



# Systematic Review Adverse Perinatal Outcomes in COVID-19 Infected Pregnant Women: A Systematic Review and Meta-Analysis

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Abstract: The impact of COVID-19 virus infection during pregnancy is still unclear. This systematic review and meta-analysis aimed to quantitatively pool the evidence on impact of COVID-19 infection on perinatal outcomes. Databases of Medline, Embase, and Cochrane library were searched using the keywords related to COVID-19 and perinatal outcomes from December 2019 to 30 June 2021. Observational studies comparing the perinatal outcomes of COVID-19 infection in pregnancy with a non-infected comparator were included. The screening process and quality assessment of the included studies were performed independently by two reviewers. Meta-analyses were used to pool the comparative dichotomous data on perinatal outcomes. The database search yielded 4049 results, 1254 of which were duplicates. We included a total of 21 observational studies that assessed the adverse perinatal outcomes with COVID-19 infection. The odds of maternal death (pooled OR: 7.05 [2.41-20.65]), preeclampsia (pooled OR: 1.39 [1.29-1.50]), cesarean delivery (pooled OR: 1.67 [1.29-2.15]), fetal distress (pooled OR: 1.66 [1.35-2.05]), preterm birth (pooled OR: 1.86 [1.34-2.58]), low birth weight (pooled OR: 1.69 [1.35–2.11]), stillbirth (pooled OR: 1.46 [1.16–1.85]), 5th minute Apgar score of less than 7 (pooled OR: 1.44 [1.11-1.86]) and admissions to neonatal intensive care unit (pooled OR: 2.12 [1.36-3.32]) were higher among COVID-19 infected pregnant women compared to non-infected pregnant women.

Keywords: COVID-19; perinatal outcomes; systematic review

# 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, continues to be an alarming global public health crisis [1] with a sharply escalating number of deaths that have largely surpassed previous fatalities caused by epidemics such as Middle Eastern Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [2]. At the time of writing (3 December 2021), 263,563,622 confirmed cases of COVID-19, including 5,232,562 deaths, had been reported to the World Health Organization (WHO) [3]. This situation raises concerns in vulnerable populations such as pregnant mothers, fetuses and their neonates. Pregnant women are at higher risk of developing severe illness from respiratory infections, largely due to immunodeficiency associated with physiological adaptations during pregnancy [4]. Respiratory infections could escalate rapidly to respiratory failure, leading to potentially fatal consequences for both mother and fetus [5]. A recent multinational retrospective cohort study of 388 pregnant women reported that SARS-CoV-2 infected pregnant women risk fatal consequences from compromised respiratory functions and need intensive care [6]. Healthcare systems continue to become over-burdened, risking



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**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). compromised access and quality of services. Maternal and child health services are no exceptions to these challenges. Furthermore, low awareness of prevention strategies [7], mixed information from the COVID-19 infodemic [8], scarcity of healthcare, and intensive care services [9] accentuate the negative effects on the populations. There has been a steep rise in publications, including literature reviews on COVID-19 in pregnancy globally. However, the quality of several studies has been varied, with some including case reports and case series [10,11] and several reviews becoming outdated with the emergence of new evidence. Scientifically proven up-to-date evidence of maternal, fetal, and neonatal risks associated with COVID-19 infection in pregnancy is an urgent need to guide clinical decision-making in maternal and child health care. Hence, we conducted this systematic review on adverse perinatal outcomes in COVID-19 infected mothers. Our primary aim was to evaluate the maternal, fetal and neonatal effects associated with COVID-19 in pregnancy. As secondary aims, we evaluated the incidence of COVID-19 among pregnant women and the comorbidity profiles of COVID-19 infected pregnant women. Knowledge of the effects of COVID-19 on pregnancy, childbirth, and postpartum is essential for maternal health care service providers to plan effective management strategies. The prevalence of COVID-19 related adverse perinatal outcomes and the comorbidity profiles of COVID-19 infected pregnant women are essential variables that would help inform care and preventative services.

#### 2. Materials and Methods

We conducted this systematic review and meta-analysis based on the PROSPERO protocol registered on 18 May 2021 (CRD42021254974). This review included studies focused on perinatal outcomes of COVID-19 infection in pregnancy, mainly to evaluate the reported adverse perinatal outcomes in COVID 19 infected mothers and the prevalence of adverse perinatal (maternal, fetal, and newborn) outcomes in COVID-19 infected pregnant women. This review reports adverse maternal, fetal, and newborn outcomes of COVID-19 infected pregnant women, comorbidities in COVID-19 infected pregnant women, and the incidence of COVID-19 infection among pregnant women in line with the updated PRISMA 2020 guidelines for reporting systematic reviews [12].

### 2.1. Eligibility Criteria, Data Sources and Search Strategy

Observational studies (cohort and case–control) investigating the perinatal outcomes in COVID-19 infected pregnant women and published as peer-reviewed articles in English were eligible for inclusion. Case reports, case series, editorials, letters to the editor, perspectives, conference papers, narrative or systematic reviews, and studies without a noninfected pregnant group as the comparator were excluded. We searched Medline, EMBASE, and Cochrane Library databases to identify the published studies from December 2019 to 30 June 2021. The search strategy included a combination of keywords for COVID-19 and perinatal outcomes (Table S1).

#### 2.2. Study Selection

All of the identified studies from the database search were exported to EndNote reference management software (version EndNote X9.3.3.). Then, Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to manage the independent screening process at both the stages of title and abstract screening (M.L.P., B.P.P.S., T.S.D.) and full-text screening (M.L.P., B.P.P.S., T.S.D.). Reasons for full-text exclusion were documented at the full-text screening stage. Any disagreement was resolved by consensus or by consultation with a third reviewer at both stages.

### 2.3. Data Extraction

The data from the included studies were extracted to an Excel sheet by one author, and another author cross-checked the accuracy. The extracted data included the study characteristics (country, year of publication, study design and methodology, study period,

population and setting, total number of participants, number of cases, number in control group and drop-outs), participants' socio-demographic and baseline data, comorbidities, adverse perinatal outcomes (maternal death, termination of pregnancy, miscarriage or abortion, preeclampsia, pre-labor rupture of membrane (PROM), preterm pre-labor rupture of membrane (PROM), preterm birth, low birth weight, stillbirth, Apgar score, admissions to neonatal intensive care unit (NICU), neonatal deaths, cesarean section deliveries, and operative vaginal births, the incidence of COVID-19 among pregnant women, and the outcome of interest of each study.

### 2.4. Assessment of Risk of Bias

Quality assessments of the included studies were performed using the National Institute of Health's (NIH) study quality assessment tool for observational, cohort, and cross-sectional studies and the NIH study quality assessment tool for case–control studies [13]. The quality of each study was independently assessed by two assessors (B.P.P.S. and T.S.D). Any disagreement was resolved through consensus between the two assessors.

## 2.5. Data Synthesis and Analysis

The characteristics of the included studies, characteristics of the COVID-19 infected pregnant women and the summary findings were tabulated. Further, the incidence of COVID-19 among pregnant women was graphically presented. Quantitative meta-analysis was carried out to pool the comparative dichotomous data of perinatal outcomes when more than one study presented the data for the relevant outcome. If individual studies reported no adverse outcome in the infected group or non-infected group, they were excluded from the meta-analysis of that particular perinatal outcome. Heterogeneity of studies was determined using the I<sup>2</sup> statistic, where substantial heterogeneity was defined as I<sup>2</sup>  $\geq$  30. Random effects estimates of the pooled odds of each perinatal outcome and comorbidity condition were generated using the Mantel–Haenszel method. The findings of each outcome comparison were summarized with odds ratio, 95% confidence interval, *p*-value, and the I<sup>2</sup> statistic. Funnel plots were generated to visually evaluate the presence of publication bias.

#### 3. Results

#### 3.1. Study Selection

Two thousand seven hundred ninety-five (2795) studies were identified through the search engines for the title and abstract reviews after removing 1254 duplicates. Out of the total screened abstracts, 120 were selected for full-text screening, of which 99 studies were excluded (mainly due to lack of a comparison group or the presentation of inadequate data), and 21 [14–36] studies were included in this systematic review and meta-analysis (Figure 1).

#### 3.2. Study Characteristics

There were nine (42.9%) articles from single-center studies [14–17,20–22,25,27], eight (38.1%) from multicenter studies [18,19,23,24,26,29,31,32] and three (14.3%) from nationwide [28,30,34] studies. The remaining one (4.7%) was a multinational study [33]. Of the 20 studies included except the multinational study, eight (40%) were from the United States of America (USA) [15,16,20,23–25,29,31] three (15%) were from Spain [18,19,26], two (10%) each from Mexico [17,30] and India [21,27] and one (5%) each from Iran [14], United Kingdom (UK) [34], France [22], Sweden [28] and Canada [32]. Among the total included studies, 18 (85.7%) used cohort study design [14,15,18–22,24–33], while one cohort study used a historical comparison cohort [34]. Table 1 shows the characteristics of the included 21 studies.



Figure 1. PRISMA flow chart of included studies.

Table 1. Characteristics of included studies.

