



SYSTEMIC REVIEW OF RESPIRATORY VIRAL INFECTIONS IN PREGNANT WOMEN: IMPLICATIONS FOR COVID-19

Respiratory Medicine

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ABSTRACT

Background: Our objective in undertaking this systematic evaluation is to furnish an all-encompassing comprehension of the ramifications associated with respiratory viral infections, with a specific focus on COVID-19, among pregnant women. **Methodology:** A systematic search was conducted in electronic databases, including PubMed, Embase, and Scopus, to identify relevant studies published up until August 2022. The search strategy combined keywords related to respiratory viral infections (e.g., influenza, respiratory syncytial virus, COVID-19) and pregnancy. **Results:** The search was restricted to studies in English language only. The initial search yielded a total of 1,250 hits, from which 650 studies were considered eligible for further evaluation after removing duplicates. Of these, 393 studies were excluded based on title and abstract, as they did not meet the inclusion criteria. Another 150 studies were excluded as they were not relevant to the subject of this study or setting of this review. Additionally, 60 studies were excluded as they were replies from authors, 10 studies were excluded as they were books, and 18 studies were excluded as they were reviews. At the end of the screening process, a total of 19 articles were deemed eligible for inclusion in the qualitative synthesis of the present review. **Conclusion:** This study showed that pregnant women with COVID-19 had the same symptoms reported by normal population including fever and cough. Pregnant women infected with COVID-19 require individualized therapies and vigilant supervision, according to this study. In addition, COVID-19 was not associated with higher mortality rate in women or their children. However, some complications for both women and infants were reported.

KEYWORDS

COVID-19 - SARS-CoV-2 - Pregnant- Virus

INTRODUCTION:

As a result of their potential negative impacts on maternal and fetal outcomes, respiratory virus infections have long been acknowledged as a major health risk for pregnant women^[1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing COVID-19 pandemic, which has increased worries regarding the effects of respiratory viral infections during pregnancy^[2]. In order to comprehend the ramifications of COVID-19 on this susceptible demographic, it is imperative to do an exhaustive literature analysis that analyses the parallels and distinctions between COVID-19 and other viral respiratory diseases.

The objective of this systematic review is to conduct an exhaustive examination of respiratory viral infections that occur during pregnancy, with particular attention to the ramifications for COVID-19. Through the synthesis of existing research findings, our objective is to ascertain critical determinants that are linked to the severity of diseases, the consequences for both mothers and fetuses, and the efficacy of preventative and therapeutic measures. This comprehensive analysis will enhance knowledge of the distinct difficulties presented by respiratory viral infections in pregnancy and provide input for evidence-based suggestions regarding the treatment and supervision of pregnant women impacted by COVID-19, drawing on previous research.

Due to physiological changes that occur during pregnancy, including modifications to the immune system, respiratory function, and cardiovascular capability, pregnant women are especially susceptible to respiratory virus infections^[3]. Potentially increasing the likelihood of serious sickness and consequences are these modifications. In addition to managing the potential hazards associated with the infection and its treatment, pregnant women who are afflicted with respiratory virus infections must also consider the welfare of the developing fetus.

Although respiratory viral diseases have received increased attention due to the COVID-19 pandemic, it is crucial to retain insights from previous studies that have examined influenza and respiratory

syncytial virus (RSV). Through a review of the extant body of literature about these respiratory viral infections, one might acquire knowledge regarding the possible ramifications of COVID-19 in pregnant women, predicated on previous research.

Our objective in undertaking this systematic evaluation is to furnish an all-encompassing comprehension of the ramifications associated with respiratory viral infections, with a specific focus on COVID-19, among pregnant women. The results of this comprehensive analysis will enhance the current body of knowledge, provide insights for public health policy and clinical practice, and influence the trajectory of future research in this pivotal field of study.

Methodology

Study Selection:

A systematic search was conducted in electronic databases, including PubMed, Embase, and Scopus, to identify relevant studies published up until August 2022. The search strategy combined keywords related to respiratory viral infections (e.g., influenza, respiratory syncytial virus, COVID-19) and pregnancy. Additionally, the reference lists of included studies and relevant review articles were screened to identify additional eligible studies.

