



Obstetrics and Neonatal Outcomes in Pregnant Women with COVID-19: A Systematic Review

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Abstract

Background: Considering that the obstetricians and pediatricians need to comprehensive information about the obstetric and neonatal effect of COVID-19, this review study was conducted to investigate the impact of COVID-19 on obstetrics and neonatal outcomes.

Methods: In this systematic review the international search databases following PubMed, Web of Science, Scopus, ProQuest and Embase and Google scholar were searched. All articles were reviewed by two independent researchers until 10 April 2020. After quality assessment of included studies the finding reported in 2 sections obstetrics and neonatal outcomes.

Results: The sixteen studies with a sample size of 123 pregnant women with a definitive diagnosis of COVID-19 and their neonates were evaluated. The range of gestational age was 25-40 weeks. There was no death associated with COVID-19 in pregnant women. The obstetric outcomes in pregnant women with COVID-19 include decreased fetal movement, intrauterine fetal distress, anemia, PROM, preterm labor, Multiple Organ Dysfunction Syndrome (MODS) and etc. The most common delivery mode in women affect with COVID-19 was cesarean section. Except for one case with MODS, in the majority of the studies reviewed, no severe morbidity or mortality occurred. The neonatal outcomes were stillbirth, prematurity, asphyxia, fetal distress, low birth weight, small for gestational age, large for gestational age, multiple organ dysfunction syndrome, disseminated intravascular coagulation and neonatal death. In addition, five neonates born to mothers with COVID-19 were positive for SARS-CoV-2. However, the studies report these outcomes but the exact causes of theme are not known.

Conclusion: In this systematic review, we summarize the diverse results of studies about the obstetrics and neonatal outcomes following COVID-19. This infection may cause negative outcomes in both mothers and neonates. However, there were evidence about neonate infected with COVID-19, but there is controversial information about the vertical transmission of COVID-19.

Keywords: Pregnancy; Neonate; Outcome; Coronavirus infection; COVID-19

Introduction

Coronaviruses are the enveloped and largest of positive-strand RNA viruses that are important pathogens of humans, other mammals, and birds. These viruses can cause respiratory, intestinal, liver, and nervous system diseases (1, 2). In December 2019, a high incidence of pneumonia with unknown causes was detected in Wuhan, China in January 2020 and the scientists identified the cause of this pneumonia as a new type of coronavirus called SARS-Cov-2 as the cause of 2019 novel coronavirus infectious disease (COVID-19) (3). This virus belongs to the family Coronaviridae from the Nidovirales order (4). The transmission route of this virus similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), occurs via respiratory droplets and secretions thought nosocomial contacts (5). The incidence of COVID-19 and pneumonia related to it is higher in people with weakened immune systems, such as the elderly, people with underlying diseases, and pregnant women (6).

The immunological changes during pregnancy period put the pregnant women at high risk group (7). The increased risk of viral pneumonia during pregnancy is also attributed to physiological changes that are responsible for shift cellular immunity to humoral immunity; moreover, pregnant women do not tolerate severe pneumonia combined with a significant reduction in ventilation capacity as well as non-pregnant women (8, 9).

Fetuses also poorly tolerate hypoxemia and acidosis, and these complications induce preterm labor (9). Studies showed the high rates of maternal mortality, stillbirth, abortion, and preterm labor after viral pneumonia caused by the influenza A, H1N1, MERS, and SARS viruses (10-12). Despite the criticality of these conditions, however, information on the impact of COVID-19 on obstetrics and newborn outcomes is very limited.

Despite the researchers reported some pregnancy complications of COVID-19 (6, 13-17) but be-

cause the obstetricians and pediatricians need to comprehensive information about the obstetric and neonatal effect of COVID-19, so this review study was conducted to investigate the impact of COVID-19 on obstetrics and neonatal outcomes.

Methods

Data sources

In this systematic review the international search databases following PubMed, Web of Science, Scopus, ProQuest and Embase and Google scholar were searched. All observational articles were reviewed by two independent researchers until 10 April 2020. In addition, hand searching and snowballing method were also used to identify other studies from the reference list of selected studies. This systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategies

To find relevant articles, keywords are selected based on Mesh (i.e., “Pregnancy”, “Gravidity”, “Delivery”, “Infant”, “Newborn”, “Neonate”, “Outcome”, “Complication”, “Abortion”, “Obstetric Labor, Premature”, “Cesarean Section”, “Fetal Death”, “Infant, Premature”, “SARS COV 2”, “Coronavirus Infection”, “COVID-19”) which were combined using the AND and OR operators to ensure a comprehensive and complete search process.

