

## Research Article

# Clinical Properties and Diagnostic Methods of COVID-19 Infection in Pregnancies: Meta-Analysis

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We aimed to summarize reliable medical evidence by the meta-analysis of all published retrospective studies that examined data based on the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by clinical symptoms, molecular (RT-PCR) diagnosis, and characteristic CT imaging features in pregnant women. The MEDLINE, PubMed, Scopus, ISI Web of Science, ClinicalKey, and CINAHL databases were used to select the studies. Then, 384 articles were received, including the studies until 01/May/2020. As a result of the full-text evaluation, 12 retrospective articles covering all the data related were selected. A total of 181 pregnant cases with SARS-CoV-2 infections were included in the meta-analysis within the scope of these articles. According to the results, the incidence of fever was 38.1% (95% CI: 14.2-65%) and cough was 22% (95% CI: 10.8-35.2%) among all clinical features of pregnant cases with SARS-CoV-2 infection. So, fever and cough are the most common symptoms in pregnant cases with SARS-CoV-2 infection, and 91.8% (95% CI: 76.7-99.9%) of RT-PCR results are positive. Moreover, abnormal CT incidence is 97.9% (95% CI: 94.2-99.9%) positive. No case was death. However, as this virus spreads globally, it should not be overlooked that the incidence will increase in pregnant women and maybe in the risky group. RT-PCR and CT can be used together in an accurate and safe diagnosis. In conclusion, these findings will provide important guidance for current studies regarding the clinical features and correct detection of SARS-CoV-2 infection in pregnant women, as well as whether it will create emergency tables that will require the use of a viral drug.

## 1. Introduction

Wuhan is the base of coronavirus 2 (SARS-CoV-2), an infectious pneumonia epidemic that has started rapidly in China and has spread to many countries around the world since December 2019 [1]. On January 30, 2020, the World Health Organization (WHO) announced that the SARS-CoV-2 epidemic is a critical and international public health problem. Currently, the disease caused by the SARS-CoV-2 infection in humans has exceeded the outlook in the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) outbreak in 2002 [2].

To date, the total number of cases in the world was 3,349,786, and the total number of deaths was 238,628 (last update 03/May/2020 10:00 hours, WHO, status report-104), and it is still increasing. Coronaviruses (CoV) are RNA

viruses. Until December 2019, the CoV family consisted of six human pathogenic species: SARS-CoV and MERS-CoV. The seventh human pathogenic species was added with SARS-CoV-2 [3]. The four “endemic” species (HKU1, OC43, 229E, and NL63) are of clinical importance so far, often produce cold symptoms, and are responsible for about 10% of seasonal airway diseases not caused by the flu. Besides, SARS-CoV and MERS-CoV, which caused severe airway symptoms and diseases associated with a high mortality rate (10-30%, respectively), were limited to a one-time outbreak and were predominantly of regional significance [2].

Real-time reverse transcription-polymerase chain reaction (RT-PCR) diagnostic tests have been rapidly developed on SARS-CoV-2 [4]. Through genetic sequence analysis, it was stated that SARS-CoV-2 belongs to the genus  $\beta$ -coronavirus with 79.0% nucleotide similarity and 51.8% identity

