

Clinical features, treatments and perinatal outcomes of novel coronavirus infection during pregnancy: a systematic review

Narayana Goruntla, Jyothi Suchitra, Kannan M Shanmugha, Dasaratharamaiah Jinka, Mohammad Jaffar Sadiq, Vigneshwaran Easwaran

Corresponding author: Mr. Narayana Goruntla, Assoc. Professor, Dept. of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Anantapur, Andhra Pradesh, India; Email : narayanagoruntla@gmail.com

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ABSTRACT

Objectives: To collect all studies related to COVID-19 infected pregnant women and summarize the symptoms, laboratory findings, treatments, and perinatal outcomes. **Methods:** The systematic review was conducted according to the PRISMA consensus statement. A systematic search was performed in PubMed, Scopus, Web of Science, and Cochrane databases on April 3, 2020. All studies relevant to COVID-19 infection among pregnant women are considered for inclusion. A total of 12 studies are considered for inclusion in this systematic review. Two authors extracted the data by using pre-designed, piloted, and customized data extraction form. **Results :** Fever (60.2%), cough (36.6%), and postpartum fever (23.5%) are the most common symptoms observed in pregnant women infected with COVID 19. The most common abnormal laboratory finding observed in COVID 19 infected pregnant women include; raised AST or ALT (21.0%), lymphopenia (55.8%), elevated C-reactive protein (62.2%), and abnormal chest CT scan (90.2%). Oxygen administration, antibiotic, and antiviral therapy is the mainstay of management strategy in the majority of the studies. Chloroquine and hydroxychloroquine are not advised in pregnancy due to secondary complications. The most common adverse obstetric and neonatal outcomes are preterm delivery, C-section, fetal distress, and low birth weight. There was no vertical transmission of COVID 19 from mother to fetus. **Conclusion:** Fever, cough, postpartum fever, elevated C-reactive protein, lymphopenia, and abnormal chest CT are the most common clinical and laboratory examinations in pregnant women infected with COVID-19. All healthcare professionals need to consider possible outcomes in this review and make a decision to reduce the risk of complications in both mother and fetus.

Keywords: COVID-19, novel Coronavirus, neonatal outcomes, perinatal outcomes, symptoms, lab abnormalities.

On 30th January 2020, the World Health Organization (WHO) declared the novel Coronavirus disease 2019 (COVID-19) as a public health emergency of international concern (PHEIC) after it crosses the number of infected cases beyond 2002-2003 outbreaks of severe acute respiratory syndrome (SARS) in China^{1,2}. Since its initial

detection in Wuhan, Hubei province, China, COVID-19 has now been reported from all continents except Antarctica, affecting 754,948 people in 202 countries and resulting in 36,571 deaths as of April 1, 2020. On March 11, the World Health Organization (WHO) officially changed its taxonomy of the situation from a public health emergency of

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international concern to a pandemic ³.

Evidence shows that, Corona family members lead to severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) can cause severe complications during pregnancy. A study conducted by Wong SF et al on outcomes of SARS-CoV infection in 12 pregnant women revealed, seven women had a miscarriage in 1st trimester, two of five women had fetal growth retardation in 2nd to 3rd trimester, four of five women had a preterm delivery, and three women died during pregnancy period ⁴. Similarly, a study on MERS-CoV infection in pregnancy also has shown severe adverse outcomes, like preterm delivery, maternal respiratory failure, and neonatal intensive care unit (NICU) admission ⁵. The novel Coronavirus (COVID-19), which comes from the same family viruses, can potentially cause adverse prenatal and neonatal outcomes. Emergent viral infections like, Zika virus, Ebola virus, and Marburg virus can infect fetus through vertical transmission and develops the complication in both mother and fetus ⁶⁻⁸.