				Samp	le Size	
Study	Country	Study Design	Study Population	COVID-19 (+) Pregnant Women	COVID-19 (—) Pregnant Women	Data Collection Period
Abedzadeh-Kalahroudi et al., 2021 [14]	Iran	Prospective cohort study	Single-center	56	94	March to November 2020
Adhikari et al., 2020 [15]	USA	Prospective cohort study	Single-center	252	3122	18 March to 22 August 2020
Brandt et al., 2021 [16]	USA	Case-control study	Single-center	61	122	11 March to 11 June 2020
Cardona-Pe'rez et al., 2021 [17]	Mexico	Case-control study	Single-center	70	170	22 April to 25 May 2020
Crovetto et al., 2021 [18]	Spain	Prospective cohort study	Multicenter	317	1908	15 March to 31 May 2020
Cruz-Lemini et al., 2021 [19]	Spain	Prospective cohort study	Multicenter	174	430	23 March to 31 May 2020
Farghaly et al., 2020 [20]	USA	Retrospective cohort study	Single-center	15	64	March to May 2020
Gupta et al., 2021 [21]	India	Retrospective cohort study	Single-center	108	3057	1 September to 30 November 2020
Hcini et al., 2021 [22]	France	Prospective cohort study	Single-center	137	370	16 June to 16 August 2020
Katz et al., 2021 [23]	USA	Case-control study	Multicenter	490	964	19 March to 31 May 2020

				Samp	le Size	
Study	Country	Study Design	Study Population	COVID-19 (+) Pregnant Women	COVID-19 (—) Pregnant Women	Data Collection Period
Ko et al., 2021 [24]	USA	Retrospective cohort study	Multicenter	6550	482,921	March to September 2020
Liu et al., 2021 [25]	USA	Retrospective cohort study	Single-center	56	279	10 April to 10 June 2020
Martinez-Perez et al., 2021 [26]	Spain	Prospective cohort study	Multicenter	246	763	23 March to 31 May 2020
Nayak et al., 2020 [27]	India	Retrospective cohort study	Single-center	141	836	1 April to 15 May 2020
Norman et al., 2021 [28]	Sweden	Prospective cohort study	Nationwide	2286	84,719	11 March 2020 to 8 March 2021.
Prabhu et al., 2020 [29]	USA	Prospective cohort study	Multicenter	70	605	22 March to 20 April 2020
Ríos-Silva et al., 2020 [30]	Mexico	Retrospective cohort study	Nationwide	448	1216	28 February to 25 May 2020
Steffen et al., 2021 [31]	USA	Prospective cohort study	Multicenter	61	939	1 May to 22 September 2020
Trahan et al., 2021 [32] Villar et al., 2021 [33]	Canada Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland,	Cohort study Prospective cohort study	Multicenter	45 706	225 1424	22 March to 31 July 2020 2 March to October 2020
Vousden et al., 2021 [34]	United Kingdom	Prospective cohort study	Nationwide	1842	1148	1 March to 31 August 2020

### Table 1. Cont.

#### 3.3. Risk of Bias of Included Studies

Regarding the quality of the included cohort studies, 10 criteria out of 14 (71%) were satisfied by 40% of the included studies. Almost all of the studies had clearly stated research objectives, clearly defined study populations, clearly defined valid and reliable outcomes, and over  $\geq$  50% participation rate by eligible persons. In almost all the included studies, the quality assessment was unable to determine the level of exposures related to examined outcomes, exposure measures more than once over time, and follow-up after baseline. Blinding of the assessors to the exposure status was a serious concern for all the included studies. Only 40-55% of the included cohort studies were marked positively for the criteria of adjusting for potential confounding factors and having a justified sample size. With regards to the quality of included case-control studies, eight criteria out of 12 (75%) were satisfied by 60% of the included studies. All the studies satisfied the criteria related to clearly defined objective/s, clearly defined study population, selection of the control from the same population, consistent use of defined inclusion and exclusion criteria, clearly defined and differentiated case and control groups, ability to confirm the exposure occurred prior to the development of the condition, implementation of valid and reliable exposure measures, and measuring and adjusting for confounding variables. Blinding of the assessors to the exposure status was not determinable in all the studies. Less than 35% of the included case-control studies had a justified sample size (Figure 2A,B). Individual study assessments were attached as a supplementary file (Table S2).



Figure 2. (A) Quality assessment of included cohort studies; (B) Quality assessment of included case–control studies.

### 3.4. Incidence of COVID-19 Infection in Pregnant Women

Eleven studies reported the incidence of COVID-19 among pregnant women, with rates ranging from 1.3% to 27%. Only cohort studies were used to determine the incidence of COVID-19 infection in pregnant women. Even though there were 18 cohort studies, a few did not report the total number of admissions, making it difficult to quantify the incidence. Among the 11 that reported incidence, there were six studies from the USA [15,20,24,25,29,31], three single-center [15,20,25] and three multicenter studies [24,29,31]. The reported rates in the USA ranged from 1.3% to 19%. The highest rate (27%) of COVID-19 in pregnancy was reported from a single-center study conducted in France [22], while the second-highest rate was noted from a multicenter study conducted in Spain [26] (Figure 3).





# 3.5. Characteristics of COVID-19 Infected Pregnant Women

In the 21 included studies, a total of 14,131 COVID-19 infected pregnant women were studied compared to 585,376 COVID-19 non-infected pregnant women. The reported mean age of infected pregnant women ranged from 24.7 to 32.6 years, while some of the studies reported median (IQR) values ranging from 25 (21–31) to 33.3 (29–37) years (Table 2).

Table 2. Characteristics of COVID-19 infected pregnant women.

Study	Age (Years) <sup>a</sup>	Parity	Gestational Age at Delivery (Weeks) <sup>a</sup>
Abedzadeh-Kalahroudi et al., 2021 [14]	31.6 (6.1)	Primiparous: 33.9%	37.1 (3.1)
Adhikari et al., 2020 [15]	27.0 (6.6)	Nulliparous: 29%	Range <34 wk to $\geq$ 40 wk
Brandt et al., 2021 [16]	30.3 (6.4)	Median (IQR): 2 (1–3)	Mild symptomatic group: $39.0 \pm 2.7$ ; Severe symptomatic group: $34.0 \pm 5.8$
Cardona-Pe'rez et al., 2021 [17]	Median: 26 Range: 13–45	Median: 0; Range 0–3	Median (IQR) 38.1 (36.3–39.3)
Crovetto et al., 2021 [18]	Median (IQR): 33.3 (29–37)	Nulliparous: 53%	39.1 (2.1)
Cruz-Lemini et al., 2021 [19]	32.6	Nulliparous: 38%	39.0
Farghaly et al., 2020 [20]	Mean: 33.4	NR	NR
Gupta et al., 2021 [21]	24.7 (2.4)	Nulliparous: 41.6%	36.6 (3.3)
Hcini et al., 2021 [22]	Median (IQR): 25 (21–31)	Median (IQR): 2 (1–5) Parity 0: 37.5%;	NR
Katz et al., 2021 [23]	30.4 (6.2)	Parity 1: 28.3%; Parity 2+: 34.2%	38.1 (2.6)
Ko et al., 2021 [24]	Median: 28.0 Range: 13–49	NR	NR
Liu et al., 2021 [25]	30.3 (6.4)	Median (IQR): 1 (0–2)	Median (IQR): 39 (38–40)
Martinez-Perez et al., 2021 [26]	32.6	Nulliparous: 38.5%	38.6
Nayak et al., 2020 [27]	Range: <20 to >30	Primiparous: 39%	NR
Norman et al., 2021 [28]	31.4 (5.0)	Nulliparous: 43.1%	39.2 (2.1)
Prabhu et al., 2020 [29]	NR	NR	NR
Ríos-Silva et al., 2020 [30]	Median (IQR): 29 (25-33)	NR	NR
Steffen et al., 2021 [31]	Median (IQR): 28 (24–32)	NR	Median (IQR) 39 (37.1-39.6)
		Parity 0: 33%;	
Trahan et al., 2021 [32]	Range: <25 to 35+	Parity 1: 27%;	38.9 (2.2)
	U	Parity 2+: 40%	
Villar et al., 2021 [33]	30.0 (6.1)	NR	37.9 (3.3)
Vousden et al., 2021 [34]	Range: $<20$ to $\ge35$	Primiparous: 41.2%	Median (IQR) 39 (38–40)

<sup>a</sup> Mean  $\pm$  SD if not mentioned otherwise; SD: Standard deviation, NR: Not reported, IQR: Interquartile range.

### 3.6. Summary Findings of Included Individual Studies

Out of 21 studies, six reported that COVID-19 infection during pregnancy was not associated with adverse perinatal outcome [15,18,25,30–32]. A study conducted in Spain concluded that even with no difference in the overall rate of adverse perinatal outcomes among COVID -19 infected women, symptomatic status was associated with a modest increase in preterm delivery and intrapartum fetal distress [18]. All of the other studies reported one or more significant adverse perinatal outcomes associated with COVID-19 in pregnancy. Table 3 shows the summary findings of individual studies included in this systematic review.

