Review

Association of Pregnancy With Coronavirus Cytokine Storm: Systematic Review and Meta-analysis

John Muthuka[1], BSc, MPH, PgD, PhD; Michael Kiptoo[2], BSc, MSc, PhD; Kelly Oluoch[1], BPharm, MSc, MBA, PhD; Japheth Mativo Nzioki[3], BSc, MPH, PhD; Everlyn Musangi Nyamai[4], BScN, MSN

[1]Head Quaters, Kenya Medical Training College, Nairobi, Kenya

[2]Department of Health Sciences, South Eastern University of Kenya, Kitui, Kenya

[3]College of Health Sciences, Jumeira University, Dubai, United Arab Emirates

[4]Department of Nursing, Faculty of Clinical Sciences, Kenya Medical Training College, Nairobi, Kenya

Corresponding Author:
John Muthuka, BSc, MPH, PgD, PhD
Head Quaters
Kenya Medical Training College
PO Box 30195-00100
Nairobi
Kenya
Phone: 254 724274843
Email: johnmuthuka@gmail.com

Abstract

Background: COVID-19 was first identified in Wuhan, China, in December 2019, spreading to the rest of the globe, becoming a pandemic. Some studies have shown an association between pregnancy status and severe COVID-19 with a cytokine storm, whereas others have shown contrasting results.

Objective: The aim of this study was to examine the relationship between pregnancy status and the clinical COVID-19 severity characterized by the cytokine storm through a systematic review and meta-analysis.

Methods: We searched the Google Scholar, PubMed, Scopus, Web of Science, and Embase databases to identify clinical studies suitable for inclusion in this meta-analysis. Studies reporting pregnancy status and comparing the COVID-19 severity cytokine storm outcome were included. COVID-19 severity characterized by a cytokine storm was described using parameters such as intensive care unit admission, invasive mechanical ventilation, mechanical ventilation, hospital admission, pro- and anti-inflammatory cytokine levels, consolidation on chest computed tomography scan, pulmonary infiltration, extreme fevers as characteristic of a cytokine storm, syndromic severity, higher neutrophil count indicative of a cytokine storm, and severe COVID-19 presentation.

Results: A total of 17 articles including data for 840,332 women with COVID-19 were included. This meta-analysis revealed a correlation between positive pregnancy status and severe COVID-19 with a cytokine storm (random-effects model odds ratio [OR] 2.47, 95% CI 1.63-3.73; P<.001), with a cumulative incidence of 6432 (14.1%) and 24,352 (3.1%) among pregnant and nonpregnant women with COVID-19, respectively. The fixed-effects model also showed a correlation between pregnancy status and severe COVID-19 with a cytokine storm (OR 7.41, 95% CI 7.02-7.83; P<.001). Considerable heterogeneity was found among all pooled studies (I^2=98%, P<.001). Furthermore, the updated analysis showed substantially low heterogeneity (I^2=29 %, P=.19), and the funnel plot revealed no publication bias. The subanalysis between single-center and multicenter studies demonstrated similar heterogeneity (I^2=72% and 98%, respectively). Sensitivity analysis on each subgroup revealed that pregnancy was significantly related to severe COVID-19 with a cytokine storm from single-center studies (fixed-effects model OR 3.97, 95% CI 2.26-6.95; P<.001) with very low heterogeneity (I^2=2%, P=.42).

Conclusions: Being pregnant is clearly associated with experiencing a severe course of COVID-19 characterized by a cytokine storm. The COVID-19 pandemic should serve as an impetus for further research on pregnant women diagnosed with COVID-19 to map out the salient risk factors associated with its severity.

Trial Registration: PROSPERO CRD42021242011; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=242011.

(JMIR Pediatr Parent 2022;5(4):e31579) doi: 10.2196/31579

KEYWORDS

COVID-19; pandemic; pregnancy; maternal health; cytokine; cytokine storm; immune response; infectious disease; coronavirus; respiratory; virus; pregnant

Introduction

Once considered to be an "immunosuppressed" state, pregnancy is associated with an immunological transformation, where the immune system is required to promote and support the pregnancy and growing fetus. When this protection is breached, as in a viral infection, this security is weakened and infection with microorganisms can then propagate and lead to negative outcomes such as preterm labor [1].

Pregnancy is considered a high-risk condition for COVID-19. Pregnant women are more likely to have an asymptomatic infection, accounting for 75% of SARS-CoV-2 infections during the pandemic. Even among those with symptoms, cough and fever are the main symptoms in 40% of cases, with breathing difficulty and myalgia being present in 21% and 19% of pregnant women, respectively. Severe COVID-19 usually occurs with infection in the second half of pregnancy, especially toward the end of the second trimester onward. Those at greatest risk of severe COVID-19 include women who have a higher-than-ideal BMI, those over the age of 35 years, and those who have chronic underlying conditions [2].

COVID-19 is an infectious disease caused by a newly discovered coronavirus (SAR2-CoV-2) that was first identified in Wuhan, China, in December 2019 [3]. COVID-19 subsequently rapidly spread across the world, causing a global pandemic. Between March 2020 and March 2021, this highly contagious disease infected over 25 million people worldwide and killed over 1 million patients, yielding a case fatality rate that varies between 0.7% and 12.7% (average 3.4%) [4].

Most people infected with the SARS-CoV-2 will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people above the age of 58 years and those with underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illnesses [5]. Further, infected patients experiencing cytokine storms present with fevers and shortness of breath, resulting in extreme difficulty breathing that ultimately requires ventilation assistance. Such severe presentations might also be related to pregnancy status [6].

Pregnant women who have COVID-19 appear more likely to develop respiratory complications requiring intensive care than women who are not pregnant [7]. Pregnant women are also more likely to be placed on a ventilator. Some research suggests that pregnant women with COVID-19 are also more likely to have a premature birth and cesarean delivery, and their babies are more likely to be admitted to a neonatal unit [8].

Pregnant women are a potentially highly vulnerable population due to anatomical, physiological, and immunological changes under the COVID-19 pandemic. Issues related to pregnancy with COVID-19 attracted widespread attention from researchers. A large number of articles were published aiming to elaborate on the clinical characteristics and outcomes of pregnant women infected with COVID-19 to provide evidence for management [9,10]. The existing data suggest that the overall prognosis of pregnancy with COVID-19 is promising when compared with that of other previous coronaviruses. However, there are still reports of notable maternal morbidity and mortality related to COVID-19 [9].

There are many unknowns for pregnant women during the COVID-19 pandemic. Clinical experience of pregnancies complicated with infection by other coronaviruses such as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) indicated that pregnant woman should be considered to be particularly vulnerable to severe SARS-CoV-2 infection. Physiological changes during pregnancy have a significant impact on the immune system, respiratory system, cardiovascular function, and coagulation [11].

Given divergent findings in the existing literature, we systematically reviewed English-language studies to investigate whether pregnancy was associated with a more severe clinical course of COVID-19. Specifically, the aim of this study was to establish if pregnancy status is associated with COVID-19 severity characterized by a cytokine storm.

Methods

Design

All guidelines listed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement were followed in performing this meta-analysis [12]. For this systematic review and meta-analysis, data were pooled from observational studies, including cohort, case-control, cross-sectional, and similar viable case studies. The study is registered in PROSPERO (CRD42021242011).

Search Strategy

We performed a simple search in the Google Scholar, PubMed, Scopus, Web of Science, and Embase databases to identify observational studies suitable for inclusion with the following search terms: "COVID-19" OR "SARS-COV-2" OR "novel coronavirus (CoV)" AND "pregnant" OR "gestation" AND "clinical features" OR "characteristic" AND "severity" OR "severe." Studies were restricted to those published in English from March 2020 to March 2021.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) studies that examined women within reproductive age and diagnosed with COVID-19 according to World Health Organization (WHO) criteria; (2) observational, cross-sectional, prospective, or retrospective studies; (3) studies that compared pregnant women to nonpregnant women with severe COVID-19 characterized by a cytokine storm; (4) studies evaluating the clinical prognosis in pregnancy and the immunological profile at any gestation

stage, examining the proinflammatory response in COVID-19 and a severe cytokine storm as the hallmark outcome.

Exclusion criteria were as follows: (1) unrelated, duplicated, and missing information answering our research question; (2) non-English-language studies; (3) case reports/series; (4) reviews; (5) editorials; (6) studies lacking a full text (unavailable or not yet published); (7) articles without a DOI; and (8) studies with small sample sizes (<50 patients) because of low statistical power.

