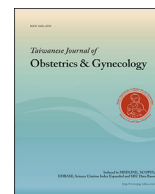




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## Review Article

# Relationship of COVID-19 with pregnancy

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### ABSTRACT

COVID-19 a pandemic disease caused by the SARS-CoV2 virus, which has been emerged in Wuhan city China from early December 2019 which subsequently spreading globally. As a consequence of the physiological adaptive changes and immunosuppressive condition during pregnancy are more susceptible to respiratory tract infection and pneumonia that perhaps makes them more at risk to COVID-19. There is scarce information available on COVID-19 pregnancy and no reliable evidence for vertical transmission. It is a concern that newborns are risk from postpartum contamination. Meanwhile, there was no vaccine and specific therapeutic drugs for COVID19. The Multidisciplinary team will manage by close supervision, isolated negative pressure room, and routinely fetal monitoring. The timing and mode of delivery depend on the critical condition of the mother and fetal. The newborns need a 14 days period of precautionary isolation. In the present study, addressed the most recent data on 149 pregnant women and 96 newborns with typical symptoms and planning of management which response to COVID-19 that will help for frontline doctor to the management of COVID-19 associated pregnancy and newborns baby. Repeated testing, contact tracing and self-isolation will assist to control the spread of SARS-CoV2 infection and COVID-19 disease until specific vaccine and pharmaceuticals drugs of COVID-19 are available.

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## Introduction

Currently, coronavirus infection 2019 (Covid-19) is spreading globally, the World Health Organization (WHO) declares on 11 March 2020 as a pandemic disease [1]. The first outbreak was revealed in Wuhan in the Hubei province of China then spreading rapidly to elsewhere of the world [2–4]. As of 25 March 2020, COVID-19 has caused more than 420,000 confirmed cases and 18,887 deaths globally, including 81,852 confirmed cases and 3287 deaths in China [5]. The outbreaks of COVID-19 with pregnancy regards as clinical characteristics and outcomes [6]. In pregnancy, the physiological alter of immunity and a cardiopulmonary system that may disproportionately be affected by any virus causes respiratory illness and an increased rate of morbidity and mortality. Previous, documented the death of pregnant women from the severe acute respiratory syndrome coronavirus (SARS-Co V) and Middle East respiratory syndrome coronavirus [7–10]. There is no confirmed evidence for intrauterine infection in late pregnancy by vertical transmission. While no available reported on COVID-19 infection in the first trimester, although about vertical

transmission there were still no acceptable laboratories and clinical finding to prove it [11–14]. There is a chance of abortion, delivery, fetal growth restriction, fetal distress, like SARS-CoV-1 infection [11,15]. The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) draw on previous knowledge and some specific management of out breaking coronavirus that may be appropriate for COVID-19 pregnant women [16,17]. Currently, many countries outbreak of COVID-19 in pregnancy, therefore we have to provide exact information of COVID-19 for awareness to the health worker, pregnant women, and the general public. Thus, the present study to review clinical aspects for managing COVID-19 infected pregnant women.

## Pathophysiology

COVID-19 as a SARS-CoV-2 belongs to the category of betaCoVs, a subfamily of Coronavirinae consisting of a single-stranded positive-sense ribonucleic acid (RNA). Previously reported all kinds of coronaviruses produced human disease either by bats or rodents [18]. The spike protein surrounded the SARS-CoV-2 to consist variable receptor-binding domain (RBD) and bind to receptor-angiotensin-converting enzyme-2(ACE-2) that available in lungs, heart, kidney and gastrointestinal tract [19]. Therefore COVID-19

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patients manifest upper and lower respiratory symptoms. The receptor-binding domain of SARS-CoV-2 shown to be a mutated version of its generally intimately associated virus according to their genomic sequence [20]. Based on pandemic laboratory trials the pathophysiological mechanism of SARS-CoV-2 are still unidentified, while the similarity of genomic sequence SARS-CoV may provide clarification for the inflammatory reaction that appears as pneumonia [13]. The structure of COVID-19 represents in (Fig. 1).

### Transmission

The animal source of SARS-CoV2 and genomic strain closely related to bats [21]. The first COVID-19 patient-related in Wuhan at the seafood wholesale market, and perhaps spread from animal to human, after while many cases existing coronavirus but this theory was failure to support. There was reliable evidence for transmission of COVID-19 from human-to-human [22,23]. The respiratory droplets and contact spreading is the main pathway for transmission. Few data exist coronavirus may cause complications mainly in the third trimester of pregnancy but may not support the vertical transmission from mother to fetus, while the newborns affected by contamination mother (Fig. 2).