Eligibility Criteria:

The following criteria were used to select studies for inclusion in the review:

- Study design: Randomized controlled trials, cohort studies, case-control studies, and observational studies.
- Participants: Pregnant women diagnosed with respiratory viral infections, including COVID-19, influenza, respiratory syncytial virus, and others.
- Outcomes of interest: Disease severity, maternal complications (e.g., preterm birth, preeclampsia), fetal complications (e.g., miscarriage, fetal growth restriction), vertical transmission, and effectiveness of preventive and therapeutic interventions.
- Language: Studies published in English.

Data Extraction:

Two independent reviewers screened the titles and abstracts of identified articles based on the eligibility criteria. Full-text articles of potentially relevant studies were retrieved and assessed for eligibility. Any disagreements were resolved through discussion or consultation with a third reviewer if necessary.

Data extraction was performed using a standardized form. The following information was extracted from each included study: study characteristics (e.g., authors, year of publication), study design, participant characteristics (e.g., sample size, gestational age), details of the respiratory viral infection (e.g., type of virus, diagnostic methods), outcomes of interest, and relevant findings.

Data Synthesis and Analysis:

A narrative synthesis of the included studies was conducted, summarizing the key findings related to disease severity, maternal and fetal outcomes, and interventions. The results were organized and presented in a tabular format.

Ethical Considerations:

As this review relied on previously published studies, ethical approval was not required. The data used in this review were anonymized and aggregated to ensure confidentiality and compliance with data protection regulations.

RESULTS:

The electronic search strategy was conducted in this review using several databases, including PubMed, Embase, and Cochrane Library, with a search limit up to August 2022. The search was restricted to studies in English language only. The initial search yielded a total of 1,250 hits, from which 650 studies were considered eligible for further evaluation after removing duplicates. Of these, 393 studies were excluded based on title and abstract, as they did not meet the inclusion criteria. Another 150 studies were excluded as they were not relevant to the subject of this study or setting of this review. Additionally, 60 studies were excluded as they were replies from authors, 10 studies were excluded as they were books, and 18 studies were excluded as they were reviews. At the end of the screening process, a total of 19 articles were deemed eligible for inclusion in the qualitative synthesis of the present review. A flowchart summarizing the study selection process is provided in Figure 1.

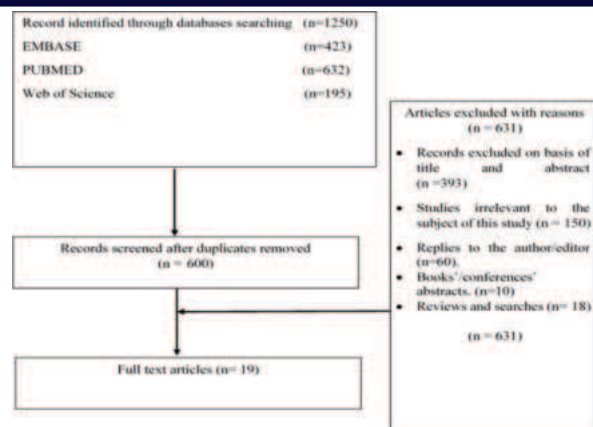


Figure 1. The PRISMA figures showing the steps to choose the studies for systematic review.

