

## Systematic Review

## Perinatal Care during the COVID-19 Pandemic

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## Abstract

**Background:** Following the pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and considering its capacity for rapid mutation, there have been many studies and articles on this novel coronavirus over the past three years. Therefore, providing knowledge and directions for management of SARS-CoV-2, for hospital staff is crucial. Hence, we collected the research information from different perspectives and summarized the guidelines for perinatal care on the topic of SARS-CoV-2, and for possible future viral pandemics. **Methods:** A systematic review aimed at assessing the publications written in English and Chinese, offering different perspectives on the topic of perinatal care concerning SARS-CoV-2, was conducted using PubMed and Google Scholar from 2020 to 2022. In addition, we summarized the guidelines from the Taiwan Association of Obstetrics and Gynecology, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, Maternal Immunization Task Force and Partners, and Academy of Breastfeeding Medicine. **Results:** Due to physiological changes, pregnant patients may be prone to have complications, especially pre-eclampsia, affecting morbidity and mortality. Most neonates of coronavirus disease (COVID-19) infected mothers did not show any clinical abnormalities due to the infection. However, compared to the general population, infected neonates needed more invasive ventilation care, while the proportion of asymptomatic neonates was less than that in the general population. Further, long term complications are still under investigation. Evidence of vertical transmission via the placenta and umbilical cord is rare but not absent. Paxlovid (nirmatrelvir/ritonavir) can be administered to patients with comorbidities, and indications for cesarean delivery does not include COVID-19 infection. Vaccination against COVID-19 should not be delayed during pregnancy and lactation. **Conclusions:** Obstetricians and gynecologists should pay more attention to pregnant women with SARS-CoV-2 because of the physiological changes and higher risks of complications, morbidity, and mortality. Early prevention with vaccination in pregnant women is the key to controlling the COVID-19 pandemic, from which we can learn how to manage the next pandemic.

**Keywords:** SARS-CoV-2; pregnancy; COVID-19; prenatal care; postpartum; pandemic

## 1. Introduction

Since the onset of the novel coronavirus pneumonia, coronavirus disease 2019 (COVID-19), in December 20, it has rapidly spread worldwide and caused a worldwide pandemic. The virus which causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been reported to be more than 80% identical to the previous human coronavirus, which also contains SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. Therefore, the mechanisms and symptoms of SARS-CoV-2, severe acute respiratory syndrome coronavirus (SARS-CoV), and MERS-CoV are similar to some extent.

From 2002 to 2003, SARS-CoV infected approximately 8098 people and claimed 776 lives globally (9.6% mortality rate) [1]. Few studies have been demonstrated on SARS-CoV-infected pregnant women. In a study in Hong Kong [2], which is the most complete study on SARS-related pregnancy, three deaths occurred among twelve patients, (fatality rate = 25%), which was much higher than that in the general population. Four of the seven patients (57%) had spontaneous miscarriages during the first trimester. Four of the five patients (80%) delivered preterm. Major medical complications among these patients included renal failure (25%), disseminated intravascular coagulopathy (25%), sepsis (16.7%), secondary bacterial pneumonia (16.7%), and adult respiratory distress



syndrome (33.3%). However, none of the newborn infants had clinical SARS, all investigations were negative for SARS, and there was no evidence of vertical transmission [2,3]. According to a case-control study of SARS [4], 6 of ten pregnant patients were admitted to the intensive care unit (ICU) (60%), and 4 of ten required endotracheal intubation (40%), as compared with a 17.5% ICU admission rate and 12.5% intubation rate in the non-pregnant group.

Concerning MERS-CoV, in a serial case report of eleven patients [5], six (54%) patients required ICU admission and three (27%) patients died during the hospitalization. However, the fatality rate was not statistically different from the overall fatality rate of 35%. Meanwhile, similar to SARS, there was no evidence of transplacental transmission [3,6].

