Review Article

Effect of COVID-19 on Mortality of Pregnant and Postpartum Women: A Systematic Review and Meta-Analysis

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Background. Based on what is known at this time, pregnant women are at an increased risk of severe illness from COVID-19 compared to nonpregnant women. Additionally, pregnant women with COVID-19 might have an increased risk of adverse pregnancy outcomes. To investigate the effects of coronavirus disease 2019 (COVID-19) on mortality of pregnant and postpartum women, we performed a systematic review of available published literature on pregnancies affected by COVID-19.

Methods. Web of Science, SCOPUS, and MEDLINE-databases were searched for original studies concerning the effect of COVID-19 on mortality of pregnant and postpartum women published by July 10, 2020. Meta-analyses of proportions were used to combine data and report pooled proportions. Results. 117 studies with a total of 11758 pregnant women were included. The age ranged between 15 and 48 years. Most subjects were infected with SARS-CoV-2 in the third trimester. Disease severity was not reported in 1125 subjects. Maternal mortality was 1.3%. In 100% of fatal cases with adequate data, fever alone or with cough was one of the presenting symptoms. Also, dyspnea (58.3%) and myalgia (50%) were the most common symptoms. Sore throat (8.3%) and gastrointestinal symptoms (anorexia, nausea) (8.3%) were rare. The rate of comorbidities was 20% among COVID-19 deaths. The majority of COVID-19-infected women who died had cesarean section (58.3%), 25% had a vaginal delivery, and 16.7% of patients were not full term. Conclusion. COVID-19 infection in pregnant women was associated with higher rates (and pooled proportions) of cesarean section and mortality. Because new data are continuously being generated and published, the findings of this study can be complete and updated with new researches. The results of this study can guide and improve prenatal counseling of COVID-19-infected pregnant women.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health crisis [1, 2]. The impact of COVID-19 on specific populations, including pregnant women and their newborns, remains mostly unknown and unstudied. There is not sufficient information about the effect of this disease in pregnant women, and most available studies have evaluated the impact of the disease in the general population. Pregnant women are at a higher risk for acquiring viral respiratory infections and severe pneumonia due to physiological changes in their immune and cardiopulmonary systems [1–3].

The observed outcomes have been different from what was seen during the H1N1 pandemic and with influenza...
outbreaks, all of which resulted in increased mortality in women who were pregnant [4]. Studies in pregnant women during coronavirus outbreaks (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) show that pregnant women are susceptible to experiencing adverse events such as requiring hospitalization or intensive care unit (ICU) admission, endotracheal intubation, and renal failure [5–7].

Worldwide, there are more than 140 million births every year, and pregnant women are potentially at risk for adverse outcomes of novel coronavirus. Although maternal mortality has been reported in some studies, limited information is available about SARS-CoV-2 infection in critically ill pregnant women hospitalized for COVID-19 [8, 9]. Also, there is a multitude of case reports of infection with SARS-CoV-2 during pregnancy but their small sample size makes it difficult to properly find potential complications [10, 11].

The findings of a study on 8207 SARS-CoV-2-infected pregnant women showed an increased risk for ICU admission and mechanical ventilation compared with nonpregnant women; however, the risk for death was similar [12]. Also, the Centers for Disease Control and Prevention surveillance report from the United States noted that pregnant women were more likely to be admitted to the ICU and receive mechanical ventilation than nonpregnant women. However, after adjusting for age, presence of underlying medical conditions, and race/ethnicity, mortality rate was not increased [12].

Based on data from the early stage of pandemic, it is reassuring that there are low rates of maternal mortality with SARS-CoV-2 [13]. However, more studies are needed to learn more about maternal mortality. This study is aimed at performing a systematic review of available published literature on pregnancies affected by COVID-19 to evaluate the effect of COVID-19 on mortality of pregnant and postpartum women.

2. Methods

2.1. Study Design. This study is a systematic scoping review based on the methodological framework of Arksey and O’Malley [14]. Five stages of the framework they adopted for conducting a scoping study are as follows: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting the results.

2.2. Research Questions. The main questions of the study included the following. What is the mortality rate of COVID-19 in pregnant and postpartum women, and how many and what type of comorbidities were found in recovered and deceased patients? What were the disease symptoms and the mode of delivery in the maternal deaths?

2.3. Search Strategy and Eligibility Criteria. We searched scientific databases of Web of Science, SCOPUS, and MEDLINE through the interface, for original studies concerning the effect of COVID-19 on maternal death published until July 10, 2020. We designed a comprehensive optimal search strategy consisted of two components related to pregnancy and COVID-19. The complete search strategy is shown in Table 1. Also, the Google Scholar engine was searched for potentially relevant articles. Eligible studies for inclusion in this systematic review were those that met all of the following criteria: (i) the analysis was performed in pregnant and postpartum women affected by COVID-19 (laboratory confirmed and/or clinically diagnosed) and (ii) the study was a full paper with original data and (iii) was written in English. Studies were excluded if they did not provide sufficient information about the patient outcome (survival or death and important related details).

2.4. Study Selection. After removing the duplicates, the search output was screened as the first step. The titles and abstracts of the articles were screened by the two authors independently according to the eligibility criteria. Then, in the secondary screening, the full texts of the retrieved articles were reviewed by the same authors. Disagreements were resolved through discussion and consensus.

2.5. Data Extraction. A data collection form was designed by the authors to extract the data of the papers in an integrated way. Characteristics of the studies were extracted, including details of the first author’s name, country, sample size, age, gestational age, comorbidities and complications in pregnancy, severity of COVID-19, ICU admission and ventilation.
need, complications during treatment of COVID-19, and maternal mortality rate. In deceased patients, more information was extracted, including presenting symptoms, mode of delivery, duration of admission to death, and the result of the polymerase chain reaction (PCR) testing of the neonates. Data extraction was performed by two authors independently, and any disagreements were resolved through discussion and team consensus.

2.6. Statistical Analysis. All analyses were conducted by STATA16 (StataCorp, College Station, Texas, USA). The study statistician performed data extraction for primary outcomes. Random effect meta-analyses were applied using restricted maximum likelihood method [15]. The random effect model was used because there may be other unknown, unregistered/unpublished studies to which we could not have access. The between-study heterogeneity was evaluated using the Cochran Q test and Tau-squared, H-squared, and I-squared statistics. Significance results of the test and values higher than 75% for I-squared were considered as substantial heterogeneity while a value of H-squared=1 indicates perfect homogeneity among the studies [16, 17]. The common effect sizes were calculated as the proportion and rate for binary and count outcomes, respectively, and their 95% confidence intervals (CIs). To assess the publication bias, the funnel plots were drawn. Additionally, Egger’s [18] and Begg’s [19] tests were conducted. A nonparametric “trim and fill” method of accounting for publication bias was performed and showed that there is no need for a modified effect size [20]. Finally, there were studies that have just one sample in some outcomes that conducted a sensitivity analysis by removing the studies with \( n=1 \) sample.