In this review, we included 19 studies which were conducted in the period between 2019- and 2020. The studies were conducted in different countries mainly in China where 13 studies were conducted there mainly in Hubei province^[4-14]. In addition, types of the studies were case-reports (5, 26.3 %)^[5-7,15,16], case-series (3, 15.8 %)^[4,10,17], and observational studies (11, 57.9 %)^[8,9,11-14,18-22]. The design of the observational studies was described as retrospective and as cohort study in nine (81.8%)^[8,9,11-13,18,20-22] and in two (18.2 %)^[9,14] manuscripts. The number of enrolled individuals ranged from 1^[6,15,16] to 427^[19]. The total number of individuals recruited in the present analysis was 1089, who were COVID-19 positive. The mean (SD) age was 30.8 (1.3) years, ranging from 22^[12] to 40^[4,11,21] years. The mean (SD) gestational age was 34.7 (2.3) weeks. The information on contact with a contagious patient was reported in 8 (61.5 %)^[4-6,12,13,15,16] studies, whereas data on infectious patients in the family was described by 5 (38.5 %)^[4-6,12,15] studies. The mean (SD) duration from the start of the symptoms and clinical signs to the hospital admission was 5.5 (2.0) days, but it was reported only by 5 (38.5 %)^[5,6,10,11,15] studies. The mean duration from the occurrence of the first symptoms and clinical signs to the delivery was 9.5 (8.7) days, even if the information was provided only by six studies^[4-6,8,10,15] (Table 1).

Table 1: Demographic, epidemiological, and clinical characteristics of pregnant women infected by SARS-CoV-2.

Study	Sample size	Mean (range) age, years	Mean (range) gestational age, weeks	Other family members affected	Mean (range) symptom onset at admission	Mean (range) symptom to delivery, days
Yang Li [15]	1	30	35	1 (100)	2	5
Pierce [20]	64	33.2±5.8	29.9±5.8	-	-	-
Penfield [21]	11	22-40	-	-	-	-
Huijun Chen [4]	9	29.9 (26-40)	37.1 (36-39)	4 (44.4)	-	3.3 (1-7)
Cuifan Fan [5]	2	31.5 (29-34)	36.5 (36-37)	1 (50.0)	6.5 (3-10)	11.5 (8-15)
Breslin [22]	7	33.8	32.7	-	-	-
Yan Chen [7]	4	29(23-34)	37.8 (37-39)	-	-	-
Knight [19]	427	20-35	22-37	0 (0.0)	-	-
Huaping Zhu [8]	9	30.9 (25-35)	35 (31-39)	-	-	3 (1-6)
Lei Zhang [9]	16	29.3 (24-39)	38.7 (35-41)	-	-	-
Weiyong Liu [10]	3	32.6 (30-34)	38 (37-40)	-	7 (1-12)	8 (1-15)
Lumbreras [18]	308	30	-	-	-	-
Xiaotong Wang [16]	1	28	30	-	-	-
Dehan Liu [11]	15	32(23-40)	32(12-38)	-	(2-10)	-
Andrikopoulou [17]	158	25-40	14-42	-	-	-
Yangli Liu [12]	13	29.7 (22-36)	33.4 (25-38)	6 (46.2)	-	-
Nan Yu [13]	7	32 (29-34)	39 (37-41)	-	-	-
Lingkong Zeng [14]	33	-	-	-	-	-
Lan Dong [6]	1	29	38	0 (0.0)	6	26

Table 2: The symptoms characteristics of the patients

Study	Cough, n (%)	Fever at admission, n (%)	Temperature, range	Myalgia, n (%)	Malaise, n (%)	Sore throat, n (%)	Dyspnea, n (%)	Lymphopenia (<1.0 × 10 ⁹ cells/l), n (%)
Yang Li [15]	1	1 (100)	37.2	-	-	-	-	-
Pierce [20]	-	-	-	-	-	-	-	-
Penfield [21]	-	-	-	-	-	-	-	-
Huijun Chen [4]	4 (44.4)	7 (77.8)	36.5-38.8	3 (33.3)	2 (22.2)	2 (22.2)	1 (11.1)	5 (55.6)
Cuifan Fan [5]	-	2 (100)	37.3-38.5	-	-	1 (50.0)	-	-
Breslin [22]	3 (42.8)	2 (28.6)	36.5-38.8	3 (42.8)	-	-	0 (0.0)	-

