 found that this virus is related to two other viruses: severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome-related coronavirus (MERS-CoV).[4,5] In pregnancy, due to physiologic and immunologic changes, there was concern for potential increased respiratory morbidity from viral pathogens similar to that from SARS-CoV-1 and MERS-CoV.[6] While most people infected with COVID-19 will be asymptomatic or only exhibit mild symptoms, progression to severe acute respiratory disorder and multiorgan failure contributes to significant morbidity and mortality especially among those with comorbidities such as diabetes and hypertension.[7]

Initial efforts to control the spread of this virus were hampered by multiple factors including asymptomatic carriage, lack of appropriate testing, and lack of knowledge due to the novel status of the virus. Within the United States, limited access to testing kits made it difficult to apply select quarantines of those spreading the virus. While testing capability has improved in the US there is continued spread of the virus with large numbers of new cases continuously being identified. In contrast, other countries such as Taiwan, Singapore, and South Korea employed more robust testing, tracking, and

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quarantine procedures leading to significantly lower infection rates and morbidity and mortality from COVID-19.[8–10] While testing for IgM and IgG antibodies to SARS-CoV-2 provides opportunity for identifying past exposures, many assays are yet to be validated with unclear test characteristics.[11]This review article will focus on the general epidemiology of the COVID-19 pandemic including geographic spread, symptomatology, transmission as well as current gaps in knowledge with a focus on the obstetric population.

Geographic distribution

At the time of this publication, there are approximately 8.6 million COVID-19 cases worldwide, with over 450,000 deaths.[12] The United States has the highest case count of any country with 2218,457 confirmed cases and 119,061 death as of June 19, 2020.[3,12] The Chinese government first acknowledged cases of the disease that would come to be called COVID-19 on December 31st, 2019, when it reported that healthcare workers were treating dozens of cases of pneumonia of an unknown cause.[13] Presumed to be a zoonotic illness from a “wet market” selling meat and seafood in Wuhan for many weeks it remained unknown whether there was viral spread from person-to-person or if transmission was only occurring by animal-to-human spread.[14] The first death from COVID-19 was reported on January 11th. By January 21st, cases had been reported in Japan, South Korea, Thailand, and in Washington State in the US. The city of Wuhan, with a population of over 11 million people, was locked down on January 23, with the cancellation of all major travel by plane and train leaving the city, and restrictions on travel within the city.[15] One week later, after thousands of cases had been reported in China, the WHO declared a global health emergency.[16]

Global response

In the weeks following the Wuhan lockdown, cases of COVID-19 emerged worldwide. The responses of individual countries and regions varied widely as they attempted to apply early lessons from China in the setting of different populations and health infrastructures. Italy was the first country outside of China with a major outbreak and experienced a high death rate. Italy’s first cases were recorded on January 31st when two Chinese tourists tested positive in Rome. A state of emergency was declared on the same day and all flights to and from China were suspended. Clusters of cases emerged starting in Northern Italy, and by the beginning of March every region was affected. Cases skyrocketed in the early weeks of March, and the Italian healthcare system was overwhelmed by demands for critical care beds and ventilators. As of June 19, 2020, Italy had over 238,011 cases and the fourth highest number of deaths of any country at 34,561.[12] Several factors were identified as contributors to the impact of the virus in Italy. Northern Italy (and Milan in particular) is a major hub for international business and tourism and has densely populated cities. Italy has a low birth rate and high life expectancy, contributing to an elderly population with 23% of the country over 65 years old. Further, Italians are likely to live in multigenerational homes, where adults live with and help care for their parents, and may commute from small towns to larger cities for work. Social customs in Italy, like cheek kissing on greeting, may also have contributed to community spread.[17,18]

In comparison to Italy, Japan experienced relatively low mortality. Japan is a country with an even larger percentage of the population aged over 65 and has densely populated cities and significant travel to and from China. But as of June 19, 2020, Japan has had only 17,658 cases and 951 deaths.[12] There may be several explanations for the low case death rates. One is a cluster-based testing approach in which clusters of infection are traced to a single source and persons with high transmissibility are isolated. In addition, there was relatively high population adherence to behavioral interventions and especially to the “three C method,” referring to avoidance of closed spaces, crowded spaces, and close contact. It has been suggested that an additional protective factor in Japan (and perhaps other East Asian countries) is the custom of wearing masks in public. This, in addition to different social customs for greeting and conversation involving less physical contact, may account for a significant difference in rates of community transmission.[19] By the time the death toll was reaching its peak in Italy, in New York the combination of international travel, high population density, and late adoption of social distancing led to an exponential increase in cases over a short period of time. On March 1st the first case was reported in NYC. By April 1st there were 83,000 cases and 1900 deaths statewide. As of June 18, 2020 there were over 382,000 cases and 26,000 deaths.[12]

