The Differences in Clinical Presentation, Management, and Prognosis of Laboratory-Confirmed COVID-19 between Pregnant and Non-Pregnant Women: A Systematic Review and Meta-Analysis

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Abstract: Background: The coronavirus disease 2019 (COVID-19) pandemic has affected millions of people across the globe. Previous coronavirus outbreaks led to worsened symptoms amongst pregnant women, suggesting that pregnant women are at greater risk. Objectives: Our aim is to investigate the differences in clinical presentation, management, and prognosis of COVID-19 infection in pregnant and non-pregnant women. Methods: We ran a search on electronic databases and analysis of the relevant articles was done using Revie Manager 5.4. Results: The review consists of nine studies comprising 591,058 women (28,797 pregnant and 562,261 non-pregnant), with most of the data derived from two large studies. The risk of experiencing fever (RR: 0.74; 95% CI: 0.64–0.85), headache (RR: 0.77; 95% CI: 0.74–0.79), myalgia (RR: 0.92; 95% CI: 0.89–0.95), diarrhea (RR: 0.40, 95% CI: 0.39–0.43), chest tightness (RR: 0.86; 95% CI: 0.77–0.95), and expectoration (RR: 0.45; 95% CI: 0.21–0.97) were greater amongst non-pregnant COVID-19-infected women. Pregnant women with COVID-19 were less likely to be obese (RR: 0.68; 95% CI: 0.63–0.73) or have a smoking history (RR: 0.32; 95% CI: 0.26–0.39). COVID-19-infected non-pregnant women had a higher frequency of comorbidity such as chronic cardiac disease (RR: 0.58; 95% CI: 0.44–0.77), renal disease (RR: 0.45; 95% CI: 0.29–0.71), and malignancy (RR: 0.82; 95% CI: 0.68–0.98), compared to COVID-19-infected pregnant women. The risk of ICU admission (RR: 2.26; 95% CI: 1.68–3.05) and requirement of invasive mechanical ventilation (RR: 2.68; 95% CI: 2.07–3.47) were significantly higher amongst pregnant women. Conclusions: Although the frequency of risk factors and the risk of experiencing clinical symptoms of COVID-19 were higher among non-pregnant women, COVID-19-infected pregnant women had a higher requirement of ICU admission and invasive mechanical ventilation compared to non-pregnant COVID-19-infected women. More well-conducted studies from varying contexts are needed to draw conclusions. Prospero registration: CRD42020204638.

Keywords: COVID-19; SARS-CoV-2; coronavirus 2; pregnant; non-pregnant adults; child-bearing age women

1. Introduction

In December 2019, the coronavirus disease 2019 (COVID-19) first emerged as a cluster of pneumonia cases of unknown origin in Wuhan, China [1]. The disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was soon declared a “public health emergency of international concern” and later characterized as a pandemic by the World Health Organization (WHO) [2]. As of 13 October 2020, there have been a total of more than 40.2 million confirmed cases of COVID-19, with over 1.1 million deaths...
worldwide [3]. Since the global outbreak, several studies have been published reporting clinical characteristics, laboratory findings, and management associated with COVID-19 in the general population, focusing mainly on non-pregnant adults [4–7].

Pregnancy is a unique state in which the maternal immune system has to overcome two main challenges: protecting the fetus against an immunological attack while maintaining adequate defense against various microbial threats. Physiological and mechanical changes associated with gestation predispose pregnant women to severe forms of respiratory infections with subsequent higher maternal and fetal mortality [8,9]. During the last two decades, coronavirus has been responsible for two major epidemics: the severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV), with a case fatality of 10.5% and 34.4%, respectively [10]. It was found that these infections were associated with worsening symptoms and clinical outcomes among pregnant women ranging from severe maternal illness to spontaneous abortion, and even maternal death [8,9,11] Although SARS-CoV-2 appears to be less virulent than the aforementioned coronaviruses, its spread is far more rapid and efficient among close contacts [12]. Therefore, it has raised additional concerns in pregnant women because previous experiences with both SARS-CoV and MERS-CoV have shown severe complications in this vulnerable population.

The increased risk of viral pneumonia in the obstetric population makes it imperative to evaluate whether there is any difference in the clinical course and outcomes between pregnant and non-pregnant women infected with COVID-19. Furthermore, we found no systematic review that provides a comparison of available evidence on COVID-19 among women of reproductive age based on their pregnancy status. Therefore, in this systematic review and meta-analysis, we aim to describe the clinical characteristics, management, and prognosis of COVID-19-infected pregnant women compared to COVID-19-infected non-pregnant women. In the next section, we specify the method with which this systematic review and meta-analysis was conducted, after which we have the results section, the discussion, and finally, the conclusion. The findings of this review will facilitate healthcare workers in understanding the disease, aid in the clinical management and counseling of these patients, as well as allow policy makers to form guidelines for the general public.

2. Methodology

This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with ID number CRD42020204638 and follows the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13] (Table S1).

A systematic literature search was conducted until 25 February 2021, using PubMed, Embase, the WHO COVID-19 database, and Google Scholar. Furthermore, medRxiv and bioRxiv were screened for pre-print papers. The following terms and their variants were combined and used in devising the search strategy: “Pregnant women” OR “Pregnancy” AND “Coronavirus” OR “Covid-19” OR “SARS-CoV-2”. The full search strategy and terms used are available in Table S2. We did not apply any language restrictions; however, papers published since 31 December 2019, were included.

All observational studies (cohort, case-control, cross-sectional, or case-series) including consecutive patients with a comparison group of pregnant and non-pregnant women of reproductive age group with laboratory-confirmed SARS-CoV-2 infection and reporting clinical characteristics, management, and prognosis were considered eligible. A case-series was defined as a study with a sample size of less than ten participants. Only studies that compared pregnant women with COVID-19 with non-pregnant women with COVID-19 were eligible for inclusion. We excluded studies describing only either pregnant or non-pregnant women with COVID-19. Studies were checked for data overlapping by assessing their center of data collection and the time period during which the data were collected. When it was unclear, authors were contacted to ensure that they reported results from different centers or during different time periods. Identified overlapping papers were
further assessed and the studies with inclusion of more variables, bigger sample size, and better quality of assessment were chosen, as shown in Table S3.

Two reviewers (D.S.A.K. and A.N.P.) independently screened the titles and abstracts for eligibility. After the initial search, full texts of relevant articles were examined for inclusion and exclusion criteria. Primary studies that fulfilled the inclusion criteria were selected for this systematic review. Any disagreement among the authors was resolved through consensus or consulting a senior reviewer (Z.S.L.).

Two authors (D.S.A.K. and A.N.P.) extracted relevant information independently from included studies. The following items were extracted from each study if available: author’s name, study design, country, duration of the study, setting, total number of study participants, demographics, past medical history, presenting signs and symptoms, management, and complications. For clinical presentation, data on the number of asymptomatic and COVID-19-like symptoms were extracted. Data on management with antivirals, antibiotics, corticosteroids, or any other new medication/technique were also recorded. Complications in the two groups, be it progression to severe COVID-19 infection, requirement for ventilation, intensive care unit (ICU) admission, or death, were also considered. The quality of the studies included in this meta-analysis was assessed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool for observational cohort and case-control studies [14]. This tool helps evaluate the internal validity of a study, hence ensuring that the results are truly due to the exposure being evaluated.

