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Maternal and Neonatal Outcomes in Infected Pregnant Women with Coronavirus: A Systematic Review

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ABSTRACT

Background & aim: Novel coronavirusease 2019 (Covid-19) started in China and caused unexplained pneumonia. The risk of adverse pregnancy outcomes increase in respiratory viral infection during pregnancy. This systematic review was performed to investigate the maternal and neonatal outcomes in pregnant women infected with Covid-19.

Methods: In this systematic review, the international databases (PubMed, Cochrane Library, Web of Science, Scopus, Embase, PsycINFO, Google scholar) as well as national databases (SID and Magiran) were searched to find out the articles published from 1 September 2020 to 30 April 2021 regarding maternal and neonatal outcomes in pregnant women infected with Covid-19. Keywords were selected based on Mesh ("Pregnancy", "Gravidity", "Delivery", "Infant", "Newborn", "Neonate", "Outcome", "Complication", "Abortion", "Obstetric Labor, Premature", "Cesarean Section", "Fetal Death", "Infant, Premature", "Coronavirus Infection", "COVIDK19"). The full texts of articles were reviewed by two independent reviewers and the relevant data was extracted.

Results: 20 studies including 78 pregnant women entered in this review. All women were at third trimester of pregnancy except 2 cases who were less than 28 weeks. The most prevalent clinical symptoms were fever, cough and sore throat. The most common maternal outcomes were intrauterine distress, rupture of membranes and preterm delivery. Most infants delivered by cesarean section. The most common neonatal complications were prematurity, small for gestational age, fetal distress, low birth weight and bacterial pneumonia.

Conclusion: In this systematic review, we found some evidence to suggest that COVID-19 pneumonia causes negative maternal and neonatal outcomes in pregnant women infected with Covid-19.

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Introduction

Covid-19 started in a wet market in Wuhan, China, however it may not be the only source of this infection. In December 2019, 41 cases of unexplained pneumonia were reported in Wuhan.

This virus is a single-stranded and has 29891 nucleotides in size and encoding 9860 amino acids. Many countries have recorded the infected cases; there was no enough experience in diagnosing and managing the COVID-19. It has a very powerful pathogenicity and transmissibility (1). Now this virus is spreading in different regions, countries and continents (2). Coronavirus causes respiratory and GI tract complications in animals and human (3).

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WHO (World Health Organization) has reported the pandemic status of vovid-19 on 11th March 2020 (4).

The risk of adverse pregnancy outcomes increases in respiratory viral infection during pregnancy (5). The partial immune suppression in pregnant women makes them to be vulnerable against COVID-19. They experience immunologic and physiologic changes and might be more susceptible to viral respiratory infection(6).

Managing such pregnancy is very complicated as the infection has potential adverse effect on the mother and neonate (4). Researchers reported some risks of preterm delivery (7), PROM (premature rupture of membrane) and fetal distress when it occurs at third trimester. There is no evidence suggesting COVID-19 increases the risk of abortion, also many physicians have fear of congenital infection and tetragenocity of this virus and they would decide pregnancy termination. Of course, data and information about pregnancy outcome in infected mothers is not enough yet(2).

There is no enough evidence of vertical transmission of virus. It is still unknown if it transmits through vaginal delivery. However neonatal infection can occur after birth by close contact with infected mothers (4).

The latest studies have shown that there is no evidence for transmission of this virus through uterus. Infants who were born with identified cases of COVID-19 with no presence of this infection in cord blood and placenta, but the swabs test were positive 36 hours after birth, therefore they may be infected by droplets and contacts. Of course, this conclusion needs more research and requires more evidence (1). Although, it is yet unknown that virus shedding occurs vaginally or increases the risk of miscarriage or stillbirth (2, 8).

MERS-CoV is viral respiratory illness that is new to human and is associated with high rate of mortality (9, 10). Many studies showed adverse pregnancy outcome regarding pregnant women infected with this virus such as; maternal mortality, stillbirth, spontaneous abortion, preterm delivery, death, fetal distress, LBW (low birth weight), premature rupture of membrane (3, 5, 7, 9, 11-17). Also, high fever in early stage of pregnancy can increase the risk of certain birth defects (6).

On the other hand, some studies have shown the acceleration of some complications such as death, still birth, preeclampsia, intra uterine fetal distress in the infected pregnant women (9, 18, 19). Some researchers have reported 42% prevalence of preterm delivery in infected pregnant women, but there is no evidence regarding fetal growth or placenta pathology (20).