Notably, we included preliminary findings published as preprints given that the phenomenon in question remains very grey in the public domain and thus we presumed inclusion of such reports would be of value in converging relevant data and information.

Data Extraction

Both adjusted and nonadjusted data among pregnant versus nonpregnant cases were extracted to identify the most relevant confounding factors to be used in the analysis by subsequent pooling. One reviewer (JM) scanned study titles and abstracts obtained via an initial database search and included relevant articles in a secondary pool. Next, two independent reviewers (MK and KO) evaluated the full texts of these articles to determine whether they met the study inclusion criteria. Any disputes were resolved by discussion and negotiation with a fourth reviewer (EN). Only studies agreed upon by all reviewers were included in the final analysis.

The following data were obtained from all studies: title, first author, publication year, location, sample size, age (median), pregnancy status (pregnant or nonpregnant), and severe COVID-19 cytokine storm presentation. The analysis was then performed to determine whether the pregnant group was more likely to develop severe COVID-19 characterized by a cytokine storm.

Risk of Bias (Quality) Assessment

The National Institutes of Health tool for observational and cross-sectional studies [13] was used for methodological quality assessment. Two to three reviewers independently assessed the quality of the studies, and the scores were added to the data extraction form before inclusion in the analysis to reduce the risk of bias. To evaluate the risk of bias, the reviewers rated each of the 14 items into qualitative variables: yes, no, or not applicable. An overall score was calculated by adding the scores of all items with yes=1 and no or not applicable=0. A score was given for every paper, resulting in a classification of poor (score 0-5), fair (score 6-9), or good (score 10-14). Data were checked by reviewers who did not perform the data extraction or each reviewer was assigned an article that they had not extracted data from in previous steps; however, in rare instances, some reviewers extracted data and performed the quality assessment for the same article.

Statistical Analyses

Review Manager 5.4.1 was used to calculate odds ratios (ORs) with 95% CIs, which are depicted using forest plots. Quantitative variables are summarized in terms total numbers and percentages. The OR of a severe COVID-19 cytokine storm among pregnant and nonpregnant women was calculated. Heterogeneity was evaluated with the Cochran Q statistic and Higgins test. The Higgins test uses a fixed-effects model when the heterogeneity is <50% and a random-effects model when the heterogeneity is >50%. When heterogeneity was detected, a sensitivity adjustment was made to determine its source. This procedure was performed by leaving a study out of the analysis one at a time, with the fixed-effects model applied after excluding heterogeneity. Subgroup, cumulative analyses, and metaregression were used to test whether or not the results are consistent and to investigate the effect of confounders on the outcome (cytokine storm) and elucidate the best predictors in pregnancy status among women with COVID-19. Publication bias was evaluated using the Cochrane Risk of Bias tool.

Results

Included Articles and Quality Assessment

The initial search of international databases using the keywords described above yielded 221 articles. After excluding 70 duplicate articles, 151 articles remained. When article titles and abstracts were evaluated for appropriateness, 29 articles ultimately met the inclusion criteria. In addition, 12 articles not meeting the inclusion criteria were excluded after full-text review. A total of 17 articles met the inclusion criteria [7,14-29]. Multimedia Appendix 1 shows the PRISMA flow diagram of the study selection procedure.

Features of the Included Studies

The 17 included studies provided data for 840,417 women with COVID-19 [7,14-29] (Table 1). According to the Centers for Disease Control and Prevention reporting guidelines for COVID-19 diagnosis [30], 85 patients whose specific parameters related to the severity of COVID-19 defined according to cytokine storm status were reported as “unknown” or not tabulated were excluded from the final analysis, yielding a final group of 840,332 patients with 45,571 (5.42%) pregnant women and 794,761 (94.58%) nonpregnant women. Among the pregnant women, 14.1% (6432/45,571) had cytokine storm events reported, compared to only 3.1% (24,352/794,761) of the nonpregnant women. The cumulative incidence of a cytokine storm from all studies ranged from 0.4% to 90.7% (average 36.26%).

Table 1. Features of the studies included in the meta-analysis.

Reference	Location of patients	Study design	Parameter of comparison on COVID-19 severity with cytokine storm	Events in pregnant women/ total in cohort	Events in non-pregnant women/total in cohort	Cumulative incidence of severe COVID-19 defined by cytokine storm, n (%)
Badr et al [14]	France and Belgium	CC[a], MC[b]	ICU[c] versus no ICU admission	58/83	17/107	75 (39%)
Westgren and Acharya [15]	New York	R[d], O[e], MC	ICU versus no ICU admission	8/82	50/332	58 (14%)
CDC[f] [16]	United States	P[g], C[h], MC	ICU plus mechanical ventilation versus no ICU admission with mechanical ventilation	2583/8200	15,840/316,800	18,423 (5.7%)
Cheng et al [17]	Wuhan, China	R, SC[i]	Higher versus lower level of inflammation markers	0/31	1/80	1 (0.9%)
Collin et al [23]	Sweden	R, MC	Invasive mechanical ventilation versus no invasive mechanical ventilation	7/13	29/40	36 (68%)
Ellington et al [7]	United States	R, O MC	ICU with mechanical ventilation versus no ICU with mechanical ventilation	2587/8207	4840/83,205	7427 (8%)
Liu et al [24]	Wuhan, China	R, CC, SC	Consolidation on chest CT[j] versus no consolidation on chest CT	20/21	16/19	36 (90%)
Martinez-Portilla et al [25]	Mexico	R, MC	ICU/death versus non-ICU/death	752/5183	446/5183	1198 (12%)
Yin et al [26]	China	R, C, SC	Severe or critical COVID-19 characterized by higher levels of inflammatory indices of cytokine storm versus moderate COVID-19	19/31	11/35	30 (46%)
Mohr-Sasson et al [27]	Fuyang, China	R, C, SC	High versus low fevers	3/11	15/25	18 (50%)
Molteni et al [28]	United Kingdom, Sweden, and United States	P, O, MC	Syndromic severity versus nonsyndromic severity	87/140	1508/2515	1595 (60%)
Oakes et al [18]	Wuhan, China	R, C, SC	Hospital admission versus nonadmission	7/22	17/240	24 (9%)
Qiancheng et al [19]	Wuhan, China	R, SC	Nonsevere versus severe	2/28	1/54	3 (9.8%)
Wang et al [20]	Wuhan, China	R, SC	COVID-19 manifestations on chest CT versus no manifestations	22/30	42/42	64 (89%)
Wei et al [21]	Wuhan, China	R, SC	Higher versus lower neutrophil count as indicative of cytokine storm	15/17	24/26	39 (91%)
Xu et al [22]	Wuhan, China	R, SC	Pulmonary infiltration versus no pulmonary infiltration	17/34	3/30	20 (31%)
Zambrano et al [29]	United States	R, MC	Severe COVID-19–associated illness versus mild to moderate illness	245/23,434	1492/386,028	1737 (0.4%)

[a]CC: case-control.

[b]MC: multicenter.

[c]ICU: intensive care unit.

[d]R: retrospective.

[e]O: observational.

[f]CDC: Centers for Disease Control and Prevention.

[g]P: prospective.

[h]C: cross-sectional.

[i]SC: single-center.

[j]CT: computed tomography.

The main outcome of this meta-analysis was the possible association of pregnancy with severe COVID-19 characterized by a cytokine storm, which was indicated by a specific prognosis and event. The parameters used for assessment of COVID-19 severity were intensive care unit (ICU) admission in three studies; ICU plus mechanical ventilation in two studies; higher levels of inflammatory response markers in three studies; severe COVID-19 presentation in two studies; and consolidation on chest computed tomography scan, pulmonary infiltration, extreme fever as a characteristic of a cytokine storm, syndromic severity, hospital admission, invasive mechanical ventilation, and higher neutrophil count indicative of a cytokine storm in one study each. The study designs included retrospective (n=15, 6 multicenter and 9 single-center studies) and prospective (n=2, both multicenter). A summary of the studies included in the meta-analysis is provided in Table 1.

We assessed the quality of the included observational studies based on a modified version of the Newcastle-Ottawa Scale (NOS), which consists of 8 items with 3 subscales, and the total maximum score of these 3 subsets is 9. We considered a study that scored ≥7 to be a high-quality study since a standard criterion for what constitutes a high-quality study has not yet been universally established. The 17 studies assessed generated a mean value of 6.47, indicating that the overall quality was moderate (NOS score range 5-8), as detailed in Table 2.

Table 2. Newcastle-Ottawa scale for quality assessment and risk of bias.