Data were entered and analyzed using Review Manager (RevMan) version 5.4 [15]. Mean difference (MD) with 95% confidence intervals (CI) was used for continuous data and relative risk (RR) with 95% CI for dichotomous data. Random effect models were used and heterogeneity between the studies was explored using the $p$-value of Chi² and $I^2$. Sensitivity analysis was performed by removing one large study.

3. Results

There was a total of 4347 titles identified after the initial search, 4179 articles were excluded after screening titles and abstracts. Of the 168 studies retrieved for full text review, only 9 were found eligible for inclusion [16–24]. We excluded 159 studies on full-text review, of which 42 were authors’ perspectives or reviews, 44 were guidelines or guidance papers based on other coronavirus strains, 43 studies compared COVID-19 infected pregnant women with non-infected individuals or asymptomatic pregnant women, 26 studies did not have any outcomes of interest reported, and 4 were overlap studies conducted at the same center during the same time period, as shown in Figure 1.
3.1. Description of Included Studies

All nine studies included were observational studies, with six retrospective cohorts [16–21], one prospective cohort [24], and two case-control studies [22,23]. The data in the included studies were collected between December 2019 to February 2021 with eight papers published in the year 2020 and one in 2021 [24]. Five studies were conducted in China [16–18,20,22], one in Israel [21], one in Mexico [24], and two in the United States (US) [19,23]. Six studies were from a single center [16–18,20–22] whereas three were multicenter studies [19,23,24]. On methodological quality, it was identified that all studies mentioned their main objective, study population with uniform application of inclusion and exclusion criteria, consistency in their method of measuring exposure, and appropriate discussion of outcomes. However, only three studies took confounders into account [16,19,23].

The number of enrolled individuals in each study ranged from 36 to 409,462. Six studies had a sample size of less than 150 participants [16–18,20–23], whereas one study conducted in Mexico had a sample size of 181,088 [24] and another study conducted in the US had a total sample size of 409,462 [19], leading to the total number of participants included in this review to be 591,058. All the participants were COVID-19 positive with 28,797 pregnant women and 562,261 non-pregnant women. Characteristics of included studies are reported in Table 1 and their methodological quality in Table 2a,b. Results from the pooled analysis are presented in Table 3.
Table 1. Characteristics of included studies.

| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|----------------|--------------|-------------------------|---------|--------------|--------------|---------------------|-------------------------------|------------|---------------|
|                |              |                         |         |              | Mean age (years): | 30 ± 1.28 | Mean gestational age (weeks): | 38 ± 0.61 | First trimester: | 3 |
| Xu Qiancheng   | Retrospective cohort | Wuhan, China January to 15 March 2020 | The Central Hospital of Wuhan | Total: 82 | Pregnant: 28 | Non-pregnant: 54 | Gestational hypertension: 1 | Hypertension: 0 | Fever: 5 | Malaise: 1 | Cough: 7 | Dyspnea: 2 |
| 2020           |              |                         |         |              | Mean age (years): | 31 | Mean gestational age (weeks): | 36 | Second trimester: | 1 |
|                |              |                         |         |              | Hypertension: | 0 | Diabetes: 4 | Cough: 7 | Dyspnea: 32 | |
|                |              |                         |         |              | Chronic hepatitis: 2 |  | Chronic hepatitis B: 2 | Abdominal pain: 5 | Dyspnea: 6 | |
|                |              |                         |         |              | Hypothyroid: 1 |  | Hypothyroid: 1 | Abdominal pain: 0 | | |
|                |              |                         |         |              | Antiviral: 54 | (Ribavirin: 19) | (Umifenovir: 11) | (Riba + Umi: 7) | (Triple combo with Interferon: 7) | |
|                |              |                         |         |              | Antibiotics: 24 | (Cephalosporin: 20, Quinolone: 4) | (Cephalosporin: 9, Quinolone: 6, Cephalosporin + Quinolone: 32) | (Corticosteroid: 21) | (Corticosteroid: 19) | (Hospitalization: 7) | (Hospitalization: 19) | (Hospitalization: 0) | (Hospitalization: 0) |
| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|----------------|-------------|-------------------------|---------|--------------|--------------|---------------------|-----------------------------|------------|---------------|
| Shuang Xu 2020 | Retrospective | Wuhan, China 15 January to 15 March 2020 | Union Hospital | Total: 64 Pregnant: 34 Non-pregnant: 30 | Mean age (years): 30 ± 4.26 First trimester and second: 8 Third trimester: 26 Exposure history: 10 | Mean age: 34.77 ± 3.71 Exposure history: 2 | GDM: 2 Hypothyroidism: 1 Pre-eclampsia: 1 Fetal distress: 1 Hypertension: 0 Cardiovascular: 1 Diabetes: 2 PROM: 4 Scarred uterus: 9 | Asymptomatic: 0 Fever: 26 Cough: 23 Fatigue: 16 Sputum: 13 SOB: 10 Chest tightness: 6 Headache: 5 Myalgia: 3 Nausea/vomiting: 2 Abdominal pain: 3 Diarrhea: 2 Rash: 2 | Antibiotic: 30 Antiviral: 17 Corticosteroid: Corticosteroid: 19 Chinese medicine: 15 Oxygen therapy: 15 ICU admission: 1 | Scarred uterus: 9 Gestational Diabetes: 2 Preeclampsia: 1 ICU admission: 1 Preterm Birth: 5 Postpartum fever: 3 NO neonatal complications |
| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|---------------|--------------|-------------------------|---------|--------------|--------------|----------------------|-------------------------------|------------|---------------|
| Shaoshuai Wang 2020 [18] | Retrospective Cohort | Wuhan, China 19 January to 2 March 2020 | Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology | 43 | Mean age (years): 33.0 | Pregnant: 17 | First trimester: 1 | Fever: 8 | Antiviral therapy: 13 |
|               |              |                         |         | 26           | Mean age (years): 33.5 | Non-pregnant: 26 | Second trimester: 3 | Chills and rigors: 0 | Antibiotic therapy: 13 |
|               |              |                         |         | Healthcare workers: 13 |                      | Healthcare workers: 5 | Cough: 9 | Glucocorticoid therapy: 4 |
|               |              |                         |         |               |                      |                      | Expectoration: 3 | Headache: 1 | Immunoglobulin therapy: 1 |
|               |              |                         |         |               |                      |                      | Chest tightness: 2 | Dizziness: 0 | Cough suppressant therapy: 6 |
|               |              |                         |         |               |                      |                      | SOB: 1 | Fatigue: 4 | Oxygen support (nasal cannula): 6 |
|               |              |                         |         |               |                      |                      | Myalgia: 0 | Cough: 12 | Mechanical ventilation: 0 |
|               |              |                         |         |               |                      |                      | Diarrhea: 1 | Expectoration: 6 | Preterm birth: 2 |
|               |              |                         |         |               |                      |                      | Asymptomatic: 2 | Chest tightness: 3 | ICU admission: 0 |
|               |              |                         |         |               |                      |                      | Abdominal pain: 4 | SOB: 1 | Death: 0 |
|               |              |                         |         |               |                      |                      | Vaginal bleeding: 1 | Myalgia: 1 | ICU Admission: 0 |
|               |              |                         |         |               |                      |                      | Reduced fetal movement: 1 | Diarrhea: 4 | Mechanical ventilation: 0 |
|               |              |                         |         |               |                      |                      | Increased fetal movement: 1 | Asymptomatic: 2 | Mechanical ventilation: 0 |
| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Race/Ethnicity (%) | Race/Ethnicity (%) | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|---------------|-------------|-------------------------|---------|--------------|-------------------|-------------------|---------------------|-----------------------------|------------|---------------|
| Laura Zambrano 2020 [19] | Retrospective Cohort | United States via National Notifiable Diseases Surveillance System | Total: 489,462 Pregnant: 23,434 Non-Pregnant: 386,028 | Hispanic or Latino: 29.7 | Asian: 2.4 | Black: 14.5 | White: 23.5 | Multiple or another race: 3.1 | Known underlying medical condition status: 160,065 | Cough: 89,422 |
| | | | | | | | | | Diabetes mellitus: 427 | Fever: 68,536 |
| | | | | | | | | Chronic lung disease: 506 | Muscle aches: 78,725 |
| | | | | | | | | Cardiovascular: 304 | Chills: 50,836 |
| | | | | | | | | Chronic renal disease: 18 | Headache: 95,713 |
| | | | | | | | | Chronic liver disease: 17 | SOB: 43,234 |
| | | | | | | | | Immuno compromised: 124 | Sore throat: 89,422 |
| | | | | | | | | Psychiatric disorder: 62 | Diarrhea: 68,536 |
| | | | | | | | | Autoimmune disorder: 26 | Nausea/ vomiting: 28,999 |
| | | | | | | | | Severe obesity: 174 | Abdominal pain: 16,123 |
| | | | | | | | | N/A | N/A | ICU admissions: 245 |
| | | | | | | | | N/A | N/A | Mechanical Ventilation: 67 | Death: 412 | Death: 447 |
### Table 1. Cont.

| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|----------------|--------------|-------------------------|---------|--------------|--------------|----------------------|-------------------------------|------------|---------------|
| Biheng Cheng 2020 | Retrospective Cohort | Wuhan, China 15 January to 23 February 2020 | Renmin Hospital of Wuhan University | Total: 111 | Pregnant: trimester: 31 | Non-Pregnant: trimester: 80 | Median age (years): 33.0 | Median age (years): 29.0 | Cardiovascular disease: 1 | Fever: 15 | Antiviral: 29 |
|                |              |                        |         |              | Pregnant:          | Non-Pregnant:         |                              |            |                     | Cough: 14 | Oseltamivir: 16 |
|                |              |                        |         |              | trimester: 5      | trimester: 6         |                              |            |                     | Respiratory disease: 0 | Febrile: 2 | Arbidol: 25 |
|                |              |                        |         |              |                 |             |                              |            |                     | Diabetes: 3 | Respiratory disease: 2 | Rhinorrhea: 1 | Ribavirin: 8 |
|                |              |                        |         |              |                  |               |                              |            |                     | Malignancy: 1 | Myalgia: 8 | IV Antibiotics: 29 |
|                |              |                        |         |              |                  |               |                              |            |                     | Renal disease: 1 | Sore throat: 13 | Antifungal: 0 |
|                |              |                        |         |              |                  |               |                              |            |                     | Gastric ulcer: 0 | Headache: 2 | Corticosteroid: 20 |
|                |              |                        |         |              |                  |               |                              |            |                     | Mental sickness: 1 | Dizziness: 3 | Oxygen therapy: 2 |
|                |              |                        |         |              |                  |               |                              |            |                     | Mental sickness: 1 | SOB: 3 | Invasive ventilation: 0 |
|                |              |                        |         |              |                  |               |                              |            |                     | Digestive tract symptoms: 23 | Invasive ventilation: 2 | Non-invasive ventilation: 0 |
|                |              |                        |         |              |                  |               |                              |            |                     | Asymptomatic: 9 | ECMO: 0 | ECMO: 0 |
|                |              |                        |         |              |                  |               |                              |            |                     | Asthenia: 1 | Immunoglobulin: 7 | Immunoglobulin: 34 |

|                |              |                        |         |              |                  |               |                              |            |                     | Asthenia: 27 | ICU admission: 0 |
|                |              |                        |         |              |                  |               |                              |            |                     | ICU admission: 1 | Use of CRRT: 1 |
| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|---------------|--------------|-------------------------|---------|--------------|--------------|---------------------|------------------------------|------------|---------------|
| Aya Mohr-Sasson 2020 [21] | Retrospective Cohort | Israel, March to April 2020 | Sheba Medical Center (University Affiliated Tertiary Medical Center) | Total: 36 | Median Age: 28 All in third Trimester | Median age: 40 | N/A | N/A |
| | | | | | | | Fever: 3/11 Weakness: 5/11 Respiratory: 6/11 Gastrointestinal: 2/11 Others: 2/11 | Hospitalization: 7 Home surveillance: 4 | Intubation: 1 C-section: 2/11 (one due to symptoms related to COVID-19 and other due to non-reassuring fetal monitor) |
| Fang Liu 2020 [22] | Retrospective case-control study | Shanghai and Wuhan, China 23 January to 4 March 2020 | Xinhua Hospital and Maternal and Child Health Hospital | Total: 40 | Mean age: 31 | Mean age: 31 | N/A | N/A |
| | | | | | | Fever: 8/21 Cough: 6/21 SOB: 1/21 Fatigue: 8/21 Loss of appetite: 2/21 | Fever: 14/19 Cough: 8/19 SOB: 1/19 Fatigue: 3/19 Loss of appetite: 0/19 | N/A | ICU admission: 1/21 Mechanical ventilation: 1/21 |
| | | | | | | | | | ICU Admission: 1/19 Mechanical Ventilation: 1/19 |
### Table 1. Cont.

| Study and Year | Study Design | Country and Time Period | Setting | Total | Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|----------------|--------------|-------------------------|---------|-------|--------|--------------|----------------------|-------------------------------|------------|---------------|
| Chelsea De-Bolt 2020 [23] | Retrospective case-control study | New York and Philadelphia, United States 12 March to 5 May 2020 | NYU Langone Health, Mount Sinai Hospital, Elmhurst Hospital, Montefiore Medical center, Thomas Jefferson University Hospital | Total: 132 | Pregnant: 38 Non-pregnant: 94 | Mean age: 34.7 Mean BMI: 31.7 | N/A | N/A | N/A | N/A | N/A |
| | | | | | | | Hydroxy chloroquine: 34 Azithromycin: 25 Antivirals: 7 Tocilizumab: 3 Systemic steroids: 4 Convalescent plasma: 2 Therapeutic anticoagulation: 8 Prophylactic anticoagulation: 24 | | | | |
| | | | | | | | Hydroxy chloroquine: 76 Azithromycin: 56 Antivirals: 6 Tocilizumab: 4 Systemic steroids: 15 Convalescent plasma: 4 Therapeutic anticoagulation: 20 Prophylactic anticoagulation: 61 | | | | |
| | | | | | | | | | | N/A | N/A |
| Study and Year | Study Design | Country and Time Period | Setting | Total Number | Demographics | Past Medical History | Presenting Signs and Symptoms | Management | Complications |
|----------------|-------------|-------------------------|---------|--------------|--------------|------------------------|-------------------------------|------------|---------------|
| Martinez-Portilla 2021 [24] | Prospective cohort study | Mexico, 1 February to 28 October 2020 | Mexican National Registry of Coronavirus | Total: 181,088 Pregnant: 5183 Non-pregnant: 175905 | Mean age: 28.5 ± 5.9 | Mean age: 33.1 ± 7.5 | COPD: 10 Asthma: 112 Smoker: 91 Hypertension: 150 Cardiovascular disease: 24 Obesity: 477 Diabetes: 174 | COPD: 487 Asthma: Smoker: Hypertension: Cardiovascular disease: Obesity: Diabetes: N/A | N/A N/A N/A N/A | Death: 77 ICU admission: 154 | Death: 2589 ICU admission: 941 |
Table 2. (a) NHLBI quality assessment tool for cohort studies. (b) NHLBI quality assessment tool for case-control studies.