Vulnerable & high-risk populations

As global efforts at containment evolved, several unique populations were highlighted as particularly high-risk groups for uncontrolled transmission. By early May 2020, 40 cruise ships had confirmed cases of COVID-19 on board. The first of these to receive international press was the Diamond Princess, a 3700-person ship that was quarantined off the coast of Yokohama, Japan for several weeks after an 80 year old passenger tested positive on February 1st, six days after leaving the ship. By late February, over 500 passengers had tested positive and had overwhelmed local hospital capacity, requiring evacuation to sites where they could receive care. All passengers had left the ship by March 1st. By the end of March, testing both on and off the ship resulted in 712 positive tests out of 3711 people, or a rate of 19.2%. Cruises have often been sites of outbreaks of infectious diseases that pass quickly through a confined and closely quartered population. Factors that made them particularly dangerous for a highly infectious respiratory illness include a high average age of passengers, with approximately 40% of travelers over age 50, and that many cruise ships (unlike airplanes) do not use HEPA filters for air circulation, which require the removal of at least 99.95% of particles with a diameter of three microns or more.[20]

Residents of nursing homes are a vulnerable population for whom confinement presents its own challenges. A long-term care center in King County, Washington was the site of the first COVID-19 outbreak in the country and an early harbinger of the severity of the epidemic for the elderly in which 34 residents died with a case-fatality rate of 33.7%.[21] Safety concerns were noted at this nursing which has been penalized $600,000 dollars after health inspections[22] and subsequent measures by nursing homes across the country ranged from strict restrictions on visitation to complete lockdown with no visitors allowed, meal delivery to the doorstep, and cancellation of all group activities.

Pregnant women were initially listed as high risk populations for severe morbidity and mortality due to COVID-19. Prior experiences with related viruses (SARS-CoV-1 and MERS-CoV) demonstrated high rates of ICU admission.[23] However, as described below, moderate-sized series of COVID-19 among pregnant women do not suggest high rates of ICU admission although severe complications and death have been reported.[24,25]

Symptomatology and outcomes

General population

As testing capabilities have increased, screening efforts in the general population revealed a greater proportion of asymptomatic SARS-CoV-2 infections than previously recognized. Upon the screening of over 13,000 Icelandic citizens and nearly 3000 residents of a northern Italian city, 43% of cases identified were asymptomatic.[26,27] Of the Japanese citizens evacuated from Wuhan, 42% of those with confirmed infections were without symptoms, as were 52% of the 634 cases on the Diamond Princess cruise ship docked in Japan.[28,29]

While many SARS-CoV-2 infections appear to be asymptomatic, patterns of symptomatology among those who do develop clinical manifestations of COVID-19 have emerged as the global burden of cases grows. A report characterizing symptoms among 1099 non-obstetric patients hospitalized throughout mainland China early in the outbreak demonstrated fever and cough to be predominant symptoms present in 89% and 68% of patients respectively.[30] Fatigue was present in 38% of these patients, while shortness of breath, myalgia, headache, sore throat, and chills were present in 12−19%. Nausea, vomiting, diarrhea, and nasal congestion were present in fewer than 5% of cases. An additional review of Wuhan cases further supports these findings as does a subsequent analysis of cases in Beijing and a meta-analysis comprising nearly two thousand patients.[31-33]