Study	Year	Case selection (maximum 4)	Comparability (maximum 2)	Exposure/outcome (maximum 3)	Total score
Badr et al [14]	2020	3	2	2	7
Westgren and Acharya [15]	2020	3	2	1	6
CDC[a] [16]	2020	4	2	2	8
Cheng et al [17]	2020	3	1	2	6
Collin et al [23]	2020	4	1	2	7
Ellington et al [7]	2020	3	2	3	7
Liu et al [24]	2020	3	1	2	6
Martinez-Portilla et al [25]	2020	3	1	2	6
Yin et al [26]	2020	3	2	2	7
Mohr-Sasson et al [27]	2020	3	1	1	5
Molteni et al [28]	2020	3	1	2	6
Oakes et al [18]	2020	3	2	2	7
Qiancheng et al [19]	2020	3	1	2	6
Wang et al [20]	2020	2	2	2	6
Wei et al [21]	2020	3	1	3	7
Xu et al [22]	2020	3	2	2	6
Zambrano et al [29]	2020	3	1	3	7

[a]CDC: Centers for Disease Control and Prevention.

Pregnancy Status and COVID-19 Severity Characterized by a Cytokine Storm

The meta-analysis revealed a significant association between pregnancy status and severe COVID-19 characterized by a cytokine storm (Table 3). A sensitivity analysis was performed to explore the impact of excluding or including studies in the meta-analysis based on sample size, methodological quality, and variance. After removing eight studies (n=748,058 patients) [7,15,16,23,25,27,28,31] accounting for major causes of heterogeneity, a total of 92,274 patients were left for analysis in the remaining studies. Figure 1 and Figure 2 respectively show a shift from the random-effects model (OR 2.47, 95% CI 1.63-3.73; P<.001) to the fixed-effects model (OR 7.41, 95% CI 7.02-7.83; P<.001), revealing that pregnancy was significantly associated with severe COVID-19 characterized by a cytokine storm. Furthermore, this updated analysis showed substantially low heterogeneity (I^2=29%, P=.19). Figure 3 shows a funnel plot evaluating publication bias, which revealed considerable heterogeneity between all pooled studies (I^2=98%, P<.001). Figure 4 shows a funnel plot revealing no publication bias for the updated analysis.

Table 3. Events (cytokine storm) in pregnant and nonpregnant women.

Studies	Pregnant with COVID-19		Nonpregnant with COVID-19	
	Patients, N	Events, n (%)	Patients, N	Events, n (%)
Badr et al [14]	87	58 (66.7)	107	17 (15.9)
Westgren and Acharya [15]	82	8 (9.8)	332	50 (15.1)
CDC [16]	8200	2583 (31.5)	316,800	15,840 (5.0)
Cheng et al [17]	31	0 (0)	80	1 (1.3)
Collin et al [23]	13	7 (53.8)	40	29 (72.5)
Ellington et al [7]	8207	2587 (31.5)	83205	4840 (5.9)
Liu et al [24]	21	20 (95.3)	19	16 (84.2)
Martinez-Portilla et al [25]	5183	752 (14.5)	5183	446 (8.6)
Yin et al [26]	31	19 (61.3)	35	11 (31.4)
Mohr-Sasson et al [27]	11	3 (27.2)	25	15 (60.0)
Molteni et al [28]	140	87 (62.1)	2515	1508 (59.9)
Oakes et al [18]	22	7 (31.8)	240	17 (7.1)
Qiancheng et al [19]	28	2 (7.14)	54	1 (1.9)
Wang et al [20]	30	22 (73.3)	42	42 (100.0)
Wei et al [21]	17	15 (88.2)	26	24 (92.3)
Xu et al [22]	34	17 (50.0)	30	3 (10.0)
Zambrano et al [29]	23,434	245 (1.1)	386,028	1492 (0.4)

Figure 1. A forest plot of meta-analysis between pregnancy status and severe COVID-19 with cytokine storm.

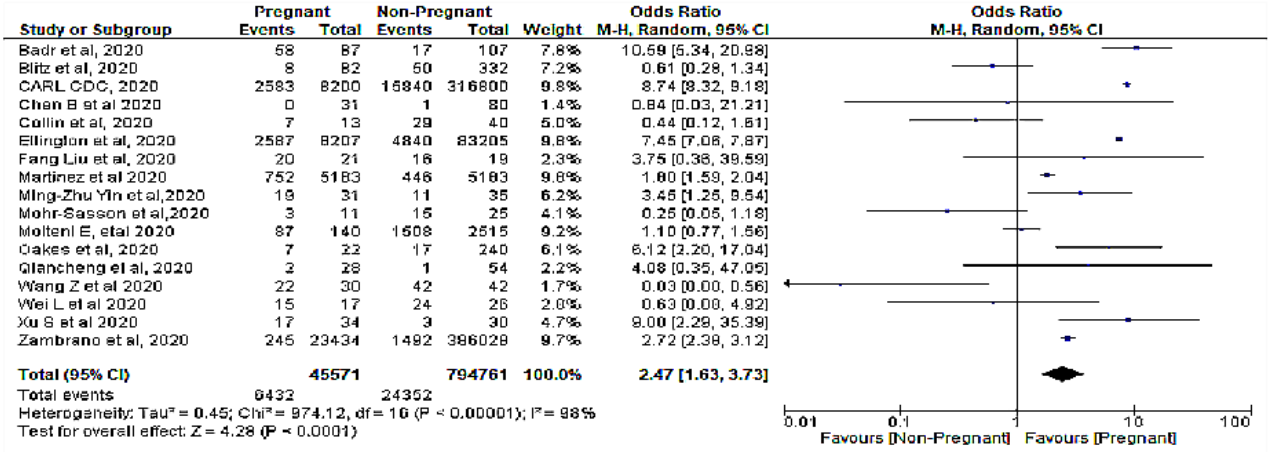


Figure 2. Forest plot of the association of pregnancy with severe COVID-19 characterized by a cytokine storm with the fixed-effects model.

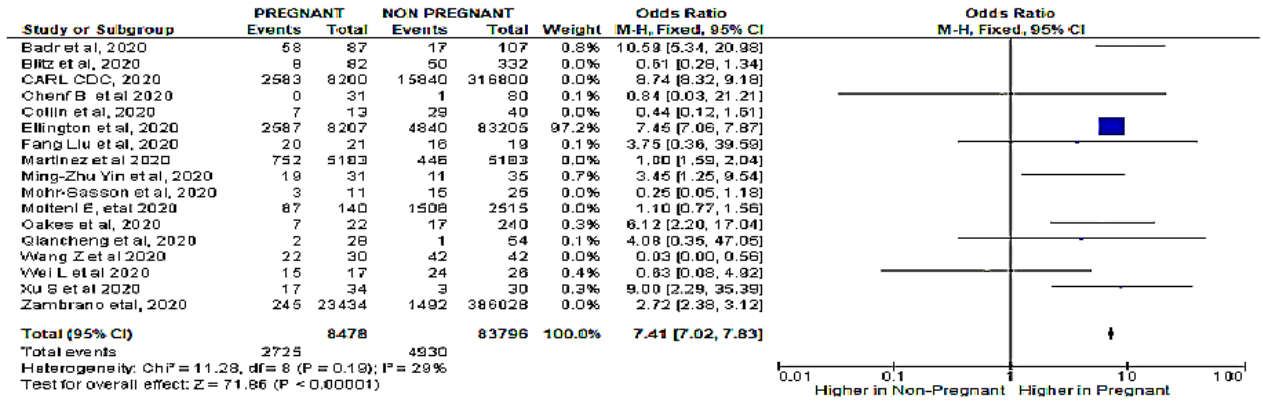


Figure 3. Funnel plot evaluating publication bias. OR: odds ratio.

