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COVID-19 in pregnancy; The fetal perspective- a systematic review

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Title Page

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Title: COVID-19 in pregnancy; The fetal perspective- a systematic review

Abstract:

Objective: We aimed to conduct a systematic review of the available literature to determine the effects of confirmed cases of COVID-19 in pregnant women from the fetal perspective by estimation of vertical transmission, perinatal outcome and possible teratogenicity.

Methods
Data sources: Eligible studies published from November 1, 2019 up to August 10, 2020 were retrieved from PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus collection databases.

Study eligibility criteria: This systematic review included English language case reports, case series and cohort studies of pregnant women who had viral RNA RT PCR confirmed SARS-CoV-2 infection, and had reported data on perinatal outcome, congenital anomalies and vertical transmission of SARS-CoV-2. A total of 35 case reports and 34 cohort/case series studies describing 1213 tested neonates were included for evidence of vertical transmission. Similarly, 26 case reports and 31 case series/cohort studies describing 1255 fetuses were included for evaluation of perinatal outcome and congenital anomalies.

Results: Our review revealed that out of 1193 neonates from SARS-CoV-2 infected mothers, 48 neonates had SARS-CoV-2 viral RNA positive nasopharyngeal swab, indicating a pooled proportion of 4.02% for vertical transmission. Cord blood samples were positive for SARS-CoV-2 viral RNA in neonatal cord blood was positive in 5.4% (3/55) of samples, 6.9% (9/130) of placenta samples, 9.5% (4/42) of amniotic fluid, 9.6% (5/52) of fecal/rectal swabs and 0% of urine samples. In the perinatal outcomes, the rate of preterm labor is 325/1255 (OR=0.12) and Cesarean delivery was 750/1255 (OR=2.20). Most common neonatal symptom was shortness of breath. There were no congenital anomalies and still birth rate was 0.9 per 1000 total births in babies born to COVID-19 mothers.

Conclusion: Chances of vertical transmission of the virus is low. The perinatal outcome for the fetus is favourable. There is very low rate of stillbirth and neonatal deaths. There were no reported congenital anomalies in babies born to SARS CoV-2 positive mothers.

Key words: COVID-19, SARS-CoV-2, vertical transmission, perinatal outcome, congenital anomaly

Key message:

A. What is known about the subject –

Studies specifically analyzing all aspects of fetus in SARS-CoV-2 positive mothers are not available. There is currently lack of large studies depicting fetal parameters and unlikely to be available in future as individual centers are still reporting cases in small

numbers.There are some systemic reviews reporting maternal outcomes and vertical transmission separately but aspects like fetal complications, teratogenicity, neonatal outcomes are missing.

B. What this study adds –

In this systematic review, we searched multiple databases to include evidence till 10th August 2020. 78 studies were included to collect data on more than 1200 fetuses. The mother to child transmission was found to be 4.02% (48/1193) by nasopharyngeal swab RT PCR testing. The risk of prematurity and caesarean delivery are high. There is evidence of fetal distress, low birth weight and neonatal respiratory symptoms in COVID-19 mothers but stillbirth is low. There are no associated congenital anomalies.

Ethical Approval/ Consent:

This is a systemic review of the available literature on the fetal perspective of COVID-19 in the mother. Since in this research, collected data is already reported with specific ethical approval and consent in each of the individual studies, and does not contain any patient identifying information, an ethical approval or consent from the patients is not required.

Research Ethics Approval: Human Participants

- Question is: Does this study involve human participants? **No**
- If ethical approval was not obtained, please provide an explanation in the free text field.
- If consent for participation was not obtained and NO is selected, please provide an explanation in the free text field.

INTRODUCTION

Novel coronavirus infection and associated coronavirus disease-2019 (COVID -19) pandemic has changed our lives forever and has compelled us to reconsider almost everything we have long taken for granted. Among the different coronaviruses severely affecting human species, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 are significant, causing MERS, SARS and COVID-19 respectively. SARS-CoV-2 strains show significant sequence homology to SARS-CoV and MERS-CoV **[1]**. As the pandemic evolved, there were significant advances in our knowledge about various aspects of the COVID-19 including epidemiology, clinical features, transmission, detection, and management modalities. Discoveries along the process of evolution are still contributing to our management practices.

There were concerns regarding the maternal and fetal effects since the beginning of the pandemic. The earlier evidence of COVID-19 in pregnancy pointed towards pregnancy being considered as low risk for the disease and no difference in disease behavior in pregnant and non-pregnant women was reported. On the contrary, a newer study involving pooled data from more than 8000 women in the USA pointed towards a significantly higher rate of intensive care unit (ICU) admission and need for mechanical ventilation in pregnant women, even when adjusted for race/ethnicity and underlying comorbid conditions **[2-4].** Similar findings were reported in another study from Sweden **[5].**

However, these studies did not specify fetal effects resulting from vertical transmission and consequent perinatal outcomes. Through this article, we want to analyze the published evidence on the fetal perspective of COVID-19 infection with respect to vertical transmission and perinatal outcome through a systematic review. This will aid in alleviating uncertainties faced while doing patient counseling and help in subsequent management during these testing times.

METHODS

Search strategy: A systematic search of PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus electronic database was done. Medical subject handling terms (MeSH) and free text term keywords like vertical transmission, perinatal outcome, congenital anomaly, teratogenicity, fetal, neonate, newborn, pregnancy were used in combination with COVID-19, 2019-nCoV, SARS-CoV-2 to search for data from 1st November 2019 till 10th July 2020. Thereafter manual update was done on weekly basis till 10th August, 2020.The references of relevant studies were also searched.

Selection criteria: The search consisted of only English language articles including case reports, case series, and letters to editors containing case information. After a thorough screening, no randomized clinical trials were found.

Inclusion criteria: The following studies were included for review.

1- Studies reporting pregnant women with confirmed COVID-19 who had delivered.

2- Studies containing the results of SARS-CoV- 2 test [including reverse transcriptase polymerase chain reaction (RT-PCR) and serological tests] in both mothers and newborns samples.

4- Studies that present the out-come of vertical transmission or perinatal outcome.

Evidence of vertical transmission is indicated by positive RT-PCR status in different samples like neonatal nasopharyngeal swab, cord blood, amniotic fluid, breast milk, and placental tissue. Perinatal outcome measures included fetal complications in SARS-CoV

2 positive pregnant women, gestational age at delivery (preterm delivery), mode of delivery, birth weight, stillbirth, neonatal death, neonatal condition at birth (APGAR scores, neonatal ICU admissions) and symptoms in the early neonatal period. Any outcome measures not explicitly mentioned was considered not to have been reported.

Exclusion criteria: Exclusions consisted of studies in pregnant women yet to deliver, duplicated studies, review articles, articles in languages other than English where English translation is unavailable, studies where infection in mothers is not confirmed, or where neonatal testing was not done. Conference abstracts, expert opinions, and critical appraisals were also excluded.

Both the authors (RD, SSK) reviewed all titles independently. Potential relevance of the studies to be included for review, were agreed upon by discussion. Selected titles and abstracts were further screened between studies to reject overlap of cases.

Full-text copies of the selected papers were obtained and the relevant data regarding study characteristics, evidence of vertical transmission, and perinatal outcomes were extracted by the same two reviewers independently. In the case of individual case reports, if the same patient was included in more than 1 study with similar characteristics and findings, only the report with a larger number of patients was included. As far as possible, single case reports were cross-checked with other reports from the same location and hospital. If a case series included multiple locations, the individual reports from the same centers were excluded. Finally, studies were screened by assessing selection, comparability and exposure for inclusion into evidence acquisition of vertical transmission and/or perinatal outcome measures **[Table-1 (a), 1 (b) in Supplementary material-1].**

Statistical analysis: Pooled proportions of categorical variables were calculated with percentage after obtaining the positive rates of each of the SARS-CoV-2 testing methods used, wherever applicable. Odds Ratio was calculated for the fetal outcome of preterm delivery and mode of delivery in the SARS-CoV-2 positive mothers from the pooled data. Percentage of most common variables were also calculated.

Public and Patient Involvement statement:

This research is not “co-produced” with patients, carers, or members of the public.

• At what stage in the research process were patients/public first involved in the research and how? – Not Applicable
• How were the research question(s) and outcome measures developed and informed by their priorities, experience, and preferences? – Not Applicable
• How were patients/public involved in the design of this study? – Not Applicable

• How were they involved in the recruitment to and conduct of the study? – Not Applicable
• Were they asked to assess the burden of the intervention and time required to participate in the research? – Not Applicable

RESULTS

1. Vertical transmission-

Vertical transmission generally includes transmission through germ cells or the placenta during pregnancy, via the birth canal during labor and delivery, and during the postpartum period through breastfeeding or close contact. The transfer of microorganisms during pregnancy is seen with many of the common pathogens with resultant effect ranging from asymptomatic infection, intrauterine growth restriction, intrauterine death, structural anomalies to a sequel of infection. Some pathogens like cytomegalovirus (CMV), or Zika virus produce mild to no symptoms in the pregnant patient but can cause congenital infection with severe consequences **[6].** Viruses specifically can be transmitted to the fetus via the maternal blood when it enters the placental villus, containing the fetal blood vessels, or by direct access to the placenta from the lower genital tract by ascending infection **[7].** Again even when transferred trans-placentally during the antenatal period, the specific timing of maternal infection can have different effects on the fetus. First trimester infections can cause severe structural anomalies whereas second and third-trimester infection is more likely to cause functional organ abnormality **[8].**

Several factors are contributing to the concerns of vertical transmission in Covid-19. It is known that the SARS-COV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors for entry into the cells. ACE-2 receptors are detected in various parts of the uterus, vagina, decidual cells and placenta **[9-12].** Congenital infection is likely If an infectious agent is detected in amniotic fluid collected before the rupture of membranes or in the cord blood at birth. Similarly, if a neonate is born with a specific structural sequel of an infection, intrauterine infection is a probability. The detection of the agent later in life signifies postnatal infection. It also depends on the presence of the agent in the genital tract and time taken from exposure to detection by definitive tests to differentiate between intrapartum and postpartum infection. Furthermore, the sensitivity of RT-PCR testing is different for detecting SARS-CoV-2 in different samples. Therefore, it is rational to test samples from multiple sites to improve detection and reduce false-negative cases **[8,13].**

Search Results:

Out of 97 records selected for full-text review, 69 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. 35 studies were case reports containing 4 or fewer number of cases and 34 studies had 5 or more number of patients **(Figure-1).** Since evidence from randomized control trials were not available until the time of the search, 34

studies having 5 or more number of patients were considered for qualitative analysis **[14,15].** The majority of earlier studies were from China but later studies contained cases from the rest of the world **[Table-1 (a),1 (b)].**

Systematic review:

Tests for diagnosis of SARS-CoV-2 was done in a total of 1213 neonates. The most common type of sample tested was neonatal nasopharyngeal samples (NP swab) (64 out of 69 studies) followed by the placenta, amniotic fluid, and cord blood. In majority, samples were taken from more than one site. In few studies, the same type of sample was repeated at different intervals (e.g., NP swab and breast milk samples) **[Table-2].**

i. Neonatal Nasopharyngeal swab

In our review, a total of 1193 neonates born to mothers with COVID-19 infection were tested by NP swabs. 48 neonates were found positive by RT-PCR test indicating a pooled proportion of 4.02 % for mother to child transmission **[Table-3].** The largest cohort study from the UK involved 427 pregnant women with COVID-19. 244 out of the 262 neonates were tested by NP swab. 6 of the neonates were positive for SARS-CoV-2 within 12 hours of birth and 6 more were positive after 12 hours of birth (12 out of 244; 4.9%) **[16].** Studies involving 181 women and 116 women in China showed 2 positive neonates out of 181 (2 out of 181; 1.1%) and no positive cases for SARS-CoV-2 in the other study **[17,18].** An analysis of 141 women from a hospital in India showed that 3 of the 131 neonates were tested positive for SARS-CoV-2 by nasopharyngeal swab **[19].** In another study in a New York Hospital, 48 neonates born to 55 women were all tested negative on Day 0 of life **[20].** However, One Italian study found three infants positive by NP swab out of 42 tested within 48 hours after birth **[21].**

One recent case report revealed that RT-PCR was positive for SARS-CoV-2 in all of the samples for amniotic fluid, vaginal swab, blood, and non-bronchoscopic bronchoalveolar lavage fluid as well as NP swab and rectal swabs collected at 1 hour of life, and then repeated at 3 days and 18 days suggesting a trans-placental transmission **[22].**

When the timing of NP swab test in the positive neonates was analyzed, it was found that only a few of the samples were positive within 24 hours of life (13 cases) **[23, 22,16, 19, 22-24]** and the majority of the cases were positive after 24 hours of life. In one study the sample collected within 24 hours was negative but the second sample collected after 24 hours was found positive **[25,26].** This indicates a strong probability of having acquired the infection, after birth.

ii. Amniotic fluid

In our review, 42 samples of amniotic fluid were tested in 18 studies with a positive result in 4 of them. The studies were case reports involving single and 2 cases. In one of these studies, the test was positive from all the maternal samples. All the neonatal samples were positive even at 18 days follow up **[22].**

iii. Placenta

A total of 19 studies were identified in our review where the placenta was examined for the presence of SARS-CoV-2 or related pathological changes. A total of 130 placental samples were tested and 9 were found positive for SARS-CoV-2. PCR for SARS-CoV-2 RNA was positive from placenta in two case reports where there were spontaneous miscarriage and dilatation and curettage respectively **[27,28].** In one of them, the umbilical cord was also positive for the virus, but the fetal organs were tested negative. The virus was confirmed to be localized mostly in the syncytiotrophoblastic cells of the placenta by immunohistochemistry for the SARS-CoV-2 spike protein as well as electron microscopy and it was identical to the typically locally isolated virus **[27].** Furthermore, in another study, electron microscopy showed the presence of the virus in the fetal side of the placenta. The virions were present in the mesenchymal core of the terminal villus and were demonstrated to be invading a syncytiotrophoblast and a microvillus. However, the neonate delivered at 28 weeks in this pregnancy was tested negative for the virus **[29].**
Evidence of probable vertical transmission was obtained in another case where the newborn was found positive for the virus by nasopharyngeal swab, plasma, and stool samples along with the placenta **[30].** Similarly, probable transplacental transmission of the virus was demonstrated by another study where SARS-CoV-2 was detected in amniotic fluid aspirated before the rupture of the membranes, vaginal swab, neonatal blood, bronchoalveolar lavage fluid, and neonatal swabs on repeated occasions at 1 hour, 3rd day and 18th day of life. The trophoblastic cells showed SARS-CoV-2 N protein on immunostaining **[22].**
Placental pathological examination showed an array of changes including vascular malperfusion, fibrin deposition, and chronic villitis, intervillositis and villous infarctions in our review. Two of these studies showed vascular malperfusion in 10 out of 20 placentas and 12 out of 15 placentas respectively but there were no assessments of placentas in these studies for the presence of SARS-CoV-2 infection. However, neonatal swabs were negative for the virus **[31,32]**. Similar pathological changes were seen in another study involving five SARS-CoV-2 positive pregnant women but the placentas were negative for the virus on direct testing for SARS-CoV-2 **[33].** Chronic intervillositis was also seen in the pathological examination of the placentas of two women where the neonates were positive for SARS-CoV2 by nasopharyngeal swab testing **[34].** Examination showed severe chronic villitis in another case where there was a stillbirth at term but direct tests of fetal tissues and placenta did not show infection with the virus **[35].**

iv. Other samples

Various other samples were tested for SARS-CoV-2 by different studies. Anal swab, rectal swab, or fecal sample was positive in 9.6% of neonates in our study. The stool sample was positive in two of the studies at Day 2 and Day 7 **[30,36].** The urine sample was tested in only 3 studies without any positive results **[37-39].** Breast milk was tested by RT-PCR in 10 of the studies with a pooled positive rate of 5.3% (3 out of 56). In one of the studies, the breast milk sample was positive in 4 consecutive days coinciding with the maternal symptoms in one woman but it was negative in milk samples of another woman. Both the babies were positive by the nasopharyngeal swab test and were symptomatic **[40].** A vaginal swab was tested in 23 women with one positive result (4.3%) **[22].** It can be argued that since IgM cannot cross placenta, elevated IgM levels in the neonate can indicate intrauterine infection, as seen in some of the neonates in this review. However, the assay of IgM for detection of infection has significant false positive results.

2. Perinatal outcome-

Evidence of COVID-19 specifically focusing on fetal and neonatal outcomes are lacking. Most of the reported literature have smaller studies. Previous systematic reviews focusing on the outcomes of all coronaviruses have reported a higher risk of preterm birth, perinatal death, miscarriage, and pre-eclampsia.

Search results:

Out of 73 records selected for full-text review, a total of 57 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. 31 studies qualified as case series/cohort and 26 studies contained 4 or fewer cases in our review **(Figure-2).** No randomized control trials were available until the time of the search.

Systematic Review:

2.1 Fetal Outcomes:

i. Fetal complications in SARS-CoV-2 +ve pregnant women

In our review, a total of 28 studies reported any fetal effects excluding all pregnancy losses or intrauterine fetal deaths (IUFD) **[Table no-4].** The most commonly reported effect was fetal distress in 36 out of 1255 pregnancies (2.8%). In addition to fetal distress, some studies have reported non-reassuring or pathological cardiotocography (CTG) (11 out of 1255; 0.87%), and some have mentioned meconium-stained amniotic fluid (3 out of 1255; 0.23%), both findings can also be considered as evidence of fetal distress **[22, 41-47]**. In another study involving 262 deliveries, the fetal compromise was seen in 37 fetuses and emergency caesarean section (CS) was done in 9 of them **[16].** Thus the

cumulative chance of fetal distress in pregnant women with a positive test for SARS-CoV-2 is 6.9%.

Premature rupture of membrane (PROM) was reported in 29 pregnancies from 12 studies. Intrauterine growth restriction (IUGR) was reported in 11 fetuses in 4 studies **[17, 25, 48, 49].** The highest number of IUGR fetuses was reported in 6 out of 10 fetuses in another study **[48]**. In addition, small for gestational age was reported in another study in 2 out of 10 fetuses **[42].** Chorioamnionitis was reported only in one study involving 3 fetuses **[4].**

ii. Mode of delivery

Mode of delivery was available for a total of 1255 pregnancies out of which 750 women delivered by CS as compared to 505 by vaginal delivery (OR=2.20) **[Table no-5].** CS was the only mode of delivery in the majority of early published case reports as in the early days of the pandemic, elective CS delivery was the mode preferred by most of the countries for maternal indications **[22-24, 26, 30, 39, 50- 65].** As the pandemic progressed, favorable outcomes were reported from vaginal delivery by many studies **[47, 49, 66-69].** It was also demonstrated that the chances of the virus being present in the vaginal fluid is very remote. In the later and larger case series, CS deliveries were only done for obstetrical indications **[19].** In a study involving 134 deliveries, there were 67 CS and 67 vaginal deliveries. The rate of CS was not statistically different in women with positive SARS-CoV-2 as compared to negative pregnancies **[19].** In yet another study, there were significantly higher rates of CS deliveries in cases (14 out of 16) as compared to the control group (57 out of 121) ($p < 0.001$) but there was no difference in the groups with regards to chronic illnesses or pregnancy complications **[70].** However, when done for maternal COVID-19 indications, the rate of cesarean was found to increase with the severity of disease **[18]**.

In the largest study in the UK, the CS delivery was seen in 156 women and vaginal birth was seen in 106 women from a total of 262 births. The indications of CS were maternal compromise (27%), fetal compromise (24%), failed induction of labor or failure to progress (19%), other obstetric reasons (16%), prior CS (10%) and maternal request (4%) **[16]**. Maternal COVID -19 related conditions were predominant indications in another larger study reporting CS for COVID-19 pneumonia in (33 out of 85), previous CS (16 out of 85), fetal distress (9 out of 85), and failure to progress in 5 out of 85 patients **[17]**. Many other studies similarly reported maternal condition requiring delivery as the commonest indication for CS **[18, 21, 62]**.

iii. Preterm Delivery

Preterm delivery is defined as delivery of a viable product of conception before 37 completed weeks of gestation. In our study, the outcome of preterm delivery was reported

in a total of 42 studies involving 1255 fetuses out of which 325 were delivered preterm (25.8%) **[Table no-5].** However, the majority of them were elective deliveries to stabilize maternal condition related to COVID-19. Spontaneous preterm labor was only seen in 23 fetuses (1.8%). The other indications included the pre-labor rupture of membranes. In a substantial number of studies, data regarding the indications were not found.In a study involving 134 deliveries in COVID -19 patients, preterm delivery was seen in 38 pregnancies with positive SARS-CoV-2 and 239 out of 836 SARS-CoV-2 negative deliveries, which was not significantly different **[19]**. A similar report was seen in another study where 4 preterm deliveries were seen out of 17 SARS-CoV-2 confirmed group as compared to 7 out of 121 in the control group **[70]**.