While these studies showed gastrointestinal symptoms to be uncommon, recent have demonstrated higher likelihood of diarrhea, nausea, vomiting, abdominal pain, or anorexia. In some cases gastrointestinal symptoms arose before respiratory symptoms, and, uncommonly, patients experienced such symptoms in the absence of any respiratory symptoms.[34,35] Olfactory and gustatory dysfunction have also emerged as highly prevalent symptoms that may have been underrecognized initially. In a study examining 417 patients with mild-to-moderate disease across European hospitals, 86% and 88% of patients endorsed anosmia/hyposmia and ageusia/hypogeusia, respectively.[36] There is also evidence that anosmia and ageusia can represent the first or only clinical manifestations for some patients, and are often present in the absence of nasal congestion or rhinorrhea.[37] In one cross-sectional survey, anosmia and ageusia were reported more frequently by females than males, and patients with these symptoms were generally younger than those without.[38]

Box 1. NIH severity of illness categories for COVID-19[39]

Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level.
Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO_2<94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%.
Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

The National Institutes of Health's criteria for classifications of disease severity (which outline mild, moderate, severe, and critical illness categories) are informed in part by symptomatology, but rely largely upon vital signs and lab or imaging findings (Box 1).[39] While several comorbidities, lab abnormalities, and imaging findings have presented themselves as consistent predictors of illness severity, evidence linking specific symptoms with patient outcomes is limited. One study examining 179 non-pregnant patients with confirmed and probable COVID-19 in Wuhan found that dyspnea, fatigue, sputum production, and headache were more frequently present in those whose infections were ultimately fatal. Another study however examining nearly two hundred confirmed cases found symptoms did not differ significantly between survivors and non-survivors.[7,40]

Obstetric population

Similar to the general population, a significant proportion of SARS-CoV-2 infected pregnant women are asymptomatic. In one study, 88% of women that screened positive upon admission for delivery hospitalizations at two New York City hospitals were without symptoms.[41] In a systematic review of 538 pregnancies complicated by COVID-19, 48% of patients experienced fever, 46% cough and 17% myalgias.[42] Dyspnea (16%), fatigue (15%) and headache (9%) were less common. There are reports of severe complications of COVID-19 among obstetric patients including cardiomyopathy,[43] need for extracorporeal membrane oxygenation,[44] and death.[45] In the aforementioned systematic review, 3 of 209 women (1.4%) were admitted to an intensive care unit. Estimates for how common critical illness is in the obstetric patient is imprecise given the rare nature of such events. In a series of 158 pregnant patients with COVID-19 in New York City, 11 women experienced symptomatic hypoxia requiring oxygen of which 9 required ICU or step-down level care. In that series there were no cases of stroke, thromboembolism, or cardiomyopathy and one women was intubated to receive general anesthesia during a complicated cesarean delivery.[24] Series of cases from China demonstrated similar results. In a similarly sized study, a similar proportion of women experienced hypoxia: of 118 women with COVID-19 infection, 9 had hypoxemia including one that required noninvasive mechanical ventilation.[25,44] Symptoms at presentation may be useful in prognosis. In the series of 158 patients from New York, 1 of 63 patients who were initially asymptomatic developed moderate or severe symptoms, compared to 13 of 75 with mild symptoms on presentation.[24] In this series, women with underlying medical conditions such as asthma were more likely to develop moderate or severe symptoms.[24]

Transmission

General transmission

According to the WHO, a large proportion of the initial cases in late December 2019 and early January 2020 were linked to a wet market where seafood, wild, and farmed animal species were sold. Many initial patients were purveyors or visitors at this market. Environmental samples taken further suggested the market in Wuhan City was the source of this outbreak. The virus could have been introduced into the human population via transmission from an animal source or an infected human could have introduced the virus that was them amplified in the market environment. According to the WHO, subsequent investigations into the first human cases from early December were not linked to this market suggesting infection through contact with other sources.[14] Whether the virus came from bats during the period in question is debated; genomic analysis of SARS-CoV-2 has found 96% nucleotide similarity with a coronavirus isolated from a bat.[35] Coronavirus has crossed species in China before.[35,46,47]

The general expert consensus is that human-to-human transmission occurs primarily through respiratory droplets which typically cannot travel more than six feet.[48-51] Studies have supported the possibility that individuals infected with COVID-19 may be contagious prior to or in the complete absence of any symptoms. A case report documented a 20-year-old woman who lived in Wuhan and without symptoms who infected two relatives with COVID-19. Additionally, she had no imaging concerns for COVID-19 on chest CT, and had normal c-reactive protein levels and lymphocyte counts. She initially tested negative on RT-PCR for SARS-CoV-2 but was then positive two days later followed by two negative retests 8 and 11 days after. Five of her relatives became ill with COVID-19, two of which developed severe pneumonia.[52] However despite this and other similar case reports, asymptomatic transmission appears to be rare according to the WHO.[53] The varying symptomatology associated with COVID-19 has made ascertaining the exact number of individuals infected and infection control measures difficult. Additional concerns related to accurate ascertainment of diagnoses include risk for false positive (which may erroneously ascribe asymptomatic transmission) and false negative results[54–57] although the case presentation above took place in an area highly endemic of COVID-19 making a false positive less likely.