2.7. Ethical Considerations. The present study complies with all the recommended principles of research ethics. The official approval of the Research Ethics Committee was not obtained for this study because it was a review of the findings of other previously published papers that were available to the public. To comply with the ethical principles, the authors did their best to avoid plagiarism and refused to manipulate the data for personal interests. Respect for the rights of other authors was provided by citing them in the text of the study when information belonging to them was expressed.
| First author’s name | Country          | $n$ | Age (y) (mean or range) | Gestational age | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 ($n$) | Death |
|---------------------|------------------|-----|-------------------------|-----------------|---------------------------------------------|----------------------|----------|-----------------|-----------------------------------------------|-------|
| Ahmed, I. [60]      | United Kingdom   | 1   | 29                      | —               | Obesity, diabetes, renal tubular acidosis, asthma, vitamin D deficiency | Severe               | 1        | 1               | Pulmonary embolism, basilar artery thrombosis | 1     |
| Al-kuraishy, H.M. [84] | Iraq            | 1   | 25                      | —               | None                                         | Nonsevere            | —        | —               | —                                             | —     |
| AlZaghal, L.A. [85]  | Jordan           | 1   | 30                      | —               | None                                         | Nonsevere            | —        | —               | —                                             | —     |
| Alzamora, M.C. [86]  | Peru             | 1   | 41                      | —               | Obesity, diabetes                            | Severe               | 1        | 1               | —                                             | —     |
| An, P. [21]         | China            | 3   | 25, 31, 33              | —               | Not reported                                 | Nonsevere            | —        | —               | —                                             | —     |
| Anderson, J. [22]    | United States    | 1   | 35                      | —               | Obesity, diabetes, asthma                    | Severe               | 1        | 1               | ARDS                                          | —     |
| Bani Hani, D.A. [87] | Jordan           | 1   | 29                      | —               | Not reported                                 | Nonsevere            | —        | —               | —                                             | —     |
| Barile, E. [52]     | Italy            | 1   | 48                      | —               | Hypertension, obesity, sickle cell trait      | Severe               | 1        | 1               | ARDS                                          | —     |
| Bastug, A. [88]      | Turkey           | 1   | 20                      | —               | None                                         | Nonsevere            | —        | —               | —                                             | —     |
| Baud, D. [61]       | Switzerland      | 1   | 28                      | —               | Obesity                                      | Nonsevere            | —        | —               | —                                             | —     |
| Blauvelt, CA [23]    | United States    | 1   | 34                      | —               | Obesity, asthma, diabetes                    | Severe               | 1        | 1               | ARDS                                          | —     |
| Breslin, N. 1 [24]   | United States    | 43  | 26.9                    | —               | Obesity ($n = 26$), asthma ($n = 8$), diabetes ($n = 3$), hypertension ($n = 3$) | Severe ($n = 6$)    | 2        | —               | Renal insufficiency ($n = 1$)                  | —     |
| Breslin, N 2 [25]    | United States    | 7   | 27-39                   | —               | Obesity ($n = 5$), diabetes ($n = 2$), asthma ($n = 1$), hypertension ($n = 1$), none ($n = 4$) | Severe ($n = 2$)    | 2        | 1               | Acute kidney injury ($n = 1$)                  | —     |
| Browne, PC [26]      | United States    | 1   | 33                      | —               | Asthma ($n = 1$)                             | Nonsevere            | —        | —               | —                                             | —     |
| Buonsenso, D. [53]   | Italy            | 4   | 31, 42, 39, 38          | —               | None                                         | Severe ($n = 1$)    | 1        | 1               | —                                             | —     |
| Cao, D. [89]         | China            | 10  | 29-35                   | —               | Diabetes ($n = 1$), preeclampsia ($n = 3$), hypothyroidism ($n = 1$), anemia ($n = 1$), none ($n = 5$) | Nonsevere ($n = 10$) | —        | —               | —                                             | —     |
| Carosso, A. [54]     | Italy            | 1   | 28                      | —               | Diabetes                                     | Nonsevere            | —        | —               | —                                             | —     |
| Chen, H. [90]        | China            | 9   | 26-40                   | —               | Hypertension ($n = 1$), preeclampsia ($n = 1$), none ($n = 7$) | Nonsevere ($n = 9$) | —        | —               | —                                             | —     |
| First author's name | Country   | n   | Age (y) (mean or range) | 1<sup>st</sup> trimester | 2<sup>nd</sup> trimester | 3<sup>rd</sup> trimester | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|-----------|-----|-------------------------|---------------------------|--------------------------|--------------------------|---------------------------------------------|---------------------|----------|-----------------|---------------------------------------------|-------|
| Chen, L. [91]       | China     | 118 | 28-34                   | 22                        | 21                       | 75                       | Not reported                               | Nonsevere (n = 109), severe (N = 9) | 1        | 1               | —                            | —     |
| Chen, R. [122]      | China     | 17  | NM                      | —                        | —                        | 17                       | Anemia (n = 5), hypertension (n = 1), diabetes (n = 2), none (n = 9) | Nonsevere (N = 17) | —        | —               | —                            | —     |
| Chen, S. [93]       | China     | 5   | 25-31                   | —                        | —                        | 5                        | Diabetes (n = 2), preeclampsia (n = 1), none (n = 2) | Nonsevere (N = 2) | —        | —               | —                            | —     |
| Chen, Y. [94]       | China     | 4   | 23-34                   | —                        | —                        | 4                        | Cholecystitis (n = 1), none (n = 3) | Not reported | 1        | 1               | —                            | —     |
| Chhabra, A. [95]    | India     | 1   | 28                      | —                        | —                        | 1                        | Obesity, diabetes | Nonsevere | —        | —               | —                            | —     |
| Cohen, J. [62]      | France    | 88  | 28-34                   | Not extractable           |                          |                          | Obesity (n = 15), diabetes (n = 7) | Severe (n = 6) | Not reported | Not reported | ARDS, endocarditis, cerebral emboli | —     |
| Collin, J. [63]     | Sweden    | 13  | 20-35                   | Not extractable           |                          |                          | Diabetes and obesity (some of the women) | Not reported | 13       | 7               | Not reported | —     |
| Cooke, W.R. [64]    | United Kingdom | 2 | 39, 28                  | —                        | —                        | 2                        | Obesity (n = 1), diabetes (n = 2) | Severe (n = 2) | —        | —               | Psychiatric sequelae (n = 2) | —     |
| De Socio, GV [55]   | Italy     | 1   | 33                      | —                        | —                        | 1                        | None | Nonsevere | —                | —                | —     |
| De Castro, A. [56]  | Italy     | 1   | 34                      | —                        | —                        | 1                        | Autoimmune thyroiditis and mitral regurgitation, Chronic hypertension (n = 1), asthma (n = 1), severe myopia (n = 1), ulcerative colitis and psoriasis (n = 1), severe scoliosis and Behçet's syndrome (n = 1), none (n = 7) | Severe Not reported | —        | —               | ARDS, endocarditis, cerebral emboli | —     |
| Dória, M. [65]      | Portugal  | 12  | 22-41                   | —                        | —                        | 12                       | Nonsevere (n = 12) | —        | —               | —                            | —     |
| Du, Y. [96]         | China     | 1   | 30                      | —                        | —                        | 1                        | None | Nonsevere | —                | —                | —     |
| Ellington, S. [12]  | United States | 8207 | 15-44              | Not reported |                          |                          | Diabetes (n = 288), lung disease (n = 409), cardiovascular (n = 262), renal disease (n = 12), liver disease (n = 8), Asymptomatic (n = 5199) | 120<sup>a</sup> | 42<sup>c</sup> | Not reported | 16<sup>d</sup> | —     |

