Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis

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Title Page with Author Information

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Outcome of Coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis

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Condensation: Pregnancy in the setting of COVID-19 disease secondary to SARS-COV-2 infection is associated with higher rates of miscarriage, preterm birth, preeclampsia, cesarean and perinatal death. There were no reported cases of vertical transmission.

Short title: Coronavirus infections in pregnancy

AJOG AT A GLANCE

A. Why was this study published?

COVID-19 disease secondary to SARS-COV-2 infection is a worldwide pandemic with an increasing number of confirmed cases everyday. Little is known about the effect of CoV (coronavirus)-related infections during pregnancy.

B. What are the key findings?

C. Pregnancy in the setting of CoV infection is associated with higher rates of miscarriage, preterm birth, preeclampsia, cesarean delivery and perinatal death (7-11%). There were no reported cases of vertical transmission.

D. What does this study add to what is already known?

This is the first systematic review exploring pregnancy and perinatal outcomes of CoV infections occurring during pregnancy. Although limited, these data can guide and enhance prenatal counselling of women with COVID-19 infection occurring during pregnancy. Evidence is accumulating rapidly, so these data may need to be updated soon.

ABSTRACT

Objective: The aim of this systematic review was to report pregnancy and perinatal outcomes of Coronavirus (CoV) spectrum infections, and particularly COVID-19 disease due to SARS-COV-2 infection during pregnancy.

Data sources: Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically utilizing combinations of word variants for “coronavirus” or “severe acute respiratory syndrome” or “SARS” or “Middle East respiratory syndrome” or “MERS” or “COVID-19” and “pregnancy”. The search and selection criteria were restricted to English language.

Study eligibility criteria: Inclusion criteria were pregnant women with a confirmed Coronavirus related illness, defined as either SARS, MERS or COVID-19.

Study appraisal and synthesis methods: We used meta-analyses of proportions to combine data and reported pooled proportions. The pregnancy outcomes observed included miscarriage, preterm birth, pre-eclampsia, preterm prelabor rupture of membranes, fetal growth restriction, and mode of delivery. The perinatal outcomes observed were fetal distress, Apgar score < 7 at five minutes, neonatal asphyxia, admission to neonatal intensive care unit, perinatal death, and evidence of vertical transmission.

Results: 19 studies including 79 women were eligible for this systematic review: 41 pregnancies (51.9%) affected by COVID-19, 12 (15.2%) by MERS, and 26 (32.9%) by SARS. An overt diagnosis of pneumonia was made in 91.8% and the most common symptoms were fever (82.6%), cough (57.1%) and dyspnea (27.0%). For all CoV infections, the rate of miscarriage was 39.1% (95% CI 20.2-59.8); the rate of preterm birth < 37 weeks was 24.3% (95% CI 12.5-38.6); premature prelabor rupture of membranes occurred in 20.7% (95% CI 9.5-34.9), preeclampsia in 16.2% (95% CI 4.2-34.1), and fetal growth restriction in 11.7% (95% CI 3.2-24.4); 84% were delivered by cesarean; the rate of perinatal death was 11.1% (95% CI 84.8-19.6) and 57.2% (95% CI 3.6-99.8) of newborns were admitted to the neonatal intensive care unit. When focusing on COVID-19, the most common adverse pregnancy outcome was preterm birth < 37 weeks, occurring in 41.1% (95% CI

25.6-57.6) of cases, while the rate of perinatal death was 7.0% (95% CI 1.4-16.3). None of the 41 newborns assessed showed clinical signs of vertical transmission.

Conclusion: In mothers infected with coronavirus infections, including COVID-19, >90% of whom also had pneumonia, PTB is the most common adverse pregnancy outcome. Miscarriage, preeclampsia, cesarean, and perinatal death (7-11%) were also more common than in the general population. There have been no published cases of clinical evidence of vertical transmission. Evidence is accumulating rapidly, so these data may need to be updated soon. The findings from this study can guide and enhance prenatal counseling of women with COVID-19 infection occurring during pregnancy.

Keywords: Coronavirus; SARS; MERS; COVID-19; SARS-COV-2; infection; pregnancy

INTRODUCTION

Coronavirus (CoV) is an enveloped, positive-stranded ribonucleic acid (RNA) virus of the family of Coronaviridae and belonging to the Nidovirales order,[1] generally causing respiratory and gastrointestinal infections that might range from mild, self-limiting conditions to more serious disorders, such as viral pneumonia with systemic impairment.[2]

In the last two decades, CoV has been responsible for two large epidemics: the Severe Acute Respiratory Syndrome (SARS) that infected 8098 people with a case-fatality rate of about 10.5%,[3] and the Middle East Respiratory Syndrome (MERS) with a total of 2519 laboratory-confirmed cases and a case–fatality rate of 34.4%.[4]

Towards the end of 2019, a novel mutation of CoV (labelled as SARS-COV-2) was identified as the cause of a severe respiratory illness – called COVID-19 - that typically presents with fever and cough.[5] Infected people show abnormal findings at diagnostic imaging, suggestive for pneumonia.