Inclusion and exclusion criteria

The inclusion criteria of this study include all studies that indicate the impact of COVID-19 on obstetrics and neonatal outcomes. The exclusion criteria were the lack of full access to articles, studies with irrelevant reports and review articles.

Data collection and extraction

An initial 3158 articles were found using the keywords. After excluding duplicate studies in Endnotes software, the title and abstract of the re-

remaining studies were reviewed by both authors independently and where article could not be excluded based on title or abstract or when there was disagreement between researchers, then the full-text of papers with eligibility criteria was retrieved and assessed (Fig. 1). After removing unrelated articles finally, 16 studies were included in

the research for the quality assessment. To extract data from the text, two authors independently extracted information. After collecting the data, the third author evaluated all forms of data extraction independently and assisted the external reviewer if the authors disagreed.

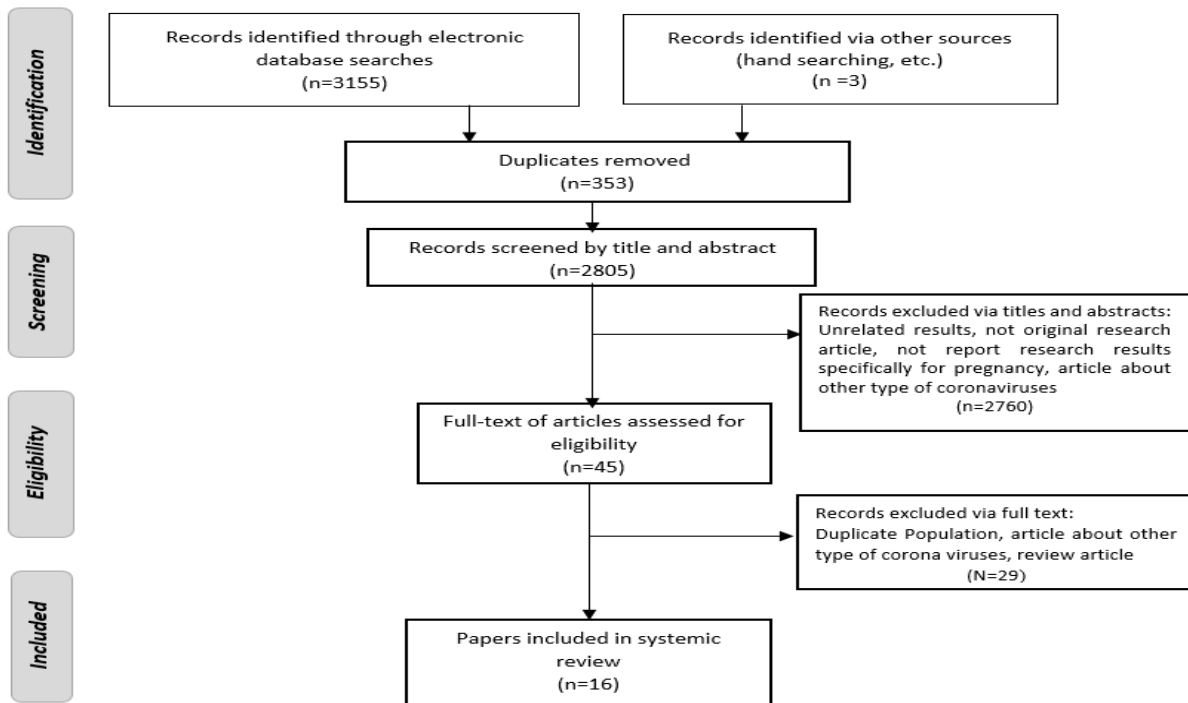


Fig.1: Flowchart for selection of studies

Quality assessment

Two authors independently assessed the quality assessment of the studies using the Newcastle-Ottawa Scale (NOS) checklist and scoring system to evaluate the quality of the case reported studies. The NOS checklist was used to assess the quality of cross-sectional, case control and cohort studies. The checklist consists of three subcategories: selection, comparability exposure, or outcome (18). A checklist designed by Kanthraj et al was used to evaluate the quality of the case report studies. The checklist includes five subcategories of goal reporting, diagnostic criteria, clinical techniques and methods, and symptom reporting, factors related to clinical existence, and the authors' conclusions (19).

