

Article type : Review Article

REVIEW ARTICLE

Maternal death related to COVID-19: A systematic review and meta-analysis focused on maternal co-morbidities and clinical characteristics

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Keywords

co-morbidities; COVID-19; maternal death; neonatal outcomes; pregnancy

Synopsis

Pregnant women with COVID-19 infection and at least one severe co-morbidity experience increased risk of death and admission to the intensive care unit.

ABSTRACT

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/IJGO.13726](https://doi.org/10.1002/IJGO.13726)

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Background: Besides reducing the quality of obstetric care, the direct impact of COVID-19 on pregnancy and postpartum is uncertain.

Objective: To evaluate the characteristics of pregnant women deceased due to COVID-19.

Search strategy: Cochrane Library, Embase, MEDLINE, Scopus, and Google Scholar were searched from inception to February 2020.

Selection criteria: Studies that compared deceased and survived pregnant women with COVID-19.

Data collection and analysis: Relevant data were extracted and tabulated. The primary outcome was maternal co-morbidity.

Main results: Thirteen studies with 154 deceased patients were included. Obesity doubled the risk of death (relative risk [RR] 2.48, 95% confidence interval [CI] 1.41–4.36, $I^2=0\%$). No differences were found for gestational diabetes (RR 5.71; 95% CI 0.77–42.44, $I^2=94\%$) or asthma (RR 2.05, 95% CI 0.81–5.15, $I^2=0\%$). Overall, at least one severe co-morbidity showed a twofold increased risk of death (RR 2.26, 95% CI 1.77–2.89, $I^2=76\%$). Admission to intensive care was related to a fivefold increased risk of death (RR 5.09, 95% CI 2.00–12.98, $I^2=56\%$), with no difference in need for respiratory support (RR 0.53, 95% CI 0.23–1.48, $I^2=95\%$) or mechanical ventilation (RR 4.34, 95% CI 0.96–19.60, $I^2=58\%$).

Conclusion: COVID-19 with at least one co-morbidity increases risk of intensive care and mortality.

1 INTRODUCTION

COVID-19 was declared a pandemic by WHO on March 11, 2020, during its 51st situation report. To date, the disease is still causing harmful consequences in almost every country [1].

The clinical course of the disease frequently starts with low-grade fever, cough, anosmia, ageusia, headache, chest pain, or pneumonia [2]. Specific consequences of the infection on pregnancy and neonatal outcomes are still uncertain since evidence regarding the disease is still ongoing. The severity of the disease ranges from asymptomatic to acute respiratory distress. The reported mortality for SARS-Cov-2 is estimated in the range of 1%–2%, less than other coronaviruses including Middle East Respiratory Syndrome

(MERS) and Severe Acute Respiratory Syndrome (SARS), for which the reported rate of death is estimated at about 35% and 10%, respectively [3]. The morbidity rate of COVID-19 in pregnant women is higher than MERS, SARS, and also influenza and Ebola [4]. Nevertheless, it seems that pregnancies affected by COVID-19 do not develop more severe symptoms compared to the general population and an increased risk for pregnant women, compared to non-pregnant women, has not been demonstrated yet [5, 6]. However, it is ascertained that pregnant women cannot avoid mandatory examinations; therefore, they cannot avoid interactions with healthcare professionals. For this reason, they could be more exposed to contagion than nonpregnant women [7]. On the contrary, women of reproductive age are expected to have 60% less access to intensive care units (ICUs) than postmenopausal women [3, 8]. Moreover, new findings from studies conducted in low-resource countries showed an increased risk of death in obstetric patients who tested positive for SARS-CoV-2 [9]. Therefore, evidence concerning the impact of pregnancy as well as its co-morbidities on COVID-19-related maternal mortality is still uncertain.

The aim of the present systematic review and meta-analysis was to investigate the clinical characteristics of pregnant women who died due to COVID-19.

2 MATERIALS AND METHODS

The research protocol was designed a priori, defining methods for searching the literature. The meta-analysis was conducted complying with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] and the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) statement guidelines [11]. The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the ID number CRD42021228455.