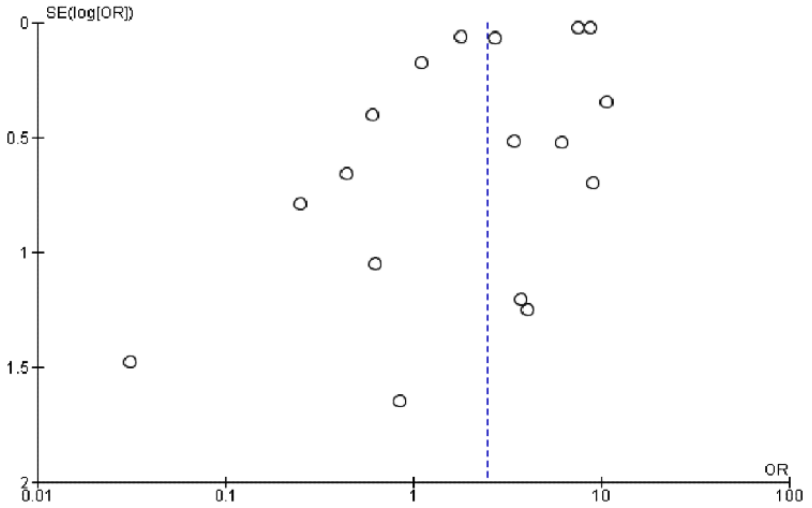
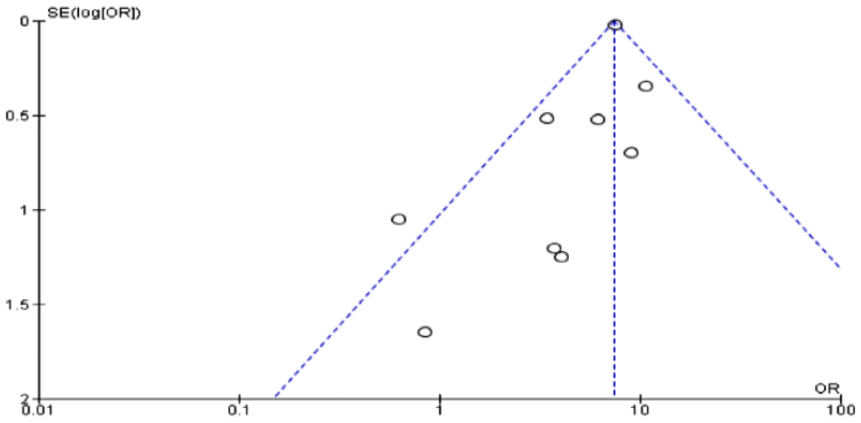


Figure 4. Funnel plot revealing no publication bias in the updated analysis. OR: odds ratio.



Subgroup Analysis and Investigation of Heterogeneity

Heterogeneity in the pooled effect estimates was considerably high for all 17 studies, contributed by 748,058 out of 840,332 (89.02%) evaluated subjects, and thus it was necessary to perform subgroup analyses to identify possible variables or characteristics moderating the results obtained. Subgroup analysis was performed according to whether it was a multicenter study, including 879,556 patients, or a single-center study with 776 patients. Figures 5 and 6 show that subgroup analysis still showed high heterogeneity (I^2=72%). The test for the overall effect for single-center studies (Z=0.91, P=.36; I^2=98) and multicenter studies (Z=3.97, P<.001) showed no significance difference (χ_1^2=0.67, P=.41; I^2=0%). This prompted further sensitivity analysis on each subgroup to ascertain the group that was most strongly associated with heterogeneity.

Figure 7 shows the sensitivity analysis on independent subgroups. In single-center studies, elimination of studies that caused the major heterogeneity ([27] and [31]; n=108) revealed that pregnancy was significantly related to severe COVID-19 with a cytokine storm represented by 668 patients (fixed-effects model OR 3.97, 95% CI 2.26-6.95; P<.001), with this updated analysis showing substantially low heterogeneity (I^2=2%, P=.42). In multicenter studies, subsequent removal of any one study did not change the heterogeneity from its original value (χ^2_7=928.90, P<.001; I^2=99%), demonstrating that multicenter studies were the main cause of heterogeneity and this was similar to the overall heterogeneity of the combined groups (fixed-effects model heterogeneity χ^2_{14}=938.26, P<.001; I^2=99%), with the test for subgroup differences being insignificant (χ^2_1=1.9, P=.17; I^2=47.4%). Figure 8 shows a funnel plot similarly demonstrating that multicenter studies were associated with heterogeneity with only one study demonstrating homogeneity.

Figure 5. Subgroup analysis according to single-center or multicenter study designs showing similarly high heterogeneity as the full meta-analysis.

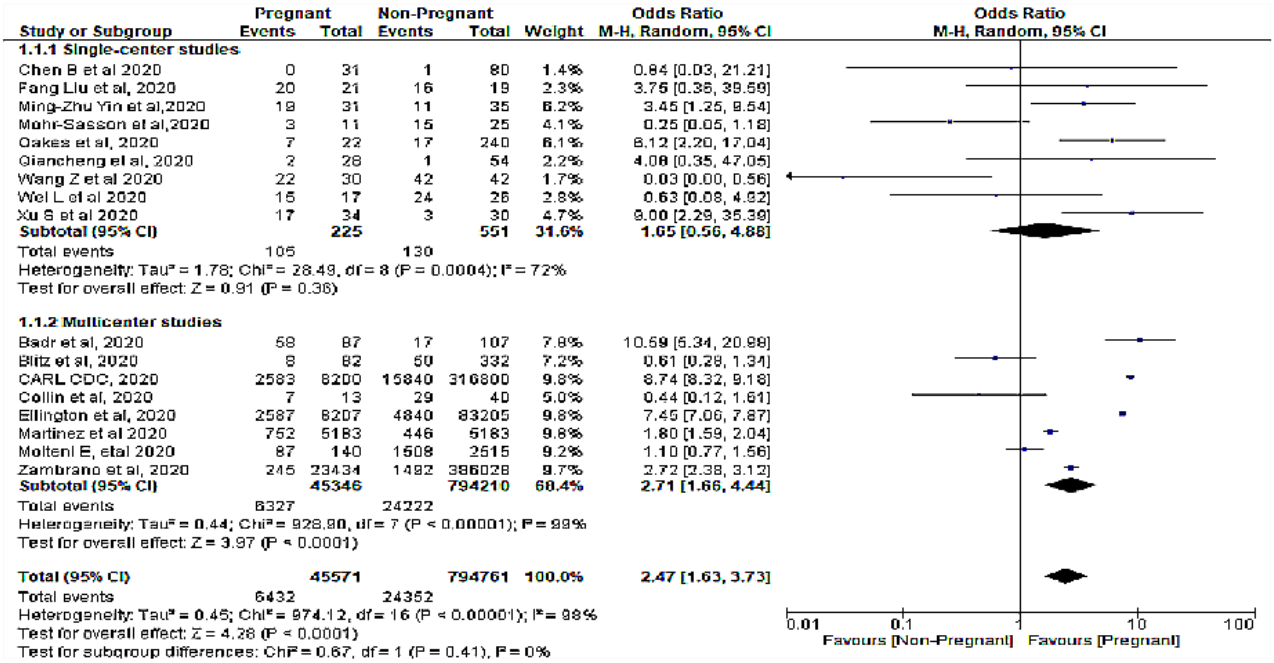


Figure 6. Funnel plot of the subgroup analysis-single-center and multicenter studies.

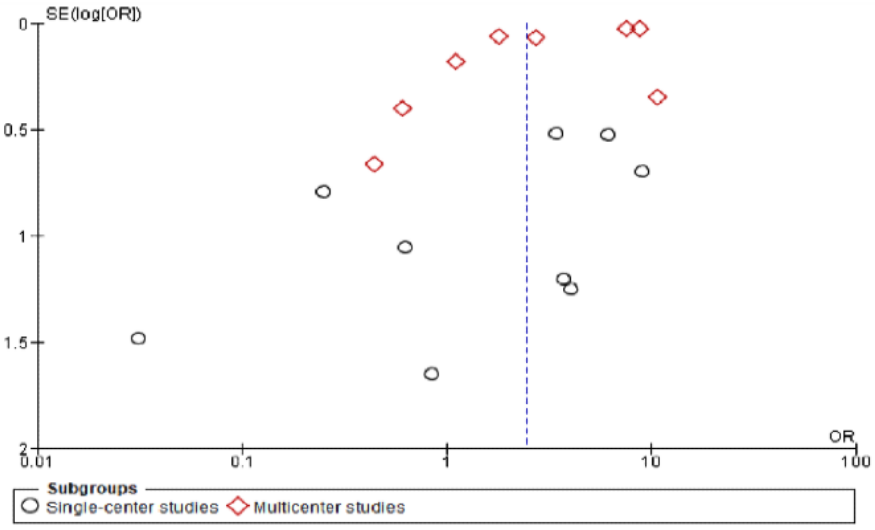


Figure 7. Sensitivity analysis on independent subgroups.