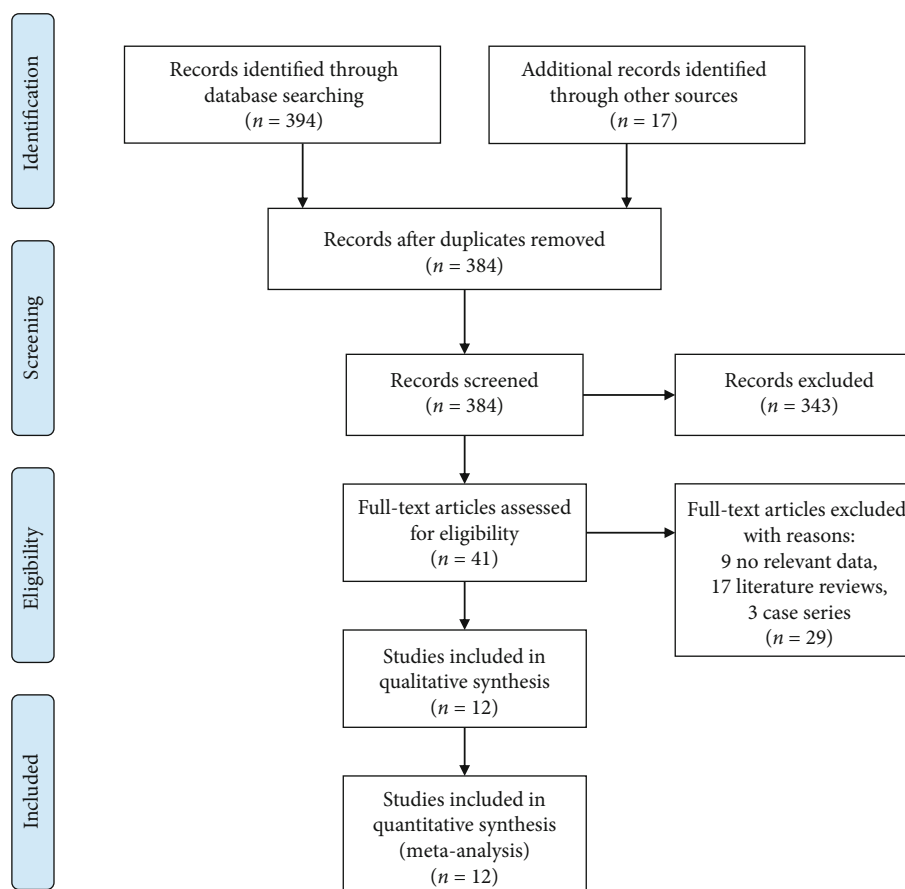


FIGURE 1: PRISMA flowchart.

with MERS-CoV and SARS-CoV [5]. Besides, it has been reported that SARS-CoV-2 is 96% identical to a bat coronavirus throughout its genome [6, 7].

The pandemic spreading can be fatal when healthcare professionals are not ready to manage the infection, as now seen in the COVID-19 outbreak. The SARS-CoV-2 virus was also isolated from asymptomatic individuals, and affected patients showed contagiousness even 2 weeks after symptoms ceased [8]. Thus, it required radical measures on all continents, including closing the country's borders.

As the epidemic of COVID-19 spreads rapidly, pregnant women have drawn attention to the prevention and control of COVID-19 infection due to being at risk of respiratory infection, especially flu. Physiological and mechanical changes in pregnancy increase susceptibility to infections in general and promote rapid progression to respiratory failure, especially when the cardiovascular system is affected. Thus, they represent a high-risk group during infectious outbreaks [8].

All these risk factors cause an essential point to examine pregnant women. Clinical features and the functionality of the methods of detection of SARS-CoV-2 infection in pregnant women are currently the focus of attention in medical studies, though, owing to the different designs of different clinical trials and small sample sizes, published trials are also various [2]. The goal of this study was to examine all these articles about the detection of SARS-CoV-2 in pregnant

women with molecular (PCR) and CT imaging methods, the frequency of occurrence of these clinical features, and also the detection correction of the methods used in diagnosis by meta-analysis.

## 2. Material and Methods

**2.1. Sources of Information.** MEDLINE, PubMed, Scopus, ClinicalKey Library, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and ISI Web of Science were searched using combined keywords: "2019-nCoV and/or pregnancy," "COVID-19 and/or pregnancy," and "SARS-CoV-2 and/or pregnancy."

**2.2. Article Selection and Publication Quality Evaluation.** Meta-analysis was elaborated according to the PRISMA guidelines [9]. The literature search and selection process are presented in Figure 1, which was conducted according to the PRISMA flowchart. The two authors (BUC, BAB) reviewed all the literature independently. The agreement on potential relevance or inconsistencies has been reached unanimously, or a decision was made by discussing with a third reviewer (ÖP).