Search strategy and study selection

Five electronic databases (Cochrane Library at the CENTRAL register, Ovid Embase, MEDLINE, Scopus, and Google Scholar) were searched from inception to February 2020. Eligible studies were identified with a combination of the following keywords and/or Medical Subject Headings (MeSH) terms: “maternal death”; “maternal mortality”; “coronavirus”; “COVID-19”; “COVID 19”; and “SARS-CoV-2”. Case reports, case series,

prospective cohort studies, and retrospective cohort studies regarding maternal mortality cases due to COVID-19 and neonatal outcomes were considered eligible if they reported at least one maternal death with the clinical characteristics of the adverse events and if they were published in a peer-reviewed journal. No language restrictions were applied.

Review articles, letters to the editor, non-peer-reviewed reports, studies with unspecified dates and places of research, suspicion of duplicate reporting and/or unreported data on maternal deaths were excluded from the study. From the selected studies, the references were also evaluated in order to find additional relevant studies.

Titles and abstracts were reviewed separately by two reviewers (MLV and FL) to identify all eligible articles. Full-text articles were retrieved for further consideration for inclusion.

Discrepancies were solved by discussion with a third author (SS).

Data extraction, quality assessment, and outcome measures

The analyzed data were selected from each relevant study and systematically collected in a database. The following information was obtained: author's name; institution and country; study design; sample size; maternal age; gestational age at admission; symptoms on admission to hospital and the days before; pregnancy co-morbidity; mode of delivery; acute respiratory distress syndrome (ARDS) developed; maternal and neonatal outcomes; chest computed tomography (CT); time between delivery and maternal death; the results of COVID-19 tests performed on the neonatal population; and the perinatal outcomes. Not all studies reported on all evaluated variables and studies that did not report on a specific outcome were recorded as not reported.

Primary and secondary outcomes

The primary outcome was maternal co-morbidities. The secondary outcomes were admission to the intensive care unit (ICU) and the need for respiratory support. When described, additional data regarding the delivery mode, onset of ARDS, chest CT, and the perinatal and neonatal outcome were also collected. All the clinical characteristics reported and information regarding the maternal and perinatal death were recorded, including the clinical manifestations of COVID-19 at admission and the days before.

Quality assessment

The methodological quality of the studies was assessed independently by the same two authors using the Joanna Briggs Institute (JBI) tool for case series and case reports [12],

and using the Newcastle-Ottawa Scale (NOS) for observational studies [13]. According to the NOS, every trial is assessed based on three crucial elements: selection of study groups; comparability of the study groups; and ascertainment of the interested outcome. Assessment of the selection of a study requires the following: estimation of the representativeness of the exposed cohort; selection of the non-exposed cohort; checking the exposure; and validation that the evaluated endpoint was not likely to occur spontaneously at the beginning of the study. The comparability of studies is judged, including the assessment of the comparability of cohorts on the design or analysis. In addition, the ascertainment of the outcome of interest is evaluated using the following: determination of the outcome; duration; and adequacy of the follow-up. According to NOS criteria, a study can be awarded a maximum of one star for each of the numbered items within the Selection and Outcome categories.

Risk of bias judgment was independently assessed by three authors (SC, GR, and MM). Any disagreement was resolved by discussion with a fourth reviewer (PDF).

Statistical analysis

In a conservative approach, the random-effects model was calculated using the DerSimonian and Laird method. Results were reported as mean differences (MD) or relative risk (RR) with 95% confidence intervals (CI). We quantified heterogeneity using the Higgins (I^2) statistics, in which 25%, 50%, and 75% were cutoffs for low, medium, and high heterogeneity, respectively. Statistical analysis was conducted using the software STATA version 14.1 (StataCorp., College Station, TX, USA). In case of descriptive studies or trials without a control group, a narrative synthesis was selected [14].

3 RESULTS

Figure 1 illustrates the selection of studies for inclusion in the meta-analysis. Out of a total of 13 600 initial records, 13 studies (including 154 women deceased due to COVID-19) that summarized co-morbidities fulfilled the inclusion criteria and were considered for the review. These included four case reports [15–18] and three case series [9, 19, 20], two prospective [21, 22] and four retrospective cohort studies [23, 24] (Table 1).

Two studies conducted in Brazil and Mexico compared the maternal death group and the survival group and were eligible for the meta-analysis [25, 26]. For the remaining 11 studies [9, 15–17, 19–24], a qualitative synthesis was performed.

Nine studies described the maternal co-morbidity at the time of admission [9, 15–20, 22, 23]. Six studies [9, 15–20, 22, 23] listed the maternal symptoms and the clinical manifestations of COVID-19 at the time of admission and in the days before. Four studies originated from Iran. Two studies originated from the USA, UK, and Brazil, and the remaining studies were from Turkey, Mexico, Europe, and India.