The lancet study conducted by Huang et al reported epidemiological, clinical, laboratory, radiological features and treatment outcomes of patients infected with novel Coronavirus (COVID-19) in Wuhan, China ⁹. This study was only focused in non-pregnant adults. The physiological and immunocompromised changes in pregnancy can increase the susceptibility of pregnant women towards COVID-19 infection ¹⁰. Currently, the evidence linked to clinical features, laboratory tests, neonatal outcomes, vertical transmission, and intrapartum care in pregnancy caused by COVID 19 is scarce. As COVID-19 is rapidly spreading, it is not only a public health issue, it is also very important to develop an obstetrical management plan to provide care for pregnant women. This systematic review is aimed to collect all studies related to COVID-19 positive pregnancy and summarize the symptoms, laboratory findings, treatment options, obstetric and neonatal outcomes. This will generate a pool of evidence for healthcare professionals to care for pregnant women and newborns.

Materials and methods

A systematic review was conducted according to the preferred reporting items for systematic review and meta-analysis (PRISMA) consensus statement ¹¹. All available and relevant studies on novel Coronavirus (COVID-19) infection among pregnant women were included in this review.

Study selection criteria: All studies relevant to COVID-19 infection among pregnant women, and reported

symptoms, laboratory findings, maternal characteristics, and neonatal outcomes. All studies which meet the above mentioned criteria, irrespective of design, and published in the English language are considered for inclusion. Review papers and studies not given any clear information about symptoms, laboratory findings, treatment, and maternal or neonatal outcomes are excluded from the review.

Search strategy: A systematic search was performed in PubMed, Scopus, Web of Science, and Cochrane databases on April 3, 2020. All studies published on from the start of COVID 19 were considered for inclusion. The collected studies were screened for COVID-19 among pregnant women and included in the study as per study criteria. Searching was made by combining text words and medical subject headings (MeSH) by using Boolean words OR, AND, NOT in title/abstract.

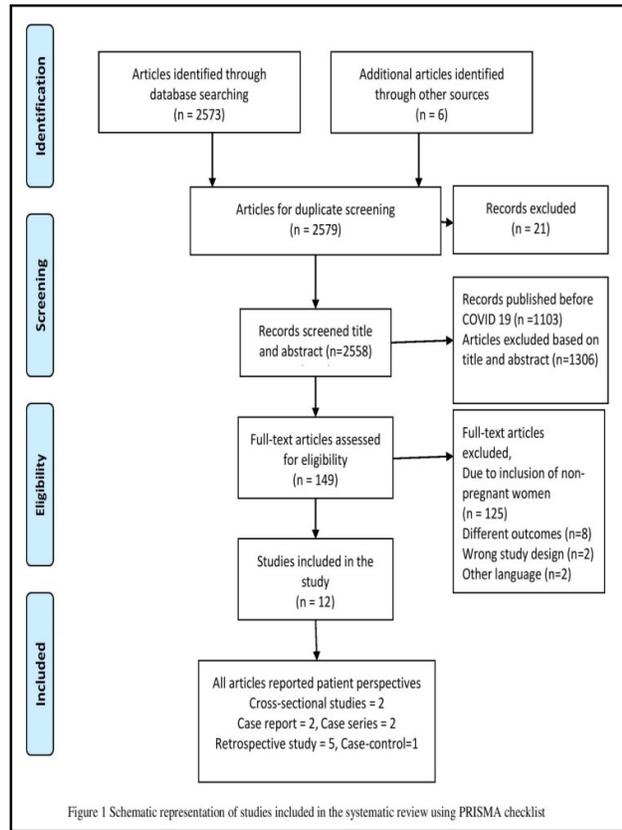
Data extraction and analysis: Two authors extracted the data by using pre-designed, piloted, and customized data extraction form. The data extraction form consists of clinical features, laboratory findings, treatment, and perinatal outcomes. The corresponding author solved any disagreement in the data extraction. The modified Newcastle-Ottawa scale was used to assess the quality of included studies. Descriptive statistics were used to represent the data.