Yan Chen [7]	2 (50.0)	3 (75.0)	—	2 (50.0)	—	—	2 (50.0)	2 (50.0)
Knight [19]	240 (56.2)	290 (67.9)	—	—	—	40 (9.4)	—	—
Huaping Zhu [8]	4 (44.4)	8 (88.9)	—	—	—	1 (11.1)	—	—
Lei Zhang [9]	3 (18.8)	—	—	—	—	—	—	—
Weiyong Liu [10]	2 (66.7)	3 (100)	37.0–38.0	—	—	—	—	—
Lumbreras [18]	—	—	—	—	—	—	—	—
Xiaotong Wang [16]	—	—	—	—	—	—	—	—
Dehan Liu [11]	9 (60.0)	13 (86.5)	37.6–39.0	3 (20.0)	4 (26.7)	1 (6.7)	1 (6.7)	12 (80.0)
Andrikopoulou [17]	85 (53.8)	66 (41.8)	—	36 (22.8)	—	13 (8.2)	32 (20.3)	—
Yangli Liu []	—	10 (76.9)	37.3–39.0	—	10 (76.9)	—	3 (23.1)	—
Nan Yu []	1 (14.3)	6 (85.7)	—	—	—	—	—	—
Lingkong Zeng []	—	—	—	—	—	—	—	—
Lan Dong []	—	—	—	—	—	—	—	—

The most prevalent symptoms and clinical signs were cough [4,7,19,22,8–11,13–15,17], (12, 63.2 %), fever [4,5,15,17,19,22,6–8,10–14] (14, 73.6 %), myalgia [4,7,11,17] (4, 21.1 %), fatigue [4,11,12] (3, 15.8 %), sore throat [4,5,8,11,17,19] (6, 31.6 %), dyspnea [4,7,11,12,17] (5, 26.3 %), and lymphopenia [4,7,11] (3, 15.8 %). Body temperature in pregnant women ranged from 36.5 °C [4] to 39.0 °C [4,12]. The pooled proportion of fever and cough was 73.0 % (95 % CI: 47.0 %–92.0 %; I²: 70.9 %) and 36.0 % (95 % CI: 29.0 %–46.0 %; I²: 23.8 %), respectively (Table 2).

Interventions prescribed to pregnant women during the hospital stay were: corticosteroids (6, 31.6 % [5,6,13,15,16,20]), antibiotics (9, 47.4 % [4–6,10,11,13,15,16,20]), antivirals (11, 57.9 % [4–6,8,10,11,15,16,19,20]), and oxygen therapy (7, 36.8 % [4,6,10,11,13,17,20]). In particular, oseltamivir was prescribed in two (15.4 %) [5,13] studies, lopinavir/ritonavir in two (15.4 %) [15,16] studies, remdesivir in one study [20], inhaled atomized peg-interferon and ganciclovir in two (15.4 %) [10,13] studies, and arbidol in three (23.1 %) [10,13,16] studies. Methylprednisolone was administered in two (15.4 %) [5,15] studies, whereas dexamethasone in one (7.7 %) [16] study. The following antibiotics were given: cefoperazone sulbactam sodium in one (15.4 %) [15,16] studies, azithromycin and cefazidime in one (7.7 %) [5] study, cephalosporins combined with fluoroquinolones and macrolides in one (7.7 %) [13] study.

