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

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Short title: Coronavirus infections in pregnancy

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

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RESEARCH IN CONTEXT

Evidence before this study

Coronavirus (CoV) is generally associated to respiratory and gastrointestinal infections that might range from mild to more serious disorders, such as viral. CoV has been responsible for two large epidemics in the past two decades: the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) and nowadays it has been identified as the cause of new illness, labelled as COVID-19, that is still spreading all across the world with the number of confirmed cases that is every day higher. Little is known about the effect of CoV-related infections during pregnancy. 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. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed. We used meta-analyses of proportions to combine data and reported pooled proportion. Quality assessment of the included studies focused on the selection of the study groups, the ascertainment and the causality of the outcome observed and the reporting of the case, as suggested by Murad et al for case series and case reports. The aim of this systematic review was to report pregnancy and perinatal outcomes of spectrum CoV-related infections during pregnancy.

Added value of this study

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, thus providing the best and most up-to-date evidence on this topic.

Implications of all the available evidence

COVID-19 has rapidly become pandemic, and the lack of knowledge about COVID-19 infection result is a compelling need of data to guide clinical decisions. The findings form this study show that pregnancies affected by CoV infections are more likely to experience PTB, either before 37 and 34 weeks, and miscarriage when the infection is acquired in the first and early second trimester. 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. When focusing on COVID-19, more than half of pregnant women experienced PTB, mostly occurring between 34 and 37 weeks, and the majority of these patients – more than 90% - delivered with CD. The rate of perinatal death, including

both stillbirths and neonatal deaths, was 7%, while the rates of neonatal asphyxia, low Apgar score and admission to NICU were all below 10%. More importantly, clinical evidence of vertical transmission was found in none of the newborns included. Although limited, these data can guide and enhance prenatal counselling of women with COVID-19 infection occurring during pregnancy.

SUMMARY

Background: Coronavirus (CoV) has been responsible for two large epidemics in the past two decades: the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) and nowadays it has been identified as the cause of new illness, labelled as COVID-19, that is still spreading all across the world with the number of confirmed cases that is every day higher. Maternal adaptations to pregnancy might expose women to a more severe course of pneumonia but little is known about the effect of Coronavirus infections during pregnancy. The aim of this systematic review was to report pregnancy and perinatal outcomes of Coronavirus spectrum infections and particularly COVID-19 during pregnancy.

Methods: 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. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed. We used meta-analyses of proportions to combine data and reported pooled proportion. The pregnancy outcomes observed were: preterm birth, pre-eclampsia, premature rupture of membranes, preterm premature rupture of membranes, intrauterine growth restriction, miscarriage, and mode of delivery. The perinatal outcomes observed were: fetal distress, low Apgar score Neonatal asphyxia, admission to neonatal intensive care unit, perinatal death, and evidence of vertical transmission.

Findings: 19 studies were eligible for this systematic review, including 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 symptom was fever (82.6%), cough (57.1%) and dyspnea (27%). The rate of preterm birth was 44.5% (95% CI 33.4-58.8), while the rate of miscarriage for CoV infections was 39.1% (95% CI 20.2-59.8). Premature preterm rupture of membranes occurred in 20.7% (95% CI 9.5-34.9), while the rate of pregnancies experiencing preeclampsia and intrauterine growth restriction was 16.2% (95% CI 4.2-34.1) and 11.7% (95% CI 3.2-24.4). Regarding mode of delivery, the rate of cesarean delivery was 83.9%, while the rate of vaginal delivery was 16.1%. 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 was admitted to neonatal intensive care unit. When focusing on COVID-19, the most common adverse pregnancy outcome was preterm birth, occurring in 52.7% (95% CI 36.3-68.8) of cases, while the rate of perinatal death was 7% (95% CI 1.4-16.3) and none of the newborns showed clinical signs of vertical transmission.

Interpretation: Based on the limited information from this study, pregnancy does not appear to increase maternal morbidity in case of COVID-19 infection. PTB is the most common adverse pregnancy outcome, although occurring more frequently in the late preterm period, and the rates of adverse perinatal outcomes are all below 10%, with no reported cases clinical evidence of vertical transmission. The findings from this study can guide and enhance prenatal counselling of women with COVID-19 infection occurring during pregnancy.

Funding: There was no funding source for this study.

