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Review Article

Understanding Maternal COVID With Latest Treatments: A Review

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Abstract

In the late year of 2019, the Coronavirus disease (COVID-19) emerged and caused an ultimate pandemic throughout the year of 2020. Not only were cities on lockdown, but the virus caused a global scare in which families quarantined within their homes. From drastically dropping the economy to hospitalizing millions of patients, the pandemic caused a baby boom. This review paper analyzes and summarizes the pathophysiology, signs and symptoms, maternal risk factors, and the most up to date treatments of COVID-19 to maternal patients.

Keywords: *Coronavirus; COVID 19; Maternal COVID; Pandemic; Outbreak*

Introduction

COVID-19

The SARS-Cov-2 (CoVid-19), a positive-stranded RNA virus with enveloped properties, was first recognized in Wuhan, China, in December 2019; which would be the initial turning point for China and the entire world [1].

This infectious RNA virus was first categorized as an epidemic, after it solely impacted China. However, the virus spread rapidly throughout more than 200 different countries worldwide. Within months, it was able to produce approximately 508,000 fatalities [2]. The vast spread of the virus influenced the World Health Organization (WHO) to announce. COVID -19 as a global pandemic (WHO, 2020). As of 2020 December, over 10 million cases have been confirmed internationally [2]. It has been estimated for every 1000 patients infected with COVID-19, approximately 5 - 10 people will succumb to the effects (Mallapaty, 2020). The high mortality rate of COVID-19 is the differentiating factor from other viral infections. This disease puts the young, elderly, and immunocompromised individuals at risk of death (CDC, 2020). Patients infected with the virus can be admitted into the hospital for secondary illnesses, which include pneumonia, upper respiratory tract infections, respiratory depression or difficulties, sepsis and/or multi-organ disease [2].

This pandemic has put civilians' lives at risk and jeopardized the economy to a great degree. In efforts to promote social distancing, countries are laying off workers, to combat the spread of the disease (Jung, 2020). The disease itself is spreading fast, and vaccines are presently in the trial phase in 172 countries (WHO, 2020). The current status of treatment and management for COVID-19 vaccinations still requires a thorough evaluation of the effectiveness of anti-viral therapy, compared to the possible side effects.

Pathophysiology of COVID-19

The pathogenesis of COVID-19 is the same as SARS-CoV, which is another coronavirus strain [3]. It is initiated through respiratory droplets or fomite exposure (Brenneis, 2020). These droplets can be transmitted to other individuals when the infected patient coughs, sneezes, speaks or touches an infected inanimate object (Brenneis, 2020). Once this transmission comes into contact with the mucous membranes, such as the eyes, nose, or mouth, the infectious particles enter the mucus lining (Brenneis, 2020). From the mucus lining, the viral particles can then enter the host's bloodstream (Brenneis, 2020). An important structural component of the coronavirus is the spike (S) protein, which allows for it to bind to host receptors [4]. The entry depends on the binding of the surface unit, S1 component of S protein, which then facilitates viral attachment to the surface of target host cells [5]. Another key finding is that a protease is necessary to allow virus fusion, which is the TMPRSS2 protease [5]. According to Narang., *et al*., SARS-CoV-2 makes its entry into the cell via the angiotensin-converting enzyme 2 (ACE2) receptor [3]. The ACE2 receptor activity is upregulated during pregnancy.

The viral particles attached to angiotensin-converting enzyme (ACE-2) receptors are located on the surface of body cells lining the heart, kidneys, lungs, and gastrointestinal lining (Brenneis, 2020). The virus then disrupts gene transcription to alter protein assembly once the viral RNA is released, causing new proteins to be formed by cells to be transported and packaged by the endoplasmic reticulum (Brenneis, 2020). When the viral proteins get released, the incubation period, on average is 4-14 days until symptoms of viral contraction appear (Brenneis, 2020).

Different pathophysiology exists for mild, moderate and severe symptoms. In mild to moderate cases, there is an increase in ACE-2 receptors in the tissues of the lungs, kidneys and the myocardium (Brenneis, 2020). Inflammatory cells, such as neutrophils release reactive oxygen species, which results in the development of cough symptoms (Brenneis, 2020). The resulting edema in the lungs' alveolar branches influences the presentation of dyspnea (Brenneis, 2020). The edema accumulating in the interstitial space also causes decreased oxygen diffusion from the alveoli into the capillaries (Brenneis, 2020). Consequently, there is an increase in cardiac output, which increases the workload of the heart (Brenneis, 2020).