### Clinical characteristic

The limited data are available for COVID-19 infected pregnant women. Several studies have appeared in a document the common symptoms are fever, cough, lymphopenia, chest pain and a small number of patients develop diarrhea and shortness of breath [24,26–28]. The pattern of clinical characteristics of COVID-19 pregnant women has like non-pregnant with COVID-19. The expected symptoms developed 3–6 days after exposure. From the 41 hospitalized cases presented with fever, cough, fatigue approximately number of 30, 24, and 7, while fewer symptoms were loss of appetite 3 and diarrhea 1 respectively [27]. Total of 149 patients with COVID-19 included this study with symptoms such as fever 149, cough 140, fatigue 48, and malaise 29 pregnant women with complications mainly presented in the mid and late gestational weeks [12,24,26,30–36]. However, it is of note that the outbreaks of COVID-19 virus in early pregnancy are unidentified [14]. The physiology alternation of pulmonary function during pregnancy may risk for COVID-19 that implement the susceptibility and severity of pneumonia [26,37,38]. Clinical characteristic represented in (Table 1).

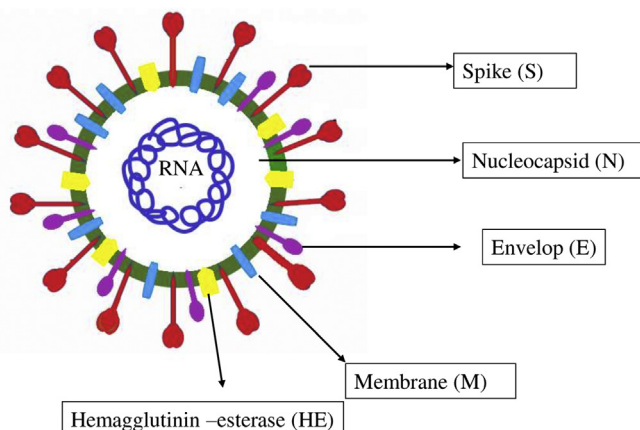


Fig. 1. Structure of COVID-19.

### Isolation and screening

The COVID-19 infected pregnant women and who had a travel-related history of COVID-19 need to immediately self-isolate for screening and testing. Currently, there is no confirmation data for either vaccine or any drugs from a clinical trial to effective treatment against COVID-19. It is strictly to avoid unnecessary moving crowded places, social distancing mandates and avoided close contact. Many women suffered a psychological impact of the outbreaks as well as higher levels of stress, depression, and anxiety which deteriorate to a critical condition. Health professionals ensuring their requirements are addressed and provide resources for psychological support to minimize the critical state of pregnancy. The identified of COVID-19 pregnant women immediately isolated in designated wards in existing hospitals with isolated negative pressure room, adequate health care resource for monitoring mother and fetus, available intensive care unit, the capability of emergency delivery and facility for newborns [39]. Isolation is another main tool for case identification besides nucleic acid testing to prevent potential outbreaks. The US Centers for Disease Control and Prevention provide supporting evidence to observe 14 days with repeated testing that may reduce precautionary self-isolation [40]. Isolation and testing strategy to ensure early diagnosis and early management of patients, therefore it may consider as a basic component of a combination approach to control COVID-19 and reduce further transmission.

### Analysis of investigated reports

The laboratory findings normal or decrease white blood cells, low lymphocyte, and increased C-reactive protein. Many women have experienced mild thrombocytopenia, raise creatine phosphokinase, and liver enzymes in addition to high alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [26]. Routinely analysis of urine and stool has a facility to detect the condition of the virus and shedding of the virus. Currently, the real-time reverse transcription-polymerase chain reaction (RT-PCR) assay used for confirmation of SARS-CoV-2 from throat swab who suspected COVID-19 [41]. United states have build 84 public health laboratories for testing of COVID-19 the specific primers of this test for SARS-CoV-2 to target their envelope, RNA-dependent RNA polymerase (RdRp), and nucleocapsid genes [42]. These detected which RdRp assay has capable the maximum analytical sensitivity. However, using the RT-PCR method to amplification of DNA and viral load in COVID-19 which may likely theoretically explanation. Regarding detecting of COVID-19 from a specimen of the lower respiratory tract has more diagnostic value comparatively upper respiratory tract [43]. WHO preferred a high significance for the detection of COVID-19 from a specimen of the lower respiratory tract such as sputum, endotracheal aspirate, or bronchoalveolar lavage. A specimen of the upper respiratory tract required when asymptomatic of the lower respiratory tract infection or situation demand. Chest radiograph or CT scan provides essential knowledge for the clinical state of COVID-19 in pregnant [43–46].