| Study ID                   | Qiancheng 2020 [18] | Xu 2020 [19] | Wang 2020 [20] | Zambrano 2020 [21] | Cheng 2020 [22] | Mohr-Sasson 2020 [23] | Martinez-Portilla 2020 [24] |
|----------------------------|---------------------|--------------|----------------|-------------------|----------------|-----------------------|-----------------------------|
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | No | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%? | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | No | No | No | No | No | No | No |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | No | No | No | No | No | No | No |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | No | No | No | No | No | No | No |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10. Was the exposure(s) assessed more than once over time? | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 13. Was loss to follow-up after baseline 20% or less? | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes | No | No | Yes | No | No | No |
| Study ID          | Fang Liu 2020 [24] | Chelsea DeBolt 2020 [23] |
|-------------------|--------------------|--------------------------|
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes |
| 3. Did the authors include a sample size justification? | No | No |
| 4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? | Yes | Yes |
| 5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? | Yes | Yes |
| 6. Were the cases clearly defined and differentiated from controls? | Yes | Yes |
| 7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? | Yes | Yes |
| 8. Was there use of concurrent controls? | No | No |
| 9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? | No | Yes |
| 10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? | Yes | Yes |
| 11. Were the assessors of exposure/risk blinded to the case or control status of participants? | No | No |
| 12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? | No | Yes |
Table 3. Comparison of pregnant and non-pregnant women with COVID-19: summary estimates.

| Outcomes                              | Relative Risk/Mean Difference (95% CI) | No of Studies; No of Participants | Heterogeneity |
|---------------------------------------|----------------------------------------|-----------------------------------|---------------|
|                                       |                                        |                                   |               |
| **Demographics**                      |                                        |                                   |               |
| Mean age (years)                      | −2.87 (−4.61 to −1.12)                 | 6; 181,520                        | <0.00001; 92% |
| Advance maternal age (years)          | 0.55 (0.53 to 0.56)                    | 1; 409,462                        | N/A           |
| Mean BMI                              | −1.70 (−3.82 to 0.42)                  | 1; 132                            | N/A           |
| Obesity                               | 0.68 (0.63 to 0.73)                    | 2; 590,550                        | <0.00001; 99% |
| Smoking                               | 0.32 (0.26 to 0.39)                    | 2; 181,220                        | 0.80; 0%      |
| Hispanic/Latino                       | 1.34 (1.31 to 1.37)                    | 1; 409,462                        | N/A           |
| Asian                                 | 1.07 (0.99 to 1.17)                    | 1; 409,462                        | N/A           |
| Black                                 | 1.03 (1.00 to 1.06)                    | 1; 409,462                        | N/A           |
| White                                 | 0.73 (0.71 to 0.75)                    | 1; 409,462                        | N/A           |
| Other (mix)                           | 0.93 (0.87 to 1.00)                    | 1; 409,462                        | N/A           |
| **Clinical presentation**             |                                        |                                   |               |
| Asymptomatic                          | 3.94 (1.69 to 9.20)                    | 3; 218                            | 0.47; 0%      |
| Fever                                 | 0.74 (0.64 to 0.85)                    | 7; 409,838                        | 0.24; 24%     |
| Cough                                 | 0.85 (0.70 to 1.04)                    | 6; 409,802                        | 0.13; 42%     |
| Respiratory symptoms                  | 0.68 (0.38 to 1.21)                    | 1; 36                             | N/A           |
| Rhinorrhea                            | 1.43 (0.29 to 7.08)                    | 2; 409,573                        | 0.2; 39%      |
| Expectoration                         | 0.45 (0.21 to 0.97)                    | 2; 107                            | 0.30; 7%      |
| Chills                                | 0.22 (0.01 to 4.92)                    | 2; 409,505                        | 0.02; 81%     |
| Headache                              | 0.77 (0.74 to 0.79)                    | 4; 409,680                        | 0.96; 0%      |
| Fatigue                               | 0.64 (0.39 to 1.05)                    | 7; 409,747                        | 0.04; 54%     |
| Myalgia                               | 0.92 (0.89 to 0.95)                    | 4; 409,680                        | 0.71; 0%      |
| Chest tightness                       | 0.86 (0.77 to 0.95)                    | 3; 409,569                        | 0.59; 0%      |
| Wheezing                              | 0.76 (0.65 to 0.88)                    | 1; 409,462                        | N/A           |
| Diarrhea                              | 0.40 (0.39 to 0.43)                    | 3; 409,569                        | 0.91; 0%      |
| Nausea or vomiting                    | 0.84 (0.29 to 2.39)                    | 2; 409,526                        | 0.13; 55%     |
| Gastrointestinal                      | 0.63 (0.14 to 2.77)                    | 2; 147                            | 0.13; 56%     |
| Rash                                  | 4.43 (0.22 to 88.74)                   | 1; 64                             | N/A           |
| Dizziness                             | 1.19 (0.10 to 14.20)                   | 2; 154                            | 0.25; 25%     |
| Anosmia/ageusia                       | 0.85 (0.82 to 0.89)                    | 1; 409,462                        | N/A           |
| Sore throat                           | 0.64 (0.13 to 3.15)                    | 2; 409,573                        | 0.09; 66%     |
| Shortness of breath                   | 0.87 (0.65 to 1.18)                    | 6; 409,802                        | 0.32; 15%     |
| Nasal congestion                      | 0.51 (0.02 to 10.26)                   | 1; 111                            | N/A           |
| Abdominal pain                        | 1.62 (0.43 to 6.11)                    | 3; 409,608                        | 0.09; 59%     |
| Loss of appetite                      | 4.55 (0.23 to 89.08)                   | 1; 40                             | N/A           |
| Other symptoms                        | 0.65 (0.16 to 2.64)                    | 1; 36                             | N/A           |
Table 3. Cont.