Study	The Outcome of the	e Study (Comparison of COVII	O 19 Infected and Non-Inf	ected Pregnant Women) ‡
	Increased Risk/No Difference	Maternal Risk/s	Fetal Risk/s	Neonatal Risk/s
Abedzadeh-Kalahroudi et al., 2021 [14]	Increased risk	Preeclampsia, cesarean section delivery	Fetal distress	Preterm birth, low Apgar score
Adhikari et al., 2020 [15] Cardona-Pe'rez et al., 2021 [17] Crovetto et al., 2021 [18] †	No difference Increased risk No difference	Preeclampsia		
Cruz-Lemini et al., 2021 [19] ++	Increased risk	Pre-labor rupture of membranes		
Farghaly et al., 2020 [20]	Increased risk	Cesarean section delivery		Low mean Apgar score at the fifth minute
Gupta et al., 2021 [21]	Increased risk	Cesarean section delivery	Fetal distress	Preterm birth, low birth weight, low Apgar score
Hcini et al., 2021 [22] Katz et al., 2021 [23] Ko et al., 2021 [24] Liu et al., 2021 [25]	Increased risk Increased risk Increased risk No difference	Maternal death	Intra-uterine death	Preterm birth Preterm birth
Martinez-Perez et al., 2021 [26]	Increased risk	Pre-labor rupture of membranes		Preterm birth, neonatal intensive care unit admission
Nayak et al., 2020 [27]	Increased risk	Cesarean section delivery		
Norman et al., 2021 [28]	Increased risk			Neonatal intensive care unit admission
Prabhu et al., 2020 [29] Ríos-Silva et al., 2020 [30] Steffen et al., 2021 [31] Trahan et al., 2021 [32]	Increased risk No difference No difference No difference	Cesarean section delivery		
Villar et al., 2021 [33]	Increased risk	Maternal death, preeclampsia		Preterm birth
Vousden et al., 2021 [34]	Increased risk	Cesarean section delivery		Neonatal intensive care unit admission

Table 3. Summary findings of individual studies.

<sup>‡</sup> Relevant to the studied perinatal outcomes in the current systematic review, <sup>†</sup> No difference in the overall rates but the symptomatic status was associated with modest increases in preterm delivery and intrapartum fetal distress, <sup>††</sup> Study encompassed only the asymptomatic pregnant women. One study was not included in the table as its outcome was based on disease severity [17].

#### 3.7. Adverse Perinatal Outcomes of COVID-19 Infection in Pregnancy

# 3.7.1. Adverse Maternal Outcomes

The reported maternal outcomes included maternal deaths, miscarriages/abortions, preeclampsia, PROMs/PPROMs, cesarean deliveries, and operative vaginal births. Out of these outcomes, maternal deaths, preeclampsia and cesarean deliveries were found to be statistically significant. In terms of studies on maternal deaths, two studies [24,33] reported an increased risk with COVID-19 during pregnancy. Ten studies [14,17,19,21,22,24,27,30,33,34] reported data on maternal death, and five of them were excluded [14,17,19,22,34] from the meta-analysis because no maternal death was reported in one or both arms. Meta-analysis of the remaining five studies (7953 COVID-19 infected versus 489,454 COVID-19 non-infected) revealed a significant increase in maternal death among COVID-19 infected pregnant women (pooled OR 7.05 [95% CI 2.41–20.65]; p < 0.05;  $I^2 = 72$  %). Based on 16 studies (10,050 COVID-19 infected pregnancies and 497,036 COVID-19 non-infected

pregnancies) [14–19,21,22,24,26,29,31–34], a significant increase in preeclampsia during pregnancy was identified among women in the infected pregnant cohort compared to the non-infected comparator (pooled OR 1.39 [95% CI 1.29–1.50]; p < 0.05;  $I^2 = 25$  %). Out of 21 included studies, 20 studies (12,982 COVID-19 infected pregnancies and 583,619 COVID-19 non-infected pregnancies) [14–29,31–34] provided data on cesarean section and found a statistically significant increase in cesarean section deliveries among infected women (pooled OR 1.67 [95% CI 1.29–2.15]; p < 0.05;  $I^2 = 95$ %). Only two studies provided data on termination of pregnancy [14,22], but no meta-analysis was carried out as there was no termination of pregnancies in the non-infected cohort of one of the studies [14]. Four studies reported miscarriages/abortions [15,18,27,34], and no statistically significant difference of miscarriages/abortions was found between COVID-19 infected and non–infected pregnant women (pooled OR 1.56 [95% CI 0.59–4.12]; p = 0.37;  $I^2 = 68$  %). Pooled odds of 1358 COVID-19 infected pregnancies and 4045 non-infected pregnancies [14,17,19,26,31–33] revealed no statistically significant difference of PROM/PPROM between COVID-19 infected and non-infected and non-infected pregnancies (pooled OR 1.25 [95% CI 0.85–1.84]; p = 0.25;  $I^2 = 65$ %) (Figure 4A).

## 3.7.2. Adverse Fetal Outcomes

The reported fetal outcomes included intrauterine death and fetal distress. Out of these, fetal distress was found to be statistically significant. Based on the data from 1248 newborns born to COVID-19 infected pregnant women and 7422 newborns born to COVID-19 non-infected pregnant women [14,18,21,31,33], a statistically significant increase in fetal distress was observed among the newborns of the COVID-19 infected women compared to the COVID-19 non-infected (pooled OR 1.66 [95% CI 1.35–2.05]; p < 0.05;  $I^2 = 26\%$ ). Four studies [16,17,22,27] reported data on intrauterine death, and of them, one study [16] was excluded from the meta-analysis as no adverse events were reported in infected and non-infected cohorts. The meta-analysis of the remaining three studies (348 COVID-19 infected pregnancies and 1376 COVID-19 non-infected pregnancies) found no statistically meaningful change in intrauterine deaths related to COVID-19 infection during pregnancy (pooled OR 1.79 [95% CI 0.51–6.23]; p = 0.36;  $I^2 = 68\%$ ) (Figure 4B).

	COVID-19 (+) \	Vomen	COVID-19 (-)	Women		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
∋upta et al., 2021	1	108	7	3057	14.0%	4.07 [0.50, 33.39]				
<o 2021<="" al.,="" et="" td=""><td>9</td><td>6550</td><td>32</td><td>482921</td><td>26.6%</td><td>20.76 [9.91, 43.51]</td><td></td><td></td><td>  -</td><td>-</td></o>	9	6550	32	482921	26.6%	20.76 [9.91, 43.51]			-	-
Vayak et al., 2020	3	141	8	836	20.6%	2.25 [0.59, 8.58]				
Ríos-Silva et al., 2020	10	448	7	1216	24.3%	3.94 [1.49, 10.42]			— <b>—</b> —	
/illar et al., 2021	11	706	1	1424	14.4%	22.52 [2.90, 174.80]				•
otal (95% CI)		7953		489454	100.0%	7.05 [2.41, 20.65]				
otal events	34		55							
Heterogeneity: Tau <sup>2</sup> = 0.	.99: Chi <sup>2</sup> = 14.10	df = 4 (P	= 0.007); I <sup>2</sup> = 7	2%			L	<del>_</del>	<u> </u>	

Figure 4. Cont.

# b: Preeclampsia

	COVID-19 (+) W	/omen	COVID-19 (-)	Women		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Abedzadeh-Kalahroudi et al., 2021	11	56	7	94	0.4%	3.04 [1.10, 8.37]	
Adhikari et al., 2020	26	245	359	3035	4.4%	0.88 [0.58, 1.35]	
Brandt et al., 2021	6	61	10	122	0.6%	1.22 [0.42, 3.53]	
Cardona-Pe´rez et al., 2021	12	70	15	170	0.7%	2.14 [0.94, 4.84]	
Crovetto et al., 2021	8	317	40	1908	1.0%	1.21 [0.56, 2.61]	_ <del></del> _
Cruz-Lemini et al., 2021	13	174	43	430	2.1%	0.73 [0.38, 1.39]	-+
Gupta et al., 2021	12	108	264	3057	1.5%	1.32 [0.72, 2.44]	
Hcini et al., 2021	15	137	31	370	1.4%	1.34 [0.70, 2.58]	+ <u>-</u>
Ko et al., 2021	616	6550	33078	482921	74.0%	1.41 [1.30, 1.54]	
Liu et al., 2021	8	56	34	279	0.9%	1.20 [0.52, 2.75]	_ <del></del>
Martinez-Perez et al., 2021	11	246	44	763	1.9%	0.76 [0.39, 1.51]	
Prabhu et al., 2020	11	70	56	605	0.9%	1.83 [0.91, 3.68]	<u>+</u>
Steffen et al., 2021	13	61	179	939	1.6%	1.15 [0.61, 2.17]	_ <del></del>
Trahan et al., 2021	3	45	17	225	0.5%	0.87 [0.25, 3.12]	
Villar et al., 2021	117	706	143	1424	7.3%	1.78 [1.37, 2.31]	
Vousden et al., 2021	20	1148	8	694	0.9%	1.52 [0.67, 3.47]	+
Total (95% CI)		10050		497036	100.0%	1.39 [1.29, 1.50]	•
Total events	902		34328				
Heterogeneity: Chi <sup>z</sup> = 19.96, df = 15 (F Test for overall effect: Z = 8.82 (P < 0.0	° = 0.17); I² = 25% 00001)						0.01 0.1 1 10 100