### Management

The tertiary hospitals were better for the isolation with the initial management of COVID-19 infected pregnant women. The health care should be concerns about isolates negative-pressure room for confirm case, and suspected cases only need isolates. The hospitals should exist negative-pressure room in ICU and NICU [47]. All physician and medical staff should be self-protection by PPE (such as gown, N95 masks, goggles, and gloves) during dealing with patients [48]. There is no confirmed evidence for vaccine and

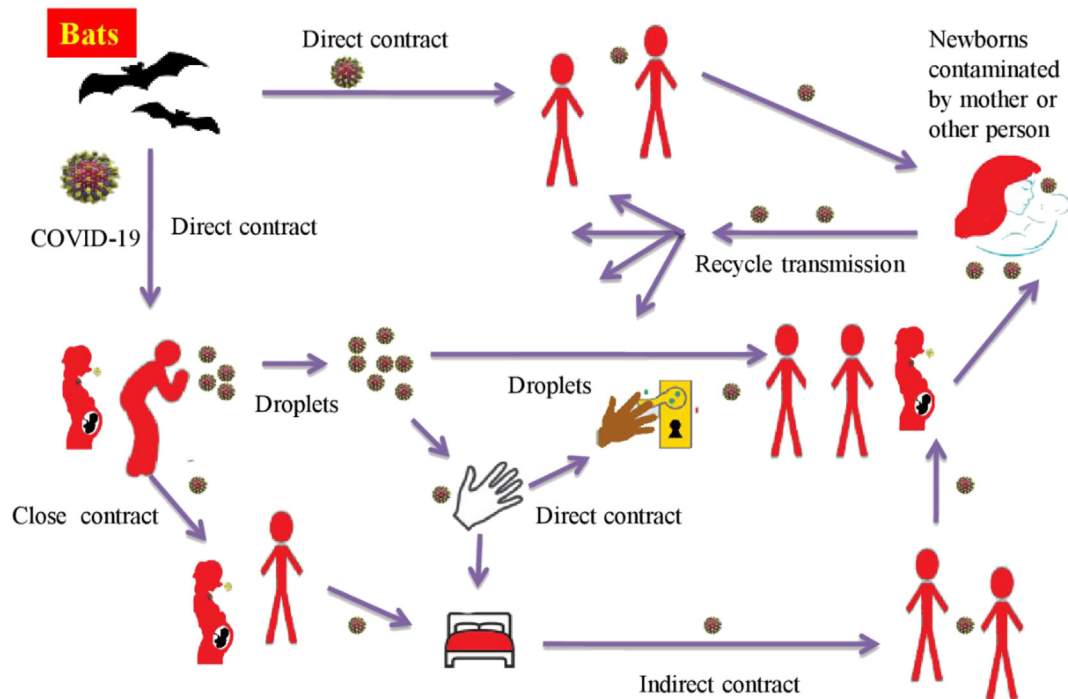


Fig. 2. Transmission pathways.

specific antiviral drugs against COVID-19. The principle treatment for severe COVID-19 infection has symptomatic and oxygen therapy. In addition to mechanical ventilation requires if respiratory failure refractory to oxygen therapy, besides, the management of septic shock by hemodynamic support. Although, no approved antiviral for COVID-19, but may propose several approaches like lopinavir or ritonavir (400/100 mg every 12 h), chloroquine (500 mg every 12 h), and hydroxychloroquine (200 mg every 12 h). Besides, Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) has used. However, COVID-19 with pneumonia treated by antibiotics [39]. It is also essential to apply supportive therapies such as the fluid infusion, adequate rest and proper nutritional diet. The management protocol represents a diagram in (Fig. 3).

### Fetal monitoring

It needs to regular monitoring of fetal heart rate by stereoscope or Doppler with compatible and dependable on gestational weeks, while ultrasound considered a stander method to determine fetal deformity, any intrauterine complication, and fetal death. Close supervision might help to make a decision, to continue a pregnancy or emergency termination and delivery.