After beginning as an epidemic in China, COVID-19 infection has rapidly spread in many other countries and the number of affected cases continues to increase significantly on a daily basis. The overall mortality rate ranges from 3% to 4% according to the World Health Organization reports,[6] but a higher rate of patients require admission to the intensive care unit (ICU).[7]

It is well known that physiologic maternal adaptations to pregnancy predispose pregnant women to a more severe course of pneumonia, with subsequent higher maternal and fetal morbidity and mortality,[1,8] but there is a lack of data in the literature about the effect of CoV infections during pregnancy, thus limiting both counseling and management of these patients.

Objective

The aim of this systematic review was to report pregnancy and perinatal outcomes of CoV spectrum infections and particularly COVID-19 during pregnancy.

METHODS

Search strategy and selection criteria

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis.[9-11] Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically on 03/13/2020, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “coronavirus” or “severe acute respiratory syndrome” or “SARS” or “Middle East respiratory syndrome” or “MERS” or “COVID-19” and “pregnancy”. The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed.[12-14]

Inclusion criteria were pregnant women with a confirmed Coronavirus spectrum illness, defined as either SARS, MERS or COVID-19 infection.

The pregnancy outcomes observed were:

- Preterm birth (PTB) (either before 37 or 34 weeks of gestation)
- Pre-eclampsia (PE)
- Preterm prelabor rupture of membranes (pPROM)
- Fetal growth restriction (FGR)
- Miscarriage, as defined by authors
- Cesarean mode of delivery

The perinatal outcomes observed were:

- Fetal distress (as defined by original authors)
- Apgar score < 7 at five minutes
- Neonatal asphyxia (as defined by original authors)
- Admission to neonatal intensive care unit (NICU)
- Perinatal death, including both stillbirth and neonatal death

- Evidence of vertical transmission, defined as the presence of clinical signs of mother-to-child transmission in the antenatal or perinatal period

Furthermore, we aimed to perform a sub-group analysis according to the trimester of pregnancy at infection and the type of Coronavirus.

Data from studies reporting the incidence of these outcomes in pregnancies with CoV spectrum infections were considered eligible for analysis. For the purpose of the analysis, we included only full-text articles with data of pregnant women who already delivered; we excluded data regarding on-going pregnancies. Furthermore, as these are relatively rare infections occurring during pregnancy with the majority of data coming from studies with small sample sizes, case reports and case series were also included in the analysis. Studies reporting cases of infective pneumonia or other respiratory disorders during pregnancy caused by other viral agents were excluded. We also excluded studies pediatric series on newborns and children from which maternal and pregnancy information could not be extrapolated.

Two authors (DDM, GS) reviewed all abstracts independently. Agreement regarding potential relevance or inconsistencies was reached by consensus or resolved by discussion with a third reviewer (FDA). Full text copies of applicable papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Data analysis

We used meta-analyses of proportions to combine data and reported pooled proportions (PP). Funnel plots (displaying the outcome rate from individual studies versus their precision (1 per SE)) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the

total number of publications included for each outcome was <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values ≥50% indicate a substantial level of heterogeneity. A random effect model was used to compute the pooled data analyses. All proportion meta-analyses were carried out by using StatsDirect version 2.7.9 (StatsDirect, Ltd, Altrincham, Cheshire, United Kingdom).

Quality assessment of the included studies was assessed using the methodological quality and synthesis of case series and case reports described by Murad et al.[15] According to this tool, each study is judged on four broad perspectives: the selection of the study groups, the ascertainment and the causality of the outcome observed, and the reporting of the case. A study can be awarded a maximum of one star for each numbered item within the Selection and Reporting categories, two stars for Ascertainment and four stars for Comparability.[15] Given emergency-need for this guidance, PROSPERO registration was not sought.

RESULTS

Study selection and characteristics

538 articles were identified, 27 were assessed with respect to their eligibility for inclusion and 19 studies were included in the systematic review (Table 1, Figure 1, Supplementary Table 1).

These 19 studies[16-34] included 79 pregnancies affected by CoV infections. The mean maternal age was 34.6. Out of the 79 pregnancies affected by CoV infections: 41 (51.9%) were affected by COVID-19, 12 (15.2%) by MERS and 26 (32.9%) by SARS.

Clinical symptoms and laboratory parameters in the overall population of pregnant with CoV infections are reported in Table 2. An overt diagnosis of pneumonia was made in 91.8% (54/57) of cases (when available, radiological findings suggestive for pneumonia are reported in

Supplementary Table 2). The most common symptom was fever that affected 82.6% (64/76) of women, followed by cough (57.1%, 44/77) and dyspnea (27%, 21/77). Lymphopenia and elevated liver enzymes were found in 79.8% (40/48) and 36.6% (9/26) of cases, respectively. 34.1% (22/70) of pregnant women affected by CoV infections were admitted to ICU and 26.3% (16/69) required mechanical ventilation. Maternal death occurred in 12.3% (9/79) of all reported CoV-related diseases cases. Of note, the rates of admission to ICU (9.3% vs 44.6% vs 53.3%), need for mechanical ventilation (5.4% vs 40.9% vs 40%) and maternal death (0% vs 28.6% vs 25.8%) were significantly lower in pregnancies affected by COVID-19, compared to MERS and SARS respectively (Supplementary Table 3).

The majority of women affected by CoV infections were usually treated first with broad spectrum antibiotics in 89.3% of cases (49/52) and then with antiviral therapy and steroids in 67.7% (37/51) and 29.8% (12/31) of cases (Table 3; Supplementary Table 4).