Furthermore, comparing the outcomes of COVID-19 pregnancies with different disease severity involving 181 pregnant women, preterm delivery was seen in 13 out of 123 (10.6%), 14 out of 29 (48.3%), and 23 out of 29 (79.3%) in women with non-severe, oxygen-requiring, and critical COVID-19, respectively. Delivery before 32 weeks was highest in 48.3% women in the critical COVID-19 group. In severe disease, urgent delivery is required to stabilize the maternal condition, even when it results in iatrogenic preterm delivery **[18]**.

iv. Birth weight

Low birth weight (LBW) is defined as less than the 3rd percentile of the average birth weight in a population. This includes preterm, and small for gestational age neonates. Small for gestational age (SGA) neonates include intrauterine growth restriction (IUGR) as well as constitutionally small babies. In this review, LBW was defined as a birth weight of less than 2500 grams. In our review birth weight was missing in many studies and only the mean weight of the babies was mentioned in some of the series. However, extracted data identified 18 studies reporting LBW. Out of these, in 11 studies the LBW was most likely to be preterm birth **[26, 31, 46, 50, 55, 60 , 62-65, 71].** LBW was significantly higher in babies born to SARS-CoV-2 infected mothers than in the control groups in yet another study **[70].** IUGR was found in 4 studies in 11 babies **[17, 25, 48, 49].** Also, SGA was found in 2 studies in 5 babies **[36, 42].** Furthermore, in one study there were 39 babies with LBW and 38 babies with preterm birth **[19].** A maximum of 6 babies had IUGR in one study but they were described as mild **[48].**

v. Miscarriage and stillbirth

Stillbirth was seen in 12 fetuses in 7 studies in our review, among which seven were second-trimester miscarriages **[16, 18, 19, 26, 35, 45, 72] [Table no-5].** 3 intrauterine deaths was observed in one of the studies which reported maternal deaths due to COVID-19 **[26].** Similarly, we found 15 spontaneous miscarriages and 4 induced miscarriages

reported in 5 studies **[16, 18, 19, 73, 74].** Induced miscarriages were done on maternal request in both studies **[73, 74].** Among the spontaneous miscarriages, 6 were seen in 141 pregnancies in one study and 5 in 181 pregnancies in another study **[18, 19].** In one of the studies, there were 3 stillbirths and they were found to be causes unrelated to COVID-19 in the mother **[16].**

2.2 Neonatal Outcomes:

The neonatal period is defined as the time period from birth until the end of the first 28 days of life. Events in the early neonatal period (first 7 days) usually are related to the pregnancy more significantly and it is also included in the definition of the perinatal period. In this review, we have assessed the neonatal outcomes using APGAR score at 1minute and 5 minutes of life, neonatal symptoms, admission into neonatal intensive care unit (ICU), and neonatal death, as the parameters **[Table no-6].**

i. Neonatal symptoms

The most common neonatal symptoms were respiratory problems **[42, 53, 56].** Respiratory distress was the most common symptom reported in 12 neonates but the test for SARS-CoV-2 was positive in only 4 neonates and negative in 8 **[21, 36, 44, 62, 63, 65, 75].** Pneumonia was seen in 5 neonates who were positive for SARS-CoV-2 and 4 neonates who were negative **[24, 26, 36, 46, 51].** Although usually respiratory symptoms are seen more in preterm babies due to pulmonary immaturity, in a single case report there were no neonatal complications in a SARS-CoV-2 positive mother who delivered a preterm baby at 29 weeks 5 days by emergency CS for maternal indications **[76].**

Diffuse bilateral granular and hazy opacities in chest radiograph and thickened lungs on x-ray were found in two neonates but the neonatal test for SARS-Cov-2 was negative in both of them **[59, 65].** In another SARS-CoV-2 +ve, newborn chest X-ray was consistent with pulmonary infection, 53 hours after birth **[73].** In another study, neonatal symptoms are extensively described. The most common first clinical symptom in the neonates of SARS-Cov-2 Positive women was shortness of breath (n=6), followed by gastrointestinal symptoms like feeding intolerance, bloating, refusing milk, and gastric bleeding (n=4). Other symptoms included fever, rapid heart rate, and vomiting. Chest radiographic abnormalities included infections (n=4), neonatal respiratory distress syndrome (n=2), and pneumothorax (n=1). Another preterm baby suffered from frequent oxygenation fluctuations and thrombocytopenia and was cured 15 days later **[42].** It was reported in yet another study that most of the complications in neonates were a result of prematurity (often iatrogenic) rather than SARS–CoV-2 infection **[36].**Other presentations in SARS-CoV-2 positive neonates included fever, cyanosis, lethargy, irritability, poor feeding, axial hypertonia, opisthotonus, and feeding difficulties **[22, 34, 36].**

ii. APGAR Score

An APGAR score of less than 7 at 1 minute and 5 minutes after birth in a newborn is defined as low APGAR score in this study **[77].** In our review, a total of 9 studies have reported a low APGAR score among babies born to SARS-CoV-2 positive mothers **[19, 21, 22, 36, 46, 56, 63-65].** Seven of the neonates were very preterm or preterm and were SARS-CoV-2 negative. The APGAR score in these is likely to be due to pulmonary immaturity **[19, 21, 22, 56, 63-65].** Two other babies were term deliveries and tested positive for SARS-CoV-2 **[36, 46].** However another study reported low APGAR scores of 0–3 in 2 babies of COVID positive mothers and in 15 babies in COVID negative mothers, indicating no statistically significant difference **[19].**

iii. ICU admissions

Admission to the neonatal ICU was done for various reasons. Majority of admissions were for observation and isolation. Neonates admitted due to complications of prematurity constitute another higher portion of the neonates. In a study, it was found that 16 babies were admitted due to low birth weight, 2 for low APGAR score, and 6 others for other uncommon reasons like ABO incompatibility, out of a total 24 ICU admissions **[19].** In another study, it was found that rates of admission to ICU increased with the severity of the disease in the mother **[18].**

iv. Neonatal death

Neonatal death was reported among 5 neonates in 4 case reports. It was unclear whether COVID-19 in mothers contributed to the deaths in 2 neonates in one of the studies **[16].** In another study, neonatal death occurred in a preterm baby on the 9th day of life who was admitted with shortness of breath and moaning and later developed refractory shock, multiple organ failure, and disseminated intravascular coagulation (DIC) **[42]**.

3. Congenital anomaly:

We could not find any studies describing structural anomalies in the fetus associated with COVID-19. Due to an evolving pandemic, the teratogenicity of the virus has not been explored adequately. However, in a few of the studies, the findings of anomaly scans during pregnancy were included and they did not show any difference between fetuses of SARS-CoV-2 positive and negative women **[42, 74].** In two case reports, multicystic dysplastic kidney was detected by antenatal ultrasound in one and after delivery in the other **[31, 44].** In another study bilateral gliosis of the deep white periventricular and subcortical matter was detected in an 11 days old neonate born to SARS-CoV-2 positive mother by magnetic resonance imaging **[22].** However, these cannot be attributed to SARS-CoV-2. Furthermore, autopsy finding in a stillborn baby born to COVID-19 mother did not show any abnormality in another report **[35].**

DISCUSSION AND CONCLUSION

The present available data do not provide a clear conclusion into the fetal outcomes and its clinical implications. The possibility of vertical transmission in pregnant women with COVID-19 infection is low (4.02%). This is in accordance with other studies **[78, 79].** There is no reported teratogenicity or congenital anomalies associated with SARS-CoV-2 infection.

The chance for cesarean delivery is more in women with COVID-19 and in most instances for maternal indications. Preterm delivery is also high (25.8%) mostly due to maternal condition, although spontaneous preterm labor is low (1.8%). This is in accordance with another study with regards to the indication but they found a trend towards spontaneous prematurity **[80].**

The outcome so far is favorable for the fetus despite the risks to the mother for ICU admissions and mechanical ventilation seen in other studies **[3].** However, fetal distress was present in 6.93% of fetuses. Maternal outcomes were not explored in our study.

There were very low rates of stillbirth and neonatal death in our study. The symptoms when present in the infected neonates were most often mild and neonatal outcomes were found to be good **[81,82].**

Though the fetal perspective seems good in the case of maternal COVID-19, it will be reasonable to consider these findings with caution. Prospective studies and randomized control trials were missing from the evidence due to the recent nature of the infection. Therefore, larger and better quality studies are required to address the knowledge gaps and to reach at a definite guideline for management.

Strengths and Limitations of the study

There are many limitations to our study. Only a limited number of available case series and cohorts were included in this review as high-quality evidence involving a higher number of subjects are lacking dues to the new kind of infection and still evolving nature of the pandemic. Almost all of the reports are retrospective reviews showing incomplete data with significant heterogeneity within the included studies with a chance of selection or recall bias. In the absence of clear guidelines for testing methods and samples, different types of samples were used for the diagnosis of SARS-CoV-2 in different studies. Though nasopharyngeal swab was used for diagnosis is most studies, there were different types of kits used. Again the same kit may have different sensitivity and specificity in different types of samples. Universal testing of pregnant women was not done in many studies, resulting in missing fetal and perinatal effects in asymptomatic women.

Nonetheless, there are many strengths to this study. The studies included in the review contained only confirmed maternal cases by RT-PCR and not the suspected cases or clinically diagnosed cases. The studies contained the results of neonatal testing. Studies included in this review were from countries across the world and not restricted to a specific region, making the findings from the study globally applicable. The case series/cohorts

were chosen only when the total number of cases was more than 4. Moreover, various aspects of vertical transmission as well as fetal and neonatal outcomes were analyzed from the chosen studies.

Future Implications:

Whether there is intrauterine infection of the fetus with respect to SARS-CoV-2 needs to be studied. What are the effects of intrauterine infection, whether there is different susceptibility at different stages of pregnancy, and whether susceptibility depends on disease severity in the mother, needs to be explored. Follow up studies are required to see long term effects of neonatal infection with SARS-CoV-2.

AUTHORSHIP STATEMENT

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the BMJ Pediatrics-open access.

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Figure-1- PRISMA 2009 Flow Diagram- Vertical transmission