Now, the number of studies reporting the infected pregnancy with covid-19 is not enough to do comparative analysis on pregnancy results (4).

Physiological and immunological changes during pregnancy are the results of shift form cell-mediated to hormonal-mediated immunity and may end to sever pneumonia in pregnancy. The outcomes of pregnancy are different in the studies and it may relate to the stage of pregnancy, maternal age, the use of drug (steroid or antiviral therapy) and potential differences in immune responses (11).

The immune response of pregnant women might change during pregnancy and postpartum, shifting from a pro-inflammatory to anti-inflammatory state. Also, we have some hormonal effects on immune system during pregnancy, for example; an increased level of progesterone is associated with several anti-inflammatory effects. Studies have shown an association of estrogen with suppression of inflammation as well as pro-inflammatory effects (21).

This systematic review study was performed with aim to determine the maternal and neonatal outcomes during pregnancy in pregnant women infected with COVID-19.

Materials and Methods

In this systematic review study, the international databases (PubMed, Cochrane Library, Web of Sciences, Scopus, Embase, and PsycINFO), national databases (SID and Magiran), and Google Scholar were searched by two independent reviewers from 1 September 2020 to 30 April 2021. Papers were selected with using the keywords of: “Pregnancy”, “Gravidity”, “Delivery”, “Infant”, “Newborn”, “Neonate”, “Outcome”, “Complication”, “Abortion”, “Obstetric Labor, Premature”, “Cesarean Section”, “Fetal Death”, “Infant, Premature”, “SARS COV 2”, “Coronavirus

Infection", and "COVID-19". All papers were entered in EndNote X9 software to identify duplications. In this study, there was no language restriction. Papers were searched manually among the relevant studies. The steps of article search were shown in Figure 1.