The results of the quality assessment of the included studies are presented in Supplementary Table 5.

Synthesis of the results

In the overall population of pregnancies infected with CoV, The rate of miscarriage for CoV infections was 39.1% (8/21 – 95% CI 20.2-59.8). The rates of PTB < 37 and 34 weeks of gestation were 24.3% (14/56 – 95% CI 12.5-38.6) and 21.8% (11/56 - 95% CI 12.5-32.9), respectively; pPROM occurred in 20.7% (6/34 – 95% CI 9.5-34.9), while the rate of pregnancies experiencing PE and FGR was 16.2% (2/19 – 95% CI 4.2-34.1) and 11.7% (2/29 – 95% CI 3.2-24.4), respectively. The rate of CD was 83.9% (50/58 – 95% CI 73.8-91.9) (Table 4; Table 5). The rate of perinatal death was 11.1% (5/60 – 95% CI 84.8-19.6) including three stillbirths and two neonatal deaths (further details are provided in Supplementary Table 6). Thirty-four point six percent (15/44 – 95% CI 20.3-49.5) of fetuses suffered from fetal distress and 57.2% (3/12 – 95% CI 3.6-99.8) of newborns was admitted to NICU. The rate of Apgar score < 7 at five minutes was 6.1% (1/48 –

95% CI 1.3-13.9), but no case of neonatal asphyxia were reported. Finally, none of the newborns showed signs of vertical transmission during the follow-up period (Table 6; Table 7).

COVID-19

Six studies[16-21] reported information on COVID-19 infection during pregnancy. There was no data on miscarriage for COVID-19 infection occurring during the first trimester. The rates of PTB < 37 and 34 weeks of gestation were 41.1% (14/32 – 95% CI 25.6-57.6) and 15% (4/32 - 95% CI 3.9-31.7), respectively. pPROM occurred in 18.8% (5/31 – 95% CI 0.8-33.5), while the rate of pregnancies experiencing PE was 13.6% (1/12 – 95% CI 1.2-36.0), with no reported cases of FGR. The rate of CD was 91% (38/41 – 95% CI 81.0-97.6) (Table 5). The rate of perinatal death was 7% (2/41 – 95% CI 1.4-16.3) including one stillbirth and one neonatal death; 43% (12/30 – 95% CI 15.3-73.4) of fetuses had fetal distress and 8.7% (1/10 – 95% CI 0.01-31.4) of newborns were admitted to NICU. The rate of Apgar score < 7 at five minutes was 4.5% (1/41 – 95% CI 0.4-12.6) and no case of neonatal asphyxia was reported. Finally, none of the newborns showed signs of vertical transmission during the follow-up period (Table 7).

MERS

Seven studies[22-28] reported information on MERS infection during pregnancy. There was no data on miscarriage for MERS infection occurring during the first trimester. The rate of PTB was 32.1% (3/11 - 95% CI 10.0-59.8), all occurring before 34 weeks of gestation. Preeclampsia occurred in 19.1% (1/7 – 95% CI 1.1-51.3) respectively, while no case of pPROM or FGR was reported in these studies. The rate of CD was 61.8% (5/8 – 95% CI 32.7-86.9) (Table 5). The rate of perinatal death was 33.2% (3/10 – 95% CI 11.2-59.9) including two stillbirths and one neonatal death (four hours after birth of an extremely preterm infant). No case of fetal distress, Apgar score < 7 at five minutes, neonatal asphyxia, and admission to NICU was reported. Finally, none of the newborns showed signs of vertical transmission during the follow-up period (Table 7).

SARS

Six studies[29-34] reported information on SARS infection during pregnancy. The rate of miscarriage for MERS infection was 39.1% (8/21 - 95% CI 20.2-59.8). The rate of PTB < 37 and 34 weeks of gestation was 15% (1/15 – 95% CI 0.3-45.6) and 28.9% (4/15 - 95% CI 10.7-51.6), respectively. pPROM and FGR occurred in 50% (1/2 – 95% CI 0.5-95.3) and 18.5% (2/15 – 95% CI 4.4-39.5) respectively, while no cases of preeclampsia were reported. The rate of CD was 72.2% (7/9 – 95% CI 44.1-93.1) (Table 5). Fetal distress occurred in 35.9% (3/9 – 95% CI 12.0-64.4) of pregnancies, while no case of perinatal death, Apgar score < 7 at five minutes, and neonatal asphyxia was reported. There were no data on rates of admission to the NICU of infants born to infected mothers. Finally, none of the newborns showed signs of vertical transmission during the follow-up period (Table 7).

It was not possible to perform a comprehensive pooled data synthesis on the incidence of pregnancy and perinatal outcomes according to the trimester of pregnancy at infection due to the very small number of included studies for each trimester of pregnancy.

COMMENT

Main findings

The findings from this systematic review show that more than 90% of hospitalized pregnant women affected by CoV infections present radiological signs suggestive for pneumonia, detected either at chest x-ray or computerized tomography and the most common symptoms are fever, cough and lymphopenia. Pregnancies affected by CoV infections have high rates of PTB before 37 and 34 weeks, and miscarriage when the infection is acquired earlier in pregnancy. Preeclampsia and cesarean delivery are also more common than in the general population. The rate of perinatal mortality is about 10%, while the most common adverse perinatal outcome is fetal distress, with more than half of the newborns admitted in NICU. Importantly, clinical evidence of vertical transmission was found in none of the newborns included.