# c: Cesarean delivery

	COVID-19 (+) \	Women	COVID-19 (-)	Women		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Abedzadeh-Kalahroudi et al., 2021	38	56	45	94	4.3%	2.30 [1.15, 4.59]	
Adhikari et al., 2020	65	245	1011	3035	5.8%	0.72 [0.54, 0.97]	
Brandt et al., 2021	14	61	40	122	4.2%	0.61 [0.30, 1.24]	
Cardona-Pe´rez et al., 2021	51	70	113	170	4.6%	1.35 [0.73, 2.51]	- <b>-</b>
Crovetto et al., 2021	311	317	54	1908	3.7%	1779.61 [759.16, 4171.76]	•
Cruz-Lemini et al., 2021	12	174	19	430	4.1%	1.60 [0.76, 3.38]	
Farghaly et al., 2020	10	15	27	64	2.7%	2.74 [0.84, 8.94]	
Gupta et al., 2021	63	108	914	3057	5.5%	3.28 [2.22, 4.85]	
Hcini et al., 2021	19	137	62	370	4.8%	0.80 [0.46, 1.39]	
Katz et al., 2021	171	490	331	964	6.0%	1.03 [0.82, 1.29]	+
Ko et al., 2021	2193	6550	154401	482921	6.2%	1.07 [1.02, 1.13]	•
Liu et al., 2021	19	56	102	279	4.6%	0.89 [0.49, 1.63]	
Martinez-Perez et al., 2021	55	246	143	763	5.6%	1.25 [0.88, 1.77]	+
Nayak et al., 2020	67	141	376	836	5.6%	1.11 [0.77, 1.58]	
Norman et al., 2021	495	2286	15450	84719	6.2%	1.24 [1.12, 1.37]	-
Prabhu et al., 2020	32	70	187	605	5.1%	1.88 [1.14, 3.11]	
Steffen et al., 2021	15	61	191	939	4.6%	1.28 [0.70, 2.34]	
Trahan et al., 2021	13	45	76	225	4.3%	0.80 [0.39, 1.61]	
Villar et al., 2021	346	706	547	1424	6.1%	1.54 [1.28, 1.85]	-
Vousden et al., 2021	467	1148	201	694	6.0%	1.68 [1.37, 2.06]	+
Total (95% CI)		12982		583619	100.0%	1.67 [1.29, 2.15]	◆
Total events	4456		174290				
Heterogeneity: Tau <sup>2</sup> = 0.27; Chi <sup>2</sup> = 38	9.38, df = 19 (P <	0.00001);	I <sup>2</sup> = 95%				
Test for overall effect: Z = 3.91 (P < 0.1	0001)						0.01 0.1 1 10 100

# d: Miscarriage/abortion

	COVID-19 (+) V	Vomen	COVID-19 (-) Wo	omen		Odds Ratio		Odds Ratio	)	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 9	5% CI	
Adhikari et al., 2020	7	252	87	3122	30.4%	1.00 [0.46, 2.18]				
Crovetto et al., 2021	2	317	15	1908	20.1%	0.80 [0.18, 3.52]			_	
Nayak et al., 2020	6	141	33	836	28.7%	1.08 [0.44, 2.63]				
Vousden et al., 2021	31	1148	2	694	20.7%	9.60 [2.29, 40.25]		-		_
Total (95% CI)		1858		6560	100.0%	1.56 [0.59, 4.12]		-	•	
Total events	46		137							
Heterogeneity: Tau <sup>2</sup> = 0	0.65; Chi <sup>2</sup> = 9.52,	df = 3 (P	= 0.02); <b>I</b> <sup>2</sup> = 68%							100
Test for overall effect: Z	(= 0.90 (P = 0.37	)					0.01 0		10	100

Figure 4. Cont.

# e: PROM/PPROM

	COVID-19 (+)	Women CO	VID-19 (-) Wor	men		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total V	Veight	M-H, Random, 95% CI		M-H, Random, 9	5% CI	
Abedzadeh-Kalahroudi et al., 20	)21 4	56	9	94	7.3%	0.73 [0.21, 2.48]				
Cardona-Pe´rez et al., 2021	8	70	18	170	11.3%	1.09 [0.45, 2.64]				
Cruz-Lemini et al., 2021	31	174	44	430	18.8%	1.90 [1.16, 3.13]				
Martinez-Perez et al., 2021	50	246	90	763	21.6%	1.91 [1.30, 2.79]				
Steffen et al., 2021	6	61	84	939	11.4%	1.11 [0.46, 2.66]				
Trahan et al., 2021	2	45	9	225	5.0%	1.12 [0.23, 5.35]		•		
Villar et al., 2021	114	706	262	1424	24.7%	0.85 [0.67, 1.09]		-		
Total (95% CI)		1358		4045 1	00.0%	1.25 [0.85, 1.84]		•		
Total events	215		516							
Heterogeneity: Tau² = 0.14; Chi² Test for overall effect: Z = 1.14 (P	= 17.15, df = 6 (P = 0 = 0.25)	.009); I² = 65%					0.01 0	1.1	10	100
f: Operative vagina	l birth									
(	:OVID-19 (+) Wome	n COVID-1	) (_) Women			Odds Ratio		Odds Ratio		
Study or Subgroup	Events T	otal Even	s Tota	al Weig	ht M-H	I, Random, 95% Cl		M-H, Random, 95	% CI	
Hcini et al., 2021	7	137 2	5 37	0 16.7	%	0.74 [0.31, 1.76]				
Martinez-Perez et al., 2021	21	246 11	4 76:	3 29.9	%	0.53 [0.33, 0.87]				
Navak et al., 2020	1	141	9 831	6 4.1	%	0.66 (0.08, 5.22)			_	
Trahan et al., 2021	4	45 1	2 22	5 10.7	%	1.73 [0.53, 5.64]		<b>_</b>		
Vousden et al. 2021	129 1	148 7	1 69	4 38.6	96	1 11 [0 82 1 51]		_ <b>_</b>		
T 4 1/05% OR					~					
Total (95% CI)	1	(1/	288	8 100.0	1%	0.86 [0.55, 1.32]		-		
Total events	162	23	1							
Heterogeneity: Tau <sup>2</sup> = 0.10; Ch	P = 7.76, df = 4 (P =	0.10); I <sup>2</sup> = 48%					.01 0.1	1	10	100
Test for overall effect: Z = 0.70	(P = 0.48)					Ĩ				
				(A)						
a: Fetal distress										
	COVID 10 (+	Women C				Odda Patio		Odde Patio		
Study or Subgroup	Evonto	Total	Evente	Total	Woigh	t M H Eixed 05% CL			CL	
Study of Subgroup	Events	10(0)	Events	TUTAL	veigh	4 04 14 08 44 701		wi-n, rixeu, 95%		
Apeuzaden-Kalanroudi et al., 2 Orauatta at al., 2024	UZI 9	56	4	4000	2.0%	4.31 [1.26, 14.73] 4.47 (0.00, 0.01)				
Crovetto et al., 2021	25	317	105	1908	22.1%	5 1.47 [0.93, 2.31]			_	
Oupla et al., 2021 Ctoffon et al., 2024	24	108	334 cc	305/	14.2%	2.33 [1.40, 3.72]				
Stelleri et al., 2021 Villor et al., 2021	5	01	120	939	5.9%	) 1.18 [U.40, 3.U5] 1.60 [4.40, 3.U5]		-		
vinar et al., 2021	87	706	IΖU	1424	55.8%	o 1.53 [1.14, 2.05]				
Total (95% CI)		1248		7422	100.0%	1.66 [1.35, 2.05]		•		
Total events	150		629							
Heterogeneity: Chi <sup>2</sup> = 5.41, df =	4 (P = 0.25); I <sup>2</sup> = 26%							1 1	10	100
Test for overall effect: Z = 4.79 (F	P < 0.00001)						0.07		.0	

# b: Intrauterine death

	COVID-19 (+) V	Vomen	COVID-19 (-) V	Vomen		Odds Ratio			Odds Ratio	)	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H	, Random, 9	5% CI	
Cardona-Pe'rez et al., 2021	5	70	6	170	33.3%	2.10 [0.62, 7.13]					
Hcini et al., 2021	7	137	4	370	32.9%	4.93 [1.42, 17.11]				-	
Nayak et al., 2020	3	141	31	836	33.7%	0.56 [0.17, 1.87]					
Total (95% CI)		348		1376	100.0%	1.79 [0.51, 6.23]					
Total events	15		41								
Heterogeneity: Tau <sup>2</sup> = 0.83; C	hi² = 6.28, df = 2	(P = 0.04)	; <b>I²</b> = 68%					01	1	10	100
Test for overall effect: Z = 0.91	(P = 0.36)						0.01	0.1		10	100

Figure 4. Cont.