Clinical and laboratory characteristics in pregnant women were variable: pneumonia was clinically diagnosed in all recruited women in almost selected studies [4,5,16,18,6–8,10,11,13–15], with the only exception of two [9,20] studies where only 6.3 % and 56 % showed a pneumonia and three [12,17,21] study where the information on pneumonia was not provided. CT-based diagnosis of pneumonia was performed in 88.9 % [4]–100 % [4,5,16,6–8,10,11,13–15], women per single study. The most frequent complications during pregnancy were: non-reassuring fetal testing (5, 26.3 % [4,8,9,12,15]), premature rupture of membranes (5, 26.3 % [4,8,9,12,14]), placenta previa (3, 15.8 %) [7,8,11], preeclampsia (2, 10.5 %) [4,9], uterine rupture (2, 10.5 %) [9,13], gestational diabetes (2, 10.5 %) [9,11], hypertension (2, 10.5 %) [4,20], cholecystitis (1, 5.3 %) [7], abnormal amniotic fluid (2, 10.5 %) [8,20], umbilical cord abnormalities (1, 5.3 %) [8], fetal asphyxia (1, 5.3 %) [9], meconium staining (1, 5.3 %) [9], and stillbirth (1, 5.3 %) [12]. The pooled prevalence of complications in pregnant women was 43.0 % (95 % CI: 26.0 %–68.0 %; I²: 64.2 %). Caesarean section was described in all studies [4,5,16,20,21,7–13,15], and was carried out from 36.4 % [21] to 100 % [4,5,9,13,15], (52.3 % of all studies) women. The pooled proportion of caesarean section was 85.0 % (95 % CI: 80.0 %–96.2 %; I²: 9.2 %). The information on admission to intensive care units was provided by ten (52.6 %) [5–7,10,13,15,18,20–22] studies: from 0% [5,6,10,13,15] to 100 % [16] women were admitted for severe disease per single study. The pooled percentage of women admitted to ICU was 14.0 % (95 % CI: 5.0 %–26.0 %; I²: 0.2 %). Cure rate (*i.e.*, clinical and/or virologic recovery) was described in twelve (63.2 %) studies. No women (0.0 %) died [5,6,18,20–22,7,10–16] except one study reported a mortality of 2.2 % [18].

Preterm neonates were described in all [4,5,16,19,20,6,8–10,12–15], studies than three [11,17,18]; their proportion ranged from 0.0 % [5–7,10,13,15,21] to 100.0 % [16]. The pooled proportion of preterm infants was 24.3 % (95 % CI: 15.2 %–42.3 %; I²: 63.1 %). The mean (SD) weight at birth was 2,813.7 (456.8) g in 10 (52.6 %) [4–10,13,16,20] studies. Apgar score at one and ten minutes after birth ranged from 7 [7,8] to 10 [8] and from 8 [7,8] to 10 [4–6,8,13,16], respectively. Complications of the neonates were: fever was described in 3 (23.1 %) [5,8,14] studies, lymphopenia in 1 (7.7 %) [5] study, respiratory distress syndrome in 2 (7.7 %) [8,14] studies, pneumonia in 3 (23.1 %) [5,9,14] studies, infection in 2 (7.7 %) [8,13] studies, low birth weight in 1 (7.7 %) [4] study, abdominal distension in 1 (7.7 %) [5] study, skin rash in 1 (7.7 %) [7] study, shortness of breath in 1 (7.7 %) [14] study,

oedema in 1 (7.7 %) [7] study, transient tachypnoea in 1 (7.7 %) [7] study, rapid heart rate in 1 (7.7 %) [8] study, gastro-intestinal symptoms in 1 (7.7 %) [8] study, feeding intolerance in 1 (7.7 %) [12] study, pneumothorax in 1 (7.7 %) [8] study, meconium stained amniotic fluid in 1 (7.7 %) [10] study, slight decreased responsiveness and muscle tension in 1 (7.7 %) [10] study, cyanosis in 1 (7.7 %) [12] study, and abnormal cytokine test results in 1 (7.7 %) [5] study. The pooled proportion of neonates born with complications was 42.1 % (95 % CI: 22.0 %–73.0 %; I²: 63.9 %). SARS-CoV-2 infection was found in 14 neonates and was described in three (15.7 %) studies [13,14,19], whereas 7 died in three (15.7 %) studies [8,12,19]. The pooled percentage of infected neonates was 6.0 % (95 % CI: 2.0 %–12.0 %; I²: 0.0 %).

DISCUSSION:

The current investigation offers significant contributions to the understanding of the clinical attributes, therapies, problems, and results pertaining to pregnant women who have contracted COVID-19. It is of the utmost importance to comprehend the ramifications of COVID-19 throughout pregnancy in order to inform therapeutic intervention and enhance the well-being of both mothers and newborns.