Strengths and limitations

To the best of our knowledge, this is the first systematic review exploring pregnancy and perinatal outcomes of CoV infections occurring during pregnancy. This comprehensive meta-analysis included all series published so far on this topic.

The small number of cases in some of the included studies, their retrospective non-randomized design, and the lack of standardized criteria for the antenatal surveillance, management and timing of delivery of pregnancies affected by CoV infections represent the major limitations of this systematic review, thus making it difficult to draw any convincing evidence on this clinical management strategies. Furthermore, there is a possibility that some patients were included in more than one report, although two authors independently reviewed all the included studies, carefully focusing on the different Institutions reporting outcomes. Moreover, when focusing on the outcomes of COVID-19 infection, and particularly perinatal outcomes, reported data are intuitively limited to a very short-term follow-up period and thus infectious that occurred proximate to the delivery. This has the potential to overestimate the magnitude of risks such as PTB and

underestimate more longitudinal risks such as FGR. Additionally, it was not possible to extrapolate data about the rate of both spontaneous and iatrogenic PTB and indications for CD, that was performed in the majority of cases; furthermore, few outcomes, i.e. “fetal distress”, were not clearly defined, thus leading to some discrepancies in the results, like the rate of PTB < 34 weeks (15%) and the rate of newborns admitted to NICU (9%), particularly in COVID-19 infection. Another limitation of the present review was the lack of stratification of the analysis according to the gestational age at CoV infection due to the very small number of included studies for each trimester of pregnancy. We cannot assume that the rate of miscarriage and PTB should be attributed solely to the virus / infection, since there are no comparable control groups of uninfected women from the same time. It may be that the stress of the situation in the community contributed to some of these outcomes. Finally, we also included case reports and case series, thus facing a higher risk publication bias and decreasing the level of the evidence of our findings.

Implications

COVID-19 is the last CoV infection identified at the end of 2019 in Wuhan, a city in the Hubei Province of China.[5] Currently, Europe has become the epicenter of the COVID-19 pandemic,[6] but the infection has spread in more than 150 countries, leading governments to adopt rigorous mitigation measures to reduce both the viral spread and its detrimental effects on healthcare systems and therefore on the whole economy of the countries.[35]

Despite the relatively low mortality, one of the main concerns related to COVID-19 infection is the development of an acute respiratory distress syndrome, often requiring invasive ventilation, that is the clinical epiphenomenon of the viral pneumonia.[6-7]

The lack of knowledge about COVID-19 infection has raised urgent questions among physicians regarding clinical management and expected outcomes of the affected patients, and therefore, there is currently a compelling need of data to guide clinical decisions.

Regarding pregnancy, the findings from this study found that radiological features suggestive for pneumonia can be found in almost all of the hospitalized pregnant women, usually presenting with fever, cough and lymphopenia similar to the non-pregnant population. Of note, serious conditions requiring admission to ICU and mechanical ventilation are significantly less common when compared with the two previous CoV infections (MERS and SARS). Similarly, we found no case of maternal death related to COVID-19 infection, while MERS and SARS infections caused a mortality rate in pregnant women ranging from 25% to 30%.

In this systematic review, women affected by COVID-19 disease had higher rates of miscarriage, preterm birth, preeclampsia, while the babies had higher rates of perinatal mortality (7-11%) and of admission to NICU.

Furthermore, as all the included studies reported data on hospitalized women, the reported rate of infection-related adverse outcomes, including either pregnancy and perinatal outcomes, might not reflect the overall population of pregnant when who got infected with SARS-COV-2, and there may be a cohort of patients with no or mild symptoms whose pregnancy outcome is, as of yet, unknown.[36]

More importantly, it should be emphasized that there are no known neonatal symptoms and therefore no clinical evidence suggestive for vertical transmission, particularly when COVID-19 infection occurs later in pregnancy. Unfortunately, the lack of data of first and early second trimester infection does not allow to determine whether in this case the infection may cause more severe perinatal outcomes and how to monitor the pregnancy once the infection has passed.[1]

Based on the limited information from this study, COVID-19 cannot be considered as an indication for delivery and therefore the timing and mode of delivery should be individualized according to maternal clinical conditions or obstetric factors as usual (and not COVID-19 status alone), and the decision should involve a multidisciplinary team including maternal fetal doctors, neonatologists, anesthesiologists, and infective disease specialists.

Conclusions

In summary, with the limited data reported to date, mothers infected with coronavirus infections, including COVID-19, >90% of whom also had pneumonia, are at increased risks of miscarriage, preterm birth, preeclampsia, cesarean delivery, and their babies at higher risk of perinatal death and admission to the NICU, compared to the general population. There have been no published cases of clinical evidence of vertical transmission. Evidence is accumulating rapidly, so these data may need to be updated soon.

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Table 1. General characteristics of the included studies.