Whether COVID-19 can be passed via airborne transmission is controversial.[58,59] Pathogens that are “airborne” are considered to be those that can survive on respiratory secretions $<5\ \mu$m and remain suspended in air for an extended period of time. Airborne pathogens are a source of inhalational exposure and present extensive challenges in public health and infection control.[60,61] One study evaluating the stability of SARS-CoV-2 in aerosols and on various surfaces created a simulated environment using a three-jet collision to generate aerosols $<5\ \mu$m containing SARS-CoV-2 into a Goldberg drum. They found detectable viable virus in aerosols three hours after initial generation. They also found that SARS-CoV-2 was more stable on plastic and stainless steel than copper and cardboard and detectable up to 72 h after application. The stability of SARS-CoV-2 was found to be similar to that of SARS-CoV-1 which was tested under the same experimental circumstances.[58] Different conditions within the atmosphere can also affect the distance of droplet spread and rate of evaporation and other studies have detected environmental virus in facilities that care for COVID-19 patients.[62,63] The degree to which these factors are generally relevant to human transmissibility is unclear.

Vertical transmission

Vertical transmission refers to transmission of a disease from an infected individual to their offspring prior to or immediately after delivery. While transmission from mother to baby is theoretically possible via both respiratory droplets and transplacental passage, risk for vertical transmission appears to be low; a systematic review found no cases of vertical transmission among 310 deliveries for which reverse-transcription polymerase chain reaction data were made available.[42] SARS-CoV-2 is known to interact with the angiotensin-converting enzyme 2 (ACE2) receptor, allowing it entry into cells to cause viral replication and infection via endocytosis. ACE2 has been found on multiple human tissues including the heart, kidneys, lung alveolar epithelial cells, the placenta and fetal organs.[64,65] Presence of ACE2 on maternal-fetal interface and fetal organs makes placental dysfunction and pregnancy loss theoretically possible in addition to vertical transmission. The most definitive evidence of intrauterine transmission would be the presence of viral DNA in the amniotic fluid or fetal blood prior to delivery. In case reviews in the published literature, intrauterine transmission of SARS-CoV-2 has not been confirmed.[66–69] Cases of positive serologies for SARS-CoV-2 IgM antibodies within fetal cord blood have been reported.[70,71] In one case a female neonate was delivered in a negative pressure isolation room with a mother in a N95 mask that had no close contact with the infant. The infant had no symptoms but did have SARS-CoV-2 IgG and IgM levels as well as elevated cytokines.[70] There was no detectable SARS-CoV-2 on serial RT-PCR tests of the neonatal nasopharyngeal swabs. While detection of IgM antibodies could be concerning for in utero transmission, the specificity and sensitivity of IgM tests vary as they are prone to false-positives and false-negatives as well as significant cross-reactivity.[72,73] Well-characterized data on neonatal outcomes with maternal COVID-19 infection in the first and second trimester is very limited.

Conclusion

The COVID-19 pandemic has resulted in all points of direct human contact coming under scrutiny. Globally, shutdowns have been instituted in an attempt to curtail spread with severe negative impacts on the economy. While decreasing non-urgent utilization of in-person healthcare may be possible for many medical specialties, provision of in-patient obstetric services needs to be continued at full capacity with both maternal and fetal/neonatal considerations. Obstetric research literature on COVID-19 is limited, but early evidence supports that pregnant women do not appear to be one of the highest risk groups for adverse outcomes even though risk is present for cardiomyopathy, ICU admission, and death, and hypoxia occurs in a significant minority of patients. With limited data, early findings on risk for vertical transmission appears to be reassuring although larger samples are required to estimate risk particularly with documented infections occurring in the first and second trimesters.

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