In more severe cases of COVID-19, cell death occurs due to the inflammatory cytokines (Brenneis, 2020). These cytokines influence the hypothalamus to excrete prostaglandins resulting in high fever (Brenneis, 2020). A high fever is indicative of an infectious pathogen interfering with normal bodily functions. Body aches are caused by apoptosis of cells triggered by an inflammatory response from the increased cytokines. Decreased oxygen diffusion due to edema can cause the heart to produce deadly arrhythmias (Brenneis, 2020).

Maternal COVID-19

Maternal COVID refers to the effect of coronavirus disease on pregnant women and breastfeeding mothers. Pregnant women and breastfeeding mothers can be classified among the most vulnerable members of society. Pregnant women undergo numerous hormonal changes within the gestational period. The hormonal changes compromise their immunity making them more susceptible to viral and bacterial infections (Cdc.gov., 2020). Shortly after giving birth, the hormones may balance, boosting the immunity of the mother. The hormones, Progesterone and Estrogen, are increased during pregnancy. The newborn child is highly dependent on the mother, and incase the mother is infected, the child will also be at a high risk of either bacterial or viral infections. Newborn babies have low innate immunity, and it is the mother's responsibility to take necessary precautions to keep safe from any infections, including the coronavirus disease. When a mother is exposed to the infection, the newborn baby is also at a greater risk of being infected.

Signs and symptoms of maternal COVID

According to Dr. Berhan's research, the symptoms of COVID among pregnant women and breastfeeding mothers are similar to those exhibited by the general public members [6]. Some of the most common symptoms seen among expectant and breastfeeding mothers

seen in the general public include tiredness, fever, and dry cough (Ehrlich, 2020). Other symptoms that may not be common to all mothers suffering from COVID are discoloration of fingers and toes, conjunctivitis, sore throat, headache, loss of the sense of smell or taste, diarrhea, rashes on the skin, and body ache [6]. Specific symptoms that indicate that the patient is in severe condition and requires more attention such as shortness of breath or difficulty in breathing, loss of movement, loss of speech, and chest pains. The signs and symptoms can take up to 14 days to show up from the day a mother was infected.

Risk factors of maternal COVID

Various factors such as lowered innate immunity expose mothers, putting them at a greater risk of contracting the coronavirus disease. The most obvious one for pregnant mothers is the lowered maternal innate immunity due to the hormonal changes that their bodies are experiencing [7]. With a lowered immunity, pregnant women are more susceptible to respiratory bacterial and viral infections. Going on with daily activities without taking COVID-19 precautions, such as social -distancing exposes expectant mothers to COVID-19. The social distancing regulation requires people to maintain a distance of 1.5 meters and avoid close contact. Expectant women have to get prenatal care by regularly visiting the doctors for routine checkups. The hospital is a high risk are and by regularly visiting the area, pregnant mothers remain at risk of getting infected. It is necessary for breastfeeding and pregnant mothers to observe safety regulations such as social distancing,

Methods

The data presented here were gathered via Research Gate, National Center for Biotechnology Information, PubMed, and Google Scholar to identify peer reviewed articles regarding Maternal Coronavirus.

Review

Hormones increasing during pregnancy and their contribution to the prevention of COVID

Despite the high risk of COVID that pregnant women are exposed to, there has been a low mortality rate in that population category. During pregnancy, the body tends to produce hormones and vitamins such as Estriol, progesterone, Vitamin D, and IL-10 [7] to ensure that the mother is protected against any infections that may arise. The hormones and vitamins are also responsible for ensuring the fetus is supplemented with appropriate nutrition.

The immune systems of pregnant women have been responding well to COVID infection. There has been evidence of positive immune response due to the increased level of interleukin-6 (IL-6) molecules in pregnant women (Cdc.gov., 2020); signifies that the body has activated its immune system. Breastfeeding mothers who have successfully fought COVID have developed antibodies that boost their level of immunity. The newborn babies can get passive immunity from their mothers as the antibodies are passed to them through the breast milk.

COVID vaccinations trial on pregnant women

Pregnant women are among the population considered to be vulnerable and likely to be at a greater risk of suffering from severe COVID. The recently released Pfizer-BioNTech COVID-19 vaccine will be tested on those at risk for example the health care workers, except pregnant women [8]. Trials of the new vaccine will not involve pregnant women because researchers are yet to find out whether the vaccine has any negative effects on the development of the fetus. Trial of the vaccine on pregnant women has been avoided because any vaccine tends to trigger an immune response.