### During pregnancy

The antiviral drugs with the regiment of Lopinavir or Ritonavir are comparatively safe during pregnancy [49,50]. The WHO proposed, before the selection of this drug for COVID-19 infection should be knowledge of their advantage and disadvantage. While remdesivir and chloroquine drugs have well, predictable to inhibit the SARS-COV-2 virus in vitro, based on this information these drugs may potentially effect on COVID-19 [51]. Above this drug started a clinical trial in China (ClinicalTrials.gov number NCT04252664 and NCT04257656) and United States (ClinicalTrials.gov number NCT04280705). Recently reported Chloroquine drug

may discontinue the coronavirus infection by excessive endosomal pH requires for cell fusion and disturbance the glycosylation of cellular receptors of SARS-CoV [51]. Chloroquine can safely prescribe whole trimesters of pregnancy and no interfere of perinatal outcomes [52]. Therefore, the recommended dose should increase maximum 500 mg twice daily in cases of COVID-19 infection. While the reported increased dose of chloroquine may cause systolic hypotension that aggravates the hemodynamic changes from supine aortocaval compression by a gravid uterus [53]. WHO declares, there was no benefit to routinely use of systemic corticosteroids because of the delay clearance of virus [16,54,55]. Currently, the U.S. National Institutes of Health (NIH) will trial mRNA-1273 vaccines (ClinicalTrials.gov number NCT 04283461) on non-pregnant women but it is uncertain to pregnant women.

### Delivery approach

There is no evidence for termination of pregnancy due to COVID-19 infection. Adequate care, proper treatment, and follow-up may continue to term pregnancy. The critical condition of patients will discontinue the pregnancy because of the endangering mother and fetus by emergency delivery on the consent of the patient's family. The clinicians should be self-protection and know the severity of risk during dealing with labor patients. The time and mode of delivery are depending on the status of the mother and fetal [56]. Currently, there was no reliable reported for vertical transmission and contraindication of vaginal delivery of COVID-19 patients [12,53]. The vaginal delivery preferred when labor will progress actively with the spontaneous onset and operative delivery concern to shortening the second stage of labor [57]. The present study review thirty-three vaginal deliveries without any difficulty, therefore it indicates vaginal delivery is possible for COVID-19 mother. Conversely, for cesarean delivery, the operative room should be confirmed with negative pressure and well ventilation. The surgeon should self-protect with (PPE) during the surgery procedure of COVID-19 patients. Besides, the cesarean section

**Table 1**  
Clinical aspects and management of COVID-19 infected pregnant women.

Authors	N = case	Age	Weeks of gestation	C/F	Progression	Treatment	Delivered	Neonatal outcomes	Neonatal complications
Chen et al. [11]	9	26–40	36–39	Fever, malaise, cough	Pneumonia	Antiviral therapy	CS	Normal	No
Nan yu et al. [24]	7	29–34	37–41	Fever, cough, fatigue	Pneumonia	Antibiotic therapy Oseltamivir (75 mg 12 h, orally), Ganciclovir (0.25 g every 12 h, intravenously), interferon (40 µg daily)	CS	1 had positive to SARS-CoV-2	No
Huang hua leu et al. [27]	41	22–42	22–40	Fever, cough, fatigue	Pneumonia	Antiviral therapy	Not reported	Normal	3 had cough, fever, 1 had fatigue
Huaping Zhu et al. [29]	9	25–34	31–39	Fever, cough, diarrhea	Pneumonia placenta previa Fetal distress	Oseltamivir, nebulized inhaled interferon	2-VD 7-CS	1 died	No
Dehan Liu et al. [36]	15	23–40	12–38	Fever, cough, sore throat, myalgia	Pneumonia	Antiviral therapy Antibiotic therapy	1-VD 10-CS 4-cont. pregnancy	Normal	No
Na Li et al. [37]	16	26–37	29–40	Fever, cough, sore throat, dyspnea	Pneumonia	Antiviral therapy Antibiotic therapy	2 -VD 14 –CS	Normal	No
Xiaotong Wang et al. [48]	1	28	30	Fever, cough	Fetal distress	Arbidol (0.2g administered orally every 8 h), Lopinavir and Ritonavir (400/100 mg administered orally every 8 h), Cefoperazone Sodium and Sulbactam Sodium (3.0g administered intravenously every 8 h)	CS	Normal	No
Weiyong LIU et al. [56]	3	30–34	38–40	Fever, cough	pneumonia Fetal distress	Atomized inhalation of interferon (40 µg, bid), Ganciclovir (0.25g, IV).	1 -VD 2 CS	Normal	1had slightly decreased responsiveness and muscle tone
E. Kalafat et al. [57]	1	32	35 + 3	Cough, dyspnea	pneumonia	Oseltamivir, Azithromycin, hydroxychloroquine	CS	Normal	No
Siyu Chen et al. [59]	5	25–31	38–41	Cough, malaise, Dyspnea, myalgia	Preeclampsia GDM	Oseltamivir, azithromycin	3 -VD 2-CS	Normal	No
Fabio Parazzin et al. [60]	42	21–44	34–37	Dyspnea, fever, cough	pneumonia	Not reported	24-VD 18-CS	Total 3 had Positivity to SARS-Cov-2, among 1 had missing information	1had gastrointestinal and respiratory symptoms