Author	Year	Study location	Study period	Study design	Pregnancies (n)	Type of Coronavirus	Mean maternal age
Chen	2020	China	2020	Retrospective	9	Sars-CoV-2	29.9
Wang	2020	China	2020	Case report	1	Sars-CoV-2	28
Zhu	2020	China	2020	Retrospective	9	Sars-CoV-2	30.9
Li	2020	China	2020	Case report	1	Sars-CoV-2	30
Liu*	2020	Hubei, China	2020	Retrospective	11	Sars-CoV-2	32.5
Liu	2020	Guangdong, China	2020	Retrospective	10	Sars-CoV-2	30.5
Alfaraj	2019	Saudi Arabia	2015	Case series	2	Mers-CoV	34
Jeong	2017	South Korea	2015	Case report	1	Mers-CoV	39
Alserehi	2016	Saudi Arabia	NR	Case report	1	Mers-CoV	33
Assiri	2016	Saudi Arabia	2012-2016	Case series	5	Mers-CoV	30.8
Malik	2016	United Arab Emirates	2013	Case report	1	Mers-CoV	32
Park	2016	South Korea	2015	Case report	1	Mers-CoV	39
Payne	2015	Jordan	2012	Case report	1	Mers-CoV	39
Yudin	2005	Canada	NR	Case report	1	Sars-CoV	33
Wong	2004	Hong Kong, China	2003	Retrospective	12	Sars-CoV	30.6
Lam	2004	China	2003	Retrospective	10	Sars-CoV	31.6
Robertson	2004	USA	2003	Case report	1	Sars-CoV	36
Schneider	2004	USA	2003	Case report	1	Sars-CoV	NR
Stockman	2004	USA	2003	Case report	1	Sars-CoV	38

N, numbers; NR, not reported.

*: preliminary data, pre-peer review version.

Table 2. Pooled proportions of the different clinical symptoms and laboratory parameters in the overall population of pregnancies infected with CoV infection.

Outcome	Studies (n)	Pregnancies (n/N)	I^2 (%)	Pooled proportions (95% CI)
Fever	17	64/76	8.2	82.57 (74.4-90.2)
Cough	18	44/77	7.3	57.10 (45.8-68.0)
Dyspnea	18	21/77	53.2	26.98 (18.2-36.8)
Chest pain	17	3/66	0	8.61 (3.4-16.0)
Pneumonia	16	54/57	0	91.84 (84.0-97.2)
Lymphopenia	10	40/48	49.1	79.87 (60.4-93.9)
Elevated liver enzymes	7	9/26	0	36.59 (20.4-54.5)
Admission to ICU	18	22/70	58.1	34.10 (17.5-53.0)
Need for mechanical ventilation	17	16/69	42.9	26.29 (13.3-41.9)
Maternal death	19	9/79	0	12.30 (6.3-19.9)

n/N, number of cases / total number of included pregnancies; CI, confidence interval; ICU, intensive care unit

Table 3. Pooled proportions of treatment used in the overall population of pregnancies infected with Coronavirus infection.

Outcome	Studies (n)	Pregnancies (n/N)	I^2 (%)	Pooled proportions (95% CI)
Antiviral therapy*	14	37/51	50	67.66 (47.2-85.1)
Antibiotic therapy	14	49/52	27.9	89.26 (76.8-97.3)
Steroids**	12	12/31	58.6	29.81 8.2-57.9)

n/N, number of cases / total number of included pregnancies; CI, confidence interval.

*Lopinavir/Ritonavir or Oseltamivir were the most common antiviral agents. Ribavirin was used in Wong et al.

**Maternal (not fetal) indications

Table 4. Pooled proportions of the different pregnancy outcomes in the overall population of pregnancies infected with Coronavirus infection.

Outcome	Studies (n)	Pregnancies (n/N)	I^2 (%)	Pooled proportions (95% CI)
PTB <37 weeks	16	14/56	25.5	24.30 (12.5-38.6)
PTB <34 weeks	16	11/56	1.9	21.79 (12.5-32.9)
PE	6	2/19	0	16.21 (4.2-34.1)
PPROM	8	6/34	0	20.72 (9.5-34.9)
FGR	10	2/29	0	11.66 (3.2-24.4)
Miscarriage	2	8/21	0	39.08 (20.2-59.8)
Cesarean delivery	17	50/58	4	83.91 (73.8-91.9)

n/N, number of cases / total number of included pregnancies; CI, confidence interval; PTB, preterm birth; PE, preeclampsia; pPROM, preterm prelabor rupture of membranes; FGR, fetal growth restriction.

Table 5. Pooled proportions of the different pregnancy outcomes explored in the present systematic review according to the type of viral infection.