As a result of the electronic database search, we received 394 articles and 17 of them were excluded due to repeated access. Finally, 12 unique studies were selected that reported on clinical properties and diagnostic methods. The meta-

analysis was done using 12 articles ([10–13]; [14–21]) with a total of 181 patients that satisfied the study criteria. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies [22]. The quality scores of all varied from 0 to 9 (Table 1).

**2.3. Statistical Analysis.** The meta-analysis of incidence rates was conducted using the “metafor” package in R version 3.6.2 [23]. It includes 12 studies, with a total of 181 patients. We employed the random-effects model according to assessing heterogeneity of the meta-analysis.

The publication bias was detected by Egger’s test. The test results and corresponding *P* values are presented in Table 2. Egger’s test indicated that publication bias exists for diarrhea and RT-PCR groups (*P* = 0.019 and *P* = 0.025, respectively).

The double arcsine method would be a more appropriate choice when the small sample size and extreme proportions need to be handled. The double arcsine transformation was applied in order to make the skewed distribution of proportions conform to the normal distribution [24, 25]. To conclude, we performed the inverse of the double arcsine transformation for proportions using the harmonic mean of the sample sizes for the back-transformation. The results are given for the summary incidence rate and confidence interval in Table 3.

### 3. Results

The incidence of fever was 38% (95% CI: 14-35%) and cough was 22% (95% CI: 10.8-35.2%) among all clinical features of pregnant cases with SARS-CoV-2 infection by meta-analysis. Dyspnea was observed in only 3.3% (95% CI: 0.3-8.2%). The incidence of positive RT-PCR is 91.8% (95% CI: 76.7-99.9%), and the incidence of abnormal computer tomography (CT) is 97.9% (95% CI: 94.2-99.9%).

Since no clinical signs of vomiting were found in any of the studies included in the analysis, the effect size was not given for it. Detailed results of the meta-analysis are shown in Table 3.

The most common symptoms are fever (38.1%) and cough (22%), and the less common symptoms are dyspnea (3.3%), myalgia and/or fatigue (3%), diarrhea (0.4%), and sore throat (0.2%). The point estimate of the runny nose was found as 0.0%. The confidence interval of a clinical finding of runny nose among pregnant women is between 0.000 and 0.010 with a 95% confidence level. The incidence of CT is higher than RT-PCR to diagnose COVID-19. Besides, the confidence interval of CT is narrower than RT-PCR.

### 4. Discussion

In the early stages of the SARS-CoV-2 epidemic, the case death rate is estimated to be approximately 2% [2]. Later, it is reported that the death rate in China was 3.8%, which was lower than that of the two commonly transmitted zoonotic CoV diseases, SARS and MERS [6].

SARS-CoV-2 infection is more likely to affect older people with comorbidity, with most deaths clustering in this particular population [6, 26, 27]. The mortality rates of SARS

and MERS infections are 9.6% [3] and 35%, respectively [28]. Xie et al. [29] stated that 45% of patients showed symptoms of pulmonary fibrosis within 1 month after infection with SARS-CoV and 30-36% after 3-6 months. These studies suggested that pulmonary fibrosis will be one of the serious complications in patients with SARS-CoV-2 infection. Furthermore, due to the low mortality rate of SARS-CoV-2 infection and rapid spread among patients compared to SARS-CoV and MERS-CoV infections, a large number of patients require treatment. In this case, health equipment and health worker competence have been essential. Thus, COVID-19 threatens preparedness and biosecurity conditions in all countries [30]. At the same time, both of these coronaviruses can cause death in a few but significant numbers of pregnant cases, but specific risk factors for a fatal outcome during pregnancy have not been clarified [2].