Quality characteristics

Publication bias was considered to be high since the vast majority of the included studies were either case series or case reports. The inclusion of two prospective cohort studies slightly decreased the paper's bias due to the vast number of included case reports and case series. A detailed quality assessment of the included studies is reported in Tables S1 and S2.

Qualitative analysis

Clinical characteristics and pregnancy complications

In the pooled data from the nine studies [15–18, 20–24], there was a mean maternal age of 29 years (95% CI 24.4–31.3). Hantoushzadeh et al. [9] reported only the age range with a value in the range of 20–44 years. Blitz et al. [19] and Nayak et al. [24] did not report the maternal age (Table 1). The mean gestational age on admission was 32 weeks (95% CI 28–35), while two studies did not report this information [19, 22] (Table 1). Eight studies [9, 15–18, 20–23] reported symptoms referred between the time of hospital admission and the days before. The predominant symptom was fever (14/15 patients, 87.5%), followed by dyspnea/shortness of breath (11/15, 68.75%) and dry cough (8/15, 50%) (Table S3). Less common symptoms were sore throat (4/15, 25%) followed by myalgia (3/15, 18.7%), rhinorrhea, fatigue, and hypertension (2/15, 12.5%). An unconscious state and diarrhea were present in 6.2% (1/14) of cases (Table S3). Seven studies [9, 15, 17, 18, 21–23] reported the results of the chest CT scans and all the patients had a positive CT result (11/11, 100%) with a finding of a bilateral patchy or ground-glass opacity on the chest CT scans (Table S4). At the time of admission, 20 of 23 patients were pregnant (86.9%) and one patient was puerperal, one was admitted after a spontaneous abortion, and one was not reported. The mode of delivery was reported for 15 patients [9, 15, 16, 18, 20, 22–24]: 13 (86.6%) had a cesarean delivery

and 2 (13.4%) had a vaginal delivery (Table 1). Death occurred in the postpartum period for 19 of 23 women (82.6%). Two deaths (8.6%) occurred during the pregnancy: one in the post-abortion period and one patient was not reported (Table 1). The time taken to develop ARDS, after admission to hospital, was 36 hours (95% CI 24–72) [9, 15, 16, 21]. In the seven studies that reported the outcome [9, 15–18, 20, 21, 23], maternal death occurred 6 days after delivery (95% CI 2.2–12) (Table 1).

Maternal co-morbidities

Nine studies reported the pregnancy co-morbidities on admission to hospital [9, 15–20, 22, 23], with a total of 18 patients. With regard to these 18 patients, 5 (27%) did not manifest any pregnancy complications. Gestational diabetes and obesity were the most frequent co-morbidity (22%, 4/20 for each patient). The second most frequent co-morbidities were maternal hypothyroidism, pre-eclampsia, and twin gestation (11%, 2/18 each). The less common were: obstructive sleep apnea, asthma, renal disease, hepatitis, cardiovascular disease, and HELLP syndrome (5.5%, 1/18 each). Two patients in this series had a twin pregnancy obtained after assisted reproduction [9]. Lumbreras-Marquez et al. [25] and Takemoto et al. [26] compared the maternal co-morbidities in the group of maternal deaths due to COVID-19 versus the maternal survival group. Lumbreras-Marquez et al. had a group of seven maternal deaths, with a mean age of 37 years (95% CI 26–39), and recorded data regarding maternal co-morbidities: diabetes; obesity; asthma; hypertension; exposure to tobacco; chronic obstructive pulmonary disease; chronic kidney disease; and other co-morbidities. Takemoto et al. recorded the deaths of 124 patients due to COVID-19, with a mean age of 32 years (95% CI 25–37). The majority of these (59.7%) happened during pregnancy.

Eight studies [9, 15–20, 23] reported data about neonatal outcomes: in 20 fetuses there were six cases of intrauterine fetal death (30% of the total). There were two neonatal deaths reported by Hantoushzadeh et al. [9], who reported death regarding a twin pregnancy that was linked to the complications of a premature birth (no evidence of COVID-19 infection was reported). For this reason, the rate of neonatal mortality of infants born from deceased mothers was 16.6% (2/12) [9, 15–18, 20, 21]. Eight newborns

were tested for the viral infection [9, 15, 16, 18, 20, 21], and 2 (25%) fetuses tested positive (Table S5) [9].