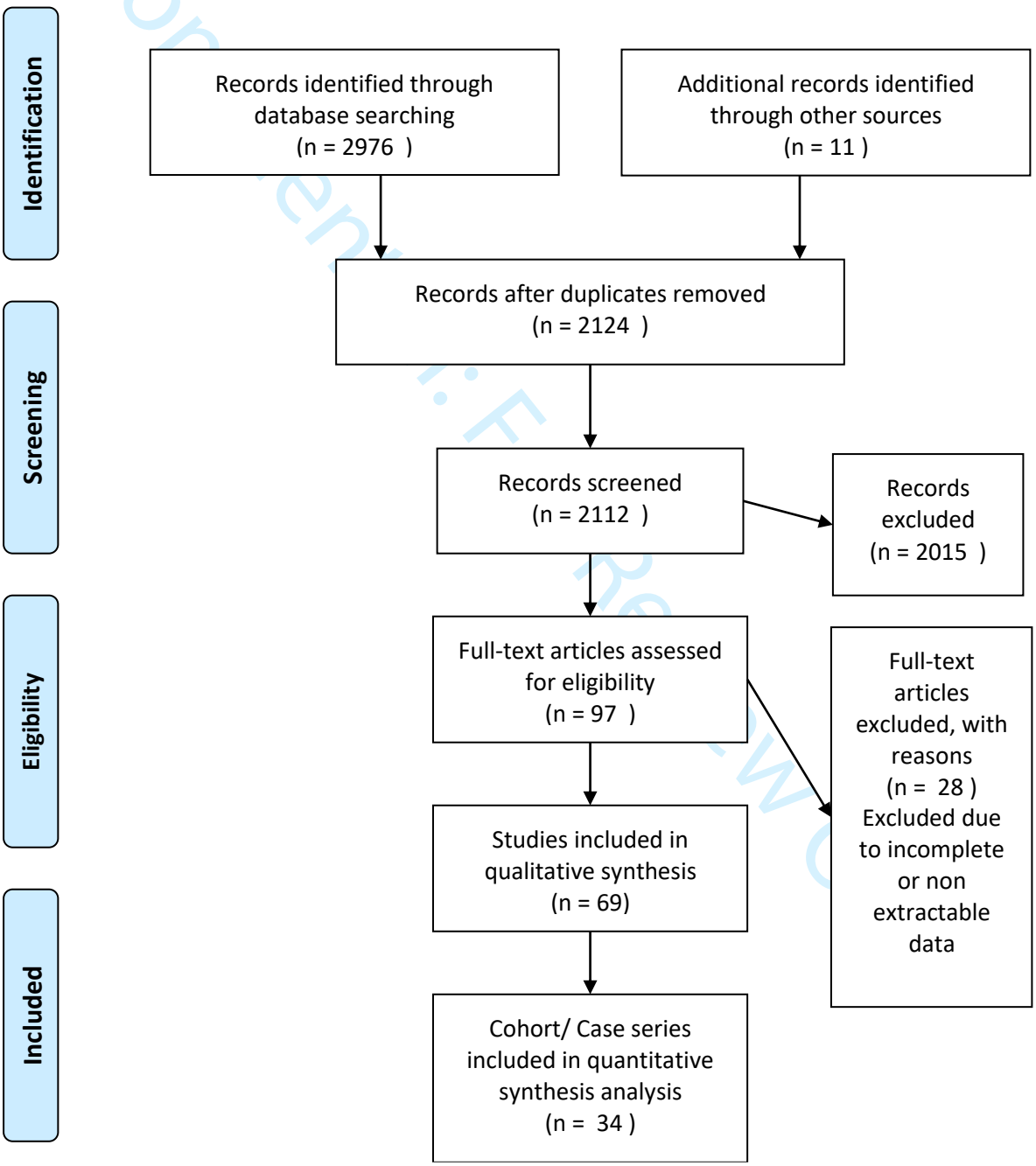

Figure-2 PRISMA 2009 Flow Diagram- Perinatal outcome

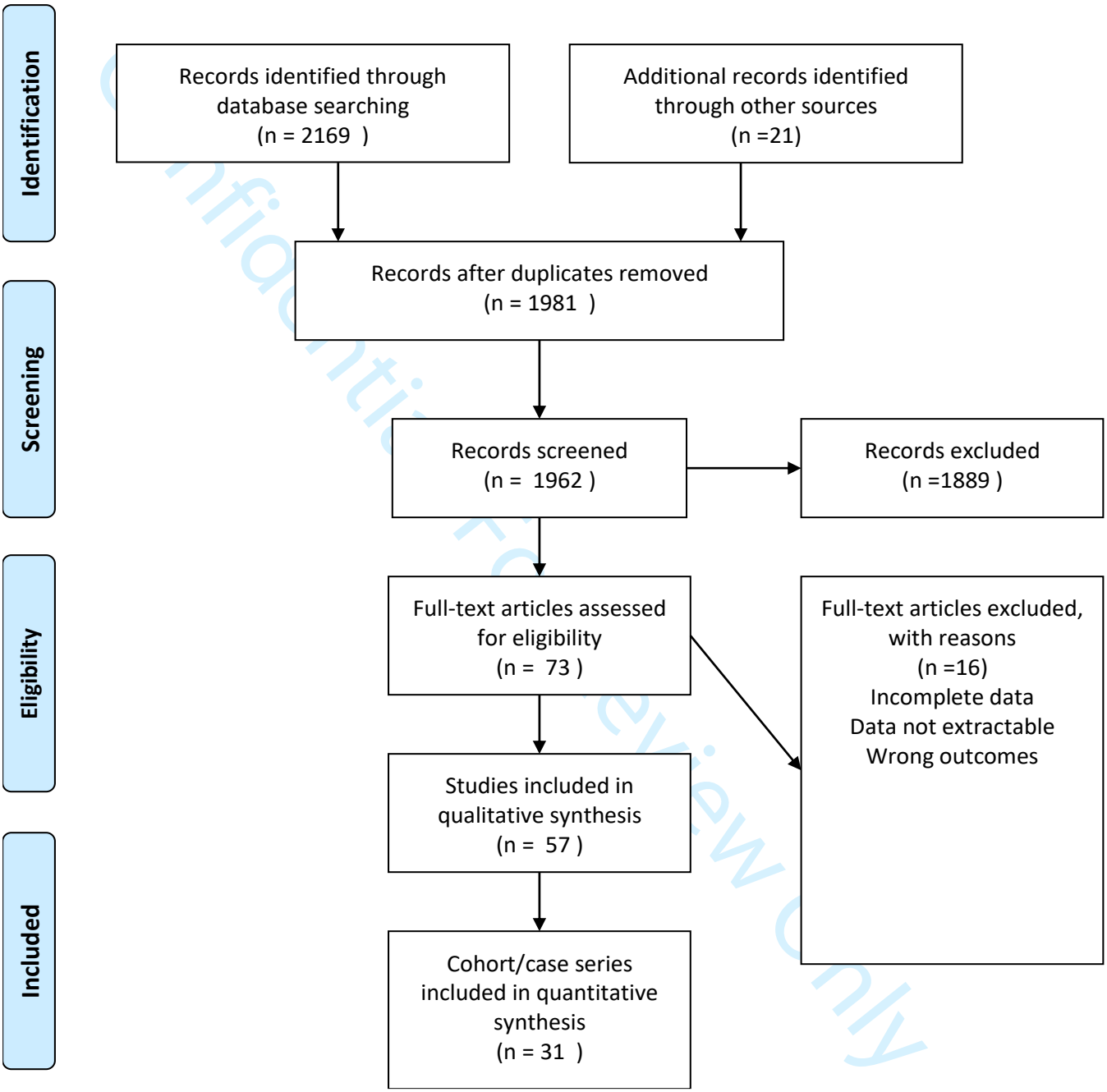

Table-1 (a): Analysis of the studies [Case series/ Cohort]

Serial number	Author (reference)	Number of pregnancies	Country	Outcomes included	Selection Contains diagnosed COVID-19 in Pregnancy	Comparability Data on pregnant women and fetus available	Outcome; Assessment and reporting	Evidence of vertical transmission	Perinatal Outcome
1.	Chen H et al (50)	9	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
2.	Zeng H et al (52)	6	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
3.	Zhu H et al (42)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
4.	Zhang I et al (83)	61	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
5.	Penfield CA et al (84)	11	China	Placental, membrane and neonatal samples	****		**	√	
6.	Liu Y et al (85)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
7.	Khan S et al (24)	17	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
8.	Zeng L et al (36)	33	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
9.	Breslin N et al (44)	18	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
10.	Qiancheng X et al (89)	23	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
11.	Yang P et al (62)	7	China	Symptoms, maternal characteristics, laboratory	****	**	***	√	√

				parameters, pregnancy and neonatal outcomes					
12.	Yang H et al (95)	55	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	*	*	√	√
13.	Wu Y et al (96)	13	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	*	*	√	
14.	Patane L et al (34)	22	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
15.	Ferrazzi E et al (21)	42	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
16.	Mulvey J et al (33)	5	USA	Placental characteristics	***			√	
17.	Govind A et al (46)	9	UK	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
18.	Vintzileos W et al (98)	32	US	Symptoms, maternal characteristics, Test results	***	*	***	√	
19.	Baergen R et al (32)	20	US	Maternal characteristics, maternal outcomes, Placental characteristics	***			√	
20.	Hantoushzadeh et al (26)	7	Iran	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
21.	Shanes E et al (31)	16	US	Symptoms, maternal characteristics, Placental pathology, pregnancy and neonatal outcomes	****	**	***	√	√
22.	Pereira A et al (75)	60	Spain	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
23.	Savasi V et al (91)	77	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
24.	London V et al (20)	68	USA	Symptoms, maternal characteristics, laboratory	****	**	***	√	√

				parameters, pregnancy and neonatal outcomes					
25.	Lokken E et al (35)	46	USA	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***		√
26.	Qadri F et al (100)	16	Michigan	Maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
27.	Yan J et al (17)	116	China	pregnancy and neonatal outcomes	****	**	***		√
28.	Knight M et al (16)	427	National, UK	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
29.	Williams R et al (25)	64	USA	Maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
30.	Kayem G et al (18)	617	France	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
31.	Nayak A et al (19)	141	India	Symptoms, maternal outcomes, neonatal outcomes	****	**	***		√
32.	Prabhu M et al (45)	70	US	Symptoms, obstetric and neonatal outcomes, and placental pathology	****	**	***	√	√
33.	Sentilhes, et al (101)	38	France	Symptoms, maternal outcomes, neonatal outcomes	****	**	***	√	√
34.	Li N et al (70)	16	China	Symptoms, maternal outcomes, neonatal outcomes	****	**	***		√
35.	Cao D et al (71)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
36.	Doria M et al (48)	10	Portugal	Symptoms, maternal characteristics, pregnancy outcomes	****	**	*		√
37.	Hu X et al (37)	7	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
38.	Breslin N et al (99)	7	US	Symptoms, maternal characteristics, test result	**	**	**	√	
39.	Nie R et al (73)	33	China	Symptoms, maternal characteristics, laboratory	****	**	***	√	√

				parameters, pregnancy outcomes					
40.	Romagano M et al (63)	7	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	*		√
41.	Yin M et al (74)	31	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√

Table-1 (b): Analysis of the studies [Case reports]

Serial number	Author (reference)	Number of preg-nancies	Country	Outcomes included	Selection Contains diagnosed COVID-19 in Pregnancy	Comparability Data on pregnant women and fetus available	Outcome; Assessment and reporting	Evidence of vertical transmission	Perinatal Outcome
1.	Alzamora et al (56)	1	china	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
2.	Li Y et al (39)	1	china	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
3.	Dong L et al (54)	1	china	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
4.	Baud D et al (28)	1	Switzerland	Symptoms, maternal characteristics, laboratory parameters, second trimester miscarriage	***	*	***	√	
5.	Wang X et al (55)	1	china	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
6.	Huang J et al (67)	1	china	Symptoms, maternal characteristics, pregnancy outcomes	***	**	***	√	√
7.	Iqbal S et al (87)	1	US	Symptoms, maternal characteristics, pregnancy outcomes	***	**	***	√	√
8.	Kalafat E et al (57)	1	Turkey	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	***	**	***	√	√