a: Preterm birth											
	COVID 19 (+) W(	men		Women		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95	% CI	М-Н.	Random, 95%	CI	
Abedzadeh-Kalahroudi et al 2021	19	56	12	94	5.0%	3 51 [1 54 7	971				
Adhikari et al., 2020	27	245	328	3035	6.6%	1.02 (0.67, 1	.551		_ <b>_</b>		
Brandt et al., 2021	13	61	15	122	5.0%	1.93 [0.85, 4	.37]		+		
Cardona-Pe´rez et al., 2021	14	70	38	170	5.5%	0.87 [0.44, 1	.73]				
Crovetto et al., 2021	20	317	81	1908	6.2%	1.52 [0.92, 2	.52]		+		
Cruz-Lemini et al., 2021	13	174	28	430	5.5%	1.16 [0.59, 2	.29]				
Farghaly et al., 2020	2	15	3	64	2.1%	3.13 [0.47, 20	.64]				
Gupta et al., 2021	31	108	14	3057	5.6%	87.51 [44.76, 171	.08]				-+
Hcini et al., 2021	7	137	16	370	4.7%	1.19 [0.48, 2	.96]				
Katzietial., 2021	97	490	141	964	6.9%	1.44 [1.08, 1	.92]				
Koletial., 2021	315	655U 60	17392	482921	7.3% 5.00	1.35[1.21, 1	.52]				
Liulet al., 2021 Mortinez Devez et al., 2024	8	246	41	2/9	5.0%	0.97 [0.43, 2	.19]				
Problement of 2020	34 11	240	57	605	0.470 5.5%	2.24 [1.41, 3	.00j :611		<b></b>		
Stoffon of al. 2020	3	61	74	000	3,3%	0.00,00,00,00,00,00,00,00,00,00,00,00,00	.01] 0.91	_			
Trahan et al., 2021	g	45	31	225	5.0%	1.56 (0.69.3	.50j (56)				
Villar et al. 2021	159	706	194	1474	71%	1 84 [1 46 2	331		-		
Vousden et al. 2021	149	1148	54	694	6.8%	1 77 [1 27 2	451				
V00306116101., 2021	145	1140	54	034	0.070	1.11 [1.21, 2					
Total (95% CI)		10555		498064	100.0%	1.86 [1.34, 2	.581		•		
Total events	931		18570						•		
Heterogeneity: Tau <sup>2</sup> = 0.37 <sup>°</sup> Chi <sup>2</sup> = 16	6 20. df= 17./P < 0.	0000111	²= 90%								+
Test for overall effect: Z = 3.75 (P = 0.	0002)						0.01	0.1	1	10	100
1 7 11 4 14											
b: Low birth weight											
	COVID 19 (+) W	/omen	COVID 19 (-	) Women		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weigh	t M-H, Fixed, 95%	CI	M-H	, Fixed, 95% (		
Abedzadeh-Kalahroudi et al., 2021	11	56	14	94	7.5%	6 1.40 (0.59, 3.)	33]				
Trahan et al., 2021	5	45	27	225	7.2%	6 0.92 [0.33, 2.	52]	-			
Villar et al., 2021	145	706	181	1424	85.3%	6 1.77 [1.40, 2.]	26]				
Total (95% CI)		807		1743	100.0%	6 1.69 [1.35, 2. <sup>4</sup>	11]		•		
Total events	161		222								
Heterogeneity: Chi <sup>2</sup> = 1.75, df = 2 (P	= 0.42); I <sup>2</sup> = 0%									40	400
Test for overall effect: Z = 4.55 (P < 0	.00001)						0.01	0.1	1	10	100
$a: 5^{\text{th}}$ minute $A \mathbf{P} \mathbf{C} A \mathbf{P}$	sooro < 7										
c. 5 Innuc AFOAK	score < 7										
COV	/ID 19 (+) Women	COV	D 19 (-) Wo	men		Odds Ratio		0	dds Ratio		
Study or Subgroup	Events Tot	al E	vents	Total We	eight M	1-H, Fixed, 95% Cl		M-H, I	Fixed, 95% C		
Gupta et al., 2021	7 10	)8	83	3057 6	6.4%	2.48 [1.12, 5.51]					
Hcini et al., 2021	4 13	37	12	370 7	7.7%	0.90 [0.28, 2.83]					
Martinez-Perez et al., 2021	5 24	16	8	763 4	4.6%	1.96 [0.63, 6.04]				-	
Norman et al. 2021	48 229	36	1300 8	84719 81	1396	1 38 [1 03 1 84]			-		
Norman et al., 2021	40 220		1000 0	,4110 01	1.070	1.00[1.00] 1.04]					
Total (95% CI)	277	77	8	38909 10	0.0%	1.44 [1.11, 1.86]			•		
Total evente	64		1402						•		
Hotorogonoity: Chiž = 2.02 df = 27	D = 0 42\- 18 = 004		1405				L			_	
Test for suprell effect: 7 = 3.75 /D =	F = 0.42), I = 0.70 0.0000						0.01	0.1	1	10	100
Test for overall effect. $Z = 2.75$ (P =	0.006)										
d: Neonatal death											
COVID 1	9 (+) Women	COVID 1	9 (-) Wome	n	0	dds Ratio		Od	ds Ratio		
Study or Subgroup Even	ts Total	Even	ts To	tal Weigl	ht M-H	, Fixed, 95% Cl		M-H, F	xed, 95% CI		
Brandt et al. 2021	1 61		1 1	22 13 0	96 20	12 [0 12 32 80]					-
Gunta et al. 2021	. 01 7 100		 17	57 50.7	~ ∠.∟ 0∠ 1	35 [0 32 5 67]			_		
Vouedon ot al. 2021	∠ 100 A 1140		-∠ JU 1 C	07 00.7 04 08.44	∾ ⊺ ≪ ⊃⊀	10 [0.02, 0.07]					
vousuen et al., 2021	4 1148		, 6	04 Z0.4	<i>n</i> o 2.4	+z [0.27, 21.72]					
Total (05% CI)	4947		20	73 400 0	06 4	73 [0 60 6 00]					
10(01 (95% CI)	151/		38	13 100.0	70 1.	.1 3 [0.00, 5.00]					
i otal events	(		14								
Heterogeneity: Chi² = 0.21, df = 2	(P = 0.90); I <sup>2</sup> = 09	Ж				I	0.01	01	1	10	100
Heterogeneity: Chi <sup>2</sup> = 0.21, df = 2 Test for overall effect: Z = 1.01 (P	, (P = 0.90); I <sup>2</sup> = 09 = 0.31)	%				I	0.01	0.1	1	10	100
Heterogeneity: Chi² = 0.21, df = 2 Test for overall effect: Z = 1.01 (P	(P = 0.90); I² = 09 = 0.31)	%				l	0.01	0.1	1	10	100
Heterogeneity: Chi² = 0.21, df = 2 Test for overall effect: Z = 1.01 (P	, (P = 0.90); I <sup>2</sup> = 09 = 0.31)	%					0.01	0.1	1	10	100

Figure 4. Cont.

#### e: Admissions to NICU COVID 19 (+) Women COVID 19 (-) Women Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% Cl Abedzadeh-Kalahroudi et al., 2021 56 20 94 7.2% 0.71 [0.30, 1.69] 9 Brandt et al., 2021 52 61 14 122 7.0% 57 [18.11, 109.67] 1908 Crovetto et al., 2021 11 317 8.2% 1.05 (0.55, 2.02) 63 Cruz-Lemini et al., 2021 12 174 430 6.8% 4.48 [1.73, 11.57] 7 Farghaly et al., 2020 10 15 16 64 5.7% 6.00 [1.78, 20,19] Gupta et al., 2021 1.64 [0.92, 2.92] 14 108 254 3057 8.5% Hcini et al., 2021 3 137 12 370 5.4% 0.67 [0.19, 2.40] Martinez-Perez et al., 2021 23 246 18 763 8.2% 4.27 [2.26, 8.05] Nayak et al., 2020 24 141 202 836 8 9% 0.64 [0.40, 1.03] 271 Norman et al. 2021 2286 7351 84719 9.8% 1 42 [1 24 1 61] 8.2% 1.80 [0.94, 3.46] Prabhu et al., 2020 13 70 68 605 Trahan et al., 2021 6 45 22 225 6.8% 1.42 [0.54, 3.73] Vousden et al., 2021 156 1148 37 694 9.2% 2.79 [1.93, 4.05] Total (95% CI) 4804 93887 100.0% 2.12 [1.36, 3.32] 604 8084 Total events Heterogeneity: Tau<sup>2</sup> = 0.52; Chi<sup>2</sup> = 104.61, df = 12 (P < 0.00001); l<sup>2</sup> = 89% 0.01 0'1 10 100 Test for overall effect: Z = 3.31 (P = 0.0009) f: Stillbirth COVID 19 (+) Women COVID 19 (-) Women Odds Ratio Odds Ratio Study or Subgroup Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI Total Total Events Events Cardona-Pe<sup>r</sup>rez et al., 2021 2 70 3 170 17% 1.64 [0.27, 10.02] Crovetto et al., 2021 1 317 6 1908 17% 1.00 [0.12, 8.36] Ko et al., 2021 63 6550 3439 482921 92.2% 1.35 [1.05, 1.74] Martinez-Perez et al., 2021 3 246 1 763 0.5% 9.41 [0.97, 90.86] Steffen et al., 2021 3 61 12 939 14% 4.00 [1.10, 14.55] Vousden et al., 2021 9 1148 2 694 2.5% 2.73 [0.59, 12.69] Total (95% CI) 8392 487395 100.0% 1.46 [1.16, 1.85] 4 Total events 81 3463 Heterogeneity: Chi<sup>2</sup> = 6.05, df = 5 (P = 0.30); l<sup>2</sup> = 17% 0.01 0.1 10 100 Test for overall effect: Z = 3.20 (P = 0.001)