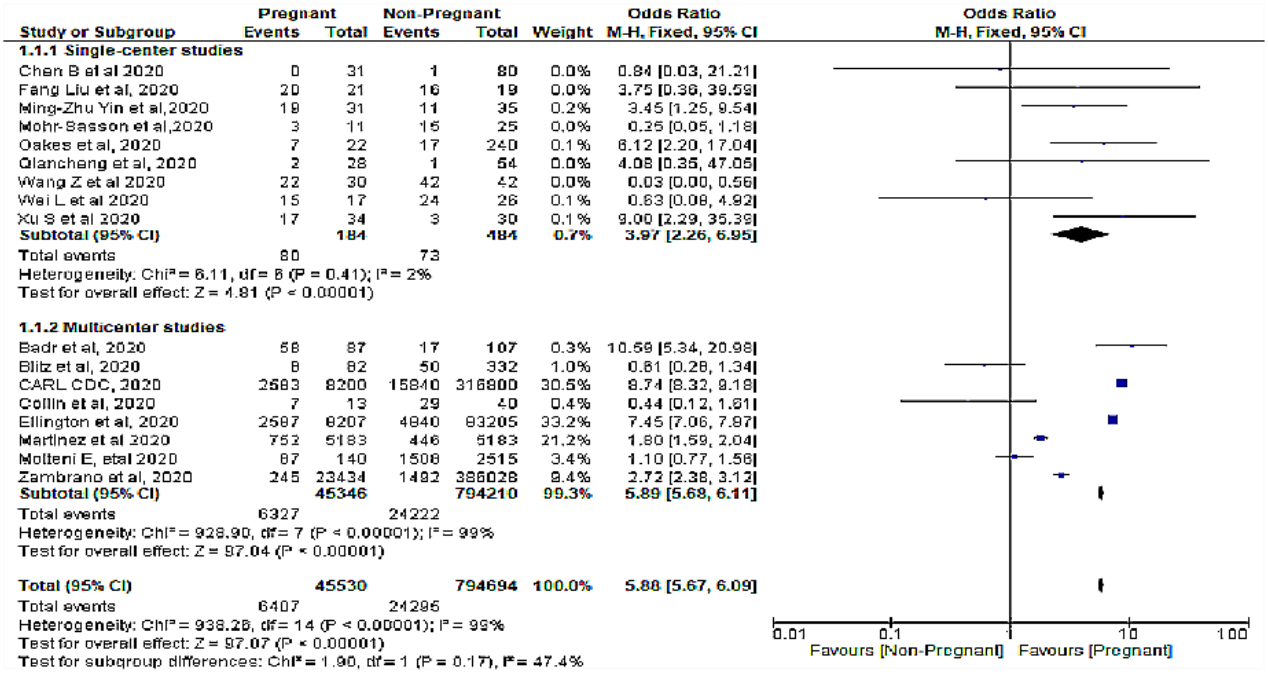
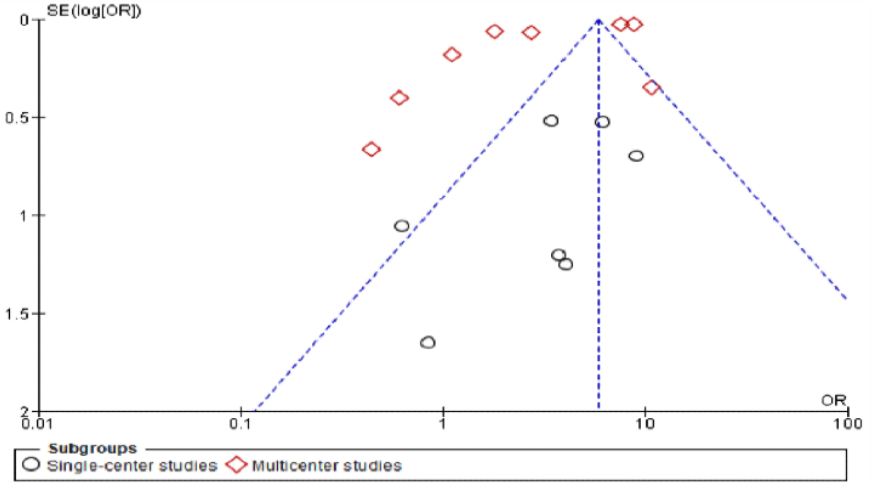


Figure 8. Funnel plot of sensitivity analysis on independent subgroups (single-center and multicenter) to evaluate publication bias.



Discussion

This review established that pregnancy is associated with an experience of severe COVID-19 characterized by a cytokine storm. Heterogeneity analysis revealed that the pooled effect estimate was considerably high considering all 17 included studies, contributed by 89% of the total patients evaluated. Further, sensitivity analysis on each subgroup indicated that single-center studies were more homogeneous in comparison to multicenter studies.

This meta-analysis included 17 studies and revealed that pregnant women had a significantly increased risk for severe COVID-19 characterized by a cytokine storm. Previous research has indicated a similar association [32,33]. Additionally, another meta-analysis reported the outcome of coronavirus spectrum infections (SARS, MERS, and COVID-19) during pregnancy, showing that COVID-19 disease severity increased during gestation [34]. This analysis adds to the extensive consensus in the literature, which should motivate more studies examining pregnancy status as a possible predictor of severe COVID-19 characterized by a cytokine storm.

Prior studies have reported results that contrast with those presented here, namely a lack of significant difference between pregnant and nonpregnant women diagnosed with COVID-19 in terms of disease severity [35,36]. In addition, a previous meta-analysis [37] failed to find a relationship between being pregnant and severe COVID-19 in 24 studies including pregnant women, and another meta-analysis indicated that COVID-19 infection during pregnancy most likely had a clinical presentation and severity resembling those in nonpregnant adults [38]. Moreover, a meta-analysis demonstrated similar trends in disease severity between pregnant people and the general population [39]. Further, two more studies showed no feasible differences in the clinical presentation of COVID-19 between pregnant and nonpregnant women [40,41]. Of concern, neither of the meta-analyses mentioned above [37,38] included an

assessment of publication bias or study quality. As such, these studies should be considered as only a preliminary quest. Hence, the present systematic meta-analysis offers a more detailed view as it covers 17 studies from diverse regions capturing both single and multiple centers. The heterogeneity was high, and after sensitivity adjustments to eliminate studies largely responsible for the heterogeneity, the association of COVID-19 severity with pregnancy was revealed with substantially low heterogeneity. Furthermore, the subgroup analysis after performing the sensitivity test in each specified subgroup (multicenter or single-center studies) showed a clear significant association between being pregnant and developing severe COVID-19 characterized by any specific parameter of a cytokine storm in single-center studies. Therefore, severe COVID-19 was observed to be almost 4 times (OR 3.97, 95% CI 2.26-6.95; $P<.001$) more frequent in pregnant women. Some previous studies, including some meta-analyses [39,42-46], support the current findings.

A recent meta-analysis revealed that SARS-CoV-2 infection may not manifest as mild symptoms during pregnancy [47]. Interestingly, this meta-analysis showed that 40 patients developed pneumonia, bilateral in most cases, with a 46.2% rate of hospitalization and 4 patients required ICU admission. The same study found a higher rate of severe forms of COVID-19, even when compared to nonpregnant women with the same baseline characteristics [47]. This appears to be because, during the gestation period, pregnant women face proinflammatory episodes that mimic the trends of a cytokine storm in the case of severe COVID-19. This has been demonstrated in recent studies where specific immune cells, especially neutrophils, and other biomarkers have been highlighted as essential effector cells in the development of COVID-19 [48-51]. In addition, pregnancy has been reported to increase the progression of COVID-19 [52]. There is growing evidence to support the WHO's statements that pregnant women are at a higher risk of developing severe COVID-19–related symptoms and possible mortality [53-56]. Indeed, pregnancy has been found to worsen the morbidity of COVID-19, and this effect becomes more prominent as pregnancy advances [57].

The association between pregnancy and illness severity due to other respiratory viruses such as MERS has been investigated previously. In one study, the case fatality (25%), ICU admission (50%), and mechanical ventilation (33%) rates were increased in the pregnant population compared with those of the nonpregnant population (20%) [58], which may be related to abnormal immune responses in pregnancy. Additionally, pregnancy may propagate respiratory infections and increase the risk of hospitalization [59]. Another study demonstrated that complications of severity with other acute respiratory distress syndromes are enhanced in pregnancy [11]. As a result, adverse effects on the pregnant woman's lungs may aggravate the symptom severity of viral infections.

The novel SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) receptor in the lungs to enter cells and cause infection. ACE2 expression and activity are enhanced during pregnancy, and transient ACE2 overexpression and its increased activity during pregnancy may be important in modulating systemic as well as local hemodynamics in the uteroplacental unit [60,61]. ACE2 upregulation may increase infectiousness and therefore infection severity risk, as the SARS-CoV-2 virus uses this receptor for host entry. Paradoxically, ACE2 upregulation has also been reported to be a protective factor against acute lung injury [62].