Abbreviations: CS = cesarean section, VD = vaginal delivery, GDM = Gestational diabetes mellitus.

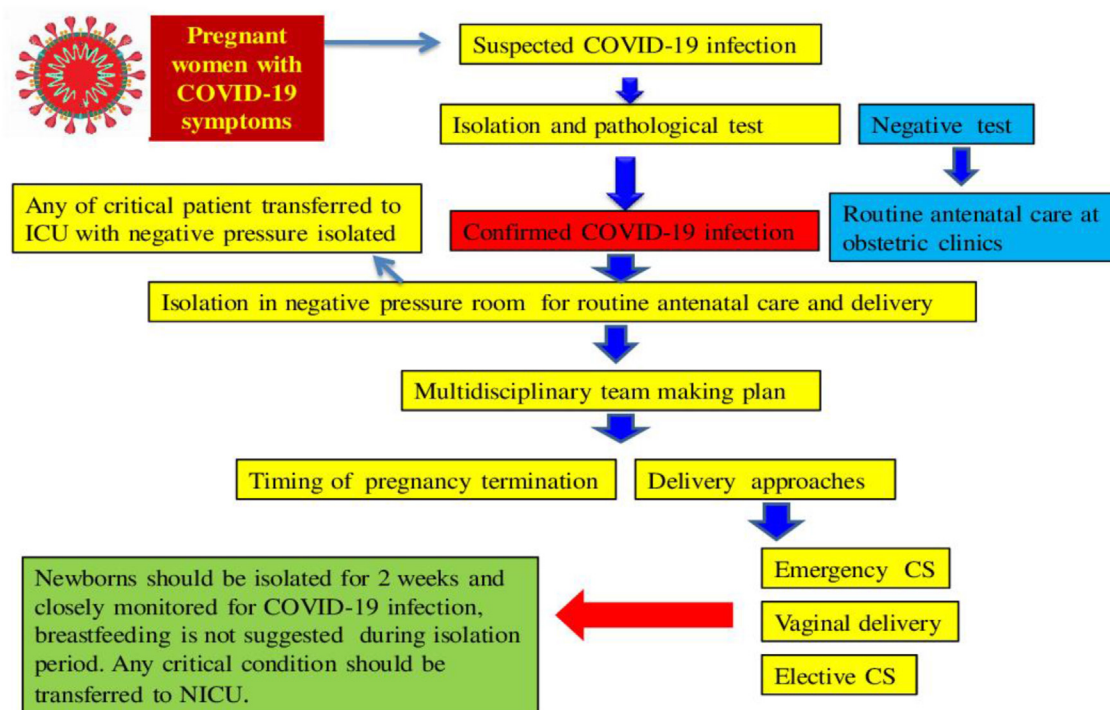


Fig. 3. Diagram of planning process for pregnant women with COVID-19 infection.

preferred in two cases of COVID-19 pregnant women due to the failure of induction and arrest of the descendent part [26]. Current reported on eleven COVID-19 patients (12–38 gestational week), among ten patients delivered by cesarean section and one patient by vaginal delivery with no complication or death of newborns. Similar reported to seven patients had CS with good neonatal outcomes except one who had positive SARS-CoV-2 (Table 1) [25,37]. Several cases of COVID-19 with pneumonia preferred either emergency or scheduled CS [29,38,58–62].