9.	Lee D et al (58)	1	Korea	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	***	**	***	√	√
10.	Liao X et al (88)	1	China	Symptoms, maternal characteristics, pregnancy outcomes	***	**	***	√	√
11.	Xiong X et al (68)	1	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	***	**	***	√	√
12.	Wang S et al (59)	1	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	***	**	***	√	√
13.	Zamaniyan M et al (60)	1	Iran	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
14.	Zambrano L et al (69)	1	Central America	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	***	**	***	√	√
15.	Song L et al (61)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	***	**	***	√	√
16.	Vivanti A et al (22)	1	France	Symptoms, maternal outcomes, neonatal outcomes	***	**	***	√	√
17.	Lowe B et al (47)	1	Australia	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	***	**	**	√	√
18.	Schnettler W et al (92)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcome	***	**	**	√	
19.	Blauvelt C et al (65)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	***	**	**	√	√
20.	Kirtsman M et al (30)	1	Canada	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	***	**	**	√	√
21.	Lyra J et al (23)	1	Portugal	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	***	**	**	√	√
22.	Algorroba et al (29)	1	US	Symptoms, maternal characteristics, laboratory	***	*	**	√	

				parameters, pregnancy outcome					
23.	Fan C et al (51)	2	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
24.	Hosier H et al(27)	1	US	Symptoms, maternal characteristics, test result	**	**	**	√	
25.	Peng Z et al(38)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
26.	Buonsenso et al (97)	4	Italy	Symptoms, maternal findings, test results	***	*	**	√	
27.	Perrone S et al (49)	4	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***		√
28.	Groß R et al (40)	2	Germany	Symptoms, maternal findings, test results	***	*	**	√	
29.	Cooke W et al (64)	2	UK	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	*		√
30.	Pulinx B et al (72)	2	Belgium	Symptoms, maternal characteristics, laboratory parameters, second trimester miscarriage	***	*	***	√	
31.	Liu W et al (41)	3	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
32.	Chen S et al (86)	3	China	Symptoms, laboratory parameters, pregnancy outcomes, samples	***	**	***	√	√
33.	Chen Y et al (43)	4	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	***	**	***	√	√
34.	Gidlöf S et al (53)	2	Sweden	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	***	**	***	√	√
35.	Khan S et al (66)	3	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	***	**	***	√	√
36.	Yu N et al (90)	2	China	Symptoms, maternal characteristics, amniotic fluid in mid pregnancy	***	*	***	√	

37.	Buonsenso D et al (94)	2	Italy	Maternal characteristics, Samples for detection	***	**	**	√	

Table -2 Studies and type of samples

	Author (reference)	Number of neonates tested	Specimen tested	Neonatal result	Positive/ Total tested
1.	Chen H et al (50)	6	NP, AF, Cord blood, BM	Negative	
2.	Fan C et al (51)	2	NP, AF, Cord blood, BM, Placenta , Vaginal swab	Negative	
3.	Liu W et al (41)	3	NP, Cord blood, Neonatal whole blood	Negative (D2)	
4.	Zhu H et al (42)	10	NP	Negative [Within 72 hours (8); Between D7-D9 (2)]	
5.	Zhang I et al (83)	10	NP	Negative	
6.	Penfield C et al (84)	11	NP, Placental and membrane	NP- Negative (D1 and D5) Placenta and membrane +ve	3/11
7.	Chen S et al (86)	3	NP, Placenta	Negative	
8.	Chen Y et al (43)	4	NP	Negative	
9.	Gidlöf S et al (53)	2	NP	Negative (34 hours and 4.5 days)	
10.	Khan S et al (66)	3	NP	RT PCR –ve	
11.	Khan S et al (24)	17	NP	+ve within 24 hours	2/17
12.	Zeng L et al (36)	33	NP , anal swab	Both +ve D2 and D4	3/33
13.	Breslin N et al (44)	18	NP	+ve at D2 and D4	3/18
14.	Breslin N et al (99)	7	NP	Negative	
15.	Qiancheng X et al (89)	23	NP	Negative	
16.	Hantoushzadeh et al (26)	4	NP	Negative at D1; +ve at D7	1/4
17.	Shanes E et al (31)	16	NP , Placenta	Negative	
18.	Pereira A et al (75)	23	NP , Placenta, BM	Negative	
19.	Savasi V et al (91)	57	NP	+ve	4/57
20.	London V et al (20)	48	NP	Negative	
21.	William R et al (25)	33	NP	Negative at 24 hours, +ve at 48 hours	1/33
22.	Knight M et al (16)	262	NP (n=244) ,Blood or aspirate	+ve at <12 hours +ve at >12 hours	6/244 6/244
23.	Kayem G et al (18)	181	NP	+ve	2/181
24.	Nayak A et al (19)	134	NP (n=131)	+ve on D1 -ve on D5	3/131
25.	Yan J et al (17)	86	NP (n=86); Cord blood (n=10),AF (n=10)	Negative	

26.	Prabhu M et al (45)	71	NP	Negative at 24 hours	
27.	Cao et al (71)	5	NP	Negative	
28.	Hu X et al (37)	7	NP, Urine	NP +ve at 36 hours	1/7
29.	Nie R et al (73)	26	NP, Cord blood, Placenta	NP +ve at 36 hours Negative - All other samples, NP (D4, D8,D15)	1/26
30.	Yin M et al (74)	17	NP (n=17), BM (n=14), AF (n=2), placenta (n=2), Anal swab (n=5)	Negative	
31.	Buonsenso et al (97)	2	NP,AF, Placenta, Cord blood, Rectal swab	NP Negative on D1,D4 and +ve on D15 Placenta, cord blood +ve Weak IgG+ve, IgM negative	1/2
32.	Yang P et al(62)	7	NP , Cord blood, AF	Negative	
33.	Yang H et al (95)	55	NP	Negative	
34.	Wu Y et al(96)	5	NP , Anal swab, BM	Negative, BM +ve	1/5
35.	Patane L et al (34)	22	NP , Placenta	NP +ve	2/22
36.	Ferrazzi E et al (21)	42	NP	NP +ve	3/42
37.	Govind A et al (46)	9	NP , Placenta, AF	NP +ve	1/9
38.	Vintzileos W et al (98)	29	NP	Negative	
39.	Baergen R et al (32)	21	NP	Negative	
40.	Lowe B et al (47)	1	NP	Negative	
41.	Schnettler W et al (92)	1	NP, AF	Negative on D1,D2	
42.	Blauvelt C et al (65)	1	NP, Rectal swab D2 Ig G and IgM	NP Negative on D1, D2, D14 Rectal swab negative on D2 Ig G and IgM negative (D5)	
43.	Alzamora M et al (56)	1	NP, Cord blood	Negative for IgM and IgG; NP +ve at 16 hours and 48hours	1/1
44.	Vivanti A et al (22)	1	NP, AF, Vaginal swab, BAL, Neonatal blood and and rectal swabs	NP +ve at 1hour, D3, D18; Rectal swab +ve at 1hour, D3, D18; Vaginal swab, NBAL, Neonatal blood +ve	1/1
45.	Song L et al (61)	1	NP, AF, Cord blood, BM	NP negative at D3,D7 All other negative	
46.	Zambrano L et al (69)	1	NP	Negative	
47.	Li Y et al (39)	1	NP, Neonatal Blood, feces, and urine	NP negative at birth and 48h All other negative	
48.	Dong L et al (54)	1	NP, Serum Vaginal swab	IgM level elevated NP negative at 2h,16h	1/1
49.	Baud D et al (28)	1	NP, AF, Placenta	Placenta +ve All other negative	1/1; 2nd trimester

			Vaginal swabs		spontaneous miscarriage
50.	Wang X et al (55)	1	NP, AF, Placenta, Cord blood, gastric juice, feces	NP negative at D1, D3, D7, D9 All other negative	
51.	Huang J et al (67)	1	NP	Negative	
52.	Iqbal S et al (87)	1	NP	Negative	
53.	Kalafat E et al (57)	1	NP, Cord blood, Placenta	Negative	
54.	Lee D et al (58)	1	NP, AF, Cord blood, Placenta, neonatal serum, anal swab	Negative	
55.	Liao X et al (88)	1	NP , AF, Cord blood, Placenta	Negative	
56.	Xiong X et al (68)	1	NP, AF, BM, rectal swab	Negative	
57.	Wang S et al (59)	1	NP , AF, Cord blood, BM	NP +ve at 36 h Negative in all others	1/1
58.	Zamaniyan M et al (60)	1	NP, Cord blood, AF	NP +ve at D2, D4, D6 AF +ve	1/1
59.	Kirtsman M et al (30)	1	NP, Placental, Stool, BM Neonatal plasma D4	NP +ve at D1, D2, D7 Placenta +ve Stool +ve D7, BM +ve	1/1
60.	Lyra J et al(23)	1	NP	+ve at 0 h,D2, D7	1/1
61.	Algorroba G et al (29)	1	NP	Negative at 0 h,D2, D7	
62.	Zeng H et al (52)	6	NP Neonatal blood	NP negative; Elevated IgM and IgG (2); Elevated IgG ,normal IgM (3)	Cytokine IL-6 elevated in all infants
63.	Peng Z et al(38)	1	NP, NBAL Fluid, Sputum, Urine	Negative	
64.	Groß R et al (40)	2	BM, NP	Both NP +ve (>D7) , BM +ve (1)	2/2,1/2
65.	Liu Y et al (85)	10	Fetal blood	Negative	
66.	Hosier H et al(27)	1	Placenta, cord blood	Both +ve	1/1; D& E at 22 weeks
67.	Pulinx B et al (72)	2	AF, Placental	Both +ve	2/2, DCDA twin at 24 weeks
68.	Mulvey J et al (33)	5	Placenta	Negative	
69.	Yu N et al (90)	2	AF in mid pregnancy	Negative	

AF= Amniotic fluid; NP= Neonatal Pharyngeal/throat swab; BM= Breast milk; NBAL= Non-bronchoscopic broncho-alveolar lavage fluid

Table-3: Vertical Transmission (Pooled result)

SAMPLE Tested by RT-PCR for SARS-CoV-2	Number of studies	Number Tested	Number Positive	Pooled Percentage

Neonatal Naso-pharyngeal swab	**64**	**1193**	**48**	**4.02%**
Placenta ± Membranes	**19**	**130**	**9**	**6.9%**
Amniotic fluid	**18**	**42**	**4**	**9.5%**
Breast milk	**10**	**56**	**3**	**5.3%**
Cord blood/ plasma	**15**	**55**	**3**	**5.4**
Other neonatal samples -Anal swab -Urine	 **11** **3**	 **52** **9**	 **5** **0**	**9.6**
Neonatal serology				
IgM	**5**	**11**	**(Elevated) 3**	**27**
IgG	**4**	**10**	**(Elevated) 6**	**60**