Facing the epidemic of SARS-CoV-2 with its capacity for rapid mutation, there have been studies and articles on this novel coronavirus for approximately 3 years. Therefore, providing knowledge and direction of management for hospital staff is crucial. Hence, we collected research from different perspectives and summarized the guidelines for perinatal care on the topic of SARS-CoV-2. In addition, we provide a summary of current knowledge and information on SARS-CoV-2 for people to face possible viral pandemics in the near future.

## 2. Materials and Methods

### 2.1 Study Design

A systemic review aimed at assessing the impacts and physiological changes of SARS-CoV-2 during pregnancy and the probability of vertical maternal–fetal transmission was performed. Second, we summarized the international guidelines for perinatal care and established a suggestive flow chart. In addition, suggestions and an overview of vaccination on the topic of SARS-CoV-2 were reviewed.

### 2.2 Search Strategies

All relevant articles were searched in the following databases, associations, and resources: PubMed, Google Scholar, Taiwan Association of Obstetrics and Gynecology, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, Maternal Immunization Task Force and Partners, and Academy of Breastfeeding Medicine. All scientific publications from 2020 to 2022 were limited to articles written in English and Chinese.

## 3. Results and Discussion

### 3.1 Physiological Change in Pregnancy and SARS-CoV-2 Infection

Physiological changes during pregnancy may deteriorate the pathogenesis and the clinical presentation of COVID-19 during pregnancy. In a multidisciplinary review of pregnancy [7], increased secretions and congestion in the mucosa of upper airways, increased chest wall circumfer-

ence, decreased residual volume due to elevation of the diaphragm, increased tidal volume contribute to physiologic dyspnea and respiratory alkalosis. In addition, the early symptoms of SARS-CoV-2 infection might mimic physiological dyspnea in pregnancy, resulting in delayed diagnosis and severe fetuses. Besides, SARS-CoV-2 enters the cell via the angiotensin-converting enzyme 2 (ACE2) receptor, which is increased on cell surface during normal pregnancy. Due to higher ACE2 expression, pregnant women might be in an elevated possibility of complications from SARS-CoV-2 infection. Upon binding to ACE2, SARS-CoV-2 leads to the receptor downregulation, thus lowering angiotensin-(1-7) levels, which could deteriorate vasoconstriction, inflammation, and procoagulopathic changes [7]. Moreover, the immune system during the pregnancy is different from that of nonpregnancy. The immune system is predominantly type 2 T helper cell (Th2) rather than type 1 T helper cell (Th1) in pregnancy, which is more humoral one and cause less protection against intracellular pathogens, such as virus [8].

### 3.2 Clinical Manifestations, Laboratory Findings, and Complications

In a meta-analysis and systemic review [3], the most clinical features were fever (66.1%), cough (52.7%), dyspnea (31.7%), and fatigue (30.3%), which were similar to those of SARS-CoV and MERS-CoV. These clinical manifestations are similar to those observed in those nonpregnant. In addition, the rate of asymptomatic COVID-19 in pregnant women may be higher than that of the general population. In a retrospective cohort study [9], the asymptomatic infection rate was 15 times higher in obstetric patients than in surgical patients, even after adjusting for age, race, and sex. In SARS-CoV-2-infected pregnancies, there are still some symptoms unrelated to respiration or the airway. For instance, headache was present in 13.1% of the patients, and abdominal pain and diarrhea accounted for 7.8% and 5.4%, respectively, which might lead to a misdiagnosis or an undiagnosis. The most common laboratory finding was lymphocytopenia (63%), followed by an elevated C-reactive protein level (approximately 56%).