| Outcomes             | Relative Risk/Mean Difference (95% CI) | No of Studies; No of Participants | Heterogeneity |
|----------------------|----------------------------------------|-----------------------------------|---------------|
|                      |                                        |                                   | Co-morbidities|
|                      |                                        |                                   |               |
| Co-morbidities       |                                        |                                   |               |
| Chronic cardiac disease | 0.58 (0.44 to 0.77)                     | 5; 590,807                       | 0.02; 66%     |
| Diabetes mellitus    | 1.02 (0.63 to 1.65)                     | 5; 590,807                       | <0.00001; 90% |
| Chronic respiratory disease | 0.74 (0.53 to 1.01)               | 4; 590,793                       | 0.003; 79%    |
| Renal disease        | 0.45 (0.29 to 0.71)                     | 2; 409,573                       | 0.21; 37%     |
| Hypothyroidism       | 1.93 (0.13 to 29.69)                   | 1; 82                             | N/A           |
| Malignancy           | 0.82 (0.68 to 0.98)                    | 2; 409,573                       | 0.98; 0%      |
| Mental sickness      | 7.59 (0.32 to 181.57)                  | 1; 111                            | N/A           |
| Chronic hepatitis B  | 1.93 (0.29 to 12.97)                   | 1; 82                             | N/A           |
| Management           |                                        |                                   |               |
| Oxygen therapy       | 0.84 (0.31 to 2.23)                    | 4; 350                            | 0.001; 81%    |
| Antivirals           | 0.87 (0.70 to 1.09)                    | 5; 432                            | 0.009; 70%    |
| Antibiotics          | 1.08 (0.95 to 1.22)                    | 5; 432                            | 0.17; 38%     |
| Corticosteroids      | 1.61 (1.02 to 2.55)                    | 5; 432                            | 0.16; 39%     |
| Immunoglobulin       | 0.46 (0.26 to 0.81)                    | 3; 236                            | 0.71; 0%      |
| Chinese medicine     | 0.88 (0.52 to 1.49)                    | 1; 64                             | N/A           |
| Complications        |                                        |                                   |               |
| Severe COVID-19      | 1.60 (0.41 to 6.28)                    | 2; 125                            | 0.37; 0%      |
| Maternal ICU admission | 2.26 (1.68 to 3.05)                | 5; 424,587                       | 0.02; 65%    |
| Invasive ventilation | 2.68 (2.07 to 3.47)                    | 3; 409,616                       | N/A           |
| Any ventilation      | 1.26 (0.50 to 3.15)                    | 3; 15,082                         | 0.03; 72%    |
| Maternal death       | 1.08 (0.89 to 1.31)                    | 2; 590,550                       | 0.31; 4%      |

The most common method of confirming COVID-19 infection was via reverse transcriptase-polymerase chain reaction test (RT-PCR) of a swab sample from either the nasopharynx or the oropharynx. Five studies confirmed COVID-19 infection only through RT-PCR alone [18,21–24]. Two studies used both RT-PCR and serological markers (IgM and IgG antibodies) to confirm COVID-19 infection [16,20]. One study with a sample size of 64 reported testing via nucleic amplification and confirmed the testing with a chest computed tomography (CT) scan [17], whereas one study vaguely mentioned using molecular amplification detection test on clinical specimens of 409,462 individuals but did not specify details [19].

3.2. Findings

Our meta-analysis found that pregnant women with COVID-19 were 2.8 years younger compared to non-pregnant counterparts with COVID-19 (Table 3). Non-pregnant women were more commonly reported to be obese (RR 0.68; 95% CI 0.63 to 0.73) and have a smoking history (RR 0.32; 95% CI 0.26 to 0.39) compared to pregnant women with COVID-19 infection. Chronic cardiac disease (RR 0.58; 95% CI 0.44 to 0.77), renal disease (RR 0.45; 95% CI 0.29 to 0.71), and malignancy (RR 0.82; 95% CI 0.68 to 0.98) were more commonly present in COVID-19-infected non-pregnant women compared to pregnant women with COVID-19 infection. There was no difference in other reported co-morbidities including diabetes mellitus, chronic respiratory disease, hypothyroidism, mental sickness, and chronic hepatitis (Figure 2).
Overall, the most common symptoms were headache (four studies, 24.5%), cough (six studies, 23.1%), myalgia (four studies, 17.7%), and fever (seven studies, 17.5%). Pregnant women were at a lower risk of experiencing fever (RR 0.74; 95% CI 0.64 to 0.85; seven studies, 409,838 participants), myalgia (RR 0.92; 95% CI 0.89 to 0.95; four studies, 409,680 participants), diarrhea (RR 0.40, 95% CI 0.39 to 0.43; three studies, 409,569 participants), chest tightness (RR 0.86; 95% CI 0.77 to 0.95; three studies, 409,680 participants), and expectoration (RR 0.45; 95% CI 0.21 to 0.97; two studies, 107 participants) as compared to non-pregnant women. The risk of being asymptomatic (RR 3.94; 95% CI 1.69 to 9.20; three studies, 218 participants) was higher amongst pregnant women as compared to non-pregnant women. The risk of other symptoms such as cough, rhinorrhea, chills, fatigue, nausea and vomiting, rash, abdominal pain, dizziness, sore throat, shortness of breath, nasal congestion, and loss of appetite were similar across both groups (Figure 3).
The risk of ICU admission was found to be significantly higher amongst pregnant women (RR 2.26; 95% CI 1.68 to 3.05; five studies, 424,587 participants) and they were also more likely to receive invasive mechanical ventilation (RR 2.68; 95% CI 2.07 to 3.47; three studies, 409,616). However, no difference in risk was found in the severity of COVID-19 infection amongst pregnant and non-pregnant women. Severe COVID-19 was reported by two articles, one of which by Qiancheng et al. who defined it as “shortness of breath with a respiratory rate greater than 30 breaths/minute, or oxygen saturation less than 93% at rest, or alveolar oxygen partial pressure/faction of inspiration \( \text{O}_2 \) (\( \text{PaO}_2/\text{FiO}_2 \)) less than 300 mmHg” [16] (R Wang et al. failed to define the “severe” COVID-19 infection). The risk of maternal mortality (RR 1.08; 95% CI 0.89 to 1.31) was found to be equal amongst pregnant and non-pregnant women [18] (Figure 4).

![Figure 4. Management among pregnant and non-pregnant women with COVID-19.](image)

Both groups were at an equal risk to be managed with oxygen therapy, antivirals, antibiotics, and Chinese medicine. However, the use of immunoglobulins (RR 0.46; 95% CI 0.26 to 0.81) was found to be lesser amongst pregnant females, whereas for corticosteroids (RR 1.61; 95% CI 1.02 to 2.55), it was higher amongst pregnant women as compared to their non-pregnant counterparts as shown in Figure 4.

Sensitivity Analysis

The studies conducted by Zambrano (2020) and Martinez-Portilla (2021) were removed and a sensitivity analysis was performed [19,24]. This was because a large sample size (n= 409,462 and n = 181,088, respectively) came from these studies, conducted across 50 states in the US and Mexico alone.

After removing Zambrano et al. and Martinez-Portilla et al., the number of enrolled individuals in each study ranged from 36 to 132. All the participants were COVID-19 positive with 180 pregnant women and 328 non-pregnant women, a combined total of 508 participants.