Results

In this review study, 16 studies with a sample size of 123 pregnant women with a definitive diagnosis of COVID-19 and their neonates were evaluated. From among the included studies, 6, 1, 4 and 5 had been done as retrospective case analysis, cohort, case series and case reports, respectively. The range of gestational age was 25-40 weeks. In all participants, diagnosis of COVID-19 was confirmed by using laboratory tests and/or imaging examinations. All studies were published in China from December 8, 2019 to March 26, 2020. The qualities of three studies

were satisfactory and the qualities of the remaining studies were excellent. After reviewing included studies, the findings were categorized ob-

stetrics and neonatal outcomes and signs and symptoms in neonates and mothers represented in Table 1.

Table 1: Study characteristics of all studies included in the systematic review

Author	Number of pregnant women/neonates	Mean of Gestational Age	Method of delivery (n)	Typical signs of viral infection (n)	Treatment
Zhang L et al (28)	16 pregnant	38.7 w (COVID-19 group)	C/S*	-	-
Chen SH et al (13)	3 pregnant	37.6w, 2d	C/S	Prenatal fever (1), postpartum fever (2), chest tightness (1)	-
Liu D et al (29)	15 pregnant	33w±1d	C/S (10), NVD**(1)	Postpartum fever (1), Cough (9), Sore throat (1), Dyspnea (1), Myalgia (3), fatigue (4), Diarrhea (1)	Oxygen support (nasal cannula), Antiviral therapy, Antibiotic therapy
Zhu H et al (27)	9 mothers/10 neonates	38w, 2d	C/S (7), NVD (2)	-	Oseltamivir and nebulized inhaled interferon
Chen H et al (20)	9 pregnant	39w, 3d	C/S (9)	Post-partum fever(6), Myalgia (3), Malaise (2), Cough (4), Dyspnea (1), Sore throat (2), Diarrhea (1)	Oxygen support (nasal cannula), Antiviral therapy, Antibiotic therapy
Song L et al (21)	1 pregnant	36w, 3d	C/S	Decreased breath sounds and rales on lung auscultation	-
Liu Y et al (6)	13 pregnant	33 w, 3d	C/S (10)	-	-
Wang X et al (24)	1 pregnant	30 w	C/S	-	Arbidol, Lopinavir and Ritonavir, Cefoperazone Sodium and Sulbactam Sodium, Human Serum Albumin
Li Y et al (25)	1 pregnant	35w	C/S	-	Antiviral treatment, Methylprednisolone to relieve inflammation effusion
Chen Y et al (22)	4 pregnant	38w,2d	C/S (3), NVD (1)	Fever (3), cough (2), fatigue (2), headache (2), mulligrubs (1), dyspnea (2)	Oxygen therapy of neonate
Fan C et al (15)	2 pregnant	36w,3d	C/S (2)	Fever persisted (1), rash (1), nasal congestion (1), sore throat (1)	Cefotiam hydrochloride, Ornidazole, Methylprednisolone; Ceftazidime, Oseltamivir, Lianhua Qingwen capsules, Methylprednisolone
Zeng L et al (26)	33 pregnant	37w, 3d	C/S (26), NVD(6)	Postpartum fever (6), Cough (10)	Mechanical ventilation, Antibiotic,
Yu N et al (23)	7 pregnant	39w, 1d	C/S (7)	Cough, Shortness of breath, Diarrhoea (1)	Oxygen support (nasal cannula), Antiviral therapy (oseltamivir, ganciclovir, interferon, arbidol tablets), Antibiotic treatment
Chen S et al (14)	5 pregnant	39w,5d	C/S (2), NVD (3)	Post-partum fever (1), Cough (1), Sputum (1), Coryza (1)	-
Khan S et al (16)	3 pregnant	37w, 1d	NVD (3)	Fever (2), Cough (3), Chest tightness (1)	Azithromycin, Oral Lianhua Qingwen capsules, Oseltamivir antiviral drugs, Oxygen inhalation
Wang S et al (30)	1 pregnant	40 w	C/S	-	Antiviral treatment (interferon α1b atomized inhalation, ganciclovir), Anti-infection (Abipenem, moxifloxacin), Methylprednisolone

*Cesarean Section; **Natural Vaginal Delivery

Obstetrics outcomes

Overall, 123 pregnant women with COVID-19 were included in this review, among whom 99 patients were delivered by cesarean section and 17 by vaginal delivery. Although most studies found that COVID-19 does not lead to vertical transmission of infection from mother to infant, but one of the causes of cesarean section in affected women were COVID-19 and its complications such as persistent fever (6, 14, 15, 20-22). Based on the results of included studies, 8 patients had combined spinal and epidural anesthesia and one received general anesthesia (21, 23, 24).