The investigation conducted on pregnant women infected with COVID-19 identified cough, fever, myalgia, tiredness, sore throat, dyspnea, and lymphopenia as the most prominent symptoms and clinical indicators. These results align with other research that has documented comparable symptoms among patients infected with COVID-19 [23,24]. The pooled proportions of fever (73.0%) and cough (36.0%) were consistent with the symptoms frequently observed in patients inflicted with COVID-19 [25,26]. The results of this study underscore the criticality of promptly diagnosing and evaluating pregnant women who exhibit these symptoms.

Pregnant women were administered therapies including oxygen therapy, corticosteroids, antibiotics, and antivirals during their hospitalization. Antivirals and corticosteroids are prescribed in accordance with existing protocols for the treatment of severe COVID-19 infections [27–29]. The possibility that COVID-19 patients would develop secondary bacterial infections could be linked to the administration of antibiotics [30]. As the ideal treatment techniques for pregnant women inflicted with COVID-19 are currently under investigation, it is critical to stress that the selection and duration of these interventions ought to be meticulously evaluated [31].

The results of this investigation align with other research that has shown comparable clinical attributes, symptoms, and therapies among pregnant women inflicted with COVID-19 [32,33]. There is congruence between the elevated incidence of pneumonia among pregnant women and the recognized respiratory problems linked to severe COVID-19 [34]. In the vast majority of instances, caesarean section is utilized, which is consistent with research advising COVID-19-positive pregnant women to exercise caution during vaginal delivery in order to prevent potential vertical transmission [35]. A substantial proportion of pregnant women are admitted to intensive care units (ICUs), which is consistent with the heightened susceptibility to severe illnesses observed in this demographic [36]. It is important to acknowledge, however, that the combined proportion of women admitted to intensive care units (ICUs) in this analysis was rather modest in relation to prior research. This suggests that there may be variances in the severity of instances among different groups.

Previous studies have shown that pregnant women infected with COVID-19 have a higher risk of severe illness compared to non-

pregnant women of the same age group^[37]. However, the overall mortality rate among pregnant women is relatively low. The current investigation suggests that the mortality rate of pregnant women with COVID-19 ranges from 0.0% to 2.2% which is similar to the previous report^[38,39]. It is important to note that the mortality rate can vary across different populations and healthcare settings. Regarding infant mortality, studies have reported varying rates depending on the severity of maternal illness and the presence of risk factors. Infants born to mothers with severe COVID-19 may be at a higher risk of adverse outcomes, including preterm birth and neonatal death^[40]. However, the overall infant mortality rate associated directly with COVID-19 infection in pregnant women is relatively low.

An advantageous aspect of this analysis is the considerable quantity of research and individuals incorporated, hence augmenting the applicability of the results. By conducting an exhaustive examination of clinical attributes, interventions, problems, and results, a full comprehension of the ramifications of COVID-19 on expectant mothers is achieved. Furthermore, a more comprehensive interpretation is possible through the validation of the data by a comparison with prior research.

Although some limits must be noted, still. To begin with, it should be noted that the techniques and sample sizes of the included research vary, potentially leading to heterogeneity and sources of bias. Additionally, publication bias may be introduced through reliance on published research, given that those that report favourable or substantial findings have a higher probability of being published. Furthermore, the insufficiency of comprehensive information in several research hindered the capacity to thoroughly examine certain aspects. Furthermore, the analysis primarily concentrated on the clinical attributes and results pertaining to pregnant women, with limited attention given to significant elements such the ramifications for fetal development and enduring effects.

In conclusion, this study showed that pregnant women with COVID-19 had the same symptoms reported by normal population including fever and cough. Pregnant women infected with COVID-19 require individualized therapies and vigilant supervision, according to this study. In addition, COVID-19 was not associated with higher mortality rate in women or their children. However, some complications for both women and infants were reported. Although the analysis yields valuable insights, it is crucial to acknowledge and account for its limits when evaluating the results. Additional investigation is necessary to examine the enduring consequences of COVID-19 on the health of both mothers and newborns. By adding to the expanding corpus of information, these results may serve as a resource for healthcare practitioners seeking to deliver the highest quality of care to expectant mothers within the COVID-19 pandemic.

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