<sup>a</sup> Journal of Pregnancy
| First author's name          | Country             | n  | Age (y) (mean or range) | 1st trimester | 2nd trimester | 3rd trimester | Comorbidities and complications in gestation                                                                 | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|-----------------------------|---------------------|----|-------------------------|---------------|---------------|---------------|-----------------------------------------------------------------------------------------------------------------|----------------------|----------|------------------|-----------------------------------------------|--------|
| Fan, C. [97]                | China               | 2  | 34, 29                  | —             | —             | 2             | None (n = 2), known comorbidities (n = 2), none (n = 15), other (n = 162)                                       | Nonsevere (n = 2)    | —        | —                | —                             |        |
| Fassett, M.J. [27]          | United States       | 17 | 33.2                    | —             | —             | 17            | Known comorbidities (n = 2), none (n = 15)                                                                       | Asymptomatic (n = 17) | —        | —                | —                             |        |
| Ferraiolo, A. [57]          | Italy               | 1  | 30                      | —             | —             | 1             | None                                                                                                             | Asymptomatic         | —        | —                | —                             |        |
| Fontanella, F. [66]         | Netherlands, Ireland| 2  | 39, 29                  | —             | —             | 2             | Obesity (n = 2), diabetes (n = 1), hepatitis B (n = 1)                                                            | Nonsevere (n = 2)    | —        | —                | Maternal sepsis (n = 1)            |        |
| Forero-Peña, D.A. [98]      | Venezuela           | 1  | 32                      | —             | —             | 1             | None                                                                                                             | Nonsevere (n = 6),   | —        | —                | —                             |        |
| Fox, N.S. [28]              | United States       | 33 | 31                      | Not extractable| —             | —             | Not reported                                                                                                     | Asymptomatic (n = 27)| —        | —                | —                             |        |
| Futterman, I. [29]          | United States       | 2  | 41, 31                  | —             | 1             | 1             | None (n = 2), obesity, diabetes, preeclampsia                                                                     | Not reported         | 1        | 1                | DIC (n = 2), ARDS, acute renal failure, sepsis (n = 2) |        |
| Gidlöf, S. [67]             | Sweden              | 1  | 34                      | —             | —             | 1             | Obesity, diabetes, preeclampsia                                                                                  | Nonsevere            | —        | —                | —                             |        |
| Goklkar I.T. [30]           | United States       | 61 | 25-38                   | —             | —             | 1             | Obesity (n = 26), asthma (n = 6), diabetes (n = 5)                                                                | Not reported         | 6        | 4                | Not reported                           |        |
| González Romero, D. [68]    | Spain               | 1  | 44                      | —             | —             | 1             | None                                                                                                             | Severe               | 1        | 1                | —                             |        |
| Govind, A. [69]             | United Kingdom      | 9  | 18-39                   | —             | 9             | 2             | Diabetes (n = 2), asthma (n = 1), none (n = 6), nonsevere (n = 7), severe (n = 2)                              | Nonsevere (n = 2)    | 2        | 2                | Not reported                          |        |
| Grimminck, K. [70]          | Netherlands         | 1  | 31                      | —             | —             | 1             | Hypertension, systemic lupus erythematos                                                                           | Nonsevere            | —        | —                | —                             |        |
| First author's name | Country       | n    | Age (y) (mean or range) | 1<sup>st</sup> trimester | 2<sup>nd</sup> trimester | 3<sup>rd</sup> trimester | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|---------------|------|-------------------------|---------------------------|--------------------------|--------------------------|---------------------------------------------|---------------------|----------|------------------|---------------------------------------------|-------|
| Gulersen, M. [31]   | United States | 65   | 29-35                   | —                         | 65                       |                          | Known comorbidity (n = 11, including asthma, chronic hypertension, diabetes, HIV, and autoimmune disorders), none (n = 54) | Asymptomatic (n = 14), nonsevere (n = 44), severe (n = 7) | 5        | Not reported    | Not reported                                | —     |
| Hantoushzadeh, S. [99] | Iran         | 9    | Not extractable         | —                         | 9                        |                          | Obesity (n = 3), underweight (n = 1), diabetes (n = 1), hypothyroidism (n = 1), none (n = 3) | Severe (n = 9)       | 9        | 9                | ARDS (n = 2), cardiopulmonary collapse (n = 2), end organ failure (n = 1), acute renal failure (n = 1), septic shock and DIC (n = 1) | 7     |
| Hirshberg, A. [32]  | United States | 5    | 27-39                   | —                         | 2                        | 3                        | Obesity (n = 3), hypertension (n = 3), asthma (n = 1), diabetes (n = 1), chronic kidney disease (n = 1) | Severe (n = 5)       | 5        | 5                | —                                           | —     |
| Hong, L. [33]       | United States | 1    | 36                      | —                         | 1                        | —                        | Hypothyroidism, obesity, hyperlipidemia | Severe              | 1        | 1                | Septic shock, cardiomyopathy, ARDS, MODS (n = 1), HF, RF, (n = 1) | —     |
| Huang, W. [100]     | China         | 8    | 27-33                   | —                         | 8                        |                          | Anemia (n = 4), preeclampsia (n = 1), none (n = 4) | Nonsevere (n = 5), severe (n = 3) | 3        | 2                | —                                           | —     |
| Iqbal, S. [34]      | United States | 1    | 34                      | —                         | —                        | 1                        | Not reported | Obesity (n = 2), polycystic ovary syndrome (n = 1) | Nonsevere           | —        | —                | —                                           | —     |
| Juusela, A. [35]    | United States | 2    | 45, 26                  | —                         | —                        | 2                        | —                                          | Not extractable | 1        | 1                | Cardiomyopathy (n = 2)                        | —     |
| Kalafat, E. [101]   | Turkey        | 1    | 32                      | —                         | —                        | 1                        | Thalassemia | Severe             | 1        | 1                | MODS                                        | —     |
| Karami, P. [102]    | Iran          | 1    | 27                      | —                         | —                        | 1                        | None                      | Severe              | 1        | 1                | MODS                                        | 1     |
| First author's name | Country    | n  | Age (y) (mean or range) | Gestational age | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|------------|----|-------------------------|-----------------|---------------------------------------------|----------------------|----------|-----------------|-----------------------------------------------|-------|
| Kayem, G. [71]      | France     | 617| Not reported            | 617             | Obesity (n = 159), asthma (n = 37), diabetes (n = 85), gestational hypertension or preeclampsia (n = 21), chronic hypertension (n = 18) | Nonsevere (n = 582), severe (n = 35) | Not reported | 45              | Not reported                                    | 1     |
| Kelly, J.C. [36]    | United States | 1 | Not reported            | —               | Obesity                                    | Severe               | 1        | 1               | —                                             | —     |
| Khan, S. [103]      | China      | 3  | 28, 33, 27             | —               | Not reported                               | Asymptomatic (n = 102), nonsevere (n = 64), severe (n = 75) | —        | —               | —                                             | —     |
| Khoury, R. [37]     | United States | 241| 18–47                  | —               | Not reported                               | Nonsevere (n = 21) | —        | —               | —                                             | —     |
| Kirtsman, M. [83]   | Canada     | 1  | 40                     | —               | Familial neutropenia, diabetes, and frequent bacterial infections | Nonsevere            | —        | —               | —                                             | —     |
| Kuhrt, K. [72]      | United Kingdom | 1 | 30                     | —               | Thyroid carcinoma                         | Nonsevere            | —        | —               | —                                             | —     |
| Lang, G. [104]      | China      | 1  | 30                     | —               | None                                      | Nonsevere (n = 3), gestational hypertension (3), hypothyroidism (2), preeclampsia (1), chronic hypertension (1), polycystic ovary syndrome (1) | —        | —               | —                                             | —     |
| Li, N. [105]        | China      | 16 | 26–37                  | —               | Nonsevere (n = 16)                        | —                    | —        | —               | —                                             | —     |
| Li, Y. [106]        | China      | 1  | 30                     | —               | Not reported                              | Nonsevere            | —        | —               | —                                             | —     |
| Liao, X. [107]      | China      | 1  | 25                     | —               | Not reported                              | Nonsevere            | —        | —               | —                                             | —     |
| Liu, D. [108]       | China      | 15 | 23–40                  | —               | Nonsevere (n = 1), diabetes (n = 1), mitral valve and tricuspid valve replacement (n = 1), none (n = 13) | Nonsevere            | —        | —               | —                                             | —     |
| First author's name | Country      | n  | Age (y) (mean or range) | Gestational age 1st trimester | Gestational age 2nd trimester | Gestational age 3rd trimester | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|--------------|----|------------------------|-------------------------------|-------------------------------|-------------------------------|----------------------------------------|---------------------|----------|----------------|----------------------------------------|-------|
| Liu, H. [109]       | China        | 41 | 22-42                  | —                             | 41                            | —                             | Diabetes (n = 4), gestational hypertension (n = 3), hepatitis B (n = 1) | Nonsevere           | —        | —              | —                                      | —     |
| Liu, Y. [110]       | China        | 13 | 22-36                  | —                             | 2                             | 11                            | Not reported Diabetess (n = 3), asthma (n = 4), hypothyroidism (n = 3), hypertension (n = 2), obese (n = 15), underweight (n = 1), Crohn’s disease (n = 1), heart valve repair (n = 1), thyroid carcinoma (n = 1), seizure disorder (n = 2) | Severe (n = 1)      | 1        | 1              | MODS (n = 1)                            | —     |
| Lokken, E.M. [38]   | United States| 46 | 26-34                  | 3                             | 20                            | 23                            | None (n = 47), known comorbidities (n = 21, including diabetes (n = 9), chronic hypertension (n = 2), asthma (n = 2), cholestasis (n = 2), preeclampsia (n = 4)) | Asymptomatic         | (n = 22), symptomatic (n = 46) | —              | —        | —              | —                                      | —     |
| London, V. [39]     | United States| 68 | 25-34                  | —                             | 3                             | 65                            | None (n = 47), known comorbidities (n = 21, including diabetes (n = 9), chronic hypertension (n = 2), asthma (n = 2), cholestasis (n = 2), preeclampsia (n = 4)) | Asymptomatic         | (n = 22), symptomatic (n = 46) | —              | —        | —              | Not reported                           | 1     |
| Lowe, B. [73]       | Australia    | 1  | 31                     | —                             | —                             | 1                             | Not reported | Nonsevere | —        | —              | —                                      | —     |
| Lu, D. [111]        | China        | 1  | 22                     | —                             | —                             | 1                             | None | Nonsevere | —        | —              | —                                      | —     |
| Lucarelli, E. [40]  | United States| 3  | 38, 26, 46             | —                             | 2                             | 1                             | Not reported | Severe (n = 3) | 3        | 3              | Acute kidney injury (n = 1)               | —     |
| Lyra, J. [74]       | Portugal     | 1  | 35                     | —                             | —                             | 1                             | None | Nonsevere | —        | —              | —                                      | —     |
| Martinelli, I. [58] | Italy        | 1  | 17                     | —                             | —                             | 1                             | Obesity | Severe | —        | —              | Pulmonary embolism                        | —     |
| Martinez-Perez, O. [75] | Spain    | 82 | 19-48                  | —                             | 82                            | —                             | Diabetes (n = 1), preeclampsia (n = 4), asthma (n = 6), hypothyroidism (n = 3), other (n = 20) | Nonsevere (n = 78), severe (n = 4) | 9        | 6              | Sepsis (n = 1)                           | —     |
| Mehta, H. [41]      | United States| 1  | 39                     | —                             | 1                             | —                             | None | Severe | 1        | 1              | ARDS                                    | —     |
| Mendoza, M. [76]    | Spain        | 42 | 26-38                  | —                             | 42                            | —                             | Diabetes (n = 1) | Nonsevere (n = 34), severe (n = 8) | 8        | Not reported | Preeclampsia-like syndrome (n = 5)        | —     |
| First author’s name | Country          | n   | Age (y)       | 1<sup>st</sup> trimester | 2<sup>nd</sup> trimester | 3<sup>rd</sup> trimester | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|------------------|-----|---------------|---------------------------|--------------------------|--------------------------|-----------------------------------------------|----------------------|----------|-----------------|-----------------------------------------------|-------|
| Mulvey, J.J. [42]  | United States    | 5   | 26-40         | —                         | —                        | 5                        | Polycystic ovary syndrome, iron deficiency anemia (n = 1), hypothyroidism (n = 1), none (n = 3) | Asymptomatic (n = 4), nonsevere (n = 1) | —        | —               | —                                             | —     |
| Naqvi, M. [43]     | United States    | 1   | 35            | —                         | 1                        | —                        | Hypertension, diabetes, asthma                | Severe               | —        | —               | —                                             | —     |
| Nesr, G. [77]      | United Kingdom   | 2   | 34            | —                         | 1                        | —                        | Immune thrombocytopenia                       | Nonsevere            | —        | —               | —                                             | —     |
| Panichaya, P. [112]| Thailand         | 1   | 43            | —                         | 1                        | —                        | None                                          | Nonsevere            | —        | —               | —                                             | —     |
| Peng, Z. [113]     | China            | 1   | 25            | —                         | —                        | 1                        | None                                          | Nonsevere            | —        | —               | —                                             | —     |
| Pereira, A. [78]   | Spain            | 60  | 22-43         | 10                        | 16                       | 32                       | HELLP syndrome (n = 1), preeclampsia (n = 2), DVT (n = 2) | Severe and critical (n = 64) | Not reported | 24               | ARDS (n = 14), cardiac arrest (n = 1)       | —     |
| Pierce-Williams, RMP [44] | United States | 64  | 33.2          | —                         | —                        | 64                       | Cardiac disease (including chronic hypertension, cardiomyopathy) (n = 11), pulmonary pathology (n = 16) | Severe and critical (n = 64) | Not reported | 24               | Pulmonary edema (n = 2)                      | —     |
| Prabhu, M. [45]    | United States    | 70  | 30.5 in symptomatic and 31.4 in asymptomatic (med) | —                         | —                        | 70                       | Chronic hypertension (n = 3), preeclampsia or gestational hypertension (n = 11), diabetes (n = 10), asthma (n = 6), obesity (n = 12) | Asymptomatic (n = 55), symptomatic (n = 15) | 1        | —               | Pulmonary edema (n = 2)                      | —     |
| Qadri, F. [5]      | United States    | 16  | 20-40         | —                         | —                        | 16                       | Obesity (n = 10)                              | Nonsevere (n = 16)    | —        | —               | —                                             | —     |
| Qiancheng, X. [114]| China            | 28  | 30            | 3                         | 1                        | 24                       | Hypertension (n = 1), diabetes (n = 2), hepatitis B (n = 2), hypothyroidism (n = 1) | Severe (n = 2)       | Not reported | Not reported | Not reported                              | —     |
| Rabice, S.R. [46]  | United States    | 1   | 36            | —                         | —                        | 1                        | Diabetes, asthma, obesity, preeclampsia       | Nonsevere            | —        | —               | Acute pancreatitis                          | —     |
| Rubin, E.S. [47]   | United States    | 1   | 26            | —                         | —                        | 1                        | Chronic hypertension                          | Nonsevere            | —        | —               | —                                             | —     |
| First author's name       | Country     | n   | Age (y) (mean or range) | 1<sup>st</sup> trimester | 2<sup>nd</sup> trimester | 3<sup>rd</sup> trimester | Comorbidities and complications in gestation                                                                                   | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------------|-------------|-----|-------------------------|---------------------------|-------------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------|---------------------|----------|----------------|---------------------------------------------|-------|
| San-Juan, R. [79]         | Spain       | 32  | 32                      | 1                         | 9                       | 22                      | None (n = 26), asthma (n = 4), obesity (n = 1), multiple sclerosis (n = 1), diabetes (n = 2)                                    | Severe (n = 18)     | 2        | 2              | ARDS (n = 8)                                      | —     |
| Savasi, V.M. [59]         | Italy       | 77  | 15–48                   | 4                         | 13                      | 50<sup>c</sup>          | Known comorbidities (n = 24 including obesity and cardiovascular, autoimmune, endocrine, and metabolic diseases)               | Asymptomatic (n = 12), severe (n = 14) | 6        | 6              | —                                           | —     |
| Schnettler, WT [48]       | United States | 1  | 39                      | —                         | —                       | 1                       | Myotonic dystrophy, bicuspid aortic valve, a prior mild cerebrovascular accident                                             | Severe              | 1        | 1              | ARDS                                        | —     |
| Sentilhes, L. [80]        | France      | 54  | 19–42                   | Not extractable           |                         |                         | Obesity (n = 4), asthma (n = 5), chronic hypertension (n = 1), other (n = 4)                                              | Nonsevere (n = 37), severe and critical (n = 17) | 5        | 5              | ARDS (n = 1)                                     | —     |
| Shojaei, S. [115]         | Iran        | 1   | 38                      | —                         | 1                       | —                       | None                                                                                                                                  | None                | 1        | 1              | Cardiac arrest (n = 1)                            | —     |
| Silverstein, J.S. [49]    | United States | 2  | 17, 34                  | —                         | —                       | 2                       | Obesity (n = 1)                                                                                                                | Severe (n = 2)      | 2        | 2              | —                                           | —     |
| Sinkey, R.G. [50]         | United States | 1  | 25                      | —                         | —                       | 1                       | Hypertension, preeclampsia, obesity, anemia                                                                                        | Not reported        | —        | —              | HF, pulmonary edema                               | —     |
| Slayton-Milam, S. [51]    | United States | 1  | 27                      | —                         | —                       | 1                       | Not reported                                                                                                                 | Severe              | 1        | 1              | Worsening anemia (n = 1)                          | —     |
| Taghizadieh, A. [116]     | Iran        | 1   | 33                      | —                         | —                       | 1                       | None                                                                                                                                  | Severe              | 1        | 1              | Acute kidney injury (n = 1)                       | —     |
| Takemoto, M.L.S. [117]    | Brazil      | 978 | 29.5 for recovered, 31.5 for died women | Not reported              |                         |                         | Cardiovascular (n = 54), diabetes (n = 89), obesity (n = 44), asthma (n = 23)                                                  | Not reported        | 207      | 317            | Not reported (n = 124)                           | 124   |
| Tutiya, C.T. [118]        | Brazil      | 2   | 44, 29                  | —                         | —                       | 3                       | Obese (n = 2), history of breast cancer (n = 1), hypertension (n = 1)                                                              | Severe              | 2        | 2              | Pulmonary microthrombi                           | —     |
| Vallejo, V. [8]           | United States | 1  | 36                      | —                         | —                       | 1                       | Obesity                                                                                                                               | Severe              | 1        | 1              | MODS (n = 1)                                      | —     |
| Vibert, F. [81]           | France      | 1   | 21                      | —                         | 1                       | —                       | None                                                                                                                                  | Severe              | 1        | 1              | —                                           | —     |
| First author's name | Country | n     | Age (y) (mean or range) | 1st trimester | 2nd trimester | 3rd trimester | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|---------|-------|-------------------------|---------------|---------------|---------------|-----------------------------------------------|---------------------|----------|-----------------|-----------------------------------------------|--------|
| Vivanti, A.J. [82]  | France  | 100   | 29-37                   | —             | 100           |               | Asthma (n = 9), diabetes (n = 7), hypertension (n = 6) | Severe (n = 10)  | 10       | 9               | ARDS (n = 6), transient hepatitis (n = 1) |        |
| Wang, X. [119]     | China   | 1     | 28                      | —             | —             | 1             | Not reported | Not reported | Severe | 1 Not reported | —                  | —      |
| Wang, Z. [120]     | China   | 30    | 29.9                    | —             | —             | 30            | Hypertension (n = 5), diabetes (n = 2), hypothyroidism (n = 1), obesity (n = 1) | Nonsevere (n = 30) | Not reported | Not reported | Not reported | —                  | —      |
| Wu, C. [121]       | China   | 8     | 26-35                   | —             | —             | 8             | Not reported | Asymptomatic (n = 4), nonsevere (n = 4) | —                  | —        | —               | —                  | —      |
| Wu, X. [122]       | China   | 23    | 21-37                   | 3             | —             | 20            | Hypothyroidism (n = 2), hepatitis B (n = 2), hypertension (n = 4), none (n = 15) | Asymptomatic (n = 15), nonsevere (n = 8) | Not reported | Not reported | Not reported | —                  | —      |
| Wu, Y. [123]       | China   | 13    | 26-40                   | 5             | 3             | 5             | Not reported | Nonsevere | —               | —                  | —      |
| Xia, H. [124]      | China   | 1     | 27                      | —             | —             | 1             | Not reported | Not reported | Not reported | —                  | —      |
| Xiong, X. [125]    | China   | 1     | 25                      | —             | —             | 1             | Not reported | Nonsevere | —               | —                  | —      |
| Xu, L. [126]       | China   | 5     | 23-34                   | —             | —             | 5             | Anemia (n = 2) | Nonsevere (n = 5) | —                  | —        | —               | —                  | —      |
| Yan, J. [127]      | China   | 116   | 24-41                   | 4             | 6             | 106           | Diabetes (n = 8), hypertensive disorders (n = 5) | Nonsevere (n = 108), severe (n = 8) | 8        | 8               | —                  | —      |
| Yang, H. [128]     | China   | 27    | 22-39                   | 4             | —             | 23            | Diabetes (n = 3), coagulopathy (n = 3), gestational hypertension (n = 2), hypothyroidism (n = 2), preeclampsia (n = 1), hypoproteinemia (n = 1), hepatitis (n = 2), schistosomiasis (n = 1) | Severe (n = 1) | —        | —               | —                  | —      |
| Yassa, M. [129]    | Turkey  | 8     | 19-41                   | 3             | 3             | 2             | Not reported | Not reported | 1 Not reported | —                  | —      |
| First author’s name | Country  | n  | Age (y) (mean or range) | Gestational age | Comorbidities and complications in gestation | Severity of COVID-19 | ICU need | Ventilation need | Complications during treatment of COVID-19 (n) | Death |
|---------------------|----------|----|------------------------|-----------------|---------------------------------------------|----------------------|----------|-----------------|---------------------------------------------|-------|
| Yu, N. [130]        | China    | 7  | 29-34                  | —               | Hypothyroidism (n = 1), polycystic ovary (n = 1), none (n = 5) | Not reported          | —        | —               | —                                           | —     |
| Zamanian, M. [131]  | Iran     | 1  | 22                     | —               | Hypothyroidism | Severe | 1   | 1               | ARDS 1                                      | —     |
| Zambrano, L.I. [132]| Honduras | 1  | 41                     | —               | Hypertension, hypothyroidism | Nonsevere            | —        | —               | —                                           | —     |
| Zeng, Y. [133]      | China    | 16 | 25-40                  | —               | Cardiac disease (n = 2), hypothyroidism (n = 2), thalassemia (n = 1) | Nonsevere (n = 16)   | Not reported | —               | Not reported                                | —     |
| Zhang, L. [134]     | China    | 18 | 24-34                  | —               | Preeclampsia (n = 1), diabetes (n = 3) | Nonsevere (n = 17), severe (n = 1) | Not reported | Not reported | —                                           | —     |

ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome; SCIM: septic-induced ischemic cardiomyopathy; HF: heart failure; RF: respiratory failure; DIC: disseminated intravascular coagulation. *Data on symptom status were missing for 2852 (35%) pregnant women. **A total of 6079 (74%) pregnant women have missing information for ICU admission and were assumed to have not been admitted to an ICU. ***A total of 6351 (77%) pregnant women have missing information for receipt of mechanical ventilation and were assumed to have not received mechanical ventilation. ****A total of 3819 (47%) pregnant women have missing information on death and were assumed to have survived. *****10 patients were postpartum women.
| Case Study (country) | Maternal age, gravida, para, gestational age (weeks) | Comorbidities | Presenting symptoms | Mode of delivery | Duration from admission to death of the neonate | Duration from admission to death of the mother | Polymerase chain reaction testing of the neonate | Polymerase chain reaction testing of mother |
|----------------------|-----------------------------------------------------|---------------|---------------------|-----------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Ahmed, I. (United Kingdom) | 29, G2P1, 29 | Yes, Yes, Yes | Renal disease, vitamin D deficiency, obesity, hypertension | Cesarean | 15 days from the first admission, 7 days from the second admission | N/A (Stillbirth) | Negative | N/A (death of both fetuses) |
| Karamim, P. (Iran) | 27, G2P1, 30 | No, No, No | Fever, cough, malaise, dyspnea | Vaginal delivery | 3 days | N/A | N/A | N/A |
| Shojaei, S. (Iran) | 36, G3P3A0, 37 | Yes, No, No | Fever, cough, dyspnea, myalgia | Cesarean delivery | 19 days | Negative | Positive | N/A |
| Vallejo, V. (United States) | 30-34, G2P1, 28 | Yes, Yes, No | Fever, cough, sore throat | Cesarean | 2 days | Negative | Positive | N/A |
| Zamaniyan, M. (United States) | 35-39, G2P1, 28 | Yes, No, Yes | Hypothyroidism, obesity, diabetes | Cesarean | 5 days | Negative | Positive | N/A |
| Hantoushzadeh, S. (Iran) | 25-29, G2P1, 30 | No, No, No | Fever, cough, dyspnea, myalgia | Cesarean | 4 days | Negative | Positive | N/A |
| 30-34, G3P0, 24 | No, Yes, No | Fever, cough, myalgia, dyspnea, anorexia | Cesarean | 15 days | Negative | Positive | N/A | N/A |
| 35-39, G2P0, 28 | Yes, No, No | Fever, cough, dyspnea, myalgia | Cesarean | 22 days | Negative | Positive | N/A | N/A |
| 45-49, G2P1, 28 | Yes, No, No | Underweight, diabetes | Cesarean | 18 days | Negative | Positive | N/A | N/A |
## Table 3: Continued.