Table-4: Fetal outcome

Serial number	Author (reference)	Number of neonates from SARS CoV-2 +ve pregnancies	Fetal complications	Mode of delivery (n)	Birth weight in grams	Preterm delivery (n)	Still birth(n)	Comments
1.	Chen H et al (50)	9	FD (2) PROM (1)	CS (9)	1880-3730	Yes (2)	-	
2.	Fan C et al (51)	2	-	CS (2)	3440-2890	Yes (1)	-	
3.	Zeng H et al (52)	6		CS (6)			-	
4.	Pulinx B et al (72)	2	IUFD (1)	VD (2)		Yes (1)	Yes (1)	DCDA twins
5.	Liu W et al (41)	3	FD (1); MSA ; chorioamnionitis	CS (2) VD (1)	3250-3670	-	-	
6.	Zhu H et al (42)	10	FD (6), PROM (3), MSA (n=2)	CS (7) VD (2)	SGA-2 LGA/Normal-8	Yes (6)	-	
7.	Chen Y et al(43)	4	DFM (1) Ab.CTG (1)	CS (3) VD(1)	3050-3550	-	-	
8.	Gildof S et al (53)	2	-	CS (2)	2680,2160	Yes (2)	-	
9.	Khan S et al (66)	3	-	VD (3)	2890-3750	Yes (1)	-	
10.	Khan S et al (24)	17	PROM	CS (17)	2300–3750 <2700-3	Yes (5)	-	
11.	Zeng L et al (36)	33	PROM (3); FD (1)	VD (7); CS (26)	SGA (3) 1580-3360	Yes(4)	-	
12.	Breslin N et al (44)	18	Ab.CTG (3)	CS (8); VD (10)		Yes (1)	-	
13.	Qiancheng X et al (89)	23	-	CS (17) VD (5)	3130 (2915–3390)	Yes(1)	-	
14.	Hantoushzadeh S et al(26)	7	IUFD (3)	CS (4)	1180-3200	Yes (3)	Yes (1)	
15.	Zambrano L et al (69)	1	-	VD(1)	1500	Yes(1)	-	
16.	Pereira A et al (75)	23	-	VD (18) CS (5)	-	Yes(2)	-	
17.	Savasi V et al (91)	57	-	VD (34) CS (22)	3160 (840-4350)	Yes(12)	-	
18.	London V et al (20)	56	DFM (1) IUFD (17 wks) (1)	CS (22) VD (33)	-	Yes(12)	-	
19.	Lokken E et al(35)	8	FD (3)	CS (3) VD (5)	-	Yes (1)	Yes(1)	
20.	Yan J et al (17)	99	FD (9); IUGR (2) PPROM (6)	CS (85) VD(14)	3108±526	Yes (21)	-	
21.	William R et al (25)	64	IUGR(2), PPROM (1)	CS (24) VD(8)	2403.3±858	Yes (19)	-	

22.	Knight M et al (16)	266	Miscarriage (4); Fetal compromise (37)	CS (156) VD (106)	-	Yes (66)	Yes (3)	
23.	Kayem G et al (18)	181	Fetal loss <21 weeks (5)	CS (87) VD (94)	-	Yes (50)	Yes (2)	
24.	Nayak A et al (19)	134	Miscarriage (6)	CS (67) VD(67)	>2500 (92) <2500 (39)	Yes (38)	Yes (3)	
25.	Prabhu M et al (45)	70	PROM and Ab.CTG (4)	CS (32) VD(38)	3060.9-3149.6	Yes (11)	Yes (1)	
26.	Li N et al (70)	17	FD(1) ; PROM (1)	CS (14) VD(2)	3078.2 ± 565.0	Yes (4)	-	
27.	Cao D et al (71)	11	FD (3); PROM (4)	CS (8) VD(2)	2050-3800	Yes (4)	-	
28.	Hu X etal(37)	7	PROM (1)	CS (6) VD(1)	3180-3670		-	
29.	Yang P et al (62)	7	-	CS(7)	2096 ± 660	Yes (4)	-	
30.	Yang H et al (95)	13	-	CS (9) VD(4)	3063.2 ± 536.4	-	-	
31.	Patane L et al (34)	2	-	VD (1) CS(1)	2660, 2686	Yes(1)	-	
32.	Ferrazzi E et al (21)	42	-	CS (18) VD(24)	2730-3226	Yes(11)	-	
33.	Govind A et al (46)	9	Ab.CTG (1)	CS (8) VD(1)	1200-4300	Yes(2)	-	
34.	Nie R et al (73)	28	FD (4); IM (1); PROM (3)	VD (5); CS (22)	2988(502)	Yes (10)	-	
35.	Yin M et al (74)	17	IM (3)	VD (4); CS (13)	2580-3035	Yes (5)	-	
36.	Doria M et al (48)	10	IUGR (6)	CS (6) VD(4)	2350–3380	-	-	
37.	Liu Y et al (85)	10	FD(3), PROM (1)	CS(10)		Yes (6)	Yes(1)	
38.	Perrone S et al (49)	4	IUGR(1)	VD(4)	2290-3790	-	-	
39.	Romagano M et al (63)	7	-	CS(7)	1290-2580 (AGA)	Yes (7)	-	
40.	Cooke W et al (64)	2	-	CS (2)	1530,1400	Yes(2)	-	
41.	Lowe B et al (47)	1	Ab.CTG (1)	VD (1)		-	-	
42.	Blauvelt C (65)	1	-	CS(1)	1880	Yes (1)	-	
43.	Kirtsman M et al (30)	1	-	CS(1)	2930	Yes (1)	-	
44.	Lyra J et al(23)	1	-	CS(1)	3110	-	-	
45.	Li Y et al (39)	1	FD(1)	CS(1)		Yes (1)	-	
46.	Dong L et al (54)	1	-	CS(1)	3120	Yes (1)	-	
47.	Wang X et al (55)	1	FD (1)	CS(1)	1830	Yes (1)	-	
48.	Alzamora M et al (56)	1	-	CS(1)	2970	-	-	
49.	Huang J et al (67)	1	-	VD(1)		-	-	
50.	Kalafat E et al (57)	1	-	CS(1)	2790	Yes (1)	-	
51.	Xiong S et al (68)	1	PROM	VD(1)	3070	-	-	
52.	Wang S et al (59)	1	FD (1)	CS(1)	3205	-	-	
53.	Zamaniyan M et al (60)	1	-	CS(1)	2350	Yes (1)	-	
54.	Song L et al (61)	1	-	CS(1)	3630	Yes (1)	-	
55.	Lee D et al (58)	1	-	CS (1)	3130	-	-	

56.	Iqbal S et al (87)	1		VD(1)				
57.	Vivanti A et al (22)	1	Ab.CTG (1)	CS(1)	2540	Yes (1)	-	

FD= Fetal distress; Ab.CTG= Non-reassuring/ Pathological fetal cardio-tocography ; PROM= Pre-labor rupture of membrane ; Fetal demise= IUFD ; MSA= Meconium stained amniotic fluid; DFM= Decreased fetal movement; IM= Induced miscarriage; CS= Caesarean Section; VD= Vaginal delivery; AGA= Appropriate for gestational age; IUGR= Intrauterine growth restriction; SGA= Small for gestational age; LGA= Large for gestational age

Table-5; Fetal outcome (Pooled data)

Number of studies	Outcomes	Indications	
Preterm birth 42 studies	Preterm birth=325 Term birth=930	Maternal indications due to COVID-19=140 Spontaneous preterm labor=23 Fetal compromise/ distress=17 Unknown/others	OR=0.12 Total Preterm birth in 25.4% of total births Spontaneous preterm birth-1.8% of total births
Mode of delivery 57 studies	CS=750 VD=505	Maternal COVID-19 related conditions most common indication	OR=2.20
Still birth 7 studies	Still birth=13	Defined as the number of fetal death beyond 24 weeks per 1000 total births	Stillbirth rate= 0.9

Table-6; Neonatal outcome

Serial number	Author (reference)	Number of neonates	APGAR score (1 minute, 5 minute)	Neonatal symptoms (n)	Neonatal ICU admission (n)	Neonatal death	Neonatal RTPCR status
1.	Alzamora M et al (56)	1	6, 8	Respiratory difficulty Cough on D6	(1) [due to maternal sedation]	-	**Negative**
2.	Chen H et al (50)	9	8-10	-	-	-	
3.	Fan C et al (51)	2	9-10	Fever, abdominal distension, lymphopenia (1) Mild NP, lymphopenia (1)	-	-	**Negative**
4.	Li Y et al (39)	1			-	-	
5.	Dong L et al (54)	1	9-10	-	-	-	
6.	Zeng H et al (52)	6	9-10		-	-	
7.	Pulinx B et al (72)	2			-	-	
8.	Liu W et al (41)	3	8-10	decreased responsiveness and decreased muscle tone	-	-	**Negative**
9.	Zhu H et al (42)	10	8-10 in all 7-8 in 1	Shortness of breath (6), vomiting (1), rash (1), Fever (3)	1	YES (1)	**Negative**
10.	Wang X et al (55)	1	9-10	-	1	-	
11.	Liu Y et al (85)	10	10	-	-	-	
12.	Chen Y et al (43)	4	8-9 (3) 7-8 (1)	Edema (2), Rash (2),Dyspnea and TTN (1)	1	-	**Negative**
13.	Gidlof S et al (53)	2	9-10	Breathing problem, cyanotic attack(1)			**Negative**

14.	Huang J et al (67)	1	8-9	-	-	-	
15.	Iqbal S et al (87)	1	9	-	-	-	
16.	Lee D et al (58)	1	9-10	-	1	-	
17.	Khan S et al (66)	3	9-10	-	-	-	
18.	Khan S et al (24)	17	9-10 (16) 7-9 (1)	NP (5)	-	-	**2 out of 5 with pneumonia were +ve**
19.	Xiong S et al (68)	1	9-10	-	-	-	
20.	Wang S et al (59)	1	8-9	Vomiting, lymphopenia, abnormal liver enzyme levels	1	-	**Negative**
21.	Zeng L et al (36)	33	Preterm newborn-3,4 Term - Normal	RD (4=3 -ve, 1+ve). Cyanosis, feeding intolerance (3=2-ve,1+ve) Fever in 2, NP in 3 of the 3 +ve Lethargy, fever(1) lethargy, fever, NP, leukocytosis, lymphocytopenia, vomiting (1) Preterm- Neonatal RDS, NP, lymphocytopenia (1)	3	-	**+ve**
22.	Zamaniyan M et al (60)	1	8,9	Fever (1)	-	-	**+ve**
23.	Breslin N et al (44)	18	>7, >9	RD/ sepsis (1)	Yes (3)	-	**+ve**
24.	Qiancheng X et al (89)	23	10,10		-	-	
25.	Hantoushzadeh S et al(26)	4	7 (2), 9-10	NP, lymphopenia (1)	Yes (1)	-	**+ve**
26.	Shanes E et al (31)	15	7(8),8(7); 9				
27.	Zambrano L et al (69)	1	-	-	Yes (1)	-	
28.	Pereira A et al (75)	23		RD(1); Hemolytic anaemia (1)	Yes(2)	-	**Negative**
29.	Savasi V et al (91)	57	10	-	Yes(9)	-	
30.	London V et al (20)	55	-	-	-	-	
31.	Song L et al (61)	1	8,9	-	-	-	
32.	Lokken E et al (35)	8					
33.	Yan J et al (16)	99	9,10	Neonatal asphyxia (1)	Yes(47)	YES (1)	**Negative**
34.	William R et al (25)	32	7.9±1.7	-	Yes (21)	-	
35.	Knight M et al (16)	262		Neonatal encephalopathy (1)	Yes (67)	YES (2)	**Unclear whether symptomatic neonate was +ve**
36.	Kayem G et al (18)	181		-	Yes (37)	YES (1)	
37.	Nayak A et al (19)	131	7–10 (128) <7 (6)	Neonatal seizures (1), MAS (1)	Yes (24)		**Unclear whether symptomatic neonates were +ve**
38.	Prabhu et al (45)	73	9	-	Yes (13)	-	**Negative**
39.	Vivanti A et al (22)	1	4,7	irritability, poor feeding, axial	Yes (1)	-	**+ve**

				hypertonia and opisthotonos			
40.	Li N et al (70)	17	9.6 ± 0.5, 10	-	-	-	
41.	Cao D et al (71)	11	8-9,10	-	-	-	
42.	Hu X et al (37)	7	7-8,8-9	-	-	-	
43.	Yang P et al (62)	7	8-9,9-10	Vomiting(1), RD (2)	Yes (5)	-	**Negative**
44.	Yang H et al (95)	13	9,10	Fever(1)	-	-	
45.	Patane L et al (34)	2	9,10	Mild feeding difficulty (1)	Yes(1)	-	**+ve**
46.	Ferrazzi E et al (21)	42	<7 (2)	Gastrointestinal symptoms, RD (2)	Yes(3)	-	**+ve**
47.	Govind A et al(46)	9	<7 (2)	NP (1)	Yes(1)	-	**+ve**
48.	Nie R et al(73)	28	8-10, 10	Pulmonary infection (1)	Yes (1)	-	**+ve**
49.	Yin M et al(74)	17	8,9	-	-	-	
50.	Doria M et al (48)	10	9,10	-	-	-	
51.	Perrone S et al (49)	4	9,10	-	-	-	
52.	Romagano M et al (63)	7	1-7,4-9	RD	Yes(7)	-	**Negative**
53.	Cooke W et al (64)	2	1-6, 3-8	Bowel perforation D6(1)	Yes(2)	-	**Negative**
54.	Lowe B et al (47)	1	9,9	-	-	-	
55.	Blauvelt C (65)	1	4,8	RD	YES	-	**Negative**
56.	Kirtsman M et al (30)	1	9,9	-		-	
57.	Lyra J et al(23)	1	8,9	-	-	-	