A systematic review by Di Mascio *et al.* [10] concluded that SARS-CoV-2 alone led to more probability of preterm birth (24.3% for <37 weeks' gestation and 21.8% for <34 weeks' gestation) and that premature pre-labor rupture of membranes, preeclampsia, and cesarean delivery occurred in 20.7%, 16.2%, and 83.9% of cases, respectively. The most notable complication is preeclampsia due to the physiological changes mentioned above [7]. In a meta-analysis [11], the odds of developing preeclampsia during pregnancy were significantly higher among SARS-CoV-2 infection than those without SARS-CoV-2 infection (7.0% vs. 4.8%;  $p < 0.00001$ ). In addition, there was a statistically significant increase in the odds of eclampsia and HELLP syndrome among pregnant women with SARS-

CoV-2 infection. A recent report from the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network demonstrated that advanced maternal age, high body mass index (BMI), chronic obstructive pulmonary disease (COPD), asthma, chronic hypertension, or gestational diabetes mellitus (GDM), were related to severe COVID-19 consequences in pregnancy [12]. In addition, a systemic review [13] demonstrated that obesity (BMI >30), asthma, and cardiovascular disease are risk factors for morbidity during pregnancy. Therefore, it is important to pay greater attention to pregnant women with these characteristics.

### 3.3 Vertical Transmission

Currently, there are rare cases of the vertical transmission of SARS-CoV-2. In an analysis of 38 pregnant women with COVID-19 and their newborns in China [14], there were no confirmed cases of intrauterine transmission of SARS-CoV-2 infection, similar to SARS and MERS. However, in these 38 pregnant women, COVID-19 did not lead to maternal deaths, unlike coronavirus infections caused by SARS-CoV (25%) and MERS-CoV (40%) [2,14,15]. This result suggested that the severity of SARS-CoV-2 is less than that of SARS-CoV and MERS-CoV. In addition, a review study [16] demonstrated that the vertical transmission of SARS-CoV-2 from mothers to fetuses was absent. According to Elshafeey *et al.* [17], regarding vertical transmission of infected pregnant women, the polymerase chain reaction test result for SARS-CoV-2 in the cord blood, amniotic fluid, and placenta were all negative. In another study of 32 studies [18], of 261 neonates, 120 were tested for infection, of whom 12 (10.0%) tested positive, but swabs from the placenta, cord blood, and vaginal secretions were negative. However, in a case study [19], the vertical transmission of SARS-CoV-2 in a neonate born to a mother infected in the third trimester was confirmed through immunohistochemistry for the SARS-CoV-2 N-protein. Several factors may help explain the rarity of transplacental infection in SARS-CoV-2 [20]. First, SARS-CoV-2 infection is not directly related to high levels of viremia. Besides, the placenta might not highly express primary receptors that facilitate SARS-CoV-2 into cells, like angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). In specific, Ouyang *et al.* [21] both ACE2 and TMPRSS2 expressed in the trophoblast, whereas furin expressed mainly in the placental villous cell types.