Expectant women, who are older in age, overweight and are having preexisting health conditions such as diabetes and hypertension are at a greater risk of suffering from severe COVID. Even though pregnant women were not involved in the first trials of the vaccine, pregnant health care workers undertook the vaccine [9]. Pregnant health workers who undertook the vaccine claimed that they "felt comfortable and satisfied" in knowing that they contributed towards creating a safe and healthy environment. As the study about the vaccine continues expanding, pregnant women will be included in the clinical trials [10]. Including pregnant women in the trials will help in clearing any doubts about the effect of the vaccine on the health of the pregnant women and the development of the fetus. Pregnant women are considered to be a complex population as the period of pregnancy is an immunocompromised state. With an immunocompromised pregnancy, women are likely to suffer severe effects of COVID as compared to non-pregnant women. This is why it is important for extensive research to be conducted about a vaccine that will help in keeping pregnant women safe from COVID.

Transmission/Path of mother to fetus

The transmission of SARS-CoV-2 from mother to fetus is still under ongoing research. However, researchers have determined three possible pathogenesis types, in relation to the transmit of COVID-19 [11]. Firstly, the intrauterine transmission may take place at any time during pregnancy. Secondly, if the mother presents with having the virus in her blood during acute infection, the virus may spread through the placenta. Placental transmission side effects on the fetus vary and depend heavily on which stage of fetal development was disturbed. If the transmission appears later in the mother's pregnancy, the fetus may present with active infection at birth. Lastly, the intrapartum transmission may occur if the mother is in close contact with an infected individual, anytime from two weeks before delivery, until two days post-birth [11].

Testing for transmission

To test for fetal transmission, doctors check for virus detection in the amniotic fluid and umbilical cord blood. When the baby is delivered, they can further draw blood samples and perform respiratory swab examinations. A negative swab examination on the day of delivery does not necessarily imply the baby is not infected. This is because the incubation period of COVID-19, which is the allotted time between exposure to virus and presenting with symptoms, can take up to fourteen days. Due to this, a positive swab can occur anytime between days two and fourteen. In addition, a positive test for antibody response to the virus during first two to three weeks, post-birth [11].

A newborn can acquire surface exposure to SARS-CoV-2 as well. In this exposure, the child may present with a positive result during a virus test, with the virus's absence. The positive result would imply that the mother has active viral infection, during either two weeks pre-delivery, or in the first two days post-delivery [11].

Positive test results/treatment

There are a few management types for newborns who test positive for COVID-19. Medical staff caring for the newborn must wear complete personal protective equipment (PPE) attire like face shields, sterilizer solution, surgical face masks, and sterile gloves. There are many different types of masks in the market, and the ones that have shown to be useful in limiting transmission of the virus are the FFP3/FFP2/N95 [12]. The surgical masks protect against the transmission of respiratory droplets [13]. The correct use of PPE's has estimated to reduce the risk by at least 80% [13]. Research published in China has shown minimal healthcare worker infections associated with tracheal intubation when PPE was appropriately used [13]. It is essential to make sure that the masks when used, are sterile; and are not reused to avoid cross-contamination. If the newborn needs to be resuscitated, it should be done under radiant heat. Moreover, if the

newborn faces respiratory distress, their treatment would follow routine management of service [14]. Currently, researchers continue efforts to make progress in management and treatment studies.

Pregnancy and Pathogenesis

The ACE 2 receptor's overactivity is one of the many hypothesized reasons why pregnant women may be at a higher risk for SARS-CoV-2 infection [3]. ACE 2 is found in the lung epithelial and endothelial cells; this finding can explain why the respiratory system has notable dysfunctions [4]. Also, ACE2 is found in the kidney, heart, tongue, ileum, and esophagus [4]. During a normal pregnancy, the renin-angiotensin system (RAAS) is activated. Estrogen and progesterone also increase angiotensinogen and renin; thus, it increases the ANG II levels [15]. There is data that suggests that the involvement of ACE2 during pregnancy leads to increased formation of ANG 1-7 [15]. ACE2 does so by degrading Ang II to ANG (1-7); and acts by regulating the balance between Ang II and ANG (1-7) [16]. Also, it serves as a clearance mechanism for Ang II [16]. The ANG 1-7 plays a crucial role in the systemic vasodilation effects during pregnancy [15].

Vertical transmission of pregnancy and fetal

Researchers have been working to find if SARS-CoV-2 can be transmitted from a pregnant woman to her fetus via vertical transmission. Maternal-fetal transmission of viral diseases is usually through the hematogenous route. The virus circulating in the maternal blood-stream enters the placenta, reaches the chorionic villous tree and fetal blood vessels, and is transmitted to the fetus [17].