	Sars-CoV					Mers-CoV					Sars-CoV-2			
Outcome	**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**
PTB <37 weeks	5	1/15	15.03 (0.3-45.6)	31.8		6	0/11	0 (0-28.9)	0		6	14/32	41.11 (25.6-57.6)	0
PTB <34 weeks	5	4/15	28.89 (10.7-51.6)	0		6	3/11	32.11 (10.0-59.8)	9.5		6	4/32	15.03 (3.9-31.7)	22.6
Pre-eclampsia	2	0/2	0 (0-67.0)	0		2	1/7	19.10 (1.1-51.3)	0		3	1/12	13.55 (1.2-36.0)	0
PPROM	2	1/2	50.0 (0.5-95.3)	46		2	0/2	0 (0-54.4)	0		5	5/31	18.78 (0.8-33.5)	0
FGR	5	2/15	18.52 (4.4-39.5)	0		3	0/4	0 (0-48.7)	0		3	0/12	0 (0-21.4)	0
Miscarriage	2	8/21	39.08 (20.2-59.8)	0		-	-	-	-		-	-	-	-
Cesarean delivery	5	7/9	72.23 (44.1-93.1)	0		6	5/8	61.79 (32.7-86.9)	0		6	38/41	91.04 (81.0-97.6)	0

n/N, number of cases / total number of included pregnancies; CI, confidence interval; PTB, preterm birth; pPROM, preterm premature rupture of membranes; FGR, fetal growth restriction.

Table 6. Pooled proportions of the different perinatal outcomes in the overall population of pregnancies infected with Coronavirus infection.

Outcome	Studies (n)	Fetuses/Newborns (n/N)	I^2 (%)	Pooled proportions (95% CI)
Fetal distress	13	15/44	13.6	34.15 (20.3-49.5)
Apgar score < 7	12	1/48	0	6.08 (1.3-13.9)
Neonatal asphyxia	9	0/27	0	0 (0-15.7)
Admission to NICU	4	3/12	76.3	57.16 (3.6-99.8)
Perinatal death	16	5/60	0	11.11 (84.8-19.6)
Vertical transmission	16	0/60	0	0 (0-10.7)

n/N, number of cases / total number of included pregnancies; CI, confidence interval; NICU, neonatal intensive care unit.

498 **Table 7.** Pooled proportions of the different perinatal outcomes explored in the present systematic review according to the type of viral infection.
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	Sars-CoV					Mers-CoV					Sars-CoV-2			
Outcome	**Studies**	**Fetuses/Newborns (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Fetuses/Newborns (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Fetuses/Newborns (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**
Fetal distress	5	3/9	35.89 (12.0-64.4)	0		4	0/5	0 (0-44.5)	0		4	12/30	43.02 (15.3-73.4)	64.7
Apgar score < 7	4	0/4	0 (0-60.2)	0		3	0/3	0 (0-56.9)	0		5	1/41	4.53 (0.4-12.6)	0
Neonatal asphyxia	4	0/4	0 (0-60.2)	0		2	0/2	0 (0-67.0)	0		3	0/21	0 (0-13.5)	0
Admission to NICU	-	-	-	-		2	0/2	0 (0-67.0)	0		2	1/10	8.71 (0.01-31.4)	81.3
Perinatal death	5	0/9	0 (0-31.4)	0		6	3/10	33.15 (11.2-59.9)	0		5	2/41	7.00 (1.4-16.3)	0
Vertical transmission	6	0/14	0 (0-24-0)	0		4	0/4	0 (0-60.2)	0		6	0/42	0 (0-9.6)	0

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502 n/N, number of cases / total number of included pregnancies; CI, confidence interval; NICU, neonatal intensive care unit.
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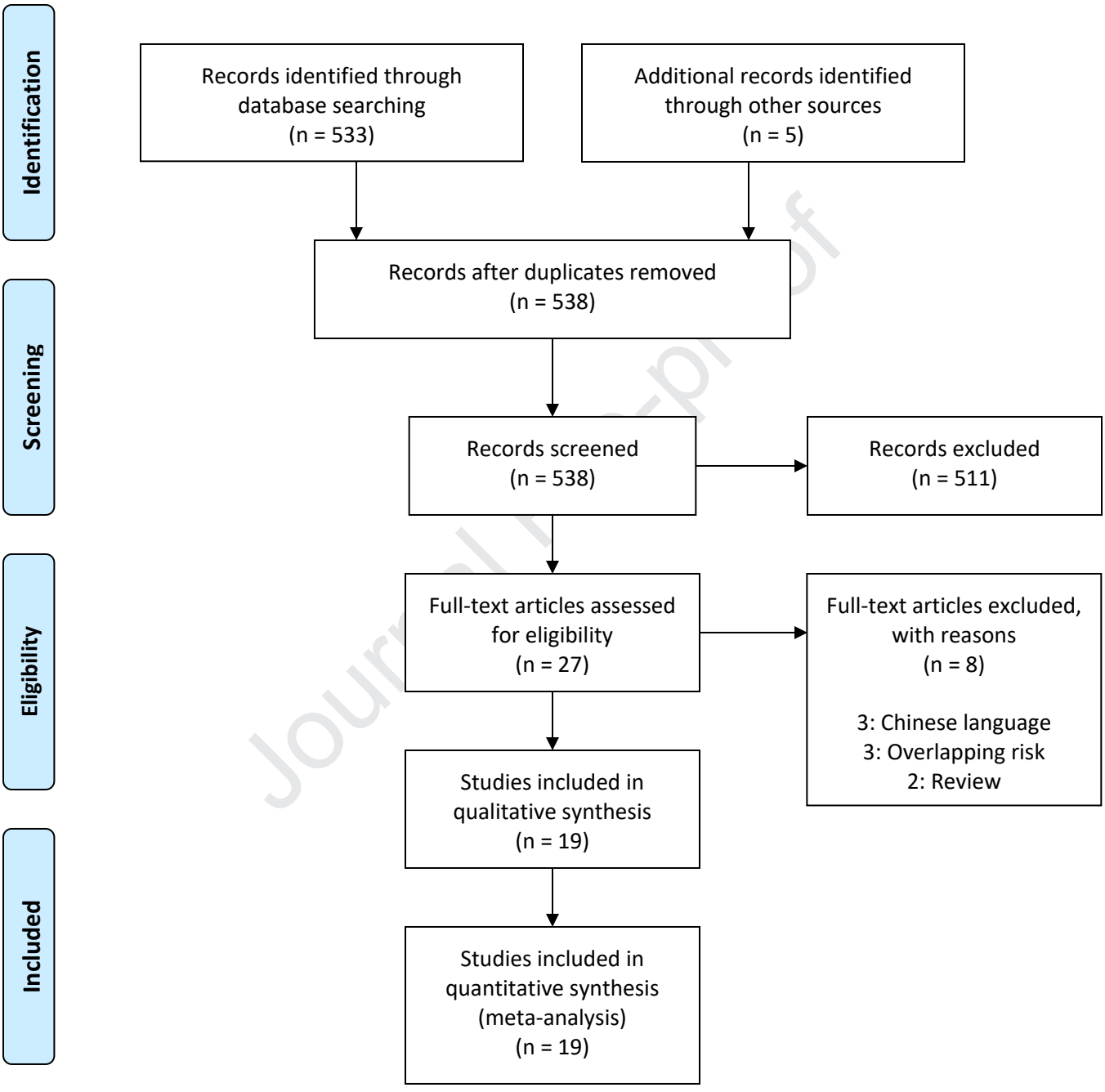
Figure legend