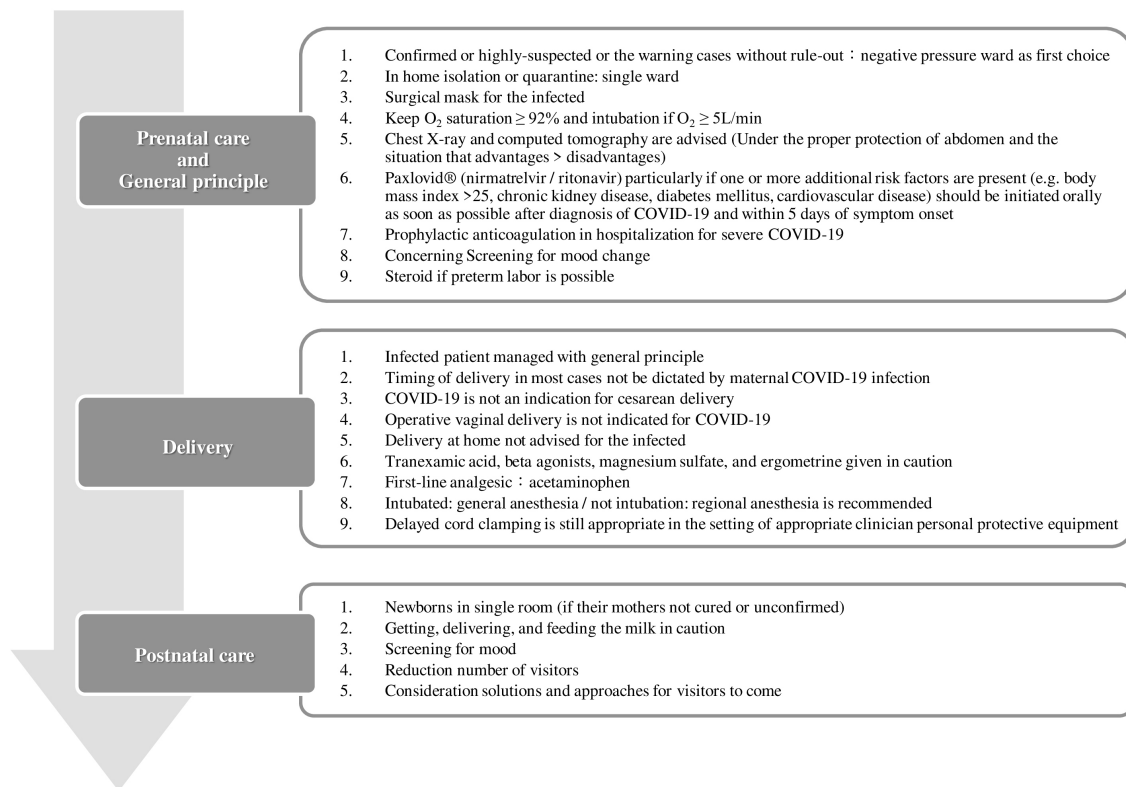
### 3.4 Offspring Clinical Presentation

No definite relationship was found between neonatal clinical abnormalities and maternal SARS-CoV-2 infection. In the meta-analysis mentioned above [18], most of neonates did not exhibit any clinical abnormalities due to the mother being infected. The most commonly symptoms were shortness of breath (42.3%), moaning (37.5%), fever (19.1%), and cough (15.4%). Other clinical presen-

tations included gastrointestinal symptoms, namely vomiting (26.1%). In total, 8.1% of neonates presented with a small gestational age (SGA), and 13.2% of the newborns suffered from intrauterine neonatal distress. However, because fever is the most common manifestation in COVID-19 patients, it might be correlated with an increased risk of miscarriage and congenital anomalies in the early trimester [22]. As mentioned previously [18], 120 neonates were surveyed and 12 of whom (10.0%) tested positive. Of these, 2 out of 12 (16.7%) cases were asymptomatic, 3 out of 12 (25.0%) cases had fever. 3 out of 12 (25.0%) cases with gastrointestinal symptoms, and 5 out of 12 (41.7%) cases presented with respiratory symptoms. Supportive management was done in 6 of 12 (50.0%) of the neonates, 2 of 12 (16.7%) received antibiotics, and 1 of 12 (8.3%) required invasive ventilation. In comparison [23], the most common symptoms in the general population were fever and cough. However, in the general population, only 10% demonstrated gastrointestinal symptoms compared with 25.0% for neonates. Only 2.3% of neonates received invasive mechanical ventilation in general, while up to 8.3% of neonates underwent invasive ventilation, which may be due to the immature neonatal lung. Concerning the asymptomatic proportion [24,25], in the general population, asymptomatic persons seem to account for approximately 40–46% of individuals with SARS-CoV-2 infection, whereas asymptomatic neonates only account for 16.7%. In summary, the severity and need for intensive care in neonates may be greater than that in the general population.