Based on the results of the included studies, obstetrics outcomes include: decreased fetal movement (22, 24, 28), increased fetal movement (23), intrauterine fetal distress (6, 20, 24, 26-28), developed anemia (22), severe dyspnea after delivery and required respiratory support (22), preeclampsia (20, 28), Premature Rupture of Membranes (PROM) (6, 20, 26-28), influenza (20), preterm labor (6, 15, 16, 20, 21, 24-29), significant increase in aminotransferase concentration (20), meconium-stained amniotic fluid (26, 28, 30), developed fever after delivery (13, 14, 20, 26, 29, 30), severely elevated liver tests such as ALT or AST (20) and MODS (6).

A study reported that there was no significant difference between the infected and non-infected women in terms of maternal outcomes. Of the 16 pregnant women, only one had severe coronavirus type, who after active treatment, she still had clear symptoms of chest tightness and shortness of breath. In this study, for COVID-19 pregnant women with uterine contraction, carbetocin or carboprost tromethamine during cesarean section was used more than the control group, and this difference was statistically significant (28).

In the majority of the studies, no severe morbidity or mortality occurred, and the clinical features and patterns of CT (computerized tomography) imaging for progression among pregnant women were similar to those of non-pregnant females (13, 20, 21, 27, 28, 30). However, one patient's condition deteriorated during hospitalization and due to MODS, including respiratory distress syndrome requiring intubation and mechanical venti-

lation, acute liver and kidney failure, and shock. Then she was admitted to the intensive care unit and supported by Extracorporeal Membrane Oxygenation (ECMO) (6). Nevertheless, no maternal deaths occurred in included studies.

Placenta change: Histopathological analysis of the placenta in one study showed that 1 case had chorioangioma and another had multifocal infarction; 3 cases had microscopic fibrin deposition in the villus interstitial or around the villi, and local syncytia nodules increased. Other tissues, including embryonic membranes and umbilical cord, were not abnormal and no chorionic inflammation and chorioamnionitis were observed. Three cases of placental tissue SARS-CoV-2 nucleic acid tests were negative (13).

Neonatal outcomes

Based on included studies, the range of neonatal weight was 1580 to 4000 gr. The weight of thirteen premature neonates was under 2500 gr (20, 24, 26, 27). In addition, 1 male neonate (39w) weighed 2810 gr, and another male neonate (38w,4d) weighed 2450 gr were small for gestational age (SGA) and one male neonate (37w) weighed 3800 gr was large for gestational age (LGA) (27). Among the studied neonates, 30 neonates were premature from 30w to 36w, 5d (6, 15, 16, 20, 21, 24-29). All of these neonates survived except one neonate (34 w) in Zhu H et al study (27). In the reviewed studies, except for one stillbirth (6), all neonates were born alive. The Apgar score of one neonate affected by COVID-19 were 3, 4, and 5 at 1, 5, and 10 minutes after birth, respectively (26). The rest of neonates obtained Apgar scores ≥ 7 at 1 and ≥ 8 at 5 minutes after birth. Only asphyxia was reported in two neonates (26, 28) which, nasopharyngeal and anal swabs for SARS-CoV-2 in one neonate were positive (26).

Vertical transmission: In most of the studies, the samples of amniotic fluid, umbilical cord blood, whole blood, plasma serum, throat swabs from neonates, and breast milk were collected and assessed for SARS-CoV-2. In majority of included studies, there was no evidence of vertical transmission and infant infection with

COVID-19 (6, 13-16, 20-22, 24, 25, 27-29). However, the result of five neonates were positive for SARS-CoV-2.