Results and observations

Study selection: A total of 2579 articles were identified by searching databases and other sources. In these articles, 21 duplicated, 1103 published prior COVID-19 incident, and 1706 not matched the abstract and title were excluded from the review. A total of 149 full text articles are selected for study eligibility screening, of which 125 articles were related to non-pregnant women, 8 articles are having different outcomes, 2 comprises wrong study design, and 2 published in other languages are subjected for exclusion. Finally, 12 articles were included in the study. The complete study selection criteria were given in the PRISMA flowchart figure 1.

The background details of the included studies were summarized in table 1. In total 12 studies, cross-sectional studies (2), case reports (2), case series (2), retrospective study (5), and case-control (1), study designs are present in the review. A total of 123 pregnant women included in the selected 12 articles, and the majority of them were in the third trimester.

Clinical manifestations of COVID 19 infected pregnant women: Fever (60.2%) and cough (36.6%) are the most



common symptoms observed in pregnant women infected with COVID 19. Some of the other and less common

raised AST or ALT (21.0%), lymphopenia (51.6%), elevated C-reactive protein (62.2%), and abnormal chest CT scan (90.2%). Even though these tests are non-specific to the COVID-19, these tests are useful to monitor the prognosis of the infection towards treatment. Maternal rt-PCR for SARS CoV-2 was positive in all pregnant women as shown in table 3.

Treatment of COVID 19 infected pregnant women: Oxygen administration, antibiotic, and antiviral therapy is the mainstay of management strategy in the majority of the studies as shown in table 3. Antiviral drugs like arbidol, oseltamivir, lopinavir, ritonavir, ganciclovir, interferon was given in the study of Wang et al, Zhu at al, and Yu et al. Antibiotics like; cefoperazone sodium, cephalosporins, quinolones, macrolides, sulbactam sodium are given in the study of Wang et al and Zhu at al. Even though corticosteroid therapy is important to control SARS, due to secondary complication in the pregnant women, majority of studies not advised steroids in pregnant women. In this review, Fan et al study had given methylprednisolone given in (20mg. IV daily) within 72 hours of delivery.

Perinatal outcomes of pregnant women infected with COVID 19: The most common perinatal outcome observed in the COVID 19 pregnancy was, fetal distress (15.5%) and low birth weight (14.4%), followed by preterm delivery (13.4), neonatal dyspnea (7.3%), bacterial pneumonia (2.4), neonatal death (2.24%) and neonatal rt-PCR for SARS-

Table 1: Characteristics of the selected studies

| Authors | Study design | Study location | Study date | Sample size | Maternal age in years(Mean ± SD) | Gestational age in week at admission (Mean ± SD) |
|--------------------------|----------------------|----------------|---------------|-------------|----------------------------------|--|
| Chen et al ²⁷ | Retrospective cohort | Wuhan, China | 12 Feb, 2020 | 9 | 29.8 ± 4.8 | 37.1±1.2 |
| Liu et al ²⁸ | Case series | Wuhan, China | 25 Feb, 2020 | 3 | 32.7 ± 2.3 | 39±1 |
| Zhu et al ²⁰ | Retrospective cohort | Hubei, China | 10 Feb 2020 | 9 | 30.9 ± 3.2 | 35.4±2.9 |
| Wang et al ¹⁹ | Case report | Suzhou, China | 28 Feb, 2020 | 1 | 35 years | 31 Weeks |
| Liu et al ²⁹ | Cross-sectional | Hubei, China | 11 Mar, 2020 | 41 | 31.0 ± 5.0 | NA |
| Liu et al ²⁶ | Cross-sectional | Hubei, China | 7 March, 2020 | 15 | 32 ± 5.0 | 32±8 |
| Yu et al ²¹ | Retrospective cohort | Wuhan, China | 24 Mar, 2020 | 7 | 32.2±2.1 | 38.7±1.4 |
| Chen et al ³⁰ | Retrospective cohort | Hubei, China | 16 Mar, 2020 | 4 | 26.5±5.8 | 37.7±0.9 |
| Khan et al ³¹ | Case series | Wuhan, China | 19, Mar, 2020 | 3 | 29.3±3.2 | 37±2.6 |
| Liu et al ³² | Retrospective cohort | Hubei, China | 27, Feb. 2020 | 13 | 29.7±4.0 | 33.8±3.9 |
| Fan et al ³⁴ | Case reports | Wuhan, China | 17, Mar, 2020 | 2 | 34 & 29 years | 37 & 36 Weeks |
| Li et al ³³ | Case control | Wuhan, China | 30, Mar, 2020 | 16 | 30.9±3.2 | 38±0.2 |