In addition, in another study ([31]), they found that in healthy lung tissue, the angiotensin-converting enzyme 2 (ACE2) SARS-CoV-2 receptor is mainly expressed by type I and type II alveolar epithelial cells. Type II alveolar cells (83%) have been reported to express ACE2. For this reason, SARS-CoV-2 infection damages most of the type II alveolar cells. The use of mechanical ventilation in the treatment of patients can also aggravate the damage of alveolar cells. However, it has also been reported that ACE2 is more expressive in pregnant women [32, 33].

Compared with past coronavirus pandemics, it has been reported that pregnancy has a significant impact on the course of the disease of SARS-CoV and the outcome of an infected patient. Therefore, the duration of the hospital stay of pregnant patients was longer. In addition to kidney failure, sepsis, or common intravascular coagulation disorder, the need for intensive care treatment was more common in pregnant women. The mortality of pregnant infected patients has also increased significantly [34]. So far, there is very little data on MERS-CoV infection during pregnancy. However, 11 reported symptomatic cases [35] showed a more severe course in pregnancy than SARS-CoV infection.

In addition to information about the effects of previous coronavirus outbreaks on pregnant women, little data is known about the clinical course, possible risks, and the validity of the methods used in the correct diagnosis for pregnant patients infected with SARS-CoV-2. In this study, a meta-analysis of the data of publications examining these possible risks and methods used in diagnosis for pregnant women suffering from SARS-CoV-2 infection was performed. The results we found in pregnant women with SARS-CoV-2 infections are common symptoms of fever, cough, shortness of breath, general myalgia, weakness, diarrhea, dyspnea, and pneumonia compared to the primary clinical symptoms in pregnant women with MERS-CoV and SARS-CoV infections [6].

When we compare our results of the meta-analysis for pregnant women with the rates of the study conducted with the nonpregnant adult group [2], respectively, the incidence of fever was 38% (89.1%), the incidence of cough was 22% (72.2%), and the incidence of myalgia and/or fatigue was 3% (42.5%). The incidence of dyspnea is 3.3% (14.8%), the incidence of abnormal CT is 98% (96.6%), and the case

TABLE 1: Characteristics of the included studies on COVID-19, 2020.

Author	Journal name	Date (M/D)	No. of patients	Study type	Age	Article quality	Clinical, molecular, and imaging findings
Chen et al.	<i>Lancet</i>	03/07	9	Retrospective	26-40	8	Fever Cough Sore throat Myalgia and/or fatigue Dyspnea Diarrhea RT-PCR CT
Liu et al.	<i>J Infect</i>	03/02	41	Retrospective	22-42	8	Fever Cough Myalgia and/or fatigue Dyspnea RT-PCR CT
Yu et al.	<i>Lancet Infect Dis</i>	03/24	7	Retrospective	29-34	7	Fever Cough Dyspnea Diarrhea RT-PCR CT
Zhu et al.	<i>Transl Pediatr</i>	02/10	9	Retrospective	25-35	6	Fever Cough Sore throat Diarrhea RT-PCR CT
Chen et al.	<i>Zhonghua Bing Li Xue Za Zhi</i>	03/01	3	Retrospective	23-34	6	Fever RT-PCR CT
Zhang et al.	<i>Zhonghua Fu Chan Ke Za Zhi</i>	03/08	16	Retrospective	24-34	7	Cough Dyspnea Diarrhea RT-PCR

TABLE 1: Continued.

Author	Journal name	Date (M/D)	No. of patients	Study type	Age	Article quality	Clinical, molecular, and imaging findings
Wu et al.	<i>Int J Gynaecol Obstet</i>	04/08	23	Retrospective	22-37	8	Fever Cough Runny nose RT-PCR CT
Liu et al.	<i>AJR Am J Roentgenol</i>	03/06	15	Retrospective	23-40	7	Fever Cough Sore throat Myalgia and/or fatigue Dyspnea Diarrhea RT-PCR CT
Chen et al.	<i>J Med Virol</i>	03/28	5	Retrospective	25-31	7	Cough Runny nose RT-PCR CT
Yang et al.	<i>J Infect</i>	04/12	13	Retrospective	30.2*	8	Fever Cough RT-PCR CT
Li et al.	<i>Clin Infect Dis</i>	03/30	34	Case-control	25-35	8	Fever Cough Sore throat Dyspnea RT-PCR CT
Wu et al.	<i>Virology Sin</i>	04/10	6	Retrospective	26-35	8	RT-PCR CT

\*Age is given as a mean value of 30.2.