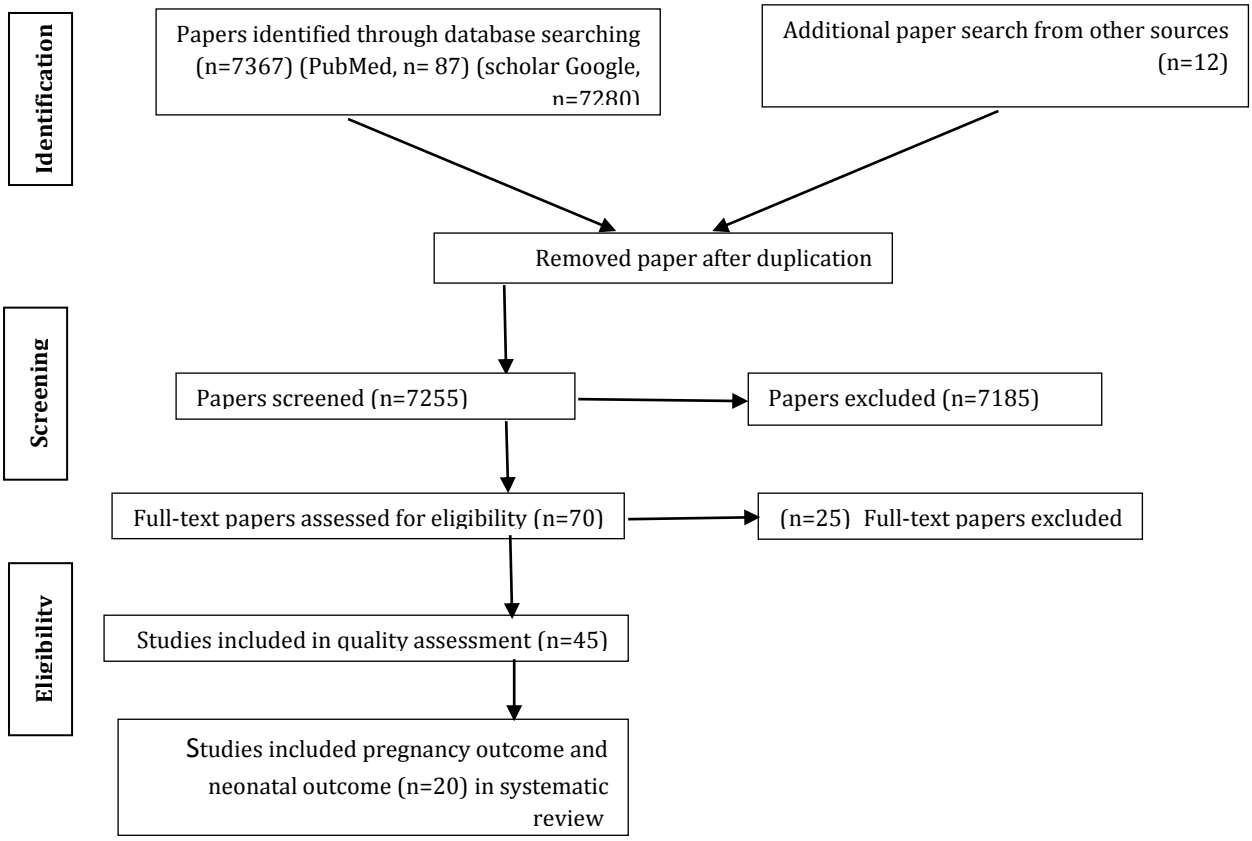

Figure 1. Flow diagram of the number of papers reviewed and include in this systematic review study

The inclusion criteria in this study were; all papers about COVID-19 during pregnancy, and the lack of full access of articles. Also, the studies with irrelevant reports and review articles were excluded from the study.

The quality assessment of this study was done by two authors individually using the Newcastle-Ottawa Scale (NOS) checklist and scoring system to evaluate the quality of the case report studies. Newcastle-Ottawa Scale (NOS) checklist was used to evaluate the quality of cross-sectional, case control and cohort studies and this scale divided the articles in terms of selection process (in 4 sections including: sample explicitness, sample size, non-response and measurement tools), comparability (one section includes: investigation of confounders and other influencing factors) and results (from two Aspect: evaluates the result and statistical tests). According to the Newcastle Ottawa scale, articles are rated from zero (weakest study) to 10 (strongest study). In order to preserve the data, studies with a score lower than the mean score (less than a score of 4) were considered to be of lower quality. The checklist consists of three sections: selection, comparability exposure, or outcome (22) . The Scoring system was designed by Kanthraj et al, and was used to evaluate the quality of the case report studies. It includes five subcategories of goal reporting, diagnostic criteria, clinical techniques and methods, and symptom reporting, factors related to clinical existence, and the authors'

conclusions (23). The quality was assessed and classified as low, medium and high.

Due to time constriction, two people (MZ, NN), conducted the search, we had searched the literature independently and read all full text, also all papers were blinded by M Gh. Disagreements were resolved by third author (ST). Evidence level was recorded blindly. Data were extracted including; demographic data, maternal imaging- diagnostic testing- outcome and perinatal and neonatal outcomes and neonatal diagnostic test.

Results

The search in databases of PubMed, Google scholar and other database selected 87, 7280 and 12 abstracts, respectively. After screening all abstracts, 124 papers were excluded due to duplication, 7185 papers were excluded because they were not about pregnant women or human or were in-vitro studies. 70 relevant studies were identified and all full texts were reviewed; finally 20 papers were included in this study (Fig.1)

Table 1. Demographic data

Refrences	Country ,year	Number of participants	Age of mother	Gestational age	Source of infection	ICU admission	CT-chest/CX Ray	Antiviral trapy
Zhu, Wang (24)	China,2020	10	30	Trimester III	-	-	yes	No
Chen, Peng (3)	China,2020	9	26-40	Trimester III	4 (Exposure to relevant environment), 5(contact with infected person)	-	-	Yes
Liu, Wang (19)	China,2020	3	30-34	Trimester III	-	-	-	-
Wang, Zhou (17)	China,2020	1	28	Trimester III	Had history of travel to Wuhan 3 weeks before admission	yes	yes	Yes
Zhang, Jiang (33)	China,2020	16	24-34	Trimester III	-	-	-	-
Li, Han (34)	China,2020	16	30.9±3.2	Trimester III	-	-	yes	Yes
Chen, Peng (3)	China,2020	4	28-34	Trimester III	-	Not mention	yes	-
Khan, Peng (7)	China,2020	3	27-33	Trimester III	3 (History of contact with infected patient)	Not mention	Not mention	Yes
Liu, Wang (19)	China,2020	3	30-34	Trimester III	-	-	yes	Yes
Liu, Chen (35)	China,2020	13	22-36	2 (less than 28 week), 11 (trimester III)		1	-	-

Data regarding the number of women, maternal age, gestational age, source of infection, ICU admission, CT-chest, CX-Ray, antiviral therapy were summarized in Table 1. Total number of women in the included papers was 1 to 16 (total number: 78). The maternal age was 22 to 40 years old. All women were at third trimester except 2 cases who were less than 28 weeks. Some of the infected women had a history of contact with infected people. Two cases had ICU admission. CT-chest, CX-Ray and antiviral therapy had been done in the cases.