Meta-analysis

Data regarding maternal diabetes, obesity, asthma, the presence of one co-morbidity or one risk factor, admission to the ICU, and respiratory support were used for the meta-analysis. Overall, maternal obesity increased the risk of maternal death by 2.48 (95% CI 1.41–4.36) with no heterogeneity ($I^2=0\%$). There were no significant changes in the risk of death in women with gestational diabetes (RR 5.71, 95% CI 0.77–42.44, $I^2=94\%$), maternal asthma (RR 2.05, 95% CI 0.81–5.15, $I^2=0\%$). The presence of one co-morbidity or one risk factor increased the risk of death twofold during COVID-19 infection (RR 2.26, 95% CI 1.77–2.89, $I^2=76\%$) (Fig. 2). Analyzing the intensive care reports, deceased women had a fivefold increased rate of admission to the ICU (RR 5.09, 95% CI 2.00–12.98, $I^2=56\%$). However, there was no difference between deceased and survived women needing respiratory support (RR 0.53, 95% CI 0.23–1.48, $I^2=95\%$) or mechanical ventilation (RR 4.34, 95% CI 0.96–19.60, $I^2=58\%$) (Fig. 3).

4 DISCUSSION

The present qualitative and quantitative synthesis showed the clinical characteristics of pregnant women deceased to COVID-19. The main symptoms at the time of admission and the days before were fever and dyspnea/shortness of breath. When carried out, the results of the chest CT scan were positive for interstitial lung infection in 100% of the cases. Almost 90% of women had a cesarean delivery, and only two vaginal deliveries were recorded. Most of the deaths occurred in the postpartum period.

Among the fetal-neonatal outcomes, intrauterine fetal death occurred in 30% of cases and there were only two postnatal deaths. These deaths were related to neonatal prematurity. Eight infants were tested for COVID-19: two were positive, with a vertical transmission rate of 25%. The presence of one maternal co-morbidity or one risk factor increased the risk of death by 156 times.

The current COVID-19 pandemic is the third zoonotic coronavirus infection in recent decades [27, 28]. During the SARS-CoV-1 pandemic, in 2002, the estimated percentage of pregnant women who died due to the pathology was estimated to be about 25% [29].

Nevertheless, complete information about SARS-CoV-2 morbidity and mortality in pregnancy is still missing. A recent review reported fever, cough, dyspnea/shortness of breath, fatigue, and myalgia between the most common symptoms of COVID-19 [30]. In contrast, a literature review that evaluated the maternal clinical presentation and outcomes of 385 women infected with COVID-19 found that 95% of them were asymptomatic or had mild symptoms, while 0.8% developed a condition requiring critical care [31].

Gestational diabetes and obesity were the most common co-morbidities. These data were also reported by Lumbreras-Marquez et al. [25] and Takemoto et al. [26], where maternal diabetes and obesity increased the risk of death threefold.

Nevertheless, knowledge in the literature on maternal susceptibility to SARS-CoV-2 is still uncertain. It was found that all the women who died after the infection had serious pulmonary damage on CT, as was also shown by Juan et al. [30], where most cases had patchy shadowing or ground-glass opacity on CT. Another meta-analysis assumed that no notable adverse outcomes for fetuses or neonates were notable [32], which is in contrast with the findings of the present study. The stillbirths reported in the present review were all related to neonatal prematurity. Regarding the risk of vertical transmission, a recent review concluded that a low rate of vertical transmission is plausible with SARS-CoV-2 infection [33].

A strength of the present review is related to the analysis of maternal mortality, which was obtained only from peer-reviewed literature. The main limitation of the meta-analysis is the limited number of studies (n=2) [25, 26] included for the quantitative analysis, and the high number of case reports and case series included for qualitative synthesis, limiting the quality of available evidence.

Moreover, although no heterogeneity was present for the primary outcome, it was reported as moderate or significant for several secondary endpoints, limiting the possible generalization of these findings. Furthermore, it is understandable that the pandemic crisis negatively influenced the quality of studies published, stressing the need for larger, prospective designed studies.