In one recent study, *ACE2* gene expression was found to be upregulated in cells specific to the maternal-fetal interface [63], thereby suggesting a mechanism by which the risk for severe COVID-19 increases in pregnancy. A role of ACE2 in COVID-19 pathophysiology has also been demonstrated, including factors influencing ACE2 expression and activity in relation to COVID-19 severity [64]. Thus, the potential impact of ACE2 expression and thus SARS-CoV-2 entry into the host in pregnancy should be further investigated [65].

The cytokine storm phenomenon has received substantial research attention recently because of the COVID-19 pandemic. Although more and more information is accumulating daily, the cytokine storm seems to be at least part of the reason that some people develop life-threatening symptoms from COVID-19. Hyperinflammatory cytokine storms in many patients with severe symptomatic cases of COVID-19 may be rooted in an atypical response to SARS-CoV-2 by dysfunctional mast cells, in a condition known as mast cell activation syndrome, rather than the typical response by normal mast cells [66]. This may be explained by systemic and chronic inflammation, diminished respiratory function and capacity, and chronic obstructive pulmonary disease–related respiratory failure in some patients. Some findings indicated an association of pro- and anti-inflammatory cytokines that play crucial roles in the development and function of preeclampsia [67]. Given this, pregnancy itself and pro- and anti-inflammatory cytokines should be considered together as a single risk factor for severe COVID-19 among pregnant women diagnosed with the novel coronavirus.

Another critical area of concern is that the cytokine storm is a critical contributor to mortality in some patients with severe COVID-19. In these patients, the levels of proinflammatory cytokines such as interleukin (IL)-1, IL-2, IL-6, IL-8, IL-17, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α are elevated, which affect the patient's clinical symptoms and severity in the general population [68]. In pregnancy, IFNs and cytokines play important roles in the immune responses promoting healthy pregnancy as well as congenital disorders and complications [69], similar to those activated during a COVID-19 cytokine storm, including TNF-α [70]. Increased levels of INF-γ, luteinizing hormone, and prolactin have been identified as the underlying cause for recurrent pregnancy losses; thus, these factors not only amplify the severity of the cytokine storm in COVID-19 but also consequentially result in adverse pregnancy outcomes [70]. This potential interaction should be clarified with future clinical research.

Several factors limit the interpretation of the present study. First, the vast majority of studies included in the meta-analysis were retrospective epidemiological studies conducted in the United States and China, with limited studies from other regions. Second, some of the included studies did not distinguish the age range of the participants as well as the stage of the gestation

period. Third, COVID-19 severity as assumed to be characterized by a cytokine storm relied on different parameters of clinical implications such as the levels of inflammatory cytokines, invasive mechanical ventilation, and ICU admission. Given these limitations, caution should be exercised when interpreting the current findings for more valid clinical practice. Future studies may respond to these issues by defining disease severity more clearly and by obtaining more detailed information on the associated inflammatory cytokines defining the COVID-19 cytokine storm.

Multiple factors are responsible for recurrent pregnancy loss, although an altered cytokine profile is known to be a major contributor, especially in the early stages of gestation. Similarly, exposure to high maternal proinflammatory cytokine concentrations in early pregnancy might play a role in several adverse effects for either the woman or infant. Thus, women expecting a pregnancy should be screened to assess the cytokine profile even prior to conception whenever possible to avoid pregnancy loss and to improve their health and social well-being, as abnormal cytokine levels could aggravate COVID-19 severity.

Finally, the interactions between the inherent inflammatory cytokines and cytokine storm due to COVID-19 should also be further examined and clarified. In addition, clinicians should pay more attention to the history of pregnancy-related altered immune responses of COVID-19 patients. Further research may aim to determine the mechanisms that drive or decrease this risk of severity by a within–pregnant population study approach.

This meta-analysis revealed that pregnancy is significantly associated with increased COVID-19 symptom severity defined by a cytokine storm. The SARS-CoV-2 epidemic should serve as an impetus for further research on pregnant women diagnosed with COVID-19, and to map out salient risk factors associated with its severity with an aim of maintaining a good pregnancy outcome and possibly evading an adverse COVID-19 clinical prognosis.

Acknowledgments

Funding for this study was provided by Kenya Medical Training College.

Authors' Contributions

JM conceptualized the study, and was responsible for data collection, collation, and retrieval; design of tables, images, and figures; major analysis and interpretation of data; and writing and drafting of the manuscript. KO performed the data collection and quality assessment. JMN played a key role in data analysis, quality assessment procedure and general review of the write-up. EMN participated in acquisition of data, quality analysis, and writing and revision of the manuscript. MK played a major role in reviewing and revising the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA (Preferred Items for Systematic Reviews and Meta-Analyses) flow diagram.
[PDF File (Adobe PDF File), 195 KB-Multimedia Appendix 1]

References

1. Silasi M, Cardenas I, Kwon J, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. Am J Reprod Immunol 2015 Mar 13;73(3):199-213 [FREE Full text] [doi: 10.1111/aji.12355] [Medline: 25582523]
2. Castro P, Matos AP, Werner H, Lopes FP, Tonni G, Araujo Júnior E. Covid-19 and pregnancy: an overview. Rev Bras Ginecol Obstet 2020 Jul;42(7):420-426 [FREE Full text] [doi: 10.1055/s-0040-1713408] [Medline: 32559801]
3. Sharma AK. Novel coronavirus disease (COVID-19). Reson 2020 Jun 05;25(5):647-668. [doi: 10.1007/s12045-020-0981-3]
4. Countries where Coronavirus has spread. Worldometer. 2020. URL: https://www.worldometers.info/coronavirus/countries-where-coronavirus-has-spread/ [accessed 2022-09-14]
5. Handayani D, Hadi DR, Isbaniah F, Burhan E, Agustin H. Corona Virus Disease 2019. J Respirol Indones 2020 Apr 30;40(2):119-129. [doi: 10.36497/jri.v40i2.101]
6. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine storm in COVID-19–immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM Consortium Position Paper. Front Immunol 2020 Jul 10;11:1648. [doi: 10.3389/fimmu.2020.01648] [Medline: 32754159]
7. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep 2020 Jun 26;69(25):769-775. [doi: 10.15585/mmwr.mm6925a1] [Medline: 32584795]
8. Barile L, Cerrano M, Locatelli A, Puppo A, Signorile AF, Barzhagi N. Prone ventilation in a 27 week pregnant woman with COVID-19 severe ARDS. Signa Vitae 2020 Jun;16(1):199-202. [doi: 10.22514/sv.2020.16.0028]
9. Chen L, Jiang H, Zhao Y. Pregnancy with COVID-19: Management considerations for care of severe and critically ill cases. Am J Reprod Immunol 2020 Nov;84(5):e13299 [FREE Full text] [doi: 10.1111/aji.13299] [Medline: 32623810]