Despite the high number of published studies, there is still an insufficient amount of accurate data to suggest there is a higher probability of acquiring the virus through vertical transmission during pregnancy [18]. To compute and make an accurate correlation, we need to draw out unbiased conclusions regarding any perinatal and neonatal complications [18-21]. In a study done by Schwartz, A sample population of females that had acquired SARS-CoV-2 was looked at [17]. Then, 29 neonates delivered to these women underwent testing from which it was found there were no cases of RT-PCR for SARS-CoV-2 infection; This was despite seeing the existence of perinatal complications in some of the infants. An outstanding observation was that when the placentas were tested for SARS-CoV-2 with RT-PCR, the results came to be negative. This lack of maternal-fetal transmission of SARS-CoV-2 is consistent with other SERS' older strains [17]. In another study by Lu., *et al.* a 22-years-old pregnant woman with asymptomatic COVID-19 was observed. The examination involved perinatal and postnatal testing (Lu., *et al*. 2020). It was found that the amniotic fluid was clear, and the placental tissue was complete. Also, no intrauterine infections were found, and this was tested multiple times via virus nucleic acid test (Lu., *et al.* 2020). This study is also consistent with previous findings where intrauterine or transplacental transmission for COVID-19 did not exist (Lu., *et al*. 2020). However, there is yet to be much more study on this topic with a much larger sample population.

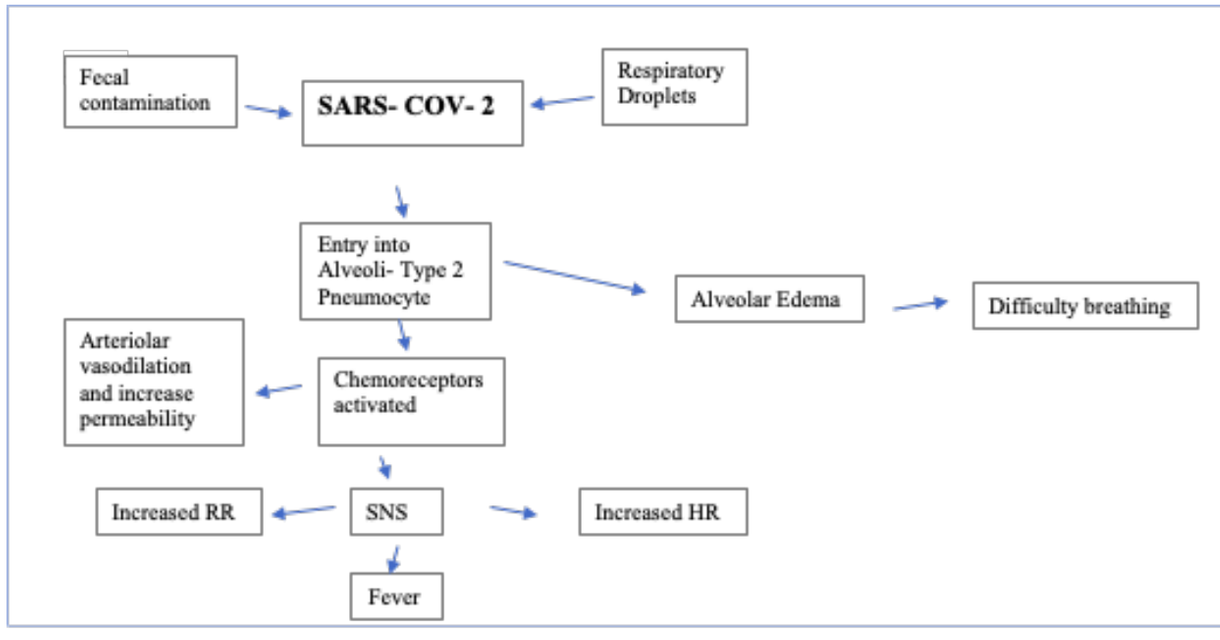

Table 1: *Flow chart of SARS- COV-2 outlining the mode of transmission, pathogenesis, and clinical presentation.*

Conclusion

COVID has spread throughout several countries and affected the entire population. However, pregnant and breastfeeding mothers are considered more vulnerable. The immune system of pregnant mothers has been responding positively to the disease; As, death rates have been quite low, in relevance to COVID. This has been allowed by the current advancement's researchers have made, as to how they can care better for expecting mothers and newborns infected COVID. More information is anticipated to come soon, as this is a significant topic in present-day research.

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