In summary, the present review showed that in the case of COVID-19 infection in pregnant women, while the majority of the admissions to hospital occurred during pregnancy, death occurred in the postpartum period. Moreover, at least one maternal co-

morbidity or one risk factor elevated the possibility of death; maternal diabetes and maternal obesity, in particular, had a negative impact on admission to the ICU. A rapid progression of disease with a short time between delivery and death was noted.

Evidence reporting the characteristics of maternal mortality and morbidity with COVID-19 is still limited and of very low quality. Therefore, it is necessary to obtain more knowledge to pursue the earlier identification of pregnant women at a higher risk for severe COVID-19 disease.

Author contributions

Study design: MLV and GR. Acquisition of data: FL, SS, and SC. Analysis and interpretation of data: MM, MLV, and FS. Drafting of the manuscript: GR and PDF.

Critical revision of the manuscript: NC, MT, and MM. All authors read and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during the present study are included in the published article and its supplementary material file.

Conflicts of interest

The authors have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram of reported studies.

Figure 2. Forest plots for maternal co-morbidities.

Figure 3. Forest plots for intensive care outcomes.

Table 1. Characteristics of included studies.

Study	Deaths (n)	Country	Mean age (years)	GA on admission (weeks)	Mode of delivery		Maternal deaths			
					Cesarean	Vaginal	Post- miscarriage	During pregnancy	Postpartum	Mean time after delivery (days)
Zamaniyan [15]	1	Iran	22	32	1	0	0	0	1	312
Vallejo [16]	1	USA	36	37	1	0	0	0	1	36
Azarkish [17]	1	Iran	19	38	0	1	0	0	1	216
Ahmed [18]	1	UK	29	29	1	0	0	0	1	144
Hantoushzadeh [9]	7	Iran	25–44	30 (4	1	0	0	7	3 (
Blitz [19]	2	USA	NR	NR	NR	NR	0	1	1	NR
Barroso Dos Reis [20]	1	Brazil	25	28	1	0	0	0	1	528
Sahin [21]	2	Turkey	28.5	27	1	0	1	0	1	125
Antoun [22]	1	UK	29	NR	1	0	0	0	1	NR
Di Mascio [23]	3	Europe	30	34	2	NR	0	1	2	192
Nayak [24]	3	India	NR	35	1	1	NR	NR	2	NR
Lumbreras- Marquez [25]	7	Mexico	NR	NR	NR	NR	NR	NR	NR	NR

Takemoto [26]	124	Brazil	32	NR	NR	NR	0	74	50	NR
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Abbreviations: GA, gestational age; NR, not reported.

Table 2. Pregnancy co-morbidities in the included studies.

Study	Pregnancy co-morbidities												
	None	Other	Obesity	OSA	Asthma	Renal disease	Hepatitis	Cardio-vascular disease	HELLP syndrome	Hypothyroidism	GDM	Pre-eclampsia	Twin gestation (DCDA) with IVF
Zamani yan [15]	0	0	0	0	0	0	0	0	0	1	0	0	0
Vallejo [16]	0	0	1	0	0	0	0	0	0	0	0	0	0
Azarkis h [17]	0	0	0	0	0	0	0	0	0	0	0	1	0
Ahmed	0	0	1	0	1	1	0	0	0	0	1	0	0