Data regarding the symptoms, time interval between the onset of symptoms until delivery, maternal outcome, type of delivery, die or survive and maternal real time PCR have been shown in Table 2.

Table2. Pregnancy outcomes

Reference	symptom	Symptom to delivery	Maternal outcome	Delivery details	Die/ surrvived	Maternal real time PCR for SARS-Cov 9(+)
Zhu, Wang (24)	Fever, cough, diarea, sore throat, cholecystitis	1 day to 6 days	6(Intrauterine distress), 2(abnormal umbilical cord), 1(placenta previa), 1(oligohydraminos), 1(polyhydraminose), 3(PROM), 1 vaginal bleeding, 1 chilecystic	7(C/S), 2(vaginal)	-	8 case
Chen, Peng (3)	Cough, dyspnoea, sore throat, diarrhea, chest pain, fever on admission, post-partum fever	1 day to 7 days	1 (gestational hypertension), 1 (preeclampsia), 2 (PROM), 2 (fetal distress)	9 (c/s)	-	9
Li, Han (34)		1 day to 13 days	1 (hypotiroidism), 1 (placenta acreta), 1 (gestational diabete)	2 (c/s)		3
Wang, Zhou (17)	fever	13 days before delivery	1 (fetal distress)	1 (c/s)	survive	1
Zhang, Jiang (33)	-	Not stated	3 (gestational diabete), 3 (PROM), 3 (preterm delivery), 2 (uterine scarring), 2(B-lynch/compression suture procedure), 1 (severe preeclampsia), 1(fetal distress), 1(fetal asphyxia), 1 (meconium staining), 1 (COVID-19 pneumonia)	16 (c/s)	-	16
Li, Han (34)	Fever on admission, fever at child birth, cough, sore throat, dyspnoea		11 complication of pregnancy	14	-	-
Chen, Peng (3)	(3)fever, (2) cough, (2) fatigue, (1) headache, (1) muligrubs, (2) dyspnea, (1) decrease of fetal movement,		-	3 cesarean section	1/3	4
Khan, Peng (7)	2(fever), 3 (cough), 1 (chest tightness),	-	1 preterm delivery	3(vaginal delivery)	3 survive	Yes
Liu, Wang (19)	2(fever), 2(cough)	-	1(chrionic fetal distress in utero, chorioamnionitis)	2 cesarean section), 1(vaginal delivery)	3 survive	Yes
Liu, Chen (35)	10 (fever), 3(dyspnea) 1 (No symptoms)	-	3(fetal distress), 1 (PROM) , 1 (still birth), 1 (still birth), 6(preterm labour)	5 cesarean section	-	-

Table 3. Fetal outcome

Reference	Country	Gender (M-F)	Fetal outcome	die	Chest radiography	symptom	Twin-singleton	Birth weight	Apgar at 1 and 5 mins	Neonatal PCR
Zhu, Wang (24)	China,2020	8- 2	6(prematurity), 2(SGA), 1 (LGA), 6 fetal distress, 2(DIC), 2 (GI bleeding), 1 (multiple organ failure), 1 (shock)	1	7(abnormality due to infection), 2 (NRDS), 1(pneumothorax)	6(SOB), 2(fever), 1(rapid heart rate), vomiting, 2(trombocytopenia with abnormal liver function), syanosis, 1 (diffused scattered rashes), 1 (edema), 1 facial skin lesion)	2-8	1520-3800 g	7-10	10 negative
Chen, Peng (3)	China,2020		1 (SGA)1 (LBW), 4 (prematurity)	0	-	-	-	1880- 3820 g	8-10	6 negative
Liu, Wang (19)	China,2020		-	-	-	-	-	3250-3670 g	8-9	negative
Wang, Zhou (17)	China,2020	M	LBW, premature	survive	-	No	Singleston	1830 g	9-10	negative
Zhang, Jiang (33)	China,2020	-	1(preterm infant), 3 (bacterial pnemonia)	-	-	-	-	2300-3750 g	Not state	10 negative
Li, Han (34)	China,2020	-	3(LBW), 4 (preterm birth), 1(intra uterine fetal distress)	-	-	-	15 singletone	3078.2± 565	(9.6± 0.5)-(10±0.0)	
Chen, Peng (3)	China,2020	3-1	(1)dyspnea, (1) oxygen therapy, (1) edema, (2) rash	0	3(2 normal , 1: TTN)	Rash	4 singletone	3050-3800 g	7-9	3 negative
Khan, Peng (7)	China,2020	Not mention	1 (prematurity)	0	no	-	3 singletone	2890-3730 g	8-10	3 negative
Liu, Wang (19)	China,2020	2 (male), 1 (female)	1(MSAF), 1(slight decreased responsiveness and muscle tention)	no	no	-	3 singletone	3250-3670 g	8-9	no
Liu, Chen (35)	China,2020	-	-	-	-	-	-	-	9 (1 score)	-

LGA: large for gestational age, **POLY**: polyhydramnios, **SGA**: small for gestational age, **SOB**: shortness of b sw3 reath, **DIC**: dissminatated intravascular coagulation, **C/W**: consistent with, **LBW**: low birth weight, **MSAF**: meconium stained amniotic fluid.