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) with 8098 people affected and a mortality 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 CoV has been identified as the cause of a severe respiratory illness mostly presenting with fever and cough, and showing abnormal findings at diagnostic imaging suggestive for pneumonia, successively labelled as COVID-19.[5]

After being epidemic in China, COVID-19 infection has rapidly spread in many other countries and the number of affected cases is still significantly increasing on a daily basis, with an actual overall mortality rate ranging from 3% to 4% according to the World Health Organization reports,[6] but a higher rate of patients requiring admission to intensive care unit (ICU).[7]

It is well known that physiologic maternal adaptations to pregnancy might expose 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 literature about the effect of CoV infections during pregnancy, thus limiting both counselling and management of these patients.

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 in 13.03.2020, 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 infection, defined as either SARS, MERS or COVID-19 infection.

The pregnancy outcomes observed were:

- Preterm birth (PTB) (either overall and before 37 or 34 weeks of gestation)
- Pre-eclampsia (PE)
- Premature rupture of membranes (PROM)
- Preterm premature rupture of membranes (pPROM)
- Intrauterine growth restriction (IUGR)
- Miscarriage, as defined by authors
- Mode of delivery, whether vaginal (VD) – also including operative delivery – or cesarean delivery (CD)

The perinatal outcomes observed were:

- Fetal distress
- Apgar score < 7 at five minutes
- Neonatal asphyxia
- 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 gestational age at infection (I, II and III trimester) 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 data of pregnant women who already delivered, while we excluded data on still on-going pregnancies. Only full-text articles were considered eligible for inclusion; furthermore, as we are focusing on a relatively rare condition occurring during pregnancy with the majority of data coming from studies with small sample size, 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 only reporting data on newborns and children from which information on pregnancy outcomes 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 those 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 proportion (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 analysis. 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. 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

Comentado [DDM1]: I mean: some of the papers on COVID19 also include pregnancies that are still ongoing. We included only data on women who already delivered

of one star for each numbered item within the Selection and Reporting categories, two stars for Ascertainment and four stars for Comparability.

Role of funding source

There was no funding source for this study.

RESULTS

Study selection and characteristics

537 articles were identified, 26 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 patients, followed by cough (57.1% - 44/77) and dyspnea (27% - 21/77). Lymphopenia and elevated liver enzymes were found respectively in 79.8% (40/48) and 36.6% (9/26) of cases. 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 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 first treated 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 S5.

Synthesis of the results

In the overall population of pregnancies infected with CoV, the rate of PTB was 44.5% (29/66 - 95% CI 33.4-58.8), with PTB < 37 and 34 weeks of gestation occurring in 24.3% (14/56 – 95% CI 12.5-38.6) and 21.8% (11/56 - 95% CI 12.5-32.9) of cases, respectively. The rate of miscarriage for CoV

infections was 39.1% (8/21 – 95% CI 20.2-59.8). pPROM and PROM occurred in 20.7% (6/34 – 95% CI 9.5-34.9) and 8.4% (2/34 – 95% CI 1.8-19.2) respectively, while the rate of pregnancies experiencing PE and IUGR was 16.2% (2/19 – 95% CI 4.2-34.1) and 11.7% (2/29 – 95% CI 3.2-24.4). Regarding mode of delivery, the rate of CD was 83.9% (50/58 – 95% CI 73.8-91.9), while the rate of VD was 16.1% (8/58 – 95% CI 8.1-26.2) (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 death. 34.6% (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 low Apgar score at five minutes was 6.1% (1/48 – 95% CI 1.3-13.9), but no case of neonatal asphyxia was 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.

The rate of PTB was 52.7% (17/32 - 95% CI 36.3-68.8), with PTB < 37 and 34 weeks of gestation occurring in 41.1% (14/32 – 95% CI 25.6-57.6) and 15% (4/32 - 95% CI 3.9-31.7) of cases, respectively. There was no data on miscarriage for COVID-19 infection occurring during the first trimester. pPROM and PROM occurred in 18.8% (5/31 – 95% CI 0.8-33.5) and 5.9% (1/31 – 95% CI 0.6-16.2) respectively, while the rate of pregnancies experiencing PE was 13.6% (1/12 – 95% CI 1.2-36.0), with no reported cases of IUGR. Regarding mode of delivery, the rate of CD was 91% (38/41 – 95% CI 81.0-97.6), while the rate of VD was 9% (3/41 – 95% CI 2.4-19.0) (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 suffered from fetal distress and 8.7% (1/10 – 95% CI 0.01-31.4) of newborns was admitted to NICU. The rate of low Apgar score 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.