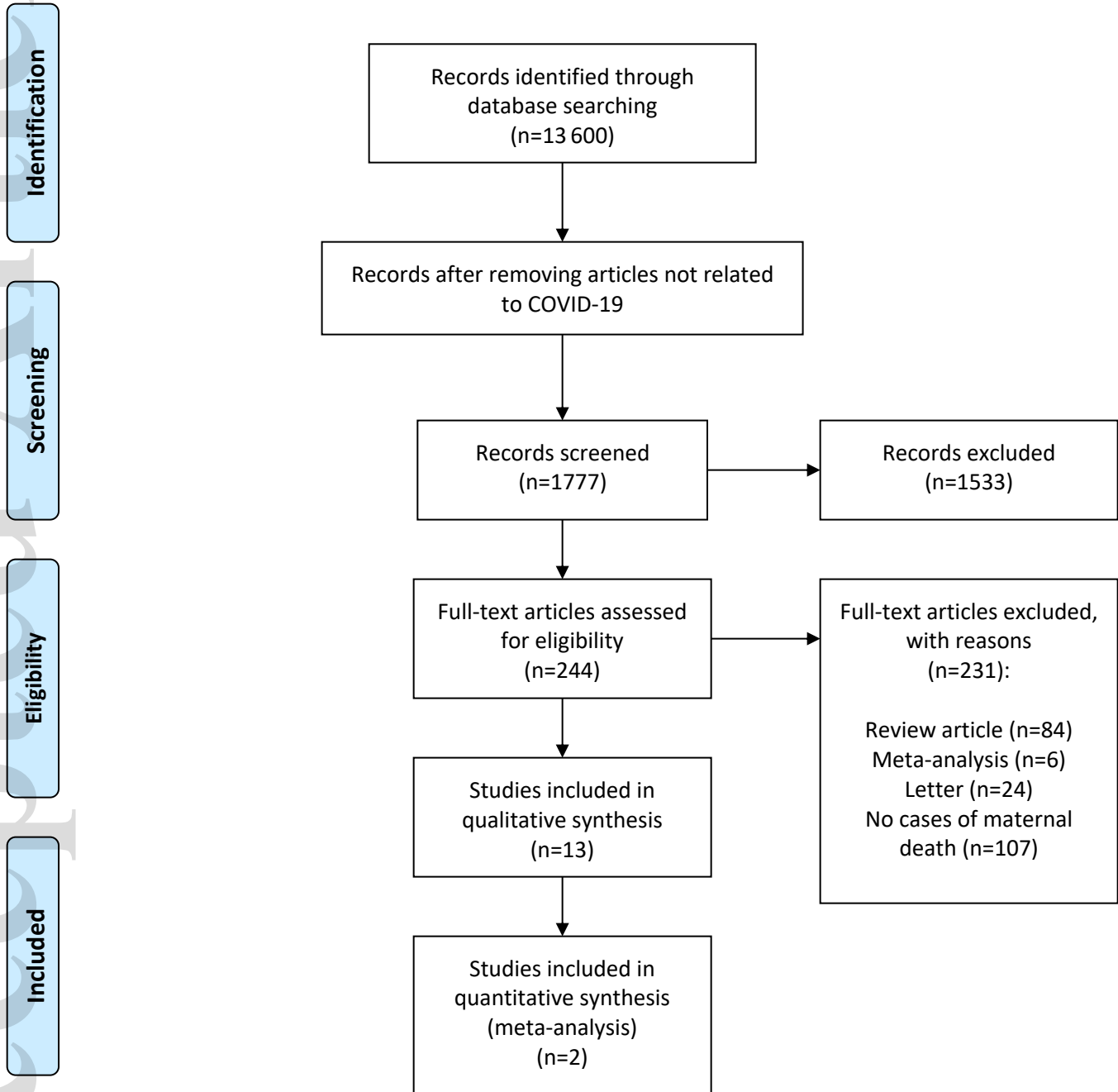
[18]														
Hantous hzadeh	0	2	1	0	0	0	0	0	0	0	1	1	0	2
[9]														
Blitz	0	1	1	1	0	0	0	0	0	0	0	0	0	0
[19]														
Barroso Dos Reis	0	1	0	0	0	0	0	0	0	0	0	0	0	0
[20]														
Sahin	1	0	0	0	0	0	0	1	0	0	0	0	0	0
[21]														
Antoun	0	0	0	0	0	0	0	0	0	0	0	1	0	0
[22]														
Di Mascio	0	1	0	0	0	0	0	0	0	0	0	1	1	0
[23]														
Nayak	1	0	0	0	0	0	1	0	1	0	0	0	0	0
[24]														
Lumbrer as- Marque z [25]	0	0	2	0	0	0	0	0	0	0	0	4	0	0

Takemo 0 60 12 0 5 0 0 26 0 0 21 0 0
to [26]

Abbreviations: DCDA, dichorionic diamniotic; GDM, gestational diabetes mellitus; IVF, in vitro fertilization; OSA, obstructive sleep apnea.