### 3.5 Long-Term Effects on Postnatal Development

Currently, the complications of SARS-CoV-2 development are still being researched. One study [26] demonstrated that inflammatory markers, especially IL-6, IL-17, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), in the umbilical cord blood, as well as in the peripheral blood of pregnant women. In addition, a recent study demonstrated gliosis in the periventricular and subcortical areas in brain images of a SARS-CoV-2-positive newborn [19]. In a cohort study using the Ages and Stages Questionnaire, 3rd Edition [27], in utero exposure to maternal SARS-CoV-2 infection was not associated with significant differences in neurodevelopment, regardless of the infection timing or severity. However, in a study in the UK [28], 3.8% of SARS-CoV-2-infected hospitalized children experienced neurologic complications also having long-term consequences, ranging from hallucinations, status epilepticus, encephalitis, chorea, Guillain-Barré/acute demyelinating syndromes and psychosis. A study of 57 infants with prenatal exposure to SARS-CoV-2 in China observed deficits in the social-emotional domain at 3 months of age [29]. A report of over 7000 infants demonstrated a relation between maternal SARS-CoV-2 exposure and neurodevelopmental diagnosis at 12 months [30]. Several studies have postulated a probable correlation between schizophrenia and autism



**Fig. 1. The suggestive flow chart for perinatal care of SARS-CoV-2 infection in pregnancy: prenatal, intra-partum and postnatal care.**

spectrum disorders [31–36] based on the influence on cytokines, complements, and cell receptors, such as ACE2 and TMPRSS2. Therefore, the impact of SARS-CoV-2 on postnatal development requires further long-term survey.

### 3.6 Comparison of Different Variants of SARS-CoV-2 and Waves in Pregnancy

The vulnerability to SARS-CoV-2 and the severity of its variants may differ among pregnant women. In a study in India [37], comparing to the first wave (April 2020 to January 2021) of SARS-CoV-2, the rates of severe COVID-19, admission to the ICU, case mortality rate, and maternal fatality ratio were higher during the second wave (February 2021 to May 2021). In a cohort study in the UK [38], the proportion of patients with moderate to severe infection significantly increased between the wild-type and Alpha periods (24.4% vs. 35.8%) and between the Alpha and Delta periods (35.8% vs. 45.0%). Compared with those admitted in the wild-type period, symptomatic pregnant patients admitted in the Alpha period required more respiratory support (27.2% vs. 20.3%), pneumonia (27.5% vs. 19.1%), and were admitted to the ICU (11.3% vs. 7.7%). An increased mortality in pregnant individuals has been reported during the Delta period compared with the pre-Delta period [39,40]. However, in a study in Spain [41], patients

in the second wave (late summer in 2020) had more probability to be treated with corticosteroids and noninvasive mechanical ventilation, and less often with conventional oxygen therapy, invasive mechanical ventilation, and anticoagulants than the first wave (spring 2020). In addition, the symptoms differed. For instance, in the second wave, patients suffered from renal and gastrointestinal symptoms more frequently. In a prospective study in Texas [42], Delta predominance was associated with increased, while Omicron was associated with decreased severe or critical illness in pregnancy compared with pre-Delta infections after adjusting for vaccination. In addition, in a retrospective study in Ireland [27], Omicron infection during pregnancy was associated with mild symptoms and minimal requirement for medical intervention. Thus, the clinical presentations and severity of different variants of SARS-CoV-2, such as Delta or Omicron, may be different, and experts and health-care providers must be cautious to minimize the impact of further waves and variants.

### 3.7 Reinfection in Pregnancy

To date, there is limited research on the reinfection of SARS-CoV-2 in pregnancy. In a case report [43], a 32-year-old previously healthy Caucasian woman was first infected at 10 + 2 weeks' gestation and then underwent a sec-



**Table 1. Timing and recommendation for the management of SARS-CoV-2 infection in pregnancy in the Taiwan Association of Obstetrics and Gynecology guidelines.**

GA <23 w or Asymptomatic or Mild symptoms	Medical treatment Observation assess the pros and cons of continuing pregnancy
Pneumonia or Sepsis	GA 24–31 w: Compose a treatment discussion with obstetrics, neonatology, internal medicine, infectious diseases, and other relevant personnel and the patient and family members GA ≥32 w: According to the severity of the disease, early delivery can be considered
With intubation	If the fetal birth prognosis is assessed to be good, considering that the condition may deteriorate rapidly, it may be considered to arrange delivery as soon as possible