In the study by Zeng et al., in 33 neonates born to mothers with COVID-19, three neonates were positive for SARS-CoV-2. In this study, two neonates were term and one was preterm. Case 1 was born at 40 weeks of gestational age by cesarean section and 2 days after birth had lethargy and fever. In physical examination, there was no remarkable result. A chest radiographic image showed pneumonia, but other laboratory tests were normal. The duration of NICU (Newborn Intensive Care Unit) was 2 days. Case 2 was born at 40 w, 4d by cesarean delivery because of confirmed maternal COVID-19. He experienced lethargy, vomiting, and fever. In physical examination, there was no remarkable result, but the laboratory tests showed leukocytosis, lymphocytopenia, and an elevated creatine kinase-MB fraction. A chest radiographic image showed pneumonia. The duration of NICU was 4 days. Case 3 was born at 31w, 2d by cesarean delivery because of fetal distress and confirmed maternal COVID-19. Following low Apgar score in 1, 5, and 10 minutes after birth, resuscitation was required. The results of chest CT-Scan showed neonatal respiratory distress syndrome and pneumonia that improved on day 14 after treatment with noninvasive ventilation, caffeine, and antibiotics. The duration of NICU was 11 days. In these three neonates, nasopharyngeal and anal swabs were positive for SARS-CoV-2 on days 2 and 4 of life and negative until day 7. All three neonates were discharged from hospital (26).

In another study, the nucleic acid test for the throat swab of one neonate was positive at 36 h after birth. This neonate was born to 34 years old mother by cesarean section. This neonate had no fever and cough, with mild shortness of breath symptoms. The result of Chest x-ray showed mild pulmonary infection. After two consecutive negative nucleic acid test results the neonate was discharged after 2 weeks (23).

Another infected infant that was born at 40w by emergency cesarean delivery, half an hour after birth, had vomiting once after feeding with for-

mula and the blood tests showed lymphopenia, deranged liver function tests, elevated total and indirect bilirubin and creatine kinase level. 36 hours after birth the results of pharyngeal swab for SARS-CoV-2 was positive. After finding evidence of neonatal infection, nucleic acid tests were performed for SARS-CoV-2 on cord blood and placental specimens and the results were negative. The mother's breast milk sample was negative for SARS-CoV-2 as well. On the sixteenth day after birth the nucleic acid tests of the pharyngeal and anal swabs for SARS-CoV-2 were negative and neonate was discharged (30).

Neonatal death: In a study, a male neonate with a gestational age of 34 w, 5 d was born to a 30-year-old mother, who underwent a cesarean section. The infant weighed 2200 g and had Apgar scores of 8 and 9 at 1 and 5 minutes after delivery, respectively. At 30 minutes after delivery, due to moaning and difficulty breathing was admitted in NICU. This neonate had intrauterine fetal distress and his first sign was an increase in heart rate. This neonate's chest X-ray was normal at admission, but 8 days later, he developed refractory shock, multiple organ failure, and disseminated intravascular coagulation (DIC), which was treated with transfusion of platelets, suspended red blood cells, and plasma. His throat swab test was negative on the ninth day of birth, and he received no antiviral treatment during this time, but he also died on this day (27).

Stillbirth: In a study, one neonate was born by cesarean section at 34 weeks of age with a dead status and zero Apgar score. During hospitalization, the condition of this neonate's mother deteriorated because of MODS and finally she was supported by ECMO (6).

Discussion

Recently the COVID-19 has become a global health concern. In this systematic review, we summarize the result of 16 studies including 123 pregnant women. Most of the women were in third trimester. The cesarean section is the common delivery method in pregnant women. This

finding is consistent with previous studies that reported emergency C-sections were pregnancy complication of women with COVID-19 (6) and MERS (31) and SARS (32). In this review, the reasons for C-section were some medical condition such as, repeat cesarean, fetal distress, PROM, Placenta issues, gestational diabetes and etc. Generally, the decision on the method of delivery should be individualized and based on gestational age, maternal and neonatal conditions (33). According to the evidence about the safety of anesthetic regimens in C-section of pregnant women with COVID-19, the both general and epidural regimes were safe in these women (34). The result of the case report of Song et al. showed that combined spinal and epidural anesthesia was effective and safe in pregnant women infected with COVID-19 and met the need for emergent cesarean delivery (21).