| Case Study (country) | Maternal age (years), gravida, para, gestational age (weeks) | Advanced maternal age | Comorbidities | Other | Presenting symptoms | Mode of delivery | Duration from admission to death | Polymerase chain reaction testing of the neonate |
|----------------------|-------------------------------------------------------------|-----------------------|---------------|-------|---------------------|-----------------|---------------------------------|-----------------------------------------------|
| Takemoto, M.L.S. (Brazil) \(^b\) | 31.5 (mean), no data about gravida or gestational age was available | Not reported | 13\(^e\) | 22\(^d\) | 5\(^e\) | 13\(^f\) | Not reported | Not reported | Not reported | Not reported |

\(^a\) Maternal age was gated in inclusive 5-year blocks (patient identification). \(^b\) 74 were pregnant and 50 were postpartum women. \(^c\) Missing/unknown (%) = 50.8. \(^d\) Missing/unknown (%) = 47.6. \(^e\) Missing/unknown (%) = 56.5. \(^f\) Missing/unknown (%) = 35.5.
3. Results

3.1. Search Results. Figure 1 shows the PRISMA flow chart for study selection. The search strategy retrieved 1348 records and 4 additional records identified through Google Scholar search. After removing 632 duplicates, 720 titles and abstracts were screened. In the second screening, 167 full texts were evaluated and a total of 117 studies were included in the systematic review.