GA, Gestational age.

ond infection of SARS-CoV-2 at a gestational age of 30 + 6 years. This woman had only mild symptoms in both episodes. In addition, the infection did not cause adverse pregnancy outcomes. During the first episode, the patient was examined negative for SARS-CoV-2 immunoglobulin G (IgG). However, it was detectable in the second episode at a gestational age of 31 + 5 years. Both the infant and mother had serum IgG antibodies at delivery and at the 2-month postnatal follow-up, and the maternal T cells was reactive to the S1 SARS-CoV-2 domain. Another case report [44] demonstrated that a 37-year-old woman developed the first episode of SARS-CoV-2 infection after delivery. The patient developed only fever but no subsequent symptoms. Anti-SARS-CoV-2 IgG was not detected from the beginning of the first episode until 4 months later. However, at the 6-month follow-up, the patient reported having COVID-19 infection again with symptoms of high fever, cough, headache, dysgeusia, anosmia, rhinorrhea, and hand frostbites. In the first episode of the two cases, anti-SARS-CoV-2 IgG was negative and the symptoms were mild. Besides, two recent studies [45,46] suggested that the antibody response of vaccination might be less efficient during pregnancy. Pregnant women need to know that a previous infection or vaccination might not guarantee total immunity to COVID-19 throughout the pregnancy.

### 3.8 Guidelines for Perinatal Care

We collected information from the Taiwan Association of Obstetrics and Gynecology (TAOG), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, and the American College of Obstetricians and Gynecologists (ACOG), as summarized in Fig. 1.

In general principle [47], for those who are confirmed or highly suspected with COVID-19 or warning cases without rule-out, the negative pressure ward is the first choice followed by a single ward, which is sufficient for people in home isolation or quarantine. For infected individuals, the surgical mask is better than the other forms of mask. In addition, oxygen saturation should be maintained at more than 92% during pregnancy with SARS-CoV-2, and patients should be intubated as soon as possible if the oxygen supply needs to be more than 5 L/min. In addition, dex-

amethasone is recommended for pregnancy with COVID-19 under advanced airway support [20]. Under the proper protection of the abdomen and the situation that advantages outweigh the disadvantages, chest radiography and computed tomography (CT). Regarding oral antiviral therapy [48], Paxlovid® (Pfizer, New York, NY, USA) (containing nirmatrelvir and ritonavir) became available only under emergency use authorization (EUA). It is recommended for patients with one or more risk factors (*e.g.*, BMI >25, diabetes mellitus, chronic kidney diseases, and cardiovascular diseases) should be prescribed orally as soon as possible after the diagnosis of COVID-19 was established. Lactation is not a contraindication for Paxlovid®. However, there are still no available human data on the use of nirmatrelvir during pregnancy for the drug-associated risk of birth defects, miscarriages, or adverse outcomes. Currently, there are no confirmed safe oral anti-COVID-19 drugs during pregnancy [47]. Due to the coagulopathy in SARS-CoV-2 and the hypercoagulable status of pregnancy, the National Institutes of Health COVID-19 Treatment Guidelines [49] recommend severe COVID-19 pregnant patients to receive prophylactic anticoagulation unless contraindicated. Steroid should be given in the condition that preterm labor is near.

According to the Taiwan Association of Obstetrics on the topic of delivery [47], infected patients can be managed with general principles, and the timing is shown in Table 1. However, according to the CDC [48], the timing of delivery in the majority of cases should not be dominated by maternal COVID-19 infection. SARS-CoV-2 infection is not an absolute indication for cesarean section, and Cesarean delivery has to be based on obstetric indications [48]. Besides, operative vaginal delivery is not an indication for COVID-19 cases. Delivery at home is not advised [47]. As SARS-CoV-2 may induce procoagulation, tranexamic acid should be administered cautiously. In addition, any medications that may cause cardiopulmonary complications, such as beta agonists, magnesium sulfate, and ergometrine, require awareness. Acetaminophen is a first-line analgesic. For intubated patients, general anesthesia is the choice, whereas for those without intubation, regional anesthesia is recommended [47]. Delayed cord clamping is still appropriate for appropriate personal protective equipment [48].