The most common clinical symptoms were fever, cough and sore throat. The time interval between symptoms until delivery was 1 to 13 daysThe most common maternal outcomes were intrauterine distress, PROM and preterm delivery. The most infants had been delivered by cesarean section.

Some information about fetal outcomes was presented in Table 3. Majority of infants was male. The most common neonatal complications were prematurity, small for gestational age, fetal distress, low birth weight and bacterial pneumonia. One infant died. Some neonates had abnormal chest radiography. The neonatal complications were fever, rapid heart rate, rash, vomiting, shortness of breath and thrombocytopenia. Most of them were singleton. The birth weight was 1520 to 3820 gr. All of them had good Apgar score and negative PCR.

Discussion

A novel coronavirus (2019-nCoV) was diagnosed in December 2019 in infected patients with severe pneumonia. The pregnant women were more susceptible to this infection (24).

In the present study, the most common neonatal complications were prematurity, small for gestational age, fetal distress, low birth weight and bacterial pneumonia. Different pregnancy outcomes have been reported in infected pregnant women with H1N1 and SARS. A study on 12 pregnant women infected by SARS in Hong Kong had reported that 50% required ICU administration, 33% needed mechanical ventilation, 57% had spontaneous abortion (women infected in first trimester) and 80% had preterm delivery (11). Also, some neonates had abnormal chest radiography. The neonatal complications were fever, rapid heart rate, rash, vomiting, shortness of breath and thrombocytopenia. Hao Hong reported that among 9 infants, four had fever, two mild upper respiratory, one asymptomatic and two had no information on symptoms (25). Regarding the source of neonatal infection, Schwartz and coworkers believed that infection can be acquired during vaginal delivery or breastfeeding, but it would be highly unusual for respiratory virus; also fetal infection will potentially transport through aerosols produced by other resource such as; coughing from mother, relatives or healthcare workers or other source in the hospital environment (5). Neonatal morbidity was more marked due to prematurity.

To date, no evidence has been derived on whether pregnancy is sensitive situation regarding COVID-19 (26). However, the immunological changes during pregnancy can cause the increased risk of illness and death from influenza (27). According to the data collected on the 1957 to 1958 influenza pandemic and the 2009 H1N1 influenza pandemic, the risk of contracting viral pneumonia was significantly higher in pregnant women than in other individuals (11, 28). During pregnancy, physiologically, the diaphragm moves upward, decreases pulmonary residual and expiratory reserve volumes, increases airway conductivity, and decreases total lung resistance (29). These conditions can elevate oxygen demand and possibly cause critical closing pressure, thereby placing women at more risk of respiratory problems (30). Additionally, the fetus has low tolerance for hypoxemia and acidosis, which can thus stimulate preterm labor after mid-pregnancy (29). The researchers showed that high rates of miscarriage, and neonatal prematurity can be traced to the contraction of viral pneumonia disorders, such as influenza A, H1N1 infection, … (31, 32). It is recommended that all pregnant women exposed to contact with a person infected with SARS-Cov2 be carefully examined. Assess pregnant women for fever and symptoms of respiratory infection, receive intensive care, use of experimental antibiotics, and research to design Dedicated nanoparticles that carry drugs, vaccines, or any effective drug that can target the mother's disease without fear of side effects on the fetus can help reduce the complications of Quid 19 in the pregnant mother and her fetus. Maternal and neonatal health are important health indicators. We can use the information of this article to plan health care for them in COVID-19.

Conclusion

In this study, we found some evidence to suggest that COVID-19 pneumonia causes negative maternal and neonatal outcomes in pregnant women infected with Covid-19. Future studies are needed to collect more robust data

to further validate or substantiate these findings, better understand the pathophysiologic pathways that explain these associations and identify effective strategies to prevent adverse outcomes in pregnant people with COVID-19.

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Conflicts of interest

Authors declared no conflicts of interest.

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