10. Schnettler WT, Al Ahwel Y, Suhag A. Severe acute respiratory distress syndrome in coronavirus disease 2019-infected pregnancy: obstetric and intensive care considerations. Am J Obstet Gynecol MFM 2020 Aug;2(3):100120 [FREE Full text] [doi: 10.1016/j.ajogmf.2020.100120] [Medline: 32363337]
11. Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, et al. Pregnancy and COVID-19. Physiol Rev 2021 Jan 01;101(1):303-318 [FREE Full text] [doi: 10.1152/physrev.00024.2020] [Medline: 32969772]
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
13. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015 Feb 25;8(1):2-10. [doi: 10.1111/jebm.12141] [Medline: 25594108]
14. Badr DA, Mattern J, Carlin A, Cordier A, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol 2020 Nov;223(5):764-768 [FREE Full text] [doi: 10.1016/j.ajog.2020.07.045] [Medline: 32730899]
15. Westgren M, Acharya G. Intensive care unit admissions for pregnant and nonpregnant women with coronavirus disease 2019. Am J Obstet Gynecol 2020 Nov;223(5):779-780 [FREE Full text] [doi: 10.1016/j.ajog.2020.07.046] [Medline: 32721395]
16. Assessing risk factors for severe COVID-19 illness. Centers for Disease Control and Prevention. 2020 Nov. URL: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/assessing-risk-factors.html [accessed 2022-09-14]
17. Cheng B, Jiang T, Zhang L, Hu R, Tian J, Jiang Y, et al. Clinical characteristics of pregnant women with coronavirus disease 2019 in Wuhan, China. Open Forum Infect Dis 2020 Aug;7(8):ofaa294 [FREE Full text] [doi: 10.1093/ofid/ofaa294] [Medline: 32760752]
18. Oakes MC, Kernberg AS, Carter EB, Foeller ME, Palanisamy A, Raghuraman N, et al. Pregnancy as a risk factor for severe coronavirus disease 2019 using standardized clinical criteria. Am J Obstet Gynecol MFM 2021 May;3(3):100319 [FREE Full text] [doi: 10.1016/j.ajogmf.2021.100319] [Medline: 33493707]
19. Qiancheng X, Jian S, Lingling P, Lei H, Xiaogan J, Weihua L, Sixth batch of Anhui medical team aiding Wuhan for COVID-19. Coronavirus disease 2019 in pregnancy. Int J Infect Dis 2020 Jun;95:376-383 [FREE Full text] [doi: 10.1016/j.ijid.2020.04.065] [Medline: 32353549]
20. Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. Int J Gynaecol Obstet 2020 Sep 03;150(3):312-317 [FREE Full text] [doi: 10.1002/ijgo.13265] [Medline: 32510581]
21. Wei L, Gao X, Chen S, Zeng W, Wu J, Lin X, et al. Clinical Characteristics and outcomes of childbearing-age women with COVID-19 in Wuhan: retrospective, single-center study. J Med Internet Res 2020 Aug 24;22(8):e19642 [FREE Full text] [doi: 10.2196/19642] [Medline: 32750000]
22. Xu S, Shao F, Bao B, Ma X, Xu Z, You J, et al. Clinical manifestation and neonatal outcomes of pregnant patients with coronavirus disease 2019 pneumonia in Wuhan, China. Open Forum Infect Dis 2020 Jul;7(7):ofaa283 [FREE Full text] [doi: 10.1093/ofid/ofaa283] [Medline: 32743014]
23. Collin J, Byström E, Carnahan A, Ahrne M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. Acta Obstet Gynecol Scand 2020 Jul 13;99(7):819-822. [doi: 10.1111/aogs.13901] [Medline: 32386441]
24. Liu F, Liu H, Hou L, Li J, Zheng H, Chi R, et al. Clinico-radiological features and outcomes in pregnant women with COVID-19 pneumonia compared with age-matched non-pregnant women. Infect Drug Resist 2020;13:2845-2854. [doi: 10.2147/IDR.S264541] [Medline: 32884308]
25. Martinez-Portilla RJ, Sotiriadis A, Chatzakis C, Torres-Torres J, Espino Y Sosa S, Sandoval-Mandujano K, 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 (COV19Mx). Ultrasound Obstet Gynecol 2021 Feb;57(2):224-231. [doi: 10.1002/uog.23575] [Medline: 33320401]
26. Yin MZ, Zhang LJ, Deng GT, Han CF, Shen MX, Sun HY, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy in China: a retrospective cohort study. MedRxiv. 2020 Apr 11. URL: https://www.medrxiv.org/content/10.1101/2020.04.07.20053744v1 [accessed 2022-09-14]
27. Mohr-Sasson A, Chayo J, Bart Y, Meyer R, Sivan E, Mazaki-Tovi S, et al. Laboratory characteristics of pregnant compared to non-pregnant women infected with SARS-CoV-2. Arch Gynecol Obstet 2020 Sep 22;302(3):629-634 [FREE Full text] [doi: 10.1007/s00404-020-05655-7] [Medline: 32572616]
28. Molteni E, Astley CM, Ma W, Sudre CH, Magee LA, Murray B, et al. SARS-CoV-2 (COVID-19) infection in pregnant women: characterization of symptoms and syndromes predictive of disease and severity through real-time, remote participatory epidemiology. medRxiv. 2020 Oct 14. URL: https://www.medrxiv.org/content/10.1101/2020.08.17.20161760v2 [accessed 2022-09-14]
29. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, CDC COVID-19 Response PregnancyInfant Linked Outcomes Team. 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 Nov 06;69(44):1641-1647. [doi: 10.15585/mmwr.mm6944e3] [Medline: 33151921]
30. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep 2020 Apr 03;69(13):382-386. [doi: 10.15585/mmwr.mm6913e2] [Medline: 32240123]
31. Wang J, Li Z, Cheng X, Hu H, Liao C, Li P, et al. Epidemiologic characteristics, transmission chain, and risk factors of severe infection of COVID-19 in Tianjin, a representative municipality city of China. Front Public Health 2020 May 20;8:198. [doi: 10.3389/fpubh.2020.00198] [Medline: 32671007]
32. Czeresnia RM, Trad ATA, Britto ISW, Negrini R, Nomura ML, Pires P, et al. SARS-CoV-2 and pregnancy: a review of the facts. Rev Bras Ginecol Obstet 2020 Sep 29;42(9):562-568 [FREE Full text] [doi: 10.1055/s-0040-1715137] [Medline: 32992359]
33. Kolkova Z, Bjurström MF, Länsberg JK, Svedas E, Hamer MA, Hansson SR, et al. Obstetric and intensive-care strategies in a high-risk pregnancy with critical respiratory failure due to COVID-19: A case report. Case Rep Womens Health 2020 Jul;27:e00240 [FREE Full text] [doi: 10.1016/j.crwh.2020.e00240] [Medline: 32714844]
34. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, 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 May;2(2):100107 [FREE Full text] [doi: 10.1016/j.ajogmf.2020.100107] [Medline: 32292902]
35. Selim M, Mohamed S, Abdo M, Abdelhaffez A. Is COVID-19 similar in pregnant and non-pregnant women? Cureus 2020 Jun 28;12(6):e8888 [FREE Full text] [doi: 10.7759/cureus.8888] [Medline: 32742855]
36. Tirmikçioğlu Z. Evaluation of updated therapeutic options for COVID-19 in pregnancy and lactation. Bezmialem Sci 2021 Feb 1;9(1):78-83. [doi: 10.14235/bas.galenos.020.4652]
37. Matar R, Alrahmani L, Monzer N, Debiane LG, Berbari E, Fares J, et al. Clinical presentation and outcomes of pregnant women with coronavirus disease 2019: a systematic review and meta-analysis. Clin Infect Dis 2021 Feb 01;72(3):521-533 [FREE Full text] [doi: 10.1093/cid/ciaa828] [Medline: 32575114]
38. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet 2020 Jul 17;150(1):47-52 [FREE Full text] [doi: 10.1002/ijgo.13182] [Medline: 32330287]
39. Kasraeian M, Zare M, Vafaei H, Asadi N, Faraji A, Bazrafshan K, et al. COVID-19 pneumonia and pregnancy; a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2022 May 19;35(9):1652-1659. [doi: 10.1080/14767058.2020.1763952] [Medline: 32429786]
40. Jafari M, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, et al. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. Rev Med Virol 2021 Sep;31(5):1-16 [FREE Full text] [doi: 10.1002/rmv.2208] [Medline: 33387448]
41. Vaezi M, Mirghafourvand M, Hemmatzadeh S. Characteristics, clinical and laboratory data and outcomes of pregnant women with confirmed SARS-CoV-2 infection admitted to Al-Zahra tertiary referral maternity center in Iran: a case series of 24 patients. BMC Pregnancy Childbirth 2021 May 17;21(1):378 [FREE Full text] [doi: 10.1186/s12884-021-03764-y] [Medline: 34001013]
42. Al-Matary A, Almatari F, Al-Matary M, AlDhaefi A, Alqahtani MHS, Alhulaimi EA, et al. Clinical outcomes of maternal and neonate with COVID-19 infection - multicenter study in Saudi Arabia. J Infect Public Health 2021 Jun;14(6):702-708 [FREE Full text] [doi: 10.1016/j.jiph.2021.03.013] [Medline: 34020209]
43. Galang RR, Chang K, Strid P, Snead MC, Woodworth KR, House LD, et al. Severe coronavirus infections in pregnancy: a systematic review. Obstet Gynecol 2020 Aug;136(2):262-272 [FREE Full text] [doi: 10.1097/AOG.0000000000004011] [Medline: 32544146]
44. Grünebaum A, McCullough LB, Litvak A, Chervenak FA. Inclusion of pregnant individuals among priority populations for coronavirus disease 2019 vaccination for all 50 states in the United States. Am J Obstet Gynecol 2021 May;224(5):536-539 [FREE Full text] [doi: 10.1016/j.ajog.2021.01.026] [Medline: 33545113]
45. Lucarelli E, Behn C, Lashley S, Smok D, Benito C, Oyelese Y. Mechanical ventilation in pregnancy due to COVID-19: a cohort of three cases. Am J Perinatol 2020 Aug 16;37(10):1066-1069 [FREE Full text] [doi: 10.1055/s-0040-1713664] [Medline: 32544963]
46. Soheili M, Moradi G, Baradaran HR, Soheili M, Mokhtari MM, Moradi Y. Clinical manifestation and maternal complications and neonatal outcomes in pregnant women with COVID-19: a comprehensive evidence synthesis and meta-analysis. J Matern Fetal Neonatal Med 2021 Feb 18:online ahead of print. [doi: 10.1080/14767058.2021.1888923] [Medline: 33602025]
47. Barbero P, Mugüerza L, Herraiz I, García Burguillo A, San Juan R, Forcén L, et al. SARS-CoV-2 in pregnancy: characteristics and outcomes of hospitalized and non-hospitalized women due to COVID-19. J Matern Fetal Neonatal Med 2022 Jul 20;35(14):2648-2654. [doi: 10.1080/14767058.2020.1793320] [Medline: 32689846]
48. Cavalcante MB, Cavalcante CTDMB, Sarno M, Barini R, Kwak-Kim J. Maternal immune responses and obstetrical outcomes of pregnant women with COVID-19 and possible health risks of offspring. J Reprod Immunol 2021 Feb;143:103250 [FREE Full text] [doi: 10.1016/j.jri.2020.103250] [Medline: 33249335]