In postnatal care [47], if mothers are not cured or unconfirmed, newborns should live in a single room without rooming-in or breastfeeding to prevent contact infection, and current evidence suggests that breastmilk is not a way to COVID-19 infection [48]. Therefore, suspected or confirmed maternal COVID-19 is not considered a contraindication for breastfeeding. Hospital staff must be cautious in obtaining, delivering, and feeding the milk.

In addition, the prevalence of perinatal depression and anxiety increased during the COVID-19 period [50,51]. To prevent perinatal mood and anxiety disorders [48], screening of all pregnant women at least once during the perinatal period for potential depression and anxiety was suggested. Although it is recommended that the number of visitors be reduced to those essential for the pregnant individual's well-being (CDC) [52], the ACOG [48] encourages collaborative approaches that ensure patients have the support and stability they need during pregnancy, during labor, and postpartum.

### 3.9 COVID-19 Vaccination for Pregnancy and Lactation

Several vaccines against SARS-CoV-2 have been developed since the first outbreak of COVID-19. These vaccines can generally be classified into three groups: traditional adjuvant-enhanced protein antigen vaccines (e.g., Novavax, Glaxo Smith Kline-Sanofi vaccines), DNA vaccines using adenoviral vectors (e.g., Sputnik V, Johnson & Johnson - Janssen and AstraZeneca/Oxford vaccine), and mRNA embedded in lipid nanoparticles (Pfizer BioNTech and Moderna vaccines) [53].

Currently, the CDC launches relatively permissive rules for use of these vaccines during pregnancy and lactation. That is, pregnant and lactating people are part of a group that is recommended to receive a COVID-19 vaccine unless contraindication, such as being allergy to the components of vaccines. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine recommend that pregnant or lactating women have access to COVID-19 vaccines, and that all eligible persons aged >12 years, receive a COVID-19 vaccine [54,55]. Additionally, COVID-19 vaccines may be administered simultaneously with other vaccines, including vaccines routinely administered during pregnancy such as Tdap and influenza (Flu shot). The Maternal Immunization Task Force indicates that all pregnant individuals to receive the COVID-19 vaccines [56]. The Taiwan Association of Obstetrics [47] also recommends pregnant and lactating women to receive the vaccine, especially the mRNA vaccine for pregnant women belonging to the high-risk group, and the antibody against SARS-CoV-2 can appear in milk. The Academy of Breastfeeding Medicine [57] suggested shared decision making while discussing immunization during and continued breastfeeding after immunization.

To date, [53] pregnancy outcomes are comparable to background rates, and “no unexpected pregnancy or infant outcomes have been observed related to COVID-19 vaccination during pregnancy”.

### 3.10 Social and Public Healthcare Issues

Since the outbreak of SARS-CoV-2 in China in 2019, there have been several social and healthcare issues related to pregnancy. It is observed that SARS-CoV-2 is more frequent low socioeconomic status. In a report from New York City [58], the risk of COVID-19 infection was higher in pregnant persons living in buildings with lower values and more residential units, and higher in neighborhoods with lower median household incomes, higher unemployment percentage, large household sizes, and greater household crowding. In a report from Atlanta [59], there was higher rates of COVID-19 infections among pregnancy correlated with Hispanic ethnicity, high neighborhood density, and lack of health insurance.