TABLE 2: Egger's test results of clinical, molecular, and imaging characteristics in pregnancy.

Fever	Cough	Dyspnea	Myalgia and/or fatigue	Diarrhea	Sore throat	Runny nose	CT	RT-PCR
0.317	0.220	0.897	0.923	0.019	0.114	0.130	0.460	0.025

TABLE 3: Meta-analysis results of clinical, molecular, and imaging characteristics in pregnancy.

Clinical, molecular, and imaging findings	Results of meta-analysis	Lower limit	Upper limit
Fever	0.381	0.142	0.650
Cough	0.220	0.108	0.352
Dyspnea	0.033	0.003	0.082
Myalgia and/or fatigue	0.030	0.000	0.115
Diarrhea	0.004	0.000	0.036
Sore throat	0.002	0.000	0.028
Runny nose	0.000	0.000	0.010
CT	0.979	0.942	0.999
RT-PCR	0.918	0.767	0.999

fatality rate of patients with SARS-CoV-2 infection is 4.3% [6, 10–12, 14–21, 27]. In addition, symptoms of diarrhea, sore throat, and runny nose are rare. Mechanical ventilation was not required in pregnant women; also, there were no reported cases of death. Egger's test was used to provide a test statistic for the presence of publication bias in the data. Egger's test was found only significant for diarrhea and RT-PCR. It appeared to be mainly caused by "study 2" with large sample size. However, we did not exclude this study for two reasons. The first reason is that Egger's test was not found significant for the others. The second reason is that removing "study 2" would decrease the total sample size.

All irregularities in the imaging results were considered abnormal for the CT result. According to our RT-PCR and CT results (91.8-97.9%, respectively), we think that both should be used when evaluating to say that the cases are correct and definite positive in pregnant women. However, it should be noted that there is radiation in the CT examination, so the question of whether the reexamination interval is necessary for the treatment of pregnant women with mild symptoms needs further discussion.

Besides, low doses during the use phase for pregnant women should be paid attention to. Based on the above, COVID-19 has mild clinical signs in pregnant women; some are asymptomatic and need to be combined with epidemiological history and nucleic acid detection. It also emphasizes that this rate (91.8%) of RT-PCR may be a false-negative result. This suggests that it may be due to early samples taken for diagnosis or asymptomatic cases.

Guan et al. [36] stated that frequent patterns in chest CT include abnormal findings in the case reports, including asymptomatic patients, with ground-glass opacity and bilateral irregular shading [6, 37, 38]. The ratio in CT (97.9%) may be due to the fact that these patterns may not be very typical images for the diagnosis of COVID-19 and may change with the eyes of the radiologist, and these nontypical patterns may also be confused with influenza-like images.

Microorganism diagnostic tests that can be done to eliminate similar images can be time-consuming.

The results of this meta-analysis study here highlight the clinical, molecular, and imaging findings of COVID-19 pregnant cases that may assist clinicians. In this way, it will prevent further contamination by implementing infection control measures, thanks to early recognition of cases and adequate intervention by clinicians. Frequent evaluation of available evidence of COVID-19, such as clinical suspicion and definitive diagnosis, has been deemed necessary to prevent contamination from health workers during close contact in pregnant women [30, 39, 40].