RD= Respiratory distress; MAS= Meconium aspiration syndrome; TTN= Transient Tachypnea of Newborn; NP= Neonatal Pneumonia

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Title Page

Article Title- COVID-19 in pregnancy; The fetal perspective- a systematic review

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Title: COVID-19 in pregnancy; The fetal perspective- a systematic review

Abstract:

Objective: We aimed to conduct a systematic review of the available literature to determine the effects of confirmed cases of COVID-19 in pregnant women from the fetal perspective by estimation of mother to child transmission, perinatal outcome and possible teratogenicity.

Methods
Data sources: Eligible studies between November 1, 2019 and August 10, 2020 were retrieved from PubMed, Embase, LitCovid, Google Scholar, EBSCO MEDLINE, CENTRAL, CINAHL, MedRXiv, BioRXiv, and Scopus collection databases.

Study eligibility criteria: English language case reports, case series and cohort studies of SARS-CoV-2 confirmed pregnant women with data on perinatal outcome, congenital anomalies and mother to child transmission were analysed. 38 case reports, 34 cohort and case series describing 1408 neonates were included for evidence acquisition of mother to child transmission. 29 case reports and 30 case series and cohort studies describing 1318 fetuses were included for the evaluation of perinatal outcome and congenital anomalies.

Results: A pooled proportion of 3.67% neonates had positive SARS-CoV-2 viral RNA nasopharyngeal swab results and 7.1 % had positive cord blood samples. 11.7% of the placenta, 6.8% of amniotic fluid, 9.6% of fecal and rectal swabs, and none of the urine samples were positive. The rate of preterm labor was 26.4% (OR=1.45, 95% CI- 1.03 to 2.03 with p = 0.03) and Cesarean delivery (CS) was 59.9% (OR=1.54, 95% CI- 1.17 to 2.03 with p = 0.002). The most common neonatal symptom was breathing difficulty (1.79%). Stillbirth rate was 9.9 per 1000 total births in babies born to COVID-19 mothers.

Conclusion: Chances of mother to child transmission of the SARS-CoV-2 virus is low. The perinatal outcome for the fetus is favorable. There is increased chances of CS but not preterm delivery.The stillbirth and neonatal death rates are low. There are no reported congenital anomalies in babies born to SARS CoV-2 positive mothers.

Keywords: COVID-19, SARS-CoV-2, mother to child transmission, perinatal outcome, congenital anomaly

KEY MESSAGE:

A. What is known about the subject –
Studies specifically analyzing all aspects of the fetus in SARS-CoV-2 positive mothers are not available. There is currently a lack of large studies depicting fetal outcomes and they are unlikely to be available in the near future as individual centers are still reporting cases in small numbers. There are some systematic reviews reporting maternal outcomes, vertical transmission and neonatal outcomes involving a lesser number of

pregnancies separately but aspects like fetal complications and teratogenicity are not adequately reported.

B. What this study adds –

In this systematic review, we searched multiple databases to include evidence until 10th August 2020. 80 studies were included to collect data on more than 1400 fetuses. The confirmed congenital transmission rate was found to be 9/1408 (0.63%). The risk of caesarean delivery is significantly higher in SARS-CoV-2 positive mothers but there is no significantly higher risk of prematurity. There is evidence of fetal distress, and neonatal respiratory symptoms in COVID-19 mothers but stillbirth is low. There are no associated congenital anomalies.

INTRODUCTION

Novel coronavirus infection and associated coronavirus disease-2019 (COVID -19) pandemic has changed our lives forever and has compelled us to reconsider almost everything we have long taken for granted. Among the different coronaviruses severely affecting human species, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2 are significant, causing MERS, SARS, and COVID-19 respectively. SARS-CoV-2 strains show significant sequence homology to SARS-CoV and MERS-CoV **[1]**. As the pandemic evolved, there were significant advances in our knowledge about various aspects of the COVID-19 including epidemiology, clinical features, transmission, detection, and management modalities. Discoveries along the process of evolution are still contributing to our management practices.

There were concerns regarding the maternal and fetal effects since the beginning of the pandemic. The earlier evidence of COVID-19 in pregnancy pointed towards pregnancy being considered as low risk for the disease and no difference in disease behavior in pregnant and non-pregnant women was reported **[2]**. On the contrary, a newer study involving pooled data from more than 8000 women in the USA pointed towards a significantly higher rate of intensive care unit (ICU) admission [adjusted relative risk (aRR) = 1.5] and need for mechanical ventilation (aRR = 1.7) in pregnant women as compared to non-pregnant women, even when adjusted for race/ethnicity and underlying comorbid conditions **[3].** Similar findings were reported from other studies from the US and Sweden **[4-6].**

However, these studies did not specify adequately fetal effects resulting from congenital or neonatal infection in SARS-CoV-2 positive mothers and consequent perinatal outcomes. Evidence of COVID-19 specifically focusing on fetal and neonatal outcomes are lacking. Most of the reported literature have smaller studies. Previous systematic reviews focusing on the outcomes of all coronaviruses have reported a higher risk of pre-eclampsia, preterm birth, miscarriage, and perinatal death.

Through this article, we want to analyze the published evidence on the fetal perspective of COVID-19 infection concerning mother to child transmission (congenital or neonatal infection) and perinatal outcome through a systematic review. This will aid in alleviating uncertainties faced while doing patient counseling and help in subsequent management during these testing times.

METHODS

Search strategy: A systematic search of PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus electronic database was done. Medical subject handling terms (MeSH) and free text term keywords like vertical transmission, perinatal outcome, fetal, neonate, newborn, pregnancy were used in combination with COVID-19, 2019-nCoV, SARS-CoV- 2 to search for data from 1st November 2019 till 10th July 2020. Thereafter manual update was done on weekly basis till 10th August 2020. The references of relevant studies were also searched.

The keywords detail and full search strategy used in each of PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus electronic database are as follows: Both medical subject headings (MeSH) and key-words: "2019 novel coronavirus infection" OR "COVID-19" OR "COVID19" OR "coronavirus disease 2019" OR "nCoV infection" OR "2019-nCoV" OR "2019 novel coronavirus" OR "2019 coronavirus" OR "novel coronavirus" OR (2019 AND coronavirus) OR "SARS CoV-2" OR "SARS CoV2" AND "vertical transmission" OR "fetal outcome" OR "perinatal outcome" OR "neonatal outcome" OR "pregnancy" OR "congenital infection" OR "mother-to-child transmission" OR "(transmission AND vertical)" OR "(transmission AND fetomaternal) " OR "teratogenicity".

Selection criteria: The search consisted of only English language articles (original English articles and other language articles with available English translation) including case reports, case series, and letters to editors containing case information. After a thorough screening, no randomized clinical trials or cohort studies were found.

Inclusion criteria: The studies fulfilling all of the following criteria (1,2 and 3) were included for review.

1- Studies reporting pregnant women with confirmed COVID-19 who had delivered.

2- Studies containing the results of the SARS-CoV-2 test [including reverse transcriptase-polymerase chain reaction (RT-PCR) and serological tests] in both mothers and newborns samples.

3- Studies that present the out-come of vertical transmission or congenital transmission or neonatal transmission or the perinatal outcome or congenital anomaly.

Exclusion criteria: Exclusions consisted of studies in pregnant women yet to deliver, duplicated studies, review articles, articles in languages other than English, studies where

infection in mothers is not confirmed, or where neonatal testing was not done. Conference abstracts, expert opinions, and critical appraisals were also excluded.

Both the authors (RD, SSK) reviewed all titles independently. The potential relevance of the studies to be included for review were agreed upon by discussion. Selected titles and abstracts were further screened between studies to reject overlap of cases.

Full-text copies of the selected papers were obtained and the relevant data regarding study characteristics, evidence of vertical transmission, and perinatal outcomes were extracted by the same two reviewers independently. In the case of individual case reports, if the same patient was included in more than 1 study with similar characteristics and findings, only the report with a larger number of patients was included. As far as possible, single case reports were cross-checked with other reports from the same location and hospital. If a case series included multiple locations, the individual reports from the same centers were excluded. Similarly, if the time-frame of the reported cases matched from the same center, the characteristics were compared to decide regarding the inclusion or exclusion from the study. Finally, studies were screened by assessing selection, comparability, and exposure for inclusion into evidence acquisition of mother to child transmission (congenital or neonatal transmission) and/or perinatal outcome measures **[Table-1a,1b].**

Study Outcomes

1. Mother to child transmission-

Evidence of mother to child transmission (congenital or neonatal transmission) is indicated by positive RT-PCR status in different samples like the neonatal nasopharyngeal swab, cord blood, amniotic fluid, breast milk, and placental tissue. Transmission of infection from mother to fetus generally includes transmission through germ cells or the placenta during pregnancy, via the birth canal during labor and delivery, and the postpartum period through breastfeeding or close contact. The transfer of microorganisms during pregnancy is seen with many of the common pathogens with resultant effects ranging from asymptomatic infection, intrauterine growth restriction, intrauterine death, and structural anomalies as a sequel of infection. Some pathogens like cytomegalovirus (CMV) or Zika virus produce mild to no symptoms in the pregnant patient but can cause congenital infection with severe consequences **[7].** Viruses specifically can be transmitted to the fetus via the maternal blood when it enters the placental villus, containing the fetal blood vessels, or by direct access to the placenta from the lower genital tract by ascending infection **[8].** Again even when transferred trans-placentally during the antenatal period, the specific timing of maternal infection can have different effects on the fetus. The first-trimester infection can cause severe structural anomalies whereas second and third-trimester infections are more likely to cause functional organ abnormalities **[9].**

Several factors are contributing to the concerns of mother to child transmission in Covid-19. It is known that the SARS-COV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors for entry into the cells. ACE-2 receptors are detected in various parts of the uterus, vagina, decidual cells, and placenta **[10-13].** Recently, the case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates has been published with a categorization of infection into confirmed, probable, possible, unlikely, and not infected groups **[14]**.