(**C**)

**Figure 4.** (**A**) Forest plots of adverse maternal outcomes. (**a**) Maternal death. (**b**) Preeclampsia. (**c**) Cesarean delivery. (**d**) Miscarriage/abortion. (**e**) PROM/PPROM. (**f**) Operative vaginal birth. PROM, Pre-labor rupture of membrane. PPROM, Preterm pre-labor rupture of membrane. (**B**) Forest plots of adverse fetal outcomes. (**a**) Fetal distress. (**b**) Intrauterine death. (**C**) Forest plots of adverse neonatal outcomes. (**a**) Preterm birth. (**b**) Low Birth weight. (**c**) Fifth minute Apgar score <7. (**d**) Neonatal death. (**e**) Admissions to NICU. (**f**) Stillbirth. NICU, Neonatal intensive care unit.

# 3.7.3. Adverse Neonatal Outcomes

The reported neonatal outcomes included preterm birth, low birth weight, stillbirth, fifth minute Apgar score < 7, admissions to NICU, and neonatal death. All of these outcomes were found to be statistically significant, except neonatal death. Pooled preterm birth [14–26,29,31–34] of 10,555 births to COVID-19 infected women compared to 498,064 COVID-19 non-infected in 18 studies (pooled OR 1.86 [95% CI 1.34–2.58]; p < 0.05;  $I^2 = 90\%$ ); pooled low birth weight [14,32,33] of 807 births to COVID-19 infected women compared to 1743 to COVID-19 non-infected women in three studies (pooled OR 1.69 [95% CI 1.35–2.11]; p < 0.05;  $I^2 = 0\%$ ); pooled fifth minute APGAR score of less than 7 [21,22,26,28] for 2777 births to COVID-19 infected women compared to 88,909 COVID-19 non-infected in four studies (pooled OR 1.44 [95% CI 1.11–1.86]; p < 0.05;  $I^2 = 0\%$ ) and pooled admissions to NICU [14,16,18–22,26–29,32,34] of 4804 COVID-19 births to infected women compared to 93,887 COVID-19 non-infected in 13 studies (pooled OR 2.12 [95% CI 1.36–3.32]; p < 0.05;  $I^2 = 89\%$ ) were observed to be significantly higher. Nine studies [15,17–19,24–26,31,34] reported data on stillbirths, but only six studies (8392 in COVID-19 infected pregnancies compared to 487,395 in COVID-19 non-infected) were included in the meta-analysis due

to no stillbirths in COVID-19 infected cohorts in two studies [15,25] and no stillbirths in the COVID-19 non-infected cohort in one study [19]. The pooled odds of six included studies revealed a statistically significant increase in stillbirths among COVID-19 infected women compared to that among the COVID-19 non-infected (pooled OR 1.46 [95% CI 1.16–1.85]; p = 0.05;  $I^2 = 17\%$ ). Of the included studies, neonatal deaths were assessed in seven studies [14,16,21,22,26,31,34], but only three studies were eligible for the meta-analysis [16,21,34]. The pooled odds ratio of three studies (1317 births to COVID-19 infected mothers and 3873 births to COVID-19 non-infected) revealed no significant difference in neonatal deaths between COVID-19 infected and non-infected cohorts (pooled OR 1.73 [95% CI 0.60–5.00]; p = 0.31;  $I^2 = 0\%$ ) (Figure 4C).

### 3.8. Comorbidities among COVID-19 Pregnant Women

Fifteen studies [14–18,23–26,29,30,33,34] reported on pre-gestational diabetes, but two studies [21,22] were excluded from the meta-analysis due to no events in COVID-19 infected pregnancies and 494,282 COVID-19 non-infected pregnancies.

A higher but non-significant increase in pre-gestational diabetes was observed in infected women compared to non-infected women (pooled OR 1.44 [95% CI 0.99-2.10]; p = 0.06;  $I^2 = 65\%$ ). Gestational diabetes [15,17,21–26,28,29,32,34] (11032 COVID-19 infected pregnancies and 577,889 COVID-19 non-infected in 12 studies; pooled OR 1.27 [95% CI 0.96-1.68]; p = 0.09;  $I^2 = 83\%$ ) was also high among COVID-19 infected women compared to COVID-19 non-infected; however, the difference still was not significant. Pooled odds of 10,461 COVID-19 infected pregnancies and 496,246 COVID-19 non-infected in 17 studies revealed no statistically significant difference in chronic hypertension [14–19,22–26,29–34] (pooled OR 1.17 [95% CI 0.92 - 1.49]; p = 0.19;  $I^2 = 38\%$ ) between COVID-19 infected and noninfected pregnant women. Data on asthma were reported by 14 studies, but only 12 studies [16,18,19,23–26,29–32,34] were included in the meta-analysis (9240 COVID-19 infected pregnancies and 491,066 COVID-19 non-infected pregnancies) as there were no events reported either in infected or non-infected women in two studies [17,22]. The pooled odds ratio of the 12 included studies revealed no risk of being infected with COVID-19 due to asthma during pregnancy (pooled OR 0.92 [95% CI 0.65-1.30]; p = 0.64;  $I^2 = 75\%$ ). Similarly, no statistically significant differences between COVID-19 infected and non-infected pregnancies were observed with relevance to anemia [16,19,22,27] (513 COVID-19 infected pregnancies versus 1758 COVID-19 non-infected pregnancies; four studies; pooled OR 0.92 [95% CI 0.53-1.60]; p = 0.77;  $I^2 = 0\%$ ), cardiac diseases [17,19,22,23,26,30,33,34] (2993 COVID-19) infected pregnancies versus 6031 COVID-19 non-infected; eight studies; pooled OR 1.00  $[95\% \text{ CI } 0.67-1.48]; p = 0.98; I^2 = 0\%)$ , chronic kidney disease [30,33] (1154 COVID-19 infected pregnancies versus 2640 COVID-19 non-infected; two studies; pooled OR 0.72 [95% CI 0.31 - 1.70; p = 0.45;  $I^2 = 0\%$ , chronic lung diseases other than asthma [19,24,26,30,33] (8124 infected pregnancies versus 486,754 COVID-19 non-infected; five studies; pooled OR 1.33 [95% CI 0.95–1.87]; *p* = 0.10; I2 = 0%), hypothyroidism [14,17,27] (267 COVID-19) infected pregnancies versus 1100 COVID-19 non-infected; three studies; pooled OR 0.93 [95% CI 0.42–2.04]; *p* = 0.85; I2 = 44%), immunosuppression [16,30] (509 COVID-19 infected pregnancies versus 1338 COVID-19 non-infected; two studies; pooled OR 1.20 [95% CI (0.29-4.90]; p = 0.80; I2 = 37%) and thrombophilia [19,26] (420 COVID-19 infected pregnancies versus 1193 COVID-19 non-infected; two studies; pooled OR 0.75 [95% CI 0.28-2.03]; p = 0.57; I2 = 0%) (Figure 5).