3.2. General Characteristics. The characteristics of the included studies are shown in Table 2. A total of 11758 pregnant and postpartum women entered the review study ranging from 1 to 8207 per study. The age range of patients was between 15 and 48 years. Most subjects were infected with SARS-CoV-2 in the third trimester. Disease severity was not reported in 1125 samples. In the remaining cases, the highest frequency was related to asymptomatic COVID-19 ($n = 5466$, $51.4\%$).

In terms of the country of origin, the highest frequencies were in China with 34 articles [8, 12, 21–52], the United States with 33 articles [5, 8, 12, 22–51], and Italy with 8 articles [52–59]. 65 studies including 10183 patients were undertaken in the high-income countries [5, 8, 12, 22–83] and 52 studies ($n = 1575$) in middle-income countries [21, 84–134].

3.3. Outcomes

3.3.1. Mortality Rate of Pregnant and Postpartum Women due to COVID-19. In total, there were 153 deaths out of 11758 pregnant and postpartum women affected by COVID-19 ($1.30\%$), of which 19 deceased patients were in high-income countries [5, 8, 12, 22–29, 31–34, 41, 42, 46, 47, 65, 66, 68–70, 72, 74–76, 83, 86, 87, 92, 94, 96, 99, 100, 104, 105, 117].

The data on 136 cases of maternal death due to COVID-19 is presented in Table 3. The highest mortality rate was reported in the study of Takemoto et al. in Brazil using the Brazilian Ministry of Health’s ARDS Surveillance System. In this study, the authors found 124 deaths in COVID-19-infected pregnant or postpartum women ($12.7\%$) [131].

3.3.2. Presenting Symptoms of COVID-19 in Pregnant and Postpartum Women Who Died of COVID-19. In all of the fatal cases with adequate data, fever alone or with cough was one of the presenting symptoms. After them, dyspnea ($58.3\%$) and myalgia ($50\%$) were the most common symptoms, respectively. Sore throat ($8.3\%$) and gastrointestinal symptoms (anorexia, nausea) ($8.3\%$) were rare.

3.3.3. Comorbidity Rate in Pregnant and Postpartum Women Who Died of COVID-19. The comorbidity rate in women who died from COVID-19 was $20\%$ (Table 3). In total, 41.7% of the deceased patients were 35 years or older (advanced maternal age), $31.1\%$ had diabetes, $21.9\%$ were obese, $14.1\%$ had cardiovascular disease (essential hypertension, gestational hypertension, preeclampsia, HELLP syndrome, drome, and heart problems), and $9.1\%$ had a history of asthma.

3.3.4. Meta-Analysis Results for Morbidities in Patients Who Died of COVID-19. The effect size in five studies for obesity...
was 0.47 (95% CI: 0.04 to 0.90, Pr value = 0.03), for diabetes was 0.29 (95% CI: -0.08 to 0.65, Pr value = 0.12), for asthma was 0.41 (95% CI: -0.06 to 0.88, Pr value = 0.09), for cardiovascular disease was 0.03 (95% CI: -0.03 to 0.10, Pr value = 0.32), for advanced maternal age was 0.61 (95% CI: 0.13 to 1.08, Pr value = 0.01), and for all comorbidity rate was 0.32 (95% CI: -0.06 to 0.88, Pr value = 0.12). Further visual inspection of the funnel plot showed a slight degree of publication bias (Figure 5).

(2) Sensitivity Analysis after Deleting the Studies with n=1. Removing these studies resulted in an effect size Pr = 0.49 (95% CI: 0.33 to 0.66, Pr value < 0.001), with a significant heterogeneity ($\tau^2 = 0.12$, $I^2 = 100.0\%$, $H^2 = 8.72e + 10$, $Q_{(df=17)} = 1.07e + 07$, $P_Q < 0.001$). Figure 6 shows the forest plot of individual effect sizes within each study. Assessment for bias by Egger’s and Begg’s tests showed no significant small-study effects (Pr = 0.308 > 0.05 and Pr = 0.054 > 0.05, respectively).

(3) Subgroup Analysis of Obesity in Recovered and Dead Pregnant and Postpartum Women. The forest plot of the individual effect size of predetermined subgroup analysis by dead/recovered is presented in Figure 7. The results indicate a higher proportion of outcome in the recovered subgroup (Pr = 0.53, 95% CI = 0.36 to 0.71), than in the deceased subgroup (Pr = 0.18, 95% CI = 0.11 to 0.25). Therefore, the test showed a significant difference between the subgroups ($Q_{(df=1)} = 13.58$, $P_Q < 0.001$). Additionally, the heterogeneity did not reduce in all subgroups ($I^2 = 93.65\%$ and $I^2 = 100\%$ in the recovered and deceased subgroups, respectively).

3.3.5. Meta-Analysis Results for Obesity

(1) Obesity in All Pregnant and Postpartum Women Affected by COVID-19. The proportion from 33 studies was 0.69 (95% CI: 0.56 to 0.82, Pr value < 0.001) based on a random effect model, with significant heterogeneity between studies ($\tau^2 = 0.14$, $I^2 = 100.0\%$, $H^2 = 1.28e + 11$, $Q_{(df=32)} = 9.68e + 11$, $P_Q < 0.001$). Figure 4 shows the forest plot of individual effect sizes within each study. Assessment for bias by Egger’s and Begg’s tests showed no significant small-study effects (Pr = 0.308 > 0.05 and Pr = 0.054 > 0.05, respectively). Further visual inspection of the funnel plot suggests a slight degree of publication bias (Figure 3).
3.3.6. Meta-Analysis Results for Diabetes (Pregestational or Gestational)

(1) Diabetes in All Pregnant and Postpartum Women Affected by COVID-19. The proportion from 38 studies was 0.38 (95% CI: 0.25 to 0.51, P value < 0.001) based on a random effect model, with significant heterogeneity between studies ($I^2 = 0.15, I^2 = 100.00\%, H^2 = 4.62e+10, Q_{(df=37)} = 5.95e + 7, P_Q < 0.001$). Figure 8 shows the forest plot of individual effect sizes within each study. Assessment for bias by Egger’s and Begg’s tests showed no significant small-study effects ($P = 0.969 > 0.05$ and $P = 0.339 > 0.05$, respectively). Further visual inspection of the funnel plot suggested a slight degree of publication bias (Figure 9).

(2) Sensitivity Analysis after Deleting the Studies with n=1. Removing these studies resulted in an effect size Pr = 0.18 (95% CI: 0.11 to 0.25, P value < 0.001), with a significant
heterogeneity ($r^2 = 0.04, I^2 = 100.0\%, H^2 = 1.76 + 5, Q_{(df=22)} = 5.95e + 07, P_Q < 0.001$). Figure 10 shows the forest plot of individual effect sizes within each study.

(3) Subgroup Analysis of Diabetes in Recovered and Dead Pregnant and Postpartum Women. The forest plot of the individual effect size of predetermined subgroup analysis by dead/recovered is presented in Figure 11. The results indicate lower proportion of outcome in the recovered subgroup ($Pr = 0.18, 95\%CI = 0.10 to 0.25$), than in the dead subgroup ($Pr = 0.18, 95\%CI = 0.11 to 0.25$), so that the test showed a nonsignificant difference between the subgroups ($Q_{(df=1)} = 0.37, P_Q = 0.54 > 0.05$). Additionally, the heterogeneity did not reduce in all subgroups ($I^2 = 100.0\%$ and $I^2 = 99.17\%$ in the recovered and dead subgroups, respectively).

3.3.7. Meta-Analysis Results for Cardiovascular Diseases

(1) Cardiovascular Diseases in All Pregnant and Postpartum Women Affected by COVID-19. The proportion from 40 studies was 0.36 (95% CI: 0.24 to 0.48, $P$ value < 0.001) based on a random effect model, with significant heterogeneity between studies ($r^2 = 0.15, I^2 = 100.0\%, H^2 = 3.52e + 10, Q_{(df=39)} = 3.42e + 8, P_Q < 0.001$). Figure 12 shows the forest plot of individual effect sizes within each study. Assessment for bias by Egger’s and Begg’s tests showed no significant small-study effects ($P = 0.942 > 0.05$ and $P = 0.129 > 0.05$, respectively). Further visual inspection of the funnel plot suggested a slight degree of publication bias (Figure 13).