There was some evidence about neonates COVID-19 in the included studies (23, 26, 30), but it is not clear whether the source of the infection in these neonates is from the mother or from the environment. In addition, there is no information about the false negative or false positive of tests. A study in China reported that the sources of SARS-CoV-2 in the neonates were maternal in origin, because strict infection control and prevention procedures were implemented during the delivery (26). However, in the majority of studies, there was no evidence of vertical transmission (6, 13-16, 20-22, 24, 25, 27-29). So, the maternal-to-neonatal vertical transmission of COVID-19 is controversial. In most studies, the neonates were separated from the mother after birth to reduce the chance of transmission, but there is also currently insufficient evidence regarding the mother/baby separation. If the mother is severely or critically ill, separation should be considered (35). The result of a review showed that in SARS vertical transmission were not seen (36). It seems that similar to the SARS and MERS the spread of COVID-19 occurs mainly via respiratory droplets (5). However, there are many unknown issue about the transmission of it.

The COVID-19 may be accompanied by some obstetrics outcomes. In the present review, the obstetric outcomes include, decreased fetal movement, intrauterine fetal distress, developed anemia, PROM, preterm labor, multiple organ dysfunction syndrome and etc. A study in Hong Kong in 2004 reported that SARS during pregnancy is associated with high incidences of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction (11). Another study showed that the pneumonia could increase the risk of low birth weight, preterm births, restricted fetal growth, and 5-minute Apgar score < 7 (37). In pregnant women, similar to other adults (38), the fever was the common clinical manifestation at the onset of COVID-19. Another symptom in the pregnant women including cough, sore throat, diarrhea, dyspnea, chills, shortness of breath. Also in SARS, which epidemic in 2002-3, the fever was the common symptom of pregnant women (39). Evidence showed that the intrapartum fever might lead to neonatal outcomes (40).

In this review, the fetoneonatal outcomes of pregnant with COVID-19 were fetal distress, prematurity, low birth weight, neonatal asphyxia, stillbirth, multiple organ failure and DIC. The preterm labor and fetal distress are the common outcomes in this study. This finding is consistent with a study which reported the fetal distress, PROM and stillbirth and preterm delivery were the pregnancy complication of women with COVID-19 (6). A rapid review reported that preterm delivery affected 42% of women with COVID-19 (41). In addition, a study showed that the pregnancy of 12 pregnant with SARS were complicated by IUGR, preterm labor and spontaneous abortion (11). Due to insufficient information, and different infection duration, severe and symptoms, different immune system of pregnant women the interpretation of studies finding and determination the causal link between neonatal complication and COVID-19 infection, is not possible.

In contrary with Wong's results, that were three deaths occurred from 12 pregnant women with SARS (11), there was not any death associated with COVID-19 in the pregnant women. The

other type of coronavirus had worsened maternal outcomes. Among 1308 patients with MERS, 5 cases were pregnant women and 2/5 (40%) of them were died (42). In addition, in 10 pregnant women during the outbreak of SARS, the adverse maternal outcomes including: renal failure, sepsis, deaths, ICU admission (39). In overall, the immune system of pregnant women was complex. Therefore, in each pregnant woman based on the gestational age, the immune system, the infection duration and severity the maternal and neonatal outcomes will be different. The equipment, physical space and human resource are necessary in management of obstetric triage (43).

The Nasal oxygen therapy is the common respiratory support for pregnant women. Maternal hypoxia might affect the brain function of neonatal in later life (44). According the world health organization recommendation, the management option in pregnant women with sever COVID-19 is oxygen therapy for achieving the $SpO_2 \geq 92-95\%$ (45). Most of women receive the treatment plan after the delivery. Antiviral therapy (such as oseltamivir) is one of the treatment options in participants of included studies. Evidence showed that there are no adverse pregnancy outcomes of oseltamivir using during pregnancy (46).

The physicians should investigate the risk-benefit of antiviral therapy in pregnant women. Overall, close collaboration and coordination between midwifery and neonatal unit are needed to management of maternal and neonatal outcome following COVID-19. The multidisciplinary team should be managed the pregnant women with COVID-19 and their newborns of these women should be isolated until 2 weeks.

Conclusion

The obstetrics and neonatal outcomes following COVID-19 were divers. It may cause negative outcomes in both mothers and neonates. However, there were evidence about neonate infected with COVID-19, but there is controversial information about the vertical transmission of

COVID-19. Therefore, due to the high transmissibility of this virus, the treatment team should be aware of the possibility of vertical transmission and they should take the necessary measures. If the mother is severely or critically ill, separation should be considered.

Although, the studies report some obstetric and neonatal outcomes but the exact causes of them are not known, and there is need the future studies to clear the causal link between these outcomes and COVID-19 infection.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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