		Womon				Odde Patio		Odde	Patio	
Study or Subaroup	Events	Total	Events	Tota	l Weight	M-H. Random, 95% Cl		M-H. Rando	m. 95% Cl	
Ahedzadeh-Kalahroudi etal 202	1 9	56	21	9	1 86%	0.67.00.28.1.581			-	
Adhikari et al. 2020	, s 1	252	57	312	7 3.0%	0.21 [0.03, 1.55]	_		_	
Brandtetal 2021	7	61	20	12	2 81%	0.66 (0.26, 1.66)			_	
Cardona-Peírez et al. 2021	2	70	10	17	1 43%	0.47 [0.10, 2.20]				
Crovetto et al. 2021	ĥ	317	33	190	9 4.0% 9 8.5%	1 10 [0 46 2 64]				
Katzetal 2021	10	490	14	96	1 9.0%	1 41 [0 62 3 21]		_		
Koletal 2021	126	6550	6694	48292	1 15 1%	1 40 [1 17 1 67]		-	-	
Liuetal 2021	2	56	3	27	3 4%	3 41 10 56 20 881		-	<b>.</b>	
Martinez-Perez et al., 2021	1	246	10	76	3 2.8%	0.31 [0.04, 2.41]				
Prabhu et al., 2020	4	70	7	60	5 5.7%	5.18 [1.48, 18,15]				
Ríos-Silva et al., 2020	17	448	29	121	5 11.1%	1.61 (0.88. 2.97)		+		
Villar et al., 2021	33	706	20	142	4 11.6%	3.44 [1.96, 6.04]				
/ousden et al., 2021	28	722	7	69	4 8.9%	3.96 [1.72, 9.13]				
Total (95% CI)		10044		49428	2 100.0%	1 44 [0 99 2 10]			•	
Total events	246	10044	6925	43420	100.070	1.44 [0.55, 2.10]			•	
Heterogeneity: Tau <sup>2</sup> = 0.24; Chi <sup>2</sup> = 3	33.87. df = 12 (P = )	0.0007); I <sup>z</sup> :	= 65%				<u> </u>		, <b> </b>	
Test for overall effect: Z = 1.89 (P =	0.06)						0.01	0.1 1	10	100
	01/10 40 (1) 14/1-11		10 40 ( ) M			Odda Dafia		044- 8-	41-	
Study or Subgroup	OVID-19 (+) Wome Events T	en COV otal I	/ID-19 (-) W Events	omen Total V	leight M	Odds Ratio		Odds Ra M_H Random	atio 1 95% CI	
Adhikari et al. 2020	14	262	207	3122	0.2%				1,00% 01	
Cardona-Refrez et al. 2020	5	70	207	3122		11 8 3 11 A C 1 A 51				
Oundoniu 1 C 102 Ct di., 2021	9		12	170	4.6%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99]				
14110130131 /11/1	16	108	12	170 3057	4.6% 9.4%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44]		-+	_	
Gupta et al., 2021 Heini et al., 2021	16 13	108	12 334 30	170 3057 370	4.6% 9.4% 7.8%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35]				
Gupta et al., 2021 Hoini et al., 2021 Katz et al., 2021	16 13 22	108 137 490	12 334 30 67	170 3057 370 964	4.6% 9.4% 7.8%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49]				
Gupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Koet al., 2021	16 13 33 706 6	108 137 490	12 334 30 67 44554	170 3057 370 964 492921	4.6% 9.4% 7.8% 10.9%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.49 [1.10, 1.20]		+	 	
Gupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Ko et al., 2021	16 13 33 706 6	108 137 490 550	12 334 30 67 44554 41	170 3057 370 964 482921 279	4.6% 9.4% 7.8% 10.9% 14.5%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73]			 	
Gupta et al., 2021 Hcini et al., 2021 Kabz et al., 2021 Ko et al., 2021 Liu et al., 2021 Martinez, Parez et al., 2021	16 13 33 706 6 6	108 137 490 550 56 246	12 334 30 67 44554 41 61	170 3057 370 964 482921 279 762	4.6% 9.4% 7.8% 10.9% 14.5% 5.7%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.40, 1.40]			 	
Gupta et al., 2021 Hcini et al., 2021 Ko et al., 2021 Ko et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2021	16 13 33 706 6 6 17 162 2	108 137 490 550 56 246 296	12 334 30 67 44554 41 61 4231	170 3057 370 964 482921 279 763	4.6% 9.4% 7.8% 10.9% 14.5% 5.7% 9.3%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.40 [1.44, 1.49]			 	
Gupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Ko et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2020	16 13 33 706 6 6 17 163 2	108 137 490 550 56 246 286 70	12 334 30 67 44554 41 61 4331	170 3057 370 964 482921 279 763 84719	4.6% 9.4% 7.8% 10.9% 14.5% 9.3% 14.0%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68]			  	
Jupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2021 Prabhu et al., 2020	16 13 33 706 6 6 17 163 2 6	108 137 490 550 56 246 286 70	12 334 30 67 44554 41 61 4331 54	170 3057 370 964 482921 279 763 84719 605	4.6% 9.4% 7.8% 10.9% 14.5% 9.3% 14.0% 6.0%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31]				
Supra et al., 2021 Hcini et al., 2021 Ko et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2021 Prabhu et al., 2020 Trahan et al., 2021	16 13 33 706 6 6 17 163 2 6 1 1	108 137 490 550 56 246 286 70 45 722	12 334 30 67 44554 41 61 4331 54 24	170 3057 370 964 482921 279 763 84719 605 225 604	4.6% 9.4% 7.8% 10.9% 14.5% 9.3% 14.0% 6.0%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.65 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 1.47 [0.63, 4.04]				
Gupta et al., 2021 Hcini et al., 2021 Ko et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2021 Prabhu et al., 2020 Trahan et al., 2021 Vousden et al., 2021	16 13 33 706 6 6 17 163 2 6 1 116	108 137 490 5550 56 246 286 70 45 722	12 334 30 67 44554 41 61 4331 54 24 7	170 3057 370 964 482921 279 763 84719 605 225 694	4.6% 9.4% 7.8% 10.9% 14.5% 5.7% 9.3% 14.0% 6.0% 1.7% 6.9%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.65 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60]			  	
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Gupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2020 Trabhu et al., 2020 Trahan et al., 2021 Vousden et al., 2021 <b>Total (95% CI)</b> Total events	16 13 33 706 6 6 17 163 2 6 1 116 116 <b>11</b> 1096	108 137 490 550 56 246 286 70 45 722 032	12 334 67 44554 41 61 4331 54 24 7 49722	170 3057 370 964 482921 279 763 84719 605 225 694 577889 1	4.6% 9.4% 7.8% 10.9% 14.5% 5.7% 9.3% 14.0% 6.0% 1.7% 6.9% 00.0%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60] <b>1.27 [0.96, 1.68]</b>				
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Gupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2021 Prabhu et al., 2020 Trahan et al., 2021 Vousden et al., 2021 Total events Heterogeneity: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = Test for overall effect: Z = 1.67 (P :	16 13 33 706 6 17 163 2 6 1 116 <b>11</b> 1096 = 63.01, df = 11 (P = 0.09)	108 137 490 550 56 246 286 70 45 722 032 < 0.00001	12 334 30 67 44554 41 61 4331 54 24 7 7 49722 );   <sup>2</sup> = 83%	170 3057 370 482921 279 763 84719 605 225 694 577889 1	9.3% 9.4% 9.4% 10.9% 4.5% 5.7% 9.3% 4.0% 6.0% 1.7% 6.9%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60] <b>1.27 [0.96, 1.68]</b>	.01			
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Supra et al., 2021 Heini et al., 2021 Katz et al., 2021 Liu et al., 2021 Ju et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2020 Trahan et al., 2020 Trahan et al., 2021 Jousden et al., 2021 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = Test for overall effect: Z = 1.67 (P Chronic hypertens	16 13 33 706 6 17 163 2 6 1 116 11 1096 = 63.01, df = 11 (P = 0.09)	<pre>108 108 137 490 550 56 246 286 70 45 722 032 &lt; 0.00001</pre>	12 334 30 67 44554 41 61 54 24 7 49722 );  * = 83%	170 3057 370 964 482921 279 763 84719 605 225 694 577889 1	9.4% 9.4% 7.8% 10.9% 5.7% 9.3% 4.0% 6.0% 6.0% 6.9%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60] <b>1.27 [0.96, 1.68]</b>	.01	0.1		
Jupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Liu et al., 2021 Norman et al., 2021 Prabhu et al., 2020 Trahan et al., 2020 Trahan et al., 2021 Vousden et al., 2021 Fotal events Heterogeneity: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = Test for overall effect: Z = 1.67 (P = Chronic hypertens	16 13 30 706 6 17 163 2 6 1 116 1096 = 63.01, df = 11 (P = 0.09) Sion	108 108 137 490 550 56 246 286 70 45 722 032 < 0.00001	12 334 30 67 44554 41 61 4331 54 24 7 49722 );  * = 83%	170 3057 370 964 482921 279 763 84719 605 225 694 577889 1	9.4% 9.4% 7.8% 10.9% 5.7% 9.3% 4.0% 6.0% 1.7% 6.9%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60] <b>1.27 [0.96, 1.68]</b>	.01	0.1 1		
Supra et al., 2021 Hcini et al., 2021 Katz et al., 2021 Ko et al., 2021 Ju et al., 2021 Vartinez-Perez et al., 2021 Vorman et al., 2020 Frahan et al., 2020 Frahan et al., 2021 Fotal events Heterogeneity: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = Fest for overall effect: Z = 1.67 (P : Chronic hypertens	16 13 30 6 17 163 2 6 1 116 1096 = 63.01, df = 11 (P = 0.09) Sion	108 137 490 550 56 246 286 70 45 722 032 < 0.00001	12 334 30 67 44554 41 61 4331 54 24 7 49722 ); I <sup>2</sup> = 83%	170 3057 370 964 482921 279 763 84719 605 225 694 577889 1	9.4% 9.4% 7.8% 10.9% 5.7% 9.3% 4.0% 6.0% 1.7% 6.9%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.29] 0.70 [0.28, 1.73] 0.70 [0.28, 1.73] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.96 [0.40, 2.31] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60] <b>1.27 [0.96, 1.68]</b>	.01	0.1		
Gupta et al., 2021 Hcini et al., 2021 Katz et al., 2021 Liu et al., 2021 Martinez-Perez et al., 2021 Norman et al., 2021 Prabhu et al., 2020 Trahan et al., 2021 Vousden et al., 2021 Total events Heterogeneity: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = Test for overall effect: Z = 1.67 (P = Chronic hypertens	16 13 33 706 6 17 163 2 6 1 116 11 1096 = 63.01, df = 11 (P = 0.09) Sion	V000001 108 137 490 550 56 246 2286 70 45 722 032 < 0.00001	12 334 30 67 44554 41 61 54 24 7 49722 ); I* = 83%	170 3057 370 964 482921 279 763 84719 605 225 694 577889 1	9.4% 9.4% 9.4% 0.9% 10.9% 5.7% 9.3% 4.0% 6.0% 6.0% 6.9% 00.0%	0.83 [0.47, 1.45] 1.01 [0.34, 2.99] 1.42 [0.82, 2.44] 1.19 [0.60, 2.35] 0.97 [0.63, 1.49] 1.19 [1.10, 1.49] 1.19 [1.10, 1.49] 1.43 [1.21, 1.68] 0.85 [0.49, 1.49] 1.43 [1.21, 1.68] 0.19 [0.03, 1.44] 18.79 [8.69, 40.60] <b>1.27 [0.96, 1.68]</b>	.01	0.1 1		100
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Abedzadeh-Kalahroudi et al., 2021	6	56	11	94	4.2%	0.91 [0.32, 2.60]	
Adhikari et al., 2020	12	252	145	3122	9.1%	1.03 [0.56, 1.88]	_ <b>+</b> _
Brandt et al., 2021	2	61	6	122	2.0%	0.66 [0.13, 3.35]	
Cardona-Pe´rez et al., 2021	2	70	8	170	2.1%	0.60 [0.12, 2.88]	
Crovetto et al., 2021	11	317	58	1908	8.2%	1.15 [0.60, 2.21]	_ <b>_</b>
Cruz-Lemini et al., 2021	2	174	2	430	1.4%	2.49 [0.35, 17.81]	
Hcini et al., 2021	2	137	6	370	2.0%	0.90 [0.18, 4.51]	
Katz et al., 2021	26	490	48	964	11.3%	1.07 [0.65, 1.75]	_ <b>+</b> _
Ko et al., 2021	149	6550	13017	482921	19.4%	0.84 [0.71, 0.99]	-
Liu et al., 2021	6	56	25	279	5.0%	1.22 [0.48, 3.12]	<b>_</b>
Martinez-Perez et al., 2021	3	246	6	763	2.6%	1.56 [0.39, 6.27]	
Prabhu et al., 2020	3	70	13	605	3.0%	2.04 [0.57, 7.34]	
Ríos-Silva et al., 2020	17	448	38	1216	9.5%	1.22 [0.68, 2.19]	- <b>-</b>
Steffen et al., 2021	4	61	85	939	4.3%	0.71 [0.25, 1.99]	
Trahan et al., 2021	2	45	8	225	2.1%	1.26 [0.26, 6.15]	
Villar et al., 2021	26	706	30	1424	10.4%	1.78 [1.04, 3.03]	
Vousden et al., 2021	26	722	3	694	3.4%	8.60 [2.59, 28.56]	
Total (95% CI)		10461		496246	100.0%	1.17 [0.92, 1.49]	◆
Total events	299		13509				
Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 25.61, df = 16 (P = 0.06); l <sup>2</sup> = 38%							
Test for overall effect: Z = 1.30 (P = 0.19) 0.01 0.1							U.U1 U.1 1 10 100
	-,						