In addition, the pandemic has had a great impact on pregnancy outcomes, even in those not diagnosed with SARS-CoV-2. In a global systematic review [60] comparing the time before the pandemic, increases in stillbirths and maternal deaths, declines in maternal mental health, and an increased rate of ruptured ectopic pregnancies were observed. In addition, in a cohort study, birth during the pandemic was associated with differences in neurodevelopment at the age of 6 months, namely lower scores on gross motor, fine motor, and personal-social. Thus, there is an essential need to develop safe, accessible, and equitable maternity care in the strategic response to this pandemic and in future health crises.

## 4. Conclusions

Due to physiological changes during pregnancy, such as upregulation of ACE2 in the respiratory tract, the severity of SARS-CoV-2 may increase, and pregnant patients may be at greater risk of morbidity, mortality, and complications. Although in some studies, neonates were diagnosed with SARS-CoV-2, evidence of vertical transmission via the placenta and umbilical cord is rare but not absent. Therefore, it is crucial to determine how neonates are infected. Most neonates did not show any clinical abnormalities because of their infected mothers. The most commonly described clinical features were dyspnea, moaning, fever, and cough. In infected neonates, the most common clinical manifestations are respiratory and gastrointestinal symptoms and fever. Compared to the general population, infected neonates needed more invasive ventilation care, while the proportion of asymptomatic neonates was less than that in the general population. Some physiological mechanisms and cytokines have been identified as probable damage to developmental status, especially in the neuropsychiatric domain. Owing to the novelty of SARS-CoV-2, long-term complications should be noted and followed up.

Considering the influence of different variants and waves of COVID-19, there is still no consensus on whether a later epidemic has a more devastating impact than the former. However, increased mortality in pregnant individuals has been reported during the Delta period compared to the pre-Delta period, while the severity of Omicron was less than that of Delta, which health care workers should be cautious of. Nowadays, studies on re-infection with COVID-19 in the perinatal period are limited. In both case reports we collected, the second episode was more severe, and anti-SARS-CoV-2 IgG was positive only in the second episode. Pregnant women and the caregivers need to aware that a previous infection or vaccination might not guarantee immunity to SARS-CoV-2 throughout the pregnancy.

Considering the management of pregnancy in the duration the epidemic of SARS-CoV-2, for those highly suspected or confirmed or warning cases, negative pressure is the first choice, while a single ward is enough for those in quarantine or in isolation. With proper abdominal protection, chest radiography and computer tomography can be performed in some situations. The O<sub>2</sub> saturation of infected pregnant women should be maintained at more than 92%, and if the O<sub>2</sub> flow needs to be greater than 5 L/min, the patients should be intubated. To date, there are no confirmed safe oral antiviral medications for COVID-19. However, Paxlovid (nirmatrelvir/ritonavir) can be administered to patients with comorbidities.

Concerning delivery, the infected patient can be managed using general principles, and SARS-CoV-2 is not an indication for cesarean delivery. Newborns whose mothers are not cured or confirmed are not recommended to be rooming-in or breastfed by their mothers. Because the advantages outweigh the disadvantages, all pregnant and lactating women should undergo vaccination for SARS-CoV-2, especially mRNA vaccines. In addition, obstetricians and related caregivers should pay attention to the tendency of anxiety and depression in pregnancy during the pandemic of SARS-CoV-2.

### Limitations

We reviewed the articles without using any statistical tools or methods. We referred to the guidelines from the American College of Obstetricians and Gynecologists, Taiwan Association of Obstetrics and Gynecology, the Centers for Disease Control and Prevention (CDC), National Institutes of Health, Society for Maternal-Fetal Medicine, Maternal Immunization Task Force and Partners, and Academy of Breastfeeding Medicine, which represented the major associations around the world and Taiwan. However, we did not include all the guidelines worldwide.

### Author Contributions

CCC and CCL designed the research study. CCL performed the research. LYF provided help and advice on writing the manuscript. SHW analyzed the data. FHK and TFC

wrote and corrected the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

### Ethics Approval and Consent to Participate

Not applicable.

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### Conflict of Interest

The authors declare no conflict of interest.

### Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.ceog5003051>.

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