The rate of PTB was 32.1% (3/11 - 95% CI 10.0-59.8), all occurring before 34 weeks of gestation.

There was no data on miscarriage for MERS infection occurring during the first trimester. PROM and PE occurred in 35.1% (1/3 – 95% CI 20.6-81.3) and 19.1% (1/7 – 95% CI 1.1-51.3) respectively, while no case of pPROM or IUGR was reported in these studies. Regarding mode of delivery, the

rate of CD was 61.8% (5/8 – 95% CI 32.7-86.9), while the rate of VD was 38.2% (3/8 – 95% CI 13.1-67.3) (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, low Apgar score 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 PTB was 37.3% (9/25 - 95% CI 20.6-55.6), with PTB < 37 and 34 weeks of gestation occurring in 15% (1/15 – 95% CI 0.3-45.6) and 28.9% (4/15 - 95% CI 10.7-51.6) of cases, respectively. The rate of miscarriage for MERS infection was 39.1% (8/21 - 95% CI 20.2-59.8). pPROM and IUGR 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 case of PROM or PE was reported in these studies. Regarding mode of delivery, the rate of CD was 72.2% (7/9 – 95% CI 44.1-93.1) while the rate of VD was 27.8% (2/9 – 95% CI 6.9-55.9) (Table 5).

Fetal distress occurred in 35.9% (3/9 – 95% CI 12.0-64.4) of pregnancies, while no case of perinatal death, low Apgar score at five minutes, and neonatal asphyxia was reported. There was no data on admission to NICU of infant born form 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 gestational age at occurrence of the infection due to the very small number of included studies for each trimester of pregnancy.

DISCUSSION

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 are more likely to experience PTB, either before 37 and 34 weeks, and miscarriage when the infection is acquired in the first and early second trimester. 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. More importantly, clinical evidence of vertical transmission was found in none of the newborns included.

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, 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 topic. Furthermore, we cannot exclude that some patients were included in more than one report, although two authors independently reviewed all the included studies, carefully focusing also on the different Institutions where data come from. 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. Another limitation of the present review was the lack of stratification of the analysis according to the cardiovascular status of the gestational age at CoV infection due to the very small number of included studies for each trimester of pregnancy. 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.

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 have raised urgent questions among physicians on clinical management and outcome 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 right as the general 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 ranging from 25% to 30%.

In this systematic review, more than half of pregnant women affected by COVID-19 experienced PTB, mostly occurring between 34 and 37 weeks, and the majority of these patients – more than 90% - delivered with CD. The rate of perinatal death, including both stillbirths and neonatal deaths, was 7%, while the rates of neonatal asphyxia, low Apgar score and admission to NICU were all below 10%.

Furthermore, as all the included studies reported data on hospitalized women, it is likely that the rate of infection-related adverse outcomes, including either pregnancy and perinatal outcomes, might be higher than the overall population of pregnant when who got infected with COVID-19, and it is quite intuitive that there could be a cohort of patients with no or mild symptoms whose pregnancy outcome is unknown.[36]

More importantly, it should be emphasized that there is no 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]

Anyway, 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, and the decision should involve a multidisciplinary team including maternal fetal doctors, neonatologists, anesthesiologists, and infective disease specialists.

To conclude, pregnancy does not appear to increase maternal morbidity in case of COVID-19 infection. PTB is the most common adverse pregnancy outcome, although occurring more frequently in the late preterm period, and the rates of adverse perinatal outcomes are all below 10%, with no reported cases clinical evidence of vertical transmission. The findings from this study can guide and enhance prenatal counselling of women with COVID-19 infection occurring during pregnancy.

Declaration of interest

The authors declare no competing interests.

Authors' individual contributions

Daniele Di Mascio: study conception and design; acquisition of data and interpretation of findings; drafting of the manuscript. Asma Khalil: critical revision. Gabriele Saccone: acquisition of data and interpretation of findings. Danilo Buca: drafting of manuscript. Marco Liberati: critical revision. Jacopo Vecchiet: critical revision. Vincenzo Berghella: critical revision. Francesco D'Antonio: study conception and design; analysis and interpretation of data.

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Figure legend

Figure 1. Systematic review flowchart

Figure 2. …