symptoms are also reported by the women; postpartum fever (23.5%), dyspnea (9.7%), fatigue (12.2%), diarrhea (4.1%), myalgia (4.9%), sore throat (4.1%), poor appetite (2.4%), headache (1.6%), malaise (1.6%), and skin rash (0.1%) as shown in table 2.

Laboratory findings of COVID 19 infected pregnant women: The most common abnormal laboratory finding observed in COVID 19 infected pregnant women include;

CoV2 (1.2%). In a study conducted by Liu et al one death was reported due to multiple organ dysfunction syndrome and stillbirth, whereas in Zhu et al study one more death was reported due to multiple organ failure, shock, gastric bleeding. The majority of the pregnant women delivered in the mode of C-section, and very few are normal delivery mode. According to the Apgar score, all babies were normal; there was no distress at one and five minute points. Other

Table 2: Symptoms of pregnant women infected with COVID-19 (n=123)

| Symptoms | No. (%) |
|------------------|-----------|
| Fever | 74 (60.2) |
| Postpartum fever | 29 (23.5) |
| Cough | 45 (36.6) |
| Myalgia | 6 (4.9) |
| Sore throat | 5 (4.1) |
| Malaise | 2 (1.6) |
| Diarrhea | 5 (4.1) |
| Dyspnea | 12 (9.7) |
| Fatigue | 15 (12.2) |
| Headache | 2 (1.6) |
| Poor appetite | 3 (2.4) |
| Skin rash | 1 (0.1) |

studies and reviews of COVID-19 in normal adults and children^{13, 14}.

Up to the present day, there was no specific treatment or prevention strategy to deal with COVID-19 infection in all groups of the population. As we know that, pregnant women are at high risk for adverse effects of the drugs, put healthcare providers in an additional challenge. The currently available off labeled chloroquine and hydroxy chloroquine use in COVID-19 are a risk to the fetus^{15, 16}. Even these drugs can excrete through breast milk and increases the risk of adverse effects in infants^{17, 18}. Supportive and symptomatic therapy is very important in

Table 3: Laboratory findings and treatment of COVID-19 infected pregnant women

| Laboratory finding | Studies mentioned test and treatment findings | Sample size | No (%) |
|---------------------------------------|---|-------------|------------|
| Elevated C-reactive protein (>10mg/L) | Chen et al ²⁷ , Liu et al ²⁸ , Liu et al ²⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Li et al ³³ | 98 | 61 (62.2) |
| Raised AST or ALT | Chen et al ²⁷ , Liu et al ²⁸ , Chen et al ³⁰ , Khan et al ³¹ | 19 | 4 (21.0) |
| Lymphopenia | Chen et al ²⁷ , Liu et al ²⁸ , Liu et al ²⁹ , Liu et al ²⁶ , Chen et al ³⁰ , Khan et al ³¹ , Fan et al ³⁴ , Li et al ³³ | 93 | 48 (51.6) |
| Abnormal chest CT | All studies | 123 | 111 (90.2) |
| Maternal rt-PCR for SARS-CoV-2 | All studies | 123 | 123 (100) |
| Treatment | | | |
| Oxygen therapy | Chen et al ²⁷ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Fan et al ³⁴ , Li et al ³³ | 59 | 35 (51.3) |
| Antibiotic | Chen et al ²⁷ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Fan et al ³⁴ , Li et al ³³ | 59 | 48 (81.3) |
| Antiviral | Chen et al ²⁷ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Fan et al ³⁴ , Li et al ³³ | 59 | 33 (55.9) |
| Corticosteroid | Chen et al ²⁷ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Fan et al ³⁴ , Li et al ³³ | 59 | 2 (3.4) |