Figure 1. Systematic review flowchart

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplementary Table 1. Excluded studies and reason for the exclusion

Author	Year	Title	Reason for the exclusion
Chen	2020	Pregnant Women With New Coronavirus Infection: A Clinical Characteristics and Placental Pathological Analysis of Three Cases	Chinese language; A series of 11 cases from the same institution was published by Liu et al and was included in this systematic review
Zhang	2020	Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province	Chinese language
Liu	2020	Coronavirus disease 2019 (COVID-19) during pregnancy: a case series	Overlapping risk with Liu 2020 (included with preliminary, pre-peer review data)
Chen	2020	Infant born to mothers with a new Coronavirus (COVID-19)	Same Institution of Zhu 2020 that was included in this systematic review
Li	2005	Severe acute respiratory syndrome in neonates and children	Review about pediatric outcomes
Ng	2004	SARS in newborns and children	Review; Data on newborns born from infected mothers are reported in papers already included in this systematic review
Shek	2003	Infant born to mothers with SARS	It is likely that all – or the majority – of the cases presented in this series are also included in Wong 2004, that is already included in this systematic review
Zhang	2003	Clinical analysis of pregnancy in second and third trimesters complicated severe acute respiratory syndrome	Chinese language

Supplementary Table 2. Radiological findings for the diagnosis of pneumonia

Author	Year	Type of CoV	Diagnosis of pneumonia
Chen	2020	Sars-CoV-2	Typical sign of viral respiratory infection at CT
Wang	2020	Sars-CoV-2	Bilateral ground glass opacities at CT
Zhu	2020	Sars-CoV-2	Bilateral ground glass opacities, patchy consolidation, blurred borders at CT
Li	2020	Sars-CoV-2	Patchy infiltrations at CXR
Liu	2020	Sars-CoV-2	Ground glass opacities, crazy paving, consolidations at CT
Jeong	2017	Mers-CoV	Diffuse opacity in the lower lung area at CXR
Alserehi	2016	Mers-CoV	Bilateral infiltrates and lower lobe opacity at CXR
Assiri	2016	Mers-CoV	Bilateral infiltrates and lower lobe opacity at CXR
Malik	2016	Mers-CoV	Bilateral consolidations at CT
Park	2016	Mers-CoV	Patchy opacities in the lower lobes at CXR
Yudin	2005	Sars-CoV	Patchy lobe infiltrates at CXR
Wong	2004	Sars-CoV	Features suggestive for progressive air-space disease at CXR
Lam	2004	Sars-CoV	Features suggestive for atypical pneumonia at CXR
Robertson	2004	Sars-CoV	Bilateral lower lobe infiltrates at CXR
Schneider	2004	Sars-CoV	Progressive pulmonary infiltrates at CXR
Stockman	2004	Sars-CoV	Diffuse infiltrates at CXR

CoV, coronavirus; CT, computerized tomography; CXR, chest x-ray.

Supplementary Table 3. Pooled proportions of the different clinical symptoms and laboratory parameters according to the type of viral infection.