(2) Sensitivity Analysis after Deleting the Studies with $n=1$. Removing these studies resulted in an effect size $Pr = 0.14\%$ (95% CI: 0.10 to 0.18, $P$ value < 0.001), with a significant heterogeneity ($r^2 = 0.01, I^2 = 100.0\%, H^2 = 2.15e + 4, Q_{(df=29)} = 2.57e + 04, P_Q < 0.001$). Figure 14 shows the forest plot of individual effect sizes within each study.

(3) Subgroup Analysis of Cardiovascular Diseases in Recovered and Dead Pregnant and Postpartum Women. The forest plot of the individual effect size of predetermined subgroup analysis by dead/recovered is presented in Figure 15. The results indicate lower proportion of outcome in the recovered subgroup ($Pr = 0.14, 95\%CI = 0.10 to 0.18$), than in the dead subgroup ($Pr = 0.16, 95\%CI = 0.16 to 0.17$), so that the test showed a nonsignificant difference between the subgroups ($Q_{(df=1)} = 1.28, P_Q = 0.26 > 0.05$). Additionally,
the heterogeneity did not reduce in all subgroup especially ($I^2 = 100.0\%$ and $I^2 = \text{noncomputable}$ in the recovered and dead subgroups, respectively).

3.3.8. Mode of Delivery in Pregnant and Postpartum Women Who Died of COVID-19. The mode of delivery in deceased cases with sufficient data ($n = 12$) was as follows: 58.3% had cesarean section, 25% had vaginal delivery, and 16.7% were not full term. Meta-analysis for mode of delivery in the fatal cases showed that the proportion from 6 studies was 0.00 (95% CI: -0.03 to 0.04, $P = 0.96$) based on a random effect model, with nonsignificant heterogeneity between studies ($t^2 = 0.00$, $I^2 = 0.03\%$, $H^2 = 1$, $Q_{(df=5)} = 2.99$, $P = 0.70$). Figure 16 shows the forest plot of individual effect sizes within each study.

Assessment for bias by Egger’s and Begg’s tests showed no significant small-study effects ($P = 0.084 > 0.05$ and $P = 0.181 > 0.05$, respectively). Further visual inspection of the funnel plot suggested a slight degree of publication bias (Figure 17).

3.3.9. Other Findings. Duration from admission to death was between 2 and 22 days [85, 124]. The most common complication during treatment of COVID-19 in pregnant and postpartum women was acute respiratory distress syndrome (ARDS). In fatal cases, PCR testing of the neonate was not indicated in 41.6% of cases (stillbirth, undelivered). In 41.6%, it was negative, and in 16.7% of the cases, the result of the initial test was negative and the second test was positive [124, 134].
4. Discussion

In this study, we systematically investigated 117 published reports involving 117,589 pregnant women from the high- and middle-income countries assessing the effect of COVID-19 on the risk of mortality.

In this systematic review, the mortality rate of COVID-19 in pregnant and postpartum women was 1.30% and the rate of severe pneumonia was reported from 0 to 14%. The majority of the patients were admitted to the ICU, and the maternal death was consistent with reported outcomes from other severe viral lower respiratory tract infections [5, 135–140].

Unlike the current study, in some studies, the mortality rate of COVID-19-infected pregnant women was not higher than nonpregnant women of reproductive age [13, 58, 141]. The absence of deaths was explained by the younger age pregnant women who were infected because it has been shown that the...
The mortality rate in COVID-19 patients is high in older individuals and those patients with at least one comorbidity [127]. Also, the number of cases in these studies was relatively small and all women were in their third trimester of pregnancy and most of them gave birth earlier than seven days after diagnosis of the disease. Hence, this clinical manifestation-to-delivery time may be too short to affect pregnancies [142]. Additionally, this discrepancy may be due to the data available at the time of publication in our study. The pregnancy-related immunological changes may be one of the causes of maternal vulnerability to COVID-19, but this did not significantly affect the response against SARS-CoV-2 [142]. In addition, maternal mortality rates were lower in high-income compared with low-income countries. In this systematic review, most of the studies were from China. It is possible that our study reported a higher mortality rate than other studies because our sample size was larger. Similar to this finding, it was shown that the incidence of maternal mortality rate in middle-income countries seems at least six times higher than that in high-income countries [142]. These findings indicate the weaknesses of maternity services in low-income countries. In addition, major barriers for a more equitable delivery of critical care in low-income countries may be an important factor, such that in Brazil—a middle-income country—only 72% of COVID-19-infected pregnant or postpartum women with COVID-19 were admitted to the ICU and 15% of them did not receive ventilation support [131]. In Mexico, only two out of seven deaths had been admitted to the ICU and received invasive respiratory assistance [143].

Viral pneumonia is one of the leading causes of pregnancy deaths worldwide [12].
in pregnant women are not different from others [144]. Maternal deaths due to cardiopulmonary complications, sometimes with multiorgan failure, have been reported in the previous literatures [9, 31, 102, 145]. In one study, pregnant women with SARS-CoV-2 infection in their second or third trimester of pregnancy died due to cardiopulmonary complications [9].

In all of the fatal cases, fever alone or with cough, dyspnea, and myalgia were the most common symptoms, respectively. Sore throat and gastrointestinal symptoms were rare. In accordance with this finding in another systematic review, the most common symptoms at presentation were fever, cough, dyspnea/shortness of breath, fatigue, and myalgia [146]. Data from nonpregnant adults have described the

| Study                  | Pr with 95% CI | Weight (%) |
|------------------------|---------------|------------|
| Recovered              |               |            |
| Breslin, N 1           | 0.07 [0.07, 0.07] | 3.53       |
| Breslin, N 2           | 0.29 [0.23, 0.34] | 3.46       |
| Cao, D                 | 0.10 [0.08, 0.12] | 3.53       |
| Chen, R                | 0.12 [0.11, 0.13] | 3.53       |
| Chen, S                | 0.40 [0.31, 0.49] | 3.34       |
| Cohen, J               | 0.08 [0.08, 0.08] | 3.53       |
| Cooke, WR              | 1.00 [1.00, 1.00] | 3.53       |
| Fontanella, F          | 0.50 [0.26, 0.74] | 2.52       |
| Goldfarb, IT           | 0.08 [0.08, 0.08] | 3.53       |
| Govind, A              | 0.22 [0.18, 0.26] | 3.50       |
| Hantoushzadeh, S       | 0.50 [0.26, 0.74] | 2.52       |
| Hirshberg, A           | 0.20 [0.14, 0.26] | 3.44       |
| Li, N                  | 0.19 [0.17, 0.21] | 3.53       |
| Liu, D                 | 0.07 [0.06, 0.07] | 3.53       |
| Liu, H                 | 0.10 [0.09, 0.10] | 3.53       |
| Lokken, E.M            | 0.07 [0.06, 0.07] | 3.53       |
| Martinez-Perez, O      | 0.01 [0.01, 0.01] | 3.53       |
| Mendoza, M             | 0.02 [0.02, 0.02] | 3.53       |
| Prabhu, M              | 0.14 [0.14, 0.15] | 3.53       |
| Qiancheng, X           | 0.07 [0.07, 0.08] | 3.53       |
| San-Juan, R            | 0.06 [0.06, 0.07] | 3.53       |
| Takemoto, M.L.S        | 0.21 [0.21, 0.21] | 3.53       |
| Vivanti, A.J           | 0.07 [0.07, 0.07] | 3.53       |
| Wang, Z                | 0.07 [0.06, 0.07] | 3.53       |
| Yan, J (11)            | 0.07 [0.07, 0.07] | 3.53       |
| Yang, H (22)           | 0.11 [0.10, 0.12] | 3.53       |
| Zhang, L               | 0.17 [0.15, 0.18] | 3.53       |
| Heterogeneity: $\tau^2 = 0.04$, $I^2 = 100.00\%$, $H^2 = 199181.86$ | 0.18 [0.10, 0.25] | 3.53 |

| Study                  | Pr with 95% CI | Weight (%) |
|------------------------|---------------|------------|
| Died                   |               |            |
| Hantoushzadeh, S       | 0.14 [0.11, 0.18] | 3.51       |
| Takemoto, M.L.S        | 0.34 [0.33, 0.35] | 3.53       |
| Heterogeneity: $\tau^2 = 0.02$, $I^2 = 99.17\%$, $H^2 = 120.37$ | 0.24 [0.05, 0.43] | 3.53 |

| Study                  | Pr with 95% CI | Weight (%) |
|------------------------|---------------|------------|
| Overall                | 0.18 [0.11, 0.25] | 3.54       |

Heterogeneity: $\tau^2 = 0.04$, $I^2 = 100.00\%$, $H^2 = 175967.18$

Test of group differences: $Q_0 (1) = 0.37$, $P = 0.54$

Random-effects REML model

Figure 11: Forest plot of individual effect size for obesity by subgroups.
most common presenting symptoms of COVID-19 as fever, cough, and dyspnea [147, 148]. In contrast with our review, in some other systematic reviews, the symptoms were significantly different with fever and cough occurring more than myalgia as well as dyspnea and fatigue occurring only in approximately one-sixth of symptomatic pregnant women [3, 149–153].