The findings were similar and suggested that pregnant women were at a lower risk of experiencing fever (RR 0.66; 95% CI 0.53 to 0.83; six studies, 376 participants), shortness of breath (RR 0.57; 95% CI 0.33 to 0.96; five studies, 340 participants), expectoration (RR 0.45; 95% CI 0.21 to 0.97; two studies, 107 participants), and chills (RR 0.03; 95% CI 0.00 to 0.52; one study, 43 participants) compared to non-pregnant women. The chances of being asymptomatic (RR 3.94; 95% CI 1.69 to 9.20, 3 studies, 218 participants) was higher amongst COVID-19-infected pregnant women compared to COVID-19-infected non-pregnant women. The risk of requiring ICU admission or management with medications was equal for both groups. However, the use of immunoglobulins among non-pregnant women was still higher as compared to pregnant women, while the use of corticosteroids was higher among pregnant women (Table 4).
Table 4. Summary estimates based on sensitivity analysis (removed Ellington 2020).

| Outcomes                     | Relative Risk/Mean Difference (95% CI) | No. of Studies; No. of Participants | Heterogeneity Chi² p Value; I² |
|------------------------------|----------------------------------------|-------------------------------------|--------------------------------|
| **Demographics**             |                                        |                                     |                                |
| Mean age (years)             | −2.40 (−3.82 to −0.97)                 | 5; 432                              | 0.02; 67%                      |
| Mean BMI                     | −1.70 (−3.82 to 0.42)                  | 1; 132                              | N/A                            |
| Smoking                      | 0.25 (0.03 to 1.87)                    | 1; 132                              | N/A                            |
| **Clinical presentation**    |                                        |                                     |                                |
| Asymptomatic                 | 3.94 (1.69 to 9.20)                    | 3; 218                              | 0.47; 0%                       |
| Fever                        | 0.66 (0.53 to 0.83)                    | 6; 376                              | 0.32; 15%                      |
| Cough                        | 0.77 (0.59 to 1.01)                    | 5; 340                              | 0.25; 26%                      |
| Respiratory symptoms         | 0.68 (0.38 to 1.21)                    | 1; 36                               | N/A                            |
| Rhinorrhea                   | 7.59 (0.32 to 181.57)                  | 1; 111                              | N/A                            |
| Expectoration                | 0.45 (0.21 to 0.97)                    | 2; 107                              | 0.30; 7%                       |
| Chills                       | 0.03 (0.00 to 0.52)                    | 1; 43                               | N/A                            |
| Headache                     | 0.60 (0.24 to 1.54)                    | 3; 218                              | 0.98; 0%                       |
| Fatigue                      | 0.55 (0.25 to 1.24)                    | 6; 376                              | 0.03; 58%                      |
| Myalgia                      | 0.52 (0.18 to 1.55)                    | 3; 218                              | 0.85; 0%                       |
| Chest tightness              | 0.60 (0.22 to 1.68)                    | 2; 107                              | 0.44; 0%                       |
| Diarrhea                     | 0.49 (0.13 to 1.88)                    | 2; 107                              | 0.76; 0%                       |
| Nausea or vomiting           | 0.35 (0.07 to 1.69)                    | 1; 64                               | N/A                            |
| Gastrointestinal             | 0.63 (0.14 to 2.77)                    | 2; 147                              | 2.25; 56%                      |
| Rash                         | 4.43 (0.22 to 88.74)                   | 1; 64                               | N/A                            |
| Dizziness                    | 1.19 (0.10 to 14.20)                   | 2; 154                              | 0.25; 25%                      |
| Sore throat                  | 0.20 (0.03 to 1.45)                    | 1; 111                              | N/A                            |
| Shortness of breath          | 0.57 (0.33 to 0.96)                    | 5; 340                              | 0.89; 0%                       |
| Nasal congestion             | 0.51 (0.02 to 10.26)                   | 1; 111                              | N/A                            |
| Abdominal pain               | 4.20 (0.26 to 68.93)                   | 2; 146                              | 0.09; 65%                      |
| Loss of appetite             | 4.55 (0.23 to 89.08)                   | 1; 40                               | N/A                            |
| Other symptoms               | 0.65 (0.16 to 2.64)                    | 1; 36                               | N/A                            |
| **Co-morbidities**           |                                        |                                     |                                |
| Chronic cardiac disease      | 1.53 (0.32 to 7.21)                    | 3; 257                              | 0.50; 0%                       |
| Diabetes mellitus            | 2.45 (0.62 to 9.61)                    | 3; 257                              | 0.30; 18%                      |
| Chronic respiratory disease  | 0.50 (0.19 to 1.29)                    | 2; 243                              | N/A                            |
| Renal disease                | 2.58 (0.17 to 39.99)                   | 1; 111                              | N/A                            |
| Hypothyroidism               | 1.93 (0.13 to 29.69)                   | 1; 82                               | N/A                            |
| Malignancy                   | 0.84 (0.04 to 20.17)                   | 1; 111                              | N/A                            |
| Mental sickness              | 7.59 (0.32 to 181.57)                  | 1; 111                              | N/A                            |
| Chronic hepatitis B          | 1.93 (0.29 to 12.97)                   | 1; 82                               | N/A                            |
Table 4. Cont.

| Outcomes          | Relative Risk/ Mean Difference (95% CI) | No. of Studies; No. of Participants | Heterogeneity |
|-------------------|----------------------------------------|-------------------------------------|---------------|
| Management        |                                        |                                     |               |
| Oxygen therapy    | 0.84 (0.31 to 2.23)                    | 4; 350                              | 0.001; 81%    |
| Antivirals        | 0.87 (0.70 to 1.09)                    | 5; 432                              | 0.009; 70%    |
| Antibiotics       | 1.08 (0.95 to 1.22)                    | 5; 432                              | 0.17; 38%     |
| Corticosteroids   | 1.61 (1.02 to 2.55)                    | 5; 432                              | 0.16; 39%     |
| Immunoglobulin    | 0.46 (0.26 to 0.81)                    | 3; 236                              | 0.71; 0%      |
| Chinese medicine  | 0.88 (0.52 to 1.49)                    | 1; 64                               | N/A           |
| Complications     |                                        |                                     |               |
| Severe COVID-19   | 1.60 (0.41 to 6.28)                    | 2; 125                              | 0.37; 0%      |
| Maternal ICU admission | 1.83 (0.30 to 11.38)               | 3; 215                              | 0.84; 0%      |
| Any ventilation   | 2.28 (1.07 to 4.88)                    | 2; 172                              | 0.48; 0%      |

4. Discussion

Human coronaviruses are among the most common pathogens causing viral respiratory infections. In the past two decades, the world has experienced three coronaviruses outbreaks, and the most recent strain, SARS-CoV-2, has led to the greatest public health crisis of the century. Amid this pandemic, the increasing mortality rate has called for a better understanding and protection of the vulnerable populations infected with the disease.

This systematic review summarizes the findings of 591,058 women with laboratory-confirmed COVID-19 infection, with 28,797 of them being pregnant. In the present meta-analysis; we found that in comparison with pregnant women, non-pregnant women are at a higher risk of experiencing symptoms such as headache, fever, expectoration, myalgia, chest tightness, wheezing, diarrhea, and anosmia, as primary symptoms of COVID-19. Non-pregnant women of reproductive age with COVID-19 had a higher frequency of comorbidities such as chronic cardiac diseases, renal diseases, and malignancy compared to pregnant COVID-19-infected women. The treatment modalities used in pregnant women were similar to the ones used in non-pregnant women, with a greater preference for corticosteroids in pregnant women. Pregnant women were more likely to be admitted to ICU and receive mechanical ventilation though there was no difference in the severity of the disease between both groups.