AST - Aspartate aminotransferase; ALT - Alanine aminotransferase; SARS - Severe Acute Respiratory Syndrome; CT - Computerized Tomography; PCR - Polymerized Chain Reaction

outcomes like, diffuse scattered rashes, edema, facial skin lesion, late gestational age, and disseminated intravascular coagulation was also observed in the study conducted by Zhu et al. The perinatal outcome profile was represented in table 4.

Discussion

The symptoms observed in the pregnant women were slightly different from the findings of the lancet study conducted by Huang et al in non-pregnant. In both pregnant and non-pregnant adults, fever and cough is the most common symptom⁹. In this review, we observed postpartum fever, poor appetite, dyspnea, sore throat, myalgia, fatigue, and malaise as additional symptoms. So, close monitoring of these symptoms will give a clue for the early detection of COVID 19. Similar types of symptoms are also observed in previous SARS-CoV in pregnancy¹². This review supports abnormal chest CT scan, elevated C-reactive protein, and decline lymphocyte count are the major changes observed in COVID-19 infected pregnant women. Even though these tests are non-specific to the COVID-19, these tests are useful to monitor the prognosis of the infection towards treatment. These laboratory changes are also similar to the findings of

pregnant women infected with COVID-19. Antiviral drugs like arbidol, oseltamivir, lopinavir, ritonavir, ganciclovir, interferon which were used for previous SARS in pregnancy can be recommended in COVID-19¹⁹⁻²¹. There was no evidence available on the safety of these medicines in pregnancy conditions. Corticosteroid therapy is very important to control SARS, but due to secondary complications in pregnant women, majority of studies not advised steroids in pregnant women²². In this review, Fan et al study had given methylprednisolone given in (20m. IV daily) within 72 hours of delivery in two patients. Antibiotics are recommended in the majority of the studies to treat secondary bacterial infections in COVID 19^{19, 20}.

According to WHO, 1-5% of C-section is recommended to avoid death or severe morbidity in mother and newborn^{23, 24}. In the current review, we found that the majority (77.3%) of pregnant women are delivered by C-section. Evidence suggests that, in viral infection to reduce the adverse perinatal and neonatal outcomes C-section is strongly recommended²⁵. Some other adverse obstetric and neonatal outcomes observed are preterm delivery, low birth weight, fetal distress, pre-rupture of the membrane. These outcomes

Table 4: Perinatal outcomes of pregnant women infected with COVID-19

| Categories | Studies mentioned perinatal outcomes | Sample size | No (%) |
|--------------------------------|---|-------------|-----------|
| Preterm delivery | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 11 (13.4) |
| Prerupture of membrane | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 3 (3.6) |
| Fetal distress | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 13 (15.8) |
| Neonatal dyspnea | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 6 (7.3) |
| Bacterial pneumonia | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 2 (2.4) |
| C-section | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 75 | 58 (77.3) |
| LBW | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Fan et al ³⁴ , Li et al ³³ | 69 | 10 (14.4) |
| Apgar 1 min (≥7) | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 82 (100) |
| Apgar 5 min (≥7) | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 82 (100) |
| Neonatal death | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 2 (2.4) |
| Neonatal rt-PCR for SARS-CoV-2 | Chen et al ²⁷ , Liu et al ²⁸ , Zhu et al ²⁰ , Wang et al ¹⁹ , Liu et al ²⁶ , Yu et al ²¹ , Chen et al ³⁰ , Khan et al ³¹ , Liu et al ³² , Fan et al ³⁴ , Li et al ³³ | 82 | 1 (1.2) |

LBW - Low Birth Weight; C - section – Caesarian section.

alert healthcare workers in dealing and reducing perinatal and neonatal complications of COVID-19.