Another finding in this study was the high prevalence of maternal comorbidities. The comorbidity rate in deceased women was 20%, and most of the pregnant women showed biochemical evidence of inflammation, mainly lymphopenia. However, in one study, nearly half of all patients (46%) had no baseline comorbidities [31]. In another study, approximately one out of every three women with SARS-CoV-2 infection had a comorbid condition, but no maternal deaths secondary to COVID-19 were reported [13]. High comorbidity and lack of maternal mortality may be due to the younger...
age of mothers. While similar to Khalil et al.’s study, maternal mortality in our study was higher due to advanced maternal age (35 years of age or older) [148] which makes management of comorbidities challenging. Also, these comorbidities per se could cause maternal deaths.

Advanced maternal age (age > 35) was the most prevalent comorbidity; other comorbidities included diabetes, obesity, cardiovascular disease (essential hypertension, gestational hypertension, preeclampsia, HELLP syndrome, and heart problems), and history of asthma, respectively. These comorbidities suggest that maternal morbidity is not different from nonpregnant women of reproductive age. In one study, obesity and pulmonary conditions such as asthma and obstructive sleep apnea (OSA) were the most common comorbidities. Also, maternal ICU admission was one of the other outcomes. Also, pregnant and postpartum women with COVID-19 admitted to the ICUs are at risk for maternal death, which may occur even in the absence of substantial baseline comorbidities [31, 148]. Another comorbidity was antiviral drug use [146, 148]; while these two causes were
not found in our study, the comorbidities could indirectly lead to patients’ ICU admission and administration of antiviral drugs. In contrast to our study, another study showed none of the pregnant patients had preexisting comorbidities, such as hypertension, cardiovascular disease, and asthma [9, 146].

Based on the results, the majority of deliveries in pregnant women with SARS COVID-19 were cesarean section. Similar to this result, COVID-19 infection was associated with a relatively higher cesarean delivery in other studies [10, 31, 146]. Also, in another systematic review, the rate of cesarean delivery was higher than in our study because more than 90% of cesarean sections were from China (306/332). Some articles from China have shown SARS-CoV-2 infection as an indication for cesarean delivery [154–156], thereby justifying such a difference in the rate of cesarean section.

| Study                                      | Pr with 95% CI | Weight (%) |
|--------------------------------------------|---------------|------------|
| Recovered                                  |               |            |
| Breslin, N 1                               | 0.07 [0.07, 0.07] | 3.44       |
| Breslin, N 2                               | 0.14 [0.11, 0.18] | 3.36       |
| Cao, D                                     | 0.30 [0.26, 0.34] | 3.32       |
| Chen, H                                    | 0.22 [0.18, 0.26] | 3.34       |
| Chen, R                                    | 0.12 [0.11, 0.13] | 3.43       |
| Chen, S                                    | 0.20 [0.14, 0.26] | 3.17       |
| D’oria, M                                  | 0.08 [0.07, 0.10] | 3.43       |
| Hirshberg, A                               | 0.60 [0.51, 0.69] | 2.89       |
| Huang, W                                   | 0.13 [0.10, 0.15] | 3.39       |
| Li, N                                      | 0.31 [0.29, 0.34] | 3.39       |
| Liu, D                                     | 0.07 [0.06, 0.07] | 3.44       |
| Liu, H                                     | 0.07 [0.07, 0.08] | 3.44       |
| Lokken, E.M                                | 0.07 [0.06, 0.07] | 3.44       |
| London, V                                  | 0.09 [0.09, 0.09] | 3.44       |
| Martinez-Perez, O                          | 0.07 [0.07, 0.07] | 3.44       |
| Pereira, A                                 | 0.05 [0.05, 0.05] | 3.44       |
| Pierce-Williams, RMP                       | 0.17 [0.17, 0.18] | 3.44       |
| Prabhu, M                                  | 0.20 [0.20, 0.20] | 3.44       |
| Qiancheng, X                               | 0.04 [0.03, 0.04] | 3.44       |
| Sentilhes, L                               | 0.02 [0.02, 0.02] | 3.44       |
| Takemoto, M.L.S                            | 0.05 [0.05, 0.05] | 3.44       |
| Tuttya, C.T                                | 0.50 [0.26, 0.74] | 1.50       |
| Vivanti, A.J                               | 0.06 [0.06, 0.06] | 3.44       |
| Wang, Z                                    | 0.17 [0.16, 0.18] | 3.44       |
| Wu, X                                      | 0.17 [0.16, 0.19] | 3.43       |
| Yan, J                                     | 0.04 [0.04, 0.04] | 3.44       |
| Yang, H                                    | 0.11 [0.10, 0.12] | 3.44       |
| Zeng, Y                                    | 0.13 [0.11, 0.14] | 3.43       |
| Zhang, L                                   | 0.06 [0.05, 0.06] | 3.44       |
| **Heterogeneity:** $\tau^2 = 0.01$, $I^2 = 100.00\%$, $H^2 = 22927.23$ | | |
| **Test of $\theta_i = \theta_j$:** $Q_{(28)} = 21132.48$, $P = 0.00$ | | |

| Died                                       |               |            |
| Takemoto, M.L.S                            | 0.16 [0.16, 0.17] | 3.44       |
| **Heterogeneity:** $\tau^2 = 0.00$, $I^2 = 0\%$, $H^2 = 0$ | | |
| **Test of $\theta_i = \theta_j$:** $Q_{(29)} = 25677.64$, $P = 0.00$ | | |

| Overall                                    |               |            |
| **Heterogeneity:** $\tau^2 = 0.01$, $I^2 = 100.00\%$, $H^2 = 21471.96$ | | |
| **Test of $\theta_i = \theta_j$:** $Q_{(29)} = 25677.64$, $P = 0.00$ | | |
| **Test of group differences:** $Q_{(1)} = 1.28$, $P = 0.26$ | | |

**Figure 15:** Forest plot of individual effect size for obesity by subgroups.
contrast to this finding, in Ferrazzi et al.’s study, 57% of women delivered vaginally and elective cesarean sections were performed in 43% of cases. Dyspnea or other COVID-19-related symptoms resulted in 23.8% cesarean sections among COVID-19-infected patients [157]. In the study by Khalil et al., the rate of cesarean section in mothers with COVID-19 was less than in our study. This difference can be explained by the fact that in the study by Khalil et al., the rate of comorbidity was higher than our study (32.5% vs. 20%), and this issue could be the reason for the cesarean section rate reduction.

5. Limitation

There are no data available for the first and early second trimester of pregnancy infections. Other limitation is the retrospective design (especially reports and case series) of the study. Also, we have only included studies which are reported in the English language. The strengths of this study are large number of studies, relatively high sample size, and the inclusion of studies from different countries.

6. Conclusion

COVID-19 infection was associated with higher rates (and pooled proportions) of cesarean section in pregnant women and their mortality. Based on the results of this study, COVID-19 cannot be considered as an indication for caesarian delivery. Therefore, the timing and mode of delivery should be individualized based on obstetrical indication and maternal situation. The findings of this study can be a guide to prenatal enhanced counseling for pregnant women with COVID-19.

Data Availability

Data are available from the first and corresponding authors upon a reasonable request.

Conflicts of Interest

The authors report no conflict of interest.

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