Pregnant women, due to their immunocompromised state, are more likely to experience complications of infectious diseases such as influenza, SARS, and MERS [17,18]. During the influenza A subtype H1N1 pandemic in 2009, pregnant women accounted for 5% of all H1N1-related deaths and were at an increased risk for severe disease, including hospitalization, ICU admissions, and death compared to their non-pregnant counterparts [11,25]. Similar trends were observed during the SARS and MERS outbreaks [9,26]. Lam, Chui Miu et al. [27] reported that 40% of the pregnant women affected with SARS required mechanical ventilation and had a case fatality of 30%, compared to 13% and 11% in non-pregnant individuals. Our review revealed a higher risk of ICU admissions in pregnant women; however, it did not show worsening clinical symptoms in pregnant women compared to non-pregnant women infected with COVID-19. Through the review, we found non-pregnant women to be at a higher risk of experiencing symptoms like headache, myalgia, fever, expectoration, chest tightness, wheezing, diarrhea, and anosmia compared to their pregnant counterparts. Many other studies and systematic reviews, however, reported clinical characteristics to be similar amongst COVID-19 infected pregnant and non-pregnant women [28–32]. Furthermore, in our review, both groups received similar supportive treatments irrespective of their pregnancy status. In concert with other
studies [29,33–35], most patients received oxygen therapy in addition to antiviral and antibiotic medications. Our study demonstrated a greater likelihood of corticosteroid use in pregnant women. However, despite being the most commonly reported medication in another review too [36], the use of corticosteroids for COVID-19 has generally not been recommended in pregnant women, due to the increased risk of preterm birth, low birth weight, and pre-eclampsia associated with its use in pregnancy [37,38].

Some of the limitations identified for this review are (1) a small number of studies included, (2) smaller sample size for most studies with a smaller number of pregnant women compared to non-pregnant women, (3) two isolated studies with a large sample size having a greater impact on the overall result, (4) lack of data on other significant variables such as socioeconomic status and ethnicity, (5) studies from limited developed countries, and (6) unadjusted analysis in most studies. We also identified that apart from two studies, all the other studies had small sample sizes of less than 150. There is a need for studies with a bigger sample size and a comparable number of pregnant and non-pregnant COVID-19-infected women with adjusted analysis to reach more conclusive results for the future updates of this review. Moreover, there is a need to compare data on other variables, especially demographic variables such as socioeconomic status and ethnicity. The current manuscript reports data on ethnicity from a single study and therefore, is biased towards the data from the largest sample-sized study, leading to a lack of generalizability. Future studies in the domain should also highlight whether the ICU admission or worsening state in pregnant women was more likely to be due to COVID-19 infection or a delivery complication. Multivariable analysis to identify factors associated with clinical presentation, management, and prognosis in pregnant and non-pregnant women could not be done due to insufficient data. However, if data on individual patients are provided in the future, then individual patient data meta-analysis (IPD-MA) would be the ideal approach to providing insights into recognizing and managing COVID-19 infection in pregnant women. More studies on populations across the world need to be published to prevent the chance of bias towards a particular set of people. A future update of this systematic review may then be warranted and can, therefore, help reach conclusive findings.

5. Conclusions

In conclusion, the findings of this study summarize the epidemiological and clinical characteristics, along with the management and prognosis of women of reproductive age with COVID-19 based on their pregnancy status. With the disease burden increasing every day, these data equip healthcare workers to better identify and monitor the patients who are more susceptible to the disease and to make informed decisions when treating the patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/ijerph18115613/s1, Table S1: PRISMA checklist, Table S2: Search strategy, Table S3: Overlapping studies.

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References

1. Lu, H.; Stratton, C.W.; Tang, Y.W. Outbreak of Pneumonia of Unknown Etiology in Wuhan, China: The Mystery and the Miracle. J. Med. Virol. 2020, 92, 401–402. [CrossRef] [PubMed]

2. WHO. Media Briefing on COVID-19—11 March 2020. Available online: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed on 23 October 2020).

3. WHO. WHO COVID-19 Dashboard. Available online: https://covid19.who.int/ (accessed on 23 October 2020).

4. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. Lancet 2020, 395, 497–506. [CrossRef]

5. Liao, J.; Fan, S.; Chen, J.; Wu, J.; Xu, S.; Guo, Y.; Li, C.; Zhang, X.; Wu, C.; Mou, H.; et al. Epidemiological and Clinical Characteristics of COVID-19 in Adolescents and Young Adults. Innovation 2020, 1, 100001. [CrossRef] [PubMed]

6. Chen, J.; Bai, H.; Liu, J.; Chen, G.; Liao, Q.; Yang, J.; Wu, P.; Wei, J.; Ma, D.; Chen, G.; et al. Distinct Clinical Characteristics and Risk Factors for Mortality in Female COVID-19 Inpatients: A Sex-Stratified Large-Scale Cohort Study in Wuhan, China. Clin. Infect. Dis. 2020, 71, 3188–3195. [CrossRef]

7. Liu, K.; Chen, Y.; Lin, R.; Han, K. Clinical Features of COVID-19 in Elderly Patients: A Comparison with Young and Middle-Aged Patients. J. Infect. 2020, 80, e14–e18. [CrossRef]

8. Assiri, A.; Abedi, G.R.; Al Masri, M.; Bin Saeed, A.; Gerber, S.L.; Watson, J.T. Middle East Respiratory Syndrome Coronavirus Infection during Pregnancy: A Report of 5 Cases from Saudi Arabia. Clin. Infect. Dis. 2016, 63, 951–953. [CrossRef]

9. Wong, S.F.; Chow, K.M.; Leung, T.N.; Ng, W.F.; Ng, T.K.; Shek, C.C.; Ng, P.C.; Lam, P.W.Y.; Ho, L.C.; To, W.W.K.; et al. Pregnancy and Perinatal Outcomes of Women with Severe Acute Respiratory Syndrome. Am. J. Obstet. Gynecol. 2004, 191, 292–297. [CrossRef]

10. Di Mascio, D.; Khalil, A.; Saccone, G.; Rizzo, G.; Buca, D.; Liberati, M.; Vecchiet, J.; Nappi, L.; Scambia, G.; Berghella, V.; et al. Outcome of Coronavirus Spectrum Infections (SARS, MERS, COVID-19) during Pregnancy: A Systematic Review and Meta-Analysis. Am. J. Obstet. Gynecol. MFM 2020, 2, 100107. [CrossRef]

11. Schwartz, D.A.; Graham, A.L. Potential Maternal and Infant Outcomes from Coronavirus 2019-NCOV (SARS-CoV-2) Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. Viruses 2020, 12, 194. [CrossRef]

12. Wu, Z.; McGoogan, J.M. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA 2020, 323, 1239–1242. [CrossRef]

13. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Altman, D.; Antes, G.; Atkins, D.; Barbour, V.; Barrowman, N.; Berlin, J.A.; et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009, 6, e1000097. [CrossRef] [PubMed]

14. Department of Health and Human Services. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies; National Institutes of Health, Department of Health and Human Services: Bethesda, MD, USA, 2014.

15. The Cochrane Collaboration. Review Manager (RevMan) [Computer Program]. Version 5.4. 2020. Available online: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-non-cochrane-reviews (accessed on 13 February 2021).