	Sars-CoV					Mers-CoV					Sars-CoV-2			
Outcome	**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**
Fever	6	26/26	100 (86.3-100)	0		5	6/9	64.11 (35.6-88.0)	0		6	32/41	75.56 (61.9-87.0)	0
Cough	6	20/26	74.21 (57.1-88.2)	0		6	7/10	65.59 (38.8-88.0)	0		6	17/41	42.02 (28.0-56.7)	0
Dyspnea	6	11/26	48.79 (27.5-70.3)	17.5		6	7/10	66.85 (40.1-88.8)	0		6	3/41	8.89 (2.4-19.0)	0
Chest pain	6	2/26	12.67 (3.3-27.0)	0		6	1/10	18.58 (3.0-43.2)	0		5	0/30	0 (0-11.9)	0
Pneumonia	6	26/26	100 (86.3-100)	0		6	9/11	76.59 (43.3-97.5)	36.8		4	19/20	91.68 (76.9-99.3)	0
Lymphopenia	4	24/24	100 (87.1-100)	0		2	1/2	50 (0.5-95.3)	46		4	15/22	65.59 (42.0-85.7)	18.6
Elevated liver enzymes	3	5/14	37.91 (14.7-64.5)	4.3		1	1/1	100 (25.0-100)	-		3	3/11	29.55 (8.6-56.6)	0
Admission to ICU	6	14/26	53.32 (35.3-70.9)	0		7	6/12	44.57 (16.8-74.3)	29		5	2/32	9.29 (0.6-26.8)	39.7
Need for mechanical ventilation	6	10/26	39.98 (23.2-58.1)	0		7	5/12	40.85 (17.1-67.1)	9.4		4	1/31	5.38 (0.4-15.5)	0
Maternal death	6	6/26	25.79 (11.8-42.9)	0		7	3/12	28.59 (9.6-52.8)	0		6	0/41	0 (0-9.8)	0

n/N, number of cases / total number of included pregnancies; CI, confidence interval; ICU, intensive care unit

Supplementary Table 4. Pooled proportions of the need for therapy according to the type of viral infection.

	Sars-CoV					Mers-CoV					Sars-CoV-2			
Outcome	**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**		**Studies**	**Pregnancies (n/N)**	**Pooled % (95% CI)**	**I^2 (%)**
Antiviral therapy*	5	13/16	66.87 (30.0-94.5)	41.9		4	2/4	50.0 (6.8-93.2)	0		5	22/31	74.83 (41.0-97.0)	70.9
Antibiotic therapy	6	26/26	100 (86.3-100)	0		4	2/4	50.0 (6.8-93.2)	0		4	21/22	90.29 (63.7-99.9)	50.5
Steroids**	5	11/16	50.08 (14.8-85.3)	45.4		4	0/4	0 (0-60.2)	0		3	1/11	22.83 (0.9-78.8)	63

n/N, number of cases / total number of included pregnancies; CI, confidence interval.

*Lopinavir/Ritonavir or Oseltamivir were the most common antiviral agents. Ribavirin was used in Wong et al.

**Maternal (not fetal) indications

Supplementary Table 5. Quality assessment of the included studies

Case series					
Author	**Year**	**Selection**	**Comparability**	**Outcome**	
Chen	2020	★★	★★	★★★	
Zhu	2020	★★	★★	★★	
Liu	2020	★★	★★	★★★	
Liu	2020	★★	★★	★★	
Alfaraj	2019	★★	★	★★	
Assiri	2016	★★	★	★★	
Wong	2003	★★	★★	★	
Lam	2003	★★	★★	★★	
Case reports					
Author	**Year**	**Selection**	**Ascertainment**	**Causality**	**Reporting**
Wang	2020	★	★★	★★★	★
Li	2020	★	★★	★★	★
Jeong	2017	★	★	★★	★
Alserehi	2016	★	★	★★	★
Malik	2016	★	★★	★★	★
Park	2016	★	★★	★	★
Payne	2015	★	★★	★★	★
Yudin	2005	★	★★	★★	★
Robertson	2004	★	★★	★★★	★
Schneider	2004	★	★★	★★★	★
Stockman	2004	★	★★	★★	★

Supplementary Table 6. Details on perinatal deaths

Author	Year	Type of CoV	Details on perinatal deaths
Zhu	2020	Sars-CoV-2	*1 Neonatal death*: The baby was delivered at a gestational age of 34+5 weeks and admitted 30 minutes after delivery due to shortness of breath and moaning. Eight days later, he developed refractory shock, multiple organ failure, and disseminated intravascular coagulation, which were treated by the transfusion of platelets, suspended red blood cells, and plasma; he died on the 9th day.
Liu	2020	Sars-CoV-2	*1 stillbirth*, no other available details
Assiri	2016	Mers-CoV	*1 stillbirth*: At 34 weeks, the mother complained shortness of breath since 3 days and was admitted for elevated blood pressure and 3+ proteinuria consistent with preeclampsia, and pneumonia was diagnosed by means of chest radiography. Fetal heart tones were absent, and intrauterine fetal demise was suspected. A stillborn infant was delivered the same day. *1 neonatal death*: At 24 weeks gestation, the mother presented to the hospital on 23 October with cough and myalgia, and chest radiography at admission showed a right lower lobe opacity. Her respiratory status deteriorated during hospitalization, and she was admitted to the ICU on 28 October for ARDS requiring intubation and mechanical ventilation. On 31 October, the patient delivered a 240-gram infant by cesarean delivery. The infant died 4 hours after birth.
Payne	2015	Mers-CoV	*1 stillbirth:* During the outbreak period, the mother's acute respiratory symptoms (fever, rhinorrhea, fatigue, headache, and cough) occurred concurrently with vaginal bleeding and abdominal pain on the seventh day of illness, and she spontaneously delivered a stillborn infant.

NR, not reported.