Previous studies on SARS infection suggest that, high rate of vertical transmission of SARS infection from mother to fetus^{4, 5}. But, the scenario is completely contrasted in COVID-19, only one newborn got positive toward COVID-19 infection; this happened after 36 hours of birth. The viral nucleic acid test of the placenta and cord blood was given negative for COVID-19. This suggests intrauterine vertical transmission has not occurred.

The previous studies on SARS infection confirmed that; the mortality rate is 10% in non-pregnant adults and 25% in pregnant women⁴. Current studies suggest that, the mortality rate of COVID 19 patients is 1-4%. In the study conducted by Liu et al one death was reported due to multiple organ dysfunction syndrome and stillbirth, whereas in Zhu et al study one more death was reported due to multiple organ failure, shock, gastric bleeding^{20, 26}. Other outcomes like, diffuse scattered rashes, edema, facial skin lesion, late gestational age, and disseminated intravascular coagulation was also observed in the study conducted by Zhu et al. The maternal, obstetric, and neonatal outcomes of COVID 19 are better than the previous SARS infection.

Strengths and limitations: This is the prime review highlighting clinical, laboratory, maternal, obstetric, and neonatal outcomes of the COVID-19 infected pregnant women. These findings help healthcare professionals to promote better care in COVID-19 infected pregnant women. Even though the current review included 80 pregnant women

from 10 studies, this is not a sufficient number to draw conclusions and generalize the data, because all studies are from a single province China. In the current systematic review, there was no comparative, case-control or cohort study design to support the outcomes that occurred majorly due to COVID-19 and not due to other co-morbid conditions. The majority of the women in enrolled studies are in the third trimester, so, it will not give effects of COVID-19 infected women in the 2nd and 1st trimester. The long term effects of COVID 19 in pregnant women and neonates are not explained in this systematic review.

Conclusions

The study confirms that, fever, cough, elevated C-reactive protein, lymphopenia, and abnormal chest CT are the most common clinical and laboratory examinations in pregnant women infected with COVID-19. The chloroquine and hydroxy chloroquine should not indicate in the treatment of COVID-19 in pregnant women because of the potential adverse effects on mother and fetus. Supportive therapy with oxygen, and antibiotics, and specific treatment with antiviral agents can be given but the safety profile of antiviral drug use was not established. COVID 19 increases the risk of C-section, preterm delivery, and low birth weight outcomes. All healthcare professionals need to consider possible outcomes in this review and make a decision to reduce the risk of complications in both mother and fetus. In the future, there is a need for inventions in the treatment and prevention of COVID 19 in the general population and pregnant women.

Conflict of interest: None. **Disclaimer:** Nil.

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- Swat Narayana Goruntla¹, Jyothi Suchitra², Kannan M Shanmugha³, Dasaratharamaiah Jinka⁴, Mohammad Jaffar Sadiq⁵, Vigneshwaran Easwaran⁶**
- ¹ Associate Professor, Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research (RIPER) – Autonomous, Anantapur, Andhra Pradesh, India; ² Head, Department of Obstetrics and Gynaecology, Rural Development Trust Hospital, Bathalapalli, Andhra Pradesh, India; ³ Department of Anaesthesiology, Rural Development Trust Hospital, Bathalapalli, Andhra Pradesh, India; ⁴ Head, Department of Pediatrics, Rural Development Trust Hospital, Bathalapalli, Andhra Pradesh, India; ⁵ Assistant Professor, Department of Clinical Pharmacology, Batterjee Medical College, Jeddah 21442, Kingdom of Saudi Arabia; ⁶ Assistant Professor, Clinical Pharmacy Department, College of Pharmacy, King Khalid University, Abha, Saudi Arabia.