16. Qiancheng, X.; Jian, S.; Lingling, P.; Lei, H.; Xiaogan, J.; Weihua, L.; Gang, Y.; Shirong, L.; Zhen, W.; GuoPing, X.; et al. Coronavirus Disease 2019 in Pregnancy. Int. J. Infect. Dis. 2020, 95, 376–383. [CrossRef]

17. Xu, S.; Shao, F.; Bao, B.; Ma, X.; Xu, Z.; You, J.; Zhao, P.; Liu, Y.; Ng, M.; Cui, H.; et al. Clinical Manifestation and Neonatal Outcomes of Pregnant Women with Coronavirus Disease 2019 Pneumonia in Wuhan, China. Open Forum Infect. Dis. 2020, 7, ofaa283. [CrossRef]

18. Wang, S.; Wei, L.; Gao, X.; Chen, S.; Zeng, W.; Wu, J.; Lin, X.; Zhang, H.; Sharifu, L.M.; Chen, L.; et al. Clinical Characteristics and Outcomes of Childbearingage Women with Coronavirus Disease 2019 in Wuhan: A Retrospective, Single-Center Study. JMIR Med. Hum. 2020, 22, e19642. [CrossRef]

19. Zambrano, L.D.; Ellington, S.; Strid, P.; Galang, R.R.; Oduyebo, T.; Tong, V.T.; Woodworth, K.R.; Nahabedian, J.F.; Azziz-Baumgartner, E.; Gilboa, S.M.; et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status—United States, January 22–October 3, 2020. MMWR Morb. Mortal. Wkly. Rep. 2020, 69, 1641–1642. [CrossRef]

20. Cheng, B.; Jiang, T.; Zhang, L.; Hu, R.; Tian, J.; Jiang, Y.; Huang, B.; Li, J.; Wei, M.; Yang, J.; et al. Clinical Characteristics of Pregnant Women with Coronavirus Disease 2019 in Wuhan, China. SSRN Electron. J. 2020, 7. [CrossRef]

21. Mohr-Sasson, A.; Chayo, J.; Bart, Y.; Meyer, R.; Sivan, E.; Mazaki-Tovi, S.; Yinon, Y. Laboratory Characteristics of Pregnant Compared to Non-Pregnant Women Infected with SARS-CoV-2. Arch. Gynecol. Obstet. 2020, 302, 629–634. [CrossRef] [PubMed]

22. Liu, F.; Liu, H.; Li, J.; Hou, L.; Lan, W.; Wang, D. Clinico-Radiological Features and Outcomes in Pregnant Women with COVID-19: Compared with Age-Matched Non-Pregnant Women. SSRN Electron. J. 2020, 13, 2845–2854. [CrossRef]

23. DeBolt, C.A.; Bianco, A.; Limaye, M.A.; Silverstein; J.; Penfield, C.A.; Roman, A.S.; Rosenberg, H.M.; Ferrara, L.; Lambert, C.; Khoury, R.; et al. Pregnant Women with Severe or Critical Coronavirus Disease 2019 Have Increased Composite Morbidity Compared with Nonpregnant Matched Controls. Am. J. Obstet. Gynecol. 2020, 224, 510.e1–510.e12. [CrossRef]
24. Martinez-Portilla, R.J.; Sotiriadis, A.; Chatzakis, C.; Torres-Torres, J.; Espino y Sosa, S.; Sandoval-Manudujano, K.; Castro-Bernabe, D.A.; Medina-Jimenez, V.; Monzarrez-Martín, J.C.; Figueras, E.; et al. Pregnant Women with SARS-CoV-2 Infection Are at Higher Risk of Death and Pneumonia: Propensity Score Matched Analysis of a Nationwide Prospective Cohort. *Ultrasound Obstet. Gynecol.* 2021, 57, 224–231. [CrossRef]

25. Kourtis, A.P.; Read, J.S.; Jamieson, D.J. Pregnancy and Infection. *N. Engl. J. Med.* 2014, 370, 2211–2218. [CrossRef] [PubMed]

26. Zaigham, M.; Andersson, O. Maternal and Perinatal Outcomes with COVID-19: A Systematic Review of 108 Pregnancies. *Acta Obstet. Gynecol. Scand.* 2020, 99, 823–829. [CrossRef]

27. Chui, M.L.; Shell, F.W.; Tse, N.L.; Kam, M.C.; Wai, C.Y.; Tin, Y.W.; Sik, T.L.; Lau, C.H. A Case-Controlled Study Comparing Clinical Course and Outcomes of Pregnant and Non-Pregnant Women with Severe Acute Respiratory Syndrome. *BJOG Int. J. Obstet. Gynaecol.* 2004, 111, 771–774. [CrossRef]

28. Chen, H.; Guo, J.; Wang, C.; Luo, F.; Yu, X.; Zhang, W.; Li, J.; Zhao, D.; Xu, D.; Gong, Q.; et al. Clinical Characteristics and Intrauterine Vertical Transmission Potential of COVID-19 Infection in Nine Pregnant Women: A Retrospective Review of Medical Records. *Lancet* 2020, 395, 809–815. [CrossRef]

29. Matar, R.; Alrahmani, L.; Monzer, N.; Debiane, L.G.; Berbari, E.; Fares, J.; Fitzpatrick, F.; Murad, M.H. Clinical Presentation and Outcomes of Pregnant Women With Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. *Clin. Infect. Dis.* 2020, 72, 521–533. [CrossRef]

30. Yang, H.; Wang, C.; Poon, L.C. Novel Coronavirus Infection and Pregnancy. *Ultrasound Obstet. Gynecol.* 2020, 55, 435–437. [PubMed]

31. Yang, Z.; Wang, M.; Zhu, Z.; Liu, Y. Coronavirus Disease 2019 (COVID-19) and Pregnancy: A Systematic Review. *J. Matern. Neonatal Med.* 2020, 1–4. [CrossRef]

32. Trocado, V.; Silvestre-Machado, J.; Azevedo, L.; Miranda, A.; Nogueira-Silva, C. Pregnancy and COVID-19: A Systematic Review of Maternal, Obstetric and Neonatal Outcomes. *J. Matern. Neonatal Med.* 2020, 1–13. [CrossRef]

33. Rothan, H.A.; Byrareddy, S.N. The Epidemiology and Pathogenesis of Coronavirus Disease (COVID-19) Outbreak. *J. Autoimmun.* 2020, 109, 102433. [CrossRef]

34. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Li, Z.; Xiao, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet* 2020, 395, 1054–1062. [CrossRef]

35. Yu, N.; Li, W.; Kang, Q.; Xiong, Z.; Wang, S.; Lin, X.; Liu, Y.; Xiao, J.; Liu, H.; Deng, D.; et al. Clinical Features and Obstetric and Neonatal Outcomes of Pregnant Patients with COVID-19 in Wuhan, China: A Retrospective, Single-Centre, Descriptive Study. *Lancet Infect. Dis.* 2020, 20, 559–564. [CrossRef]

36. Tobaiqy, M.; Qashqary, M.; Al-Dahery, S.; Mujallad, A.; Hershman, A.A.; Kamal, M.A.; Helmi, N. Therapeutic Management of Patients with COVID-19: A Systematic Review. *Infect. Prev. Pract.* 2020, 2, 100061. [CrossRef]

37. Russell, C.D.; Millar, J.E.; Bailie, J.K. Clinical Evidence Does Not Support Corticosteroid Treatment for 2019-NCoV Lung Injury. *Lancet* 2020, 395, 473–475. [CrossRef]

38. Luo, Y.; Yin, K. Management of Pregnant Women Infected with COVID-19. *Lancet Infect. Dis.* 2020, 20, 513–514. [CrossRef]