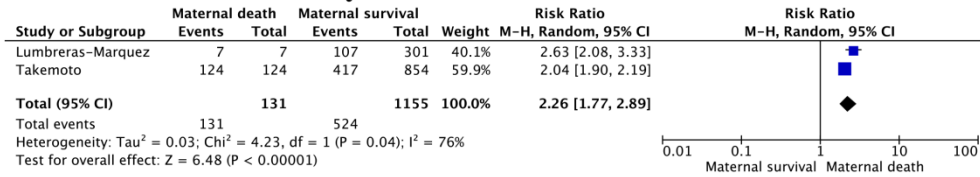


PRISMA 2009 Flow Diagram

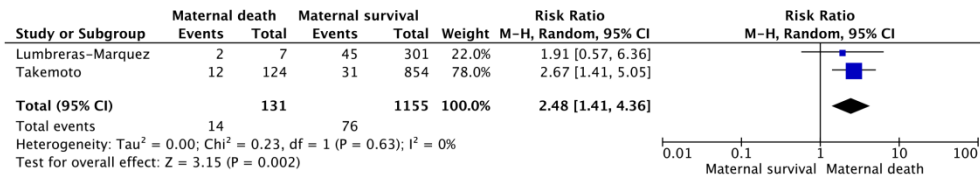


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

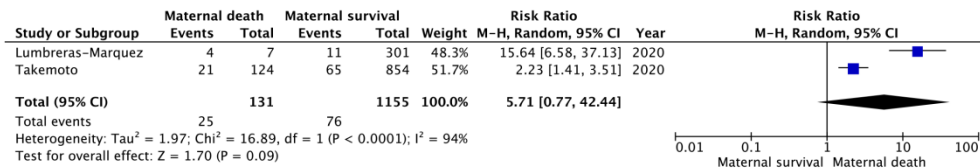
At least one comorbidity



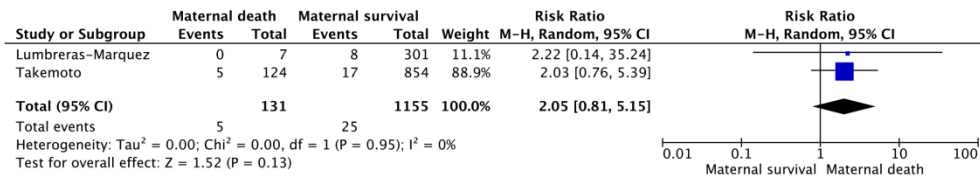
Obesity



Diabetes



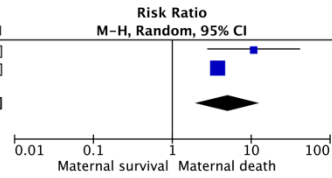
Asthma



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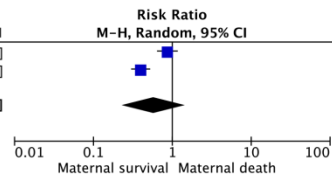
ICU Admission

Study or Subgroup	Maternal death		Maternal survival		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Lumbreras-Marquez	2	7	8	301	29.0%	10.75	[2.77, 41.73]
Takemoto	73	124	134	854	71.0%	3.75	[3.03, 4.65]
Total (95% CI)		131		1155	100.0%	5.09	[2.00, 12.98]
Total events		75	142				
Heterogeneity: Tau ² = 0.31; Chi ² = 2.26, df = 1 (P = 0.13); I ² = 56%							
Test for overall effect: Z = 3.41 (P = 0.0007)							



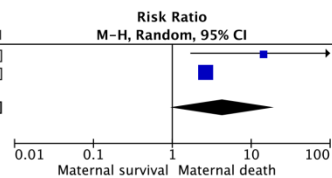
Need for respiratory support

Study or Subgroup	Maternal death		Maternal survival		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Lumbreras-Marquez	6	7	298	301	49.8%	0.87	[0.64, 1.17]
Takemoto	36	124	625	854	50.2%	0.40	[0.30, 0.52]
Total (95% CI)		131		1155	100.0%	0.59	[0.23, 1.48]
Total events		42	923				
Heterogeneity: Tau ² = 0.43; Chi ² = 20.44, df = 1 (P < 0.00001); I ² = 95%							
Test for overall effect: Z = 1.13 (P = 0.26)							



Need for mechanical ventilation

Study or Subgroup	Maternal death		Maternal survival		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Lumbreras-Marquez	1	7	3	301	29.3%	14.33	[1.69, 121.28]
Takemoto	88	124	229	854	70.7%	2.65	[2.26, 3.10]
Total (95% CI)		131		1155	100.0%	4.34	[0.96, 19.60]
Total events		89	232				
Heterogeneity: Tau ² = 0.83; Chi ² = 2.39, df = 1 (P = 0.12); I ² = 58%							
Test for overall effect: Z = 1.91 (P = 0.06)							



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