Here, we have discussed 12 articles, including 181 pregnant cases with SARS-CoV-2 infection. So far, it is the first meta-analysis to examine the factors and prenatal clinical features that may be effective in initial diagnosis in pregnant women. The quality of the literature included in this study is high. However, this review also has some limitations. As of the current period, there are few studies for the content. Data from all countries are urgently needed on this issue. Thus, it would be more appropriate to include a large number of studies in a broad geographical scope in order to obtain a more comprehensive view of COVID-19 in pregnant women as a result. Since detailed patient information was not given in all studies, especially regarding clinical findings, chronic diseases, or complications of pregnant, these factors could not be included in the meta-analysis. In particular, there were negative results, although the case showed positive clinical signs, since CT contained radiation, and its use was not preferred or repeated. The data in this analysis allow for the first synthesis of the clinical, molecular, and CT diagnostic features of COVID-19. Also, it is not included in the meta-analysis results, since deaths were not reported in pregnant women in the studies conducted. In this study, the patients were diagnosed with SARS-CoV-2 infection. However, because the clinical symptoms are rare in the findings of our study, the prevalence of asymptomatic cases may be higher among pregnant women. As there is a lack of data in newborns as part of the studies we have included, it could not be covered in this study. As a result, the importance of vertical transmission is not emphasized.

Based on the limitations reported above, the results need to be supported by more extensive studies with larger sample sizes. Further clinical data are essential to explain the clinical spectrum of the disease. Clinical experience case reports, case series, or extensive observational studies from countries with an increasing number of cases will contribute significantly.

Pregnant women are sensitive to respiratory pathogens and the development of severe pneumonia, making them more susceptible to COVID-19 infection, especially if they have chronic diseases or complications [41]. Therefore, pregnant women should be considered a critical risk group in the prevention and treatment of COVID-19. In addition to recent studies, previous pandemic experiences should be

considered in the prevention and control of this infection. Our findings will provide valuable guidance for current clinical trials. We are also of the opinion that our results can give an idea about the necessity of using a viral drug in the treatment of SARS-CoV-2 infections in pregnant women. In summary, the symptoms of pregnant women with COVID-19 are diverse; the main symptoms are fever and cough. Symptoms are relatively mild. Pregnancy did not increase the severity of COVID-19. ACE2 may not be more expressive in pregnant women. Asymptomatic individuals should be taken into consideration and should not be overlooked. CT may be more effective in diagnosis, but after evaluating the risks it carries in pregnant women, it should be administered in appropriate doses. Pregnant women with SARS-CoV-2 infection should be closely monitored for early diagnosis. Currently, pregnancy may complicate the clinical course of COVID-19, but the fact that the cases in this group are not in the risky age group defined for COVID-19 may give an idea that their condition will not be as bad as in the pregnant tables in MERS or SARS infections [2]. There may also be a need for new studies that ACE2 is not more effective in pregnant women.

## 5. Conclusion

Given the importance of this ongoing global public emergency situation, our results are limited to the small sample size, but we believe the findings reported here are important for understanding the clinical features of COVID-19 and the potential of diagnostic methods for pregnant women.

In line with our final results, it may be appropriate for correct diagnosis to evaluate both methods together with clinical symptoms in order to not miss the asymptomatic cases that may occur more frequently in pregnant women, with the false-negative results, or to not put an extra burden on the patient and health sector with false-positive results, especially for risky areas. Also, based on our findings, the question arises once again whether antiviral therapy is required for pregnant women with COVID-19, and all possible risks should be considered under the profit-loss balance, considering mild cases of viral drug use during pregnancy.

As a result, this pandemic will not be an end to the world and it will always be a priority to diagnose correctly and quickly in this vulnerable group in developing new treatment methods. We believe that this research may be critical in determining methods and even saving lives in the early diagnosis and treatment of pregnant women in current and future outbreaks.

## Data Availability

All data generated or analyzed during this study are included in this article. We also have made all our data available on an open repository figshare (<https://doi.org/10.6084/m9.figshare.12442031>).

## Disclosure

The paper is submitted in the preprint server according to the following link: <https://www.medrxiv.org/content/10.1101/2020.06.06.20123901v1>.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## Authors' Contributions

BUC designed the research model and determined the articles to be included in the study. BAB contributed to the realization of the study by applying meta-analysis. Both authors contributed to article selection and data interpretation and reviewed and approved the final article.

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