49. Da Silva CRAC, Oliveira LVD, Lopes LP, Dos Santos WAG, Agra IKR. Immunological aspects of coronavirus disease during pregnancy: an integrative review. Rev Assoc Med Bras 2020 May;66(5):696-700 [FREE Full text] [doi: 10.1590/1806-9282.66.5.696] [Medline: 32638966]
50. Figuero E, Han YW, Furuichi Y. Periodontal diseases and adverse pregnancy outcomes: mechanisms. Periodontol 2020 Jun 08;83(1):175-188. [doi: 10.1111/prd.12295] [Medline: 32385886]
51. Malinowski AK, Noureldin A, Othman M. COVID-19 susceptibility in pregnancy: Immune/inflammatory considerations, the role of placental ACE-2 and research considerations. Reprod Biol 2020 Dec;20(4):568-572 [FREE Full text] [doi: 10.1016/j.repbio.2020.10.005] [Medline: 33183974]
52. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020 Jun;222(6):521-531 [FREE Full text] [doi: 10.1016/j.ajog.2020.03.021] [Medline: 32217113]
53. Blauvelt CA, Chiu C, Donovan AL, Prahl M, Shimotake TK, George RB, et al. Acute respiratory distress syndrome in a preterm pregnant patient with coronavirus disease 2019 (COVID-19). Obstet Gynecol 2020 Jul;136(1):46-51. [doi: 10.1097/AOG.0000000000003949] [Medline: 32384385]
54. Oganyan KA, Shalepo KV, Savicheva AM, Bespalova ON, Kogan IY. New coronavirus infection and pregnancy. J Obst Women Dis 2021 Jan 25;69(6):71-80. [doi: 10.17816/JOWD69671-80]
55. Rashid F, Shahnaz S, Sharmin R, Sattar MA, Chowdhury S. Pregnancy with COVID-19: weal and woe. J SAFOG 2020;12(4):258-260. [doi: 10.5005/jp-journals-10006-1798]
56. San-Juan R, Barbero P, Fernández-Ruiz M, López-Medrano F, Lizasoáin M, Hernández-Jiménez P, et al. Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: a single-centre cohort study from Spain. EClinicalMedicine 2020 Jun;23:100407 [FREE Full text] [doi: 10.1016/j.eclinm.2020.100407] [Medline: 32632417]
57. Tug N, Yassa M, Köle E, Sakin Ö, Çakır Köle M, Karateke A, et al. Pregnancy worsens the morbidity of COVID-19 and this effect becomes more prominent as pregnancy advances. Turk J Obstet Gynecol 2020 Sep 2;17(3):149-154. [doi: 10.4274/tjod.galenos.2020.38924] [Medline: 33072417]
58. Martens M, Bharati K. Middle Eastern Respiratory Syndrome and pregnancy [18J]. Obstet Gynecol 2016;127(Supplement 1):85S-86S. [doi: 10.1097/01.AOG.0000483787.93122.d5]
59. Lokken EM, Taylor GG, Huebner EM, Vanderhoeven J, Hendrickson S, Coler B, Washington COVID-19 in Pregnancy Collaborative. Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. Am J Obstet Gynecol 2021 Jul;225(1):75.e1-75.e16 [FREE Full text] [doi: 10.1016/j.ajog.2021.02.011] [Medline: 33607103]
60. Brosnihan K, Neves L, Anton L, Joyner J, Valdes G, Merrill D. Enhanced expression of Ang-(1-7) during pregnancy. Braz J Med Biol Res 2004 Aug;37(8):1255-1262 [FREE Full text] [doi: 10.1590/s0100-879x2004000800017] [Medline: 15273828]
61. Levy A, Yagil Y, Bursztyn M, Barkalifa R, Scharf S, Yagil C. ACE2 expression and activity are enhanced during pregnancy. Am J Physiol Regul Integr Comp Physiol 2008 Dec;295(6):R1953-R1961 [FREE Full text] [doi: 10.1152/ajpregu.90592.2008] [Medline: 18945956]
62. Pathangey G, Fadadu PP, Hospodar AR, Abbas AE. Angiotensin-converting enzyme 2 and COVID-19: patients, comorbidities, and therapies. Am J Physiol Lung Cell Mol Physiol 2021 Mar 01;320(3):L301-L330 [FREE Full text] [doi: 10.1152/ajplung.00259.2020] [Medline: 33237815]
63. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One 2020 Apr 16;15(4):e0230295 [FREE Full text] [doi: 10.1371/journal.pone.0230295] [Medline: 32298273]
64. Bourgonje AR, Abdulle AE, Timens W, Hillebrands J, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol 2020 Jul 10;251(3):228-248 [FREE Full text] [doi: 10.1002/path.5471] [Medline: 32418199]
65. South AM, Brady TM, Flynn JT. ACE2 (angiotensin-converting enzyme 2), COVID-19, and ACE inhibitor and Ang II (angiotensin II) receptor blocker use during the pandemic: the pediatric perspective. Hypertension 2020 Jul;76(1):16-22 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.120.15291] [Medline: 32367746]
66. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis 2020 Nov;100:327-332 [FREE Full text] [doi: 10.1016/j.ijid.2020.09.016] [Medline: 32920235]
67. Aggarwal R, Jain AK, Mittal P, Kohli M, Jawanjal P, Rath G. Association of pro- and anti-inflammatory cytokines in preeclampsia. J Clin Lab Anal 2019 May 21;33(4):e22834 [FREE Full text] [doi: 10.1002/jcla.22834] [Medline: 30666720]
68. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020 Jun;19(6):102537 [FREE Full text] [doi: 10.1016/j.autrev.2020.102537] [Medline: 32251717]
69. Yockey LJ, Iwasaki A. Interferons and proinflammatory cytokines in pregnancy and fetal development. Immunity 2018 Sep 18;49(3):397-412 [FREE Full text] [doi: 10.1016/j.immuni.2018.07.017] [Medline: 30231982]
70. AlJameil N, Tabassum H, AlMayouf H, Alshenefy A, Almohizea MM, Ali MN. Identification of serum cytokines as markers in women with recurrent pregnancy loss or miscarriage using MILLIPLEX analysis. Biomed Res 2018;29(18):3512-3517. [doi: 10.4066/biomedicalresearch.29-18-1030]

Abbreviations

ACE2: angiotensin-converting enzyme 2
ICU: intensive care unit
IFN: interferon
IL: interleukin
MERS: Middle East respiratory syndrome
NOS: Newcastle-Ottawa Scale
OR: odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS: severe acute respiratory syndrome
TNF: tumor necrosis factor
WHO: World Health Organization

Edited by S Badawy; submitted 26.06.21; peer-reviewed by R Boyapati, A El Rifay, R Chapleau; comments to author 29.01.22; revised version received 02.03.22; accepted 22.03.22; published 04.10.22

Please cite as:
Muthuka J, Kiptoo M, Oluoch K, Nzioki JM, Nyamai EM
Association of Pregnancy With Coronavirus Cytokine Storm: Systematic Review and Meta-analysis
JMIR Pediatr Parent 2022;5(4):e31579
URL: https://pediatrics.jmir.org/2022/4/e31579
doi: 10.2196/31579
PMID: 35319475