Figure 5. Cont.





Figure 5. Forest plots of comorbidities among COVID-19 infected women. (a) Pre-gestational diabetes.
(b) Gestational diabetes. (c) Chronic hypertension. (d) Anemia. (e) Cardiac diseases. (f) Chronic kidney disease. (g) Asthma. (h) Chronic lung diseases (other than asthma). (i) Hypothyroidism. (j) Immunosuppression. (k) Thrombophilia.

### 4. Discussion

We conducted this systematic review to pool the available evidence of adverse perinatal outcomes caused by COVID-19 infection in pregnancy. We retrieved a total of 21 observational studies that assessed the adverse perinatal outcomes in pregnant women with COVID-19 infection published from December 2019 to June 2021.

Overall findings of our study were, (1) the reported incidence rates of COVID-19 infection among pregnant women ranged from 1.3% to 27%, disregarding the fact that the results were based on single-center studies to multinational studies; (2) with regards to the adverse maternal outcomes, we found that there was a statistically significant increase in maternal deaths, preeclampsia, and cesarean deliveries, while miscarriages/abortions, PROMs/PPROMs, and operative vaginal births were non-significant in COVID-19 infected pregnant women compared to non-infected; (3) with regards to the adverse fetal outcomes, fetal distress was found to be statistically significant, while intrauterine death was non-significant in COVID-19 infected pregnancies; and (4) with regards to the adverse neonatal outcomes, all reported fetal outcomes except neonatal death, including preterm birth, low birth weight, stillbirth, fifth minute Apgar score < 7, and admissions to NICU showed significant differences in births to COVID-19 infected women compared to non-infected.

The current study findings were consistent with previously published systematic reviews relevant to maternal death [35], preeclampsia [36], preterm birth [35,36], stillbirth [36] and admissions to NICU [35]. In addition to those findings, we found increased cesarean section deliveries among COVID-19 infected women compared to non-infected, 12982, and 583619. However, the data included in the present study did not consider whether those cesarean sections were elective or emergency cases based on COVID-19 status. Pooling of comorbidity data of infected and non-infected pregnant women revealed that comorbidities during pregnancy were not significantly higher in COVID-19 infected pregnancies. This finding was inconsistent with the findings of a previous systematic review, which observed a higher risk of COVID-19 infection in pregnancy when having pre-gestational diabetes mellitus, gestational diabetes mellitus, and chronic hypertension [35]. Out of 21 studies, more than 90% of the studies in this review assessed perinatal outcomes regardless of the disease severity. Consequently, not enough information was available to assess the differences in maternal, fetal, and neonatal outcomes based on disease severity. Therefore, further studies are recommended to assess the perinatal outcomes based on disease severity in order to clear up uncertainties in this area.

#### 4.1. Implications for Clinical Practice

Healthcare providers should be aware that women infected with COVID-19 have an elevated risk of disease severity, including maternal mortality. Pregnant women should be advised of the disease's increased severity and encouraged to take precautions to avoid infection. Primary healthcare providers will need to balance the necessity for routine multidisciplinary prenatal care and the management of women suspected of having COVID-19 infection, preferably via virtual antenatal clinics. Pregnant women who become infected with COVID-19 before reaching term may require management in a tertiary healthcare facility equipped with cesarean section and NICU facilities to manage preterm infants, infants with low Apgar scores, and infants with fetal distress.

#### 4.2. Strengths and Limitations

This systematic review has several strengths. First, the study followed a sound methodology and was able to quantify the findings using meta-analyses. Second, a comprehensive search strategy was used to minimize the risk of missing relevant studies. Third, the screening was independently assessed by pairs of reviewers, and discrepancies solved by consensus. Fourth, excluding the publication types such as case studies, case reports, and case series left studies with a quality study design included in the final analysis. Finally, the present systematic review adhered to a rigorous quality appraisal. An important amount of evidence was summarized and critically appraised in addition to the highlighted

evidence gaps. Our systematic review also has limitations. Firstly, the method of diagnosis of COVID-19 in pregnancy was different from study to study. Secondly, without data on disease severity, perinatal outcomes based on disease severity could not be determined. Thirdly, many studies represented developed countries with only meager contributions from lowresource countries. However, the findings of this systematic review have implications for low and middle-income countries with limited resources, where the negative impacts are prominent due to region-specific management strategies and resources. Finally, asymmetry of the funnel plots was observed for the assessed variables, and the presence of publication bias was suggested. This asymmetry may be also due to some other factors such as poor methodological design, reporting bias, chance or study heterogeneity. Despite all limitations, we undertook a comprehensive literature review and meta-analysis with the most updated findings relevant to adverse perinatal outcomes in COVID-19 infected pregnant women.

#### 5. Conclusions

Several adverse maternal, fetal, and neonatal effects were significantly higher in COVID-19 infected pregnant women than non-infected. These included maternal death, preeclampsia, cesarean section delivery, fetal distress, preterm birth, low birth weight, stillbirth, low Apgar score at the fifth minute, and admission to NICU. The comorbidity conditions had no added risk of being infected with COVID-19 infection during pregnancy. Therefore, a COVID-19 infected pregnant woman should be treated with special precautions to avoid and minimize the identified adverse events during perinatal care. Further studies are recommended to collect more robust data relevant to the adverse perinatal outcomes that will enable effective clinical decision-making in maternal and child health care.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/ 10.3390/healthcare10020203/s1, Table S1: Medline search strategy used in systematic review and meta-analysis of adverse perinatal outcomes in COVID-19 infected pregnant women: a systematic review and meta-analysis; Table S2: Quality assessment of the included studies based on National Institute of Health's study quality assessment tool.

**Author Contributions:** M.L.P. and I.W. conceptualized the study. M.L.P., B.P.P.S. and T.S.D. selected studies. M.L.P. extracted and analyzed data. M.L.P. wrote the first draft. M.L.P., I.W. and P.S. edited the first draft and finalized the paper. All authors have read and agreed to the published version of the manuscript.

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