Based on evidence from the review studies reveals that the expert recommendations for the management of COVID-19 pregnant women. A total of 149 pregnant women with COVID-19 have been reported the approaches of delivery, among 77 and 33 pregnant women by cesarean and vaginal delivery respectively. Moreover, the prescribed drug as the only antibiotic had 15, antibiotic with oral antiviral oseltamivir has prescribed 75 mg, intravenous ganciclovir 0.25 g every 12 h had 16, antibiotic with lopinavir 400 mg, ritonavir 100 mg every 8 h had 1, and arbidol 200 mg had 8 COVID-19 pregnant women. Conversely remaining 109 pregnant women prescribed antibiotics with or without antiviral drugs but the name of antiviral drugs was not reported. Most of these cases the expert suggested antibiotic and antiviral drugs because of benefited effects found to use of antibiotic as prophylaxis such as azithromycin, cefoxazole, and cephalosporin before delivery and some of the cases continued after delivery. The antiviral favipiravir drug was also used but the dosage was not mentioned. Above discussion, it was clearly understood that antibiotic along with oseltamivir and ganciclovir were vastly used may provide better outcomes. As well the multidisciplinary team recommended to start of combined antibiotic and antiviral drugs after diagnosis of cases and preferred cesarean delivery that may better improve the condition and avoided the complications of both mother and fetus. Though there was no contraindication of vaginal delivery but limited data available. Perhaps the widely used of this management has may prognosis of maternal and fetal outcomes.

### Neonatal outcomes

The Present study reviews a total one-hundred forty-nine pregnant women with COVID-19 positive who gave delivery ninety-six newborns among 1 had died due to DIC and multiple organ failure. The Apgar scores of all 95 infants had  $\geq 7$  at 1 min and  $\geq 9$  at 5 min respectively. The collected of nasopharyngeal swab from all 95 infants for COVID-19 had tested by SARS-Cov2-19 PCR. Four infants had shown COVID-19 positive among 1 had missing information, while 91 had shown COVID-19 negative. To minimize the risk of contact transmission the neonate was isolated whereas other family member and as well as nurses were taken care of them. As well, 10 neonates had breastfeeding with mother using surgical masks. The one COVID-19 positive neonate had admitted to the specialized design of children's hospital and two neonates admitted into the NICU, after two weeks one infant was discharged home by two consecutive negative nucleic acid tests, while two neonates were improved after ventilation but insufficient information about discharge.

### Neonatal complications

Total six neonate were addressed of some complication after delivery, such as three neonates had fever, cough, 1 had fatigue, 1 had gastrointestinal and respiratory symptoms and 1 had slightly decreased responsiveness and muscle tone respectively.

### Care of the newborn

To our knowledge, there was no reliable evidence for SARS-CoV-2 viral detected in conception product, fetus, amniotic fluids, placenta and breastfeeding of COVID-19 pregnant women [14]. Recent studies reported on two neonates have identified the COVID-19 infection after 36 h and 17 days of delivery due to post-partum contamination [63]. It is advisable to early umbilical cord

clamping and isolates newborns at least 14 days to reduce the viral transmission. Two COVID-19 infected mothers had breastfed without the use of surgical masks, the one newborn was infected, and one has suspected on the first and third day [62]. Newborns with suspected SARS-CoV2 need to immediately isolation with a chest CT scan, swab specimens, and nucleic acid test (NAT) [30]. The COVID-19 infected mother suffered hypoxemia that adverse effects on fetal such as birth asphyxia and premature birth. The obstetricians should concern with neonatologist during preparing for resuscitation of a neonate in the delivery room to facilitate the prognosis of the neonate. To ensure the health support to require all facility to suspected newborns.

## Conclusion

Pregnant women infected with COVID-19 need to more intensive attention. Currently, there is limited data on COVID-19 with pregnancy and found mostly during late pregnancy which is risks for mother and fetus. During late pregnancy of COVID-19 infected mother may risk of adverse obstetrical outcomes. A multi-disciplinary team contact should be adopted for dealing with these patients as it allows effectively sharing knowledge and expertise as well as responsibility. However, repeated testing, contact tracing, and self-isolation may control the spread of SARS-CoV2 and COVID-19 infection until specific treatment either by vaccine or drugs are available.

## Declaration of competing interest

None.

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