Congenital infection with intrauterine fetal death/stillbirth is **[14]**-

- confirmed from fetal tissue or autopsy material if the virus is detected by PCR from fetal or placental tissue or electron microscopic detection of the viral particle in tissue or viral growth in culture from fetal or placental tissue.
- a probable infection if the virus is detected by PCR in the surface swab from the fetus or placental swab on the fetal side.
- unlikely if it is positive in the maternal side of the placenta but fetal tissues are not tested and not present if it is not detected in fetal tissue in an autopsy.

Similarly, congenital infection in live-born symptomatic neonate is **[14]**-

- confirmed when the virus is detected by PCR in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or amniotic fluid collected prior to the rupture of the membrane.
- a probable infection when there is the detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) AND placental swab from the fetal side of the placenta in a neonate born via cesarean section before rupture of membrane or placental tissue.
- possible when there are anti-SARS-CoV-2 IgM antibodies in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or placental tissue but nasopharyngeal swab test at birth is negative.
- unlikely or absent when samples are negative within 12 hours of birth (nasopharyngeal swab, umbilical cord blood, or neonatal blood) and antibody testing is not done or negative, respectively.

If a live-born neonate has no clinical features of infection, congenital infection is **[14]**-

- confirmed by detection of the virus by PCR in cord blood or neonatal blood collected within the first 12 hours of birth.
- probable if the virus is detected by PCR in amniotic fluid collected prior to rupture of the membrane but no detection in umbilical cord blood or neonatal blood collected within the first 12 hours of birth.

- possible when there is anti-SARS-CoV-2 IgM in umbilical cord blood or detection of the virus by PCR in placental tissue but PCR in umbilical cord blood, amniotic fluid, and neonatal blood (<12hours of life) is negative.

Furthermore, infection acquired intrapartum in a symptomatic neonate is confirmed if the virus is detected by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age AND alternate explanation for clinical features excluded **[14].**

Intrapartum neonatal infection in asymptomatic neonate is confirmed by detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age **[14]**.

Postpartum infection is confirmed if a neonate shows symptoms beyond 48 hours of life and the nasopharyngeal swab is positive beyond 48hours which was negative at birth**[14]**.

If a neonate is born with a specific structural sequel of an infection, intrauterine infection is a probability. The probability of infection also depends on the presence of the agent in the genital tract and time taken from exposure to detection by definitive tests to differentiate between intrapartum and postpartum infection. Furthermore, the sensitivity of RT-PCR testing is different for detecting SARS-CoV-2 in different samples. Therefore, it is rational to test samples from multiple sites to improve detection and reduce false-negative cases **[9, 15].**

2. Perinatal outcome

Perinatal outcome measures included fetal outcomes like fetal complications in SARS-CoV 2 positive pregnant women, gestational age at delivery (preterm delivery), mode of delivery, birth weight, and stillbirth. The neonatal period is defined as the time period from birth until the end of the first 28 days of life. Events in the early neonatal period (first 7 days) usually are related to the pregnancy more significantly and it is also included in the definition of the perinatal period. In this review, we have assessed the neonatal outcomes using the APGAR score at 1 minute and 5 minutes of life, neonatal symptoms, admission into neonatal intensive care unit (ICU), and neonatal death, as the parameters. An APGAR score of less than 7 at 1 minute and 5 minutes after birth in a newborn is defined as a low APGAR score in this study **[16].** Any outcome measures not explicitly mentioned were considered not to have been reported.

- Fetal distress (FD) is assessed during labor by non-reassuring or pathological cardiotocographic (CTG) findings and meconium-stained amniotic fluid **[17, 18]**. For this research, studies reporting FD, abnormal or non-re-assuring or pathological CTG, fetal compromise, meconium-stained amniotic fluid are included

under FD. Other fetal complications were pre-labor rupture of membranes and preterm prelabor rupture of membranes.

- Preterm delivery is defined as delivery of a viable product of conception before 37 completed weeks of gestation.
- Delivery can be vaginal delivery (including instrumental) and by caesarean section (CS). For this research, instrumental vaginal deliveries and normal vaginal deliveries were considered together (VD).
- Both the Royal College of Obstetrics and Gynecology and the American College of Obstetricians and Gynecologists have adopted the definition of Intrauterine growth restriction (IUGR) is defined as an estimated fetal weight less than 10th percentile. The term is IUGR has been used interchangeably with Small for gestational age (SGA). SGA is a term commonly used for a neonate with birth weight less than 10 percent **[19,20].**
- For this research, stillbirth was considered as fetal death beyond 24 weeks of gestation, and stillbirth rate (SBR) is calculated as the number of stillbirths per 1000 total births.

Statistical analysis: Pooled proportions of categorical variables were calculated with percentage after obtaining the positive rates of each of the SARS-CoV-2 testing methods used, wherever applicable. Odds Ratio was calculated for the fetal outcome of preterm delivery and mode of delivery in the SARS-CoV-2 positive mothers from the pooled data (combining the studies where the control group of SARS-CoV-2 negative pregnant women was available) with 95% confidence interval and p values. The percentage of the most common variables were also calculated.

Public and patient involvement statement: This research is not “coproduced” with patients, carers or members of the public.

RESULTS

1. Mother to child transmission-

Search Results:

Out of 100 records selected for full-text review, 72 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. 38 studies were case reports containing 4 or fewer number of cases and 34 studies had 5 or more number of patients **(Figure-1).** Since evidence from randomized control trials were not available until the time of the search, 34 studies having 5 or more number of patients were considered for qualitative analysis **[21, 22].** However, the findings from the case reports were also noted. The majority of earlier studies were from China but later studies contained cases from the rest of the world **[Table-1a,1b].**

Table-1 (a): Analysis of the studies [Case series/ Cohort] -Supplimental material

Table-1 (b): Analysis of the studies [Case reports] -Supplimental material

Systematic review:

Tests for diagnosis of SARS-CoV-2 was done in a total of 1408 neonates. The most common type of sample tested was neonatal nasopharyngeal samples (NP swab) (67 out of 72 studies) followed by the placenta, amniotic fluid, and cord blood. In the majority, samples were taken from more than one site. In a few studies, the same type of sample was repeated at different intervals (e.g., NP swab and breast milk samples) **[Table-2].**

Table -2 Studies and type of samples -Supplimental material

i. Neonatal Nasopharyngeal swab

In our review, a total of 1388 neonates born to mothers with COVID-19 infection were tested by NP swabs. 51 neonates were found positive by the RT-PCR test constituting 3.67% of total pooled samples. **[Table-3a].**

Table-3 (a): Mother to child transmission-Test positive (Pooled result) - Supplimental material

The largest cohort study from the UK involved 427 pregnant women with COVID-19. 244 out of the 262 neonates were tested by NP swab. 6 of the neonates were positive for SARS-CoV-2 within 12 hours of birth and 6 more were positive after 12 hours of birth (12 out of 244; 4.9%) **[23].** Studies involving 181 women and 116 women in China showed 2 positive neonates out of 181 (2 out of 181; 1.1%) and no positive cases for SARS-CoV-2 in the other study **[24, 25].** An analysis of 141 women from a hospital in India showed that 3 of the 131 neonates were tested positive for SARS-CoV-2 by NP swab **[26].** In another study in a New York Hospital, 48 neonates born to 55 women were all tested negative on Day 0 of life **[27].** However, One Italian study found three infants positive by NP swab out of 42 tested within 48 hours after birth **[28].**

One recent case report revealed that RT-PCR was positive for SARS-CoV-2 in all of the samples for amniotic fluid, vaginal swab, blood, and non-bronchoscopic bronchoalveolar lavage fluid as well as NP swab and rectal swabs collected at 1 hour of life, and then repeated at 3 days and 18 days suggesting a trans-placental transmission **[29].**

As stated earlier NP swab positivity at different neonatal ages plays an important role in confirming or ruling out the viral transmission from a SARS-CoV-2 positive mother.

On further analysis of the positive samples, the congenital infection was confirmed in 5 live-born neonates, possible in 5 neonates, and probable in 2 neonates. Neonatal infection acquired intrapartum was confirmed in 2 neonates, probable in 5 neonates, and

possible in 14 neonates. Similarly, neonatal infection acquired postpartum was confirmed in 7 neonates and infection was unlikely in 1 neonate **[Table-3b].**

Table-3 (b): Analysis of evidence of congenital/ intrapartum/ postpartum transmission -Supplimental material

However, in a larger study, out of 12 neonates with positive NP result [6 within 12 hours of life and 6 at more than 12 hours of life], further analysis was not possible due to lack of followup swab results and unavailability of test results of other maternal samples like placenta and amniotic fluid **[23].**

ii. Amniotic fluid

In our review, 58 samples of amniotic fluid were tested in 19 studies with a positive result in 4 samples **[29, 30, 31]**. Congenital infection is confirmed in 2 of the studies in live-born neonates **[29, 30].** Congenital infection is also confirmed in a dichorionic, diamniotic (DCDA) twin expelled at 24 weeks by positive amniotic fluid result **[31].**

iii. Placenta

A total of 22 studies were identified in our review where the placenta was examined for the presence of SARS-CoV-2 or related pathological changes. A total of 111 placental samples were tested and 13 were found positive for SARS-CoV-2. PCR for SARS-CoV-2 RNA was positive from the placenta in two case reports where there were spontaneous miscarriage and dilatation and curettage respectively confirming a congenital infection **[32, 33].** In one of them, the umbilical cord was also positive for the virus, but the fetal organs were tested negative. The virus was confirmed to be localized mostly in the syncytiotrophoblastic cells of the placenta by immunohistochemistry for the SARS-CoV-2 spike protein as well as electron microscopy and it was identical to the typically locally isolated virus **[32].** In another study, electron microscopy showed the presence of the virus in the fetal side of the placenta. The virions were present in the mesenchymal core of the terminal villus and were demonstrated to be invading a syncytiotrophoblast and a microvillus. However, the neonate delivered at 28 weeks in this pregnancy was tested negative for the virus **[34].**

Evidence of probable mother to child transmission was obtained in another case where the newborn was found positive for the virus by nasopharyngeal swab, plasma, and stool samples along with the placenta **[35].** Similarly, confirmed congenital transmission of the virus was demonstrated by another study where SARS-CoV-2 was detected in amniotic fluid aspirated before the rupture of the membranes, vaginal swab, neonatal blood, bronchoalveolar lavage fluid, and neonatal swabs on repeated occasions at 1 hour, 3rd day and 18th day of life. The trophoblastic cells showed SARS-CoV-2 N protein on immunostaining **[29].**

Placental pathological examination showed an array of changes including vascular malperfusion, fibrin deposition, and chronic villitis, intervillositis, and villous infarctions in

our review. Two of these studies showed vascular malperfusion in 10 out of 20 placentas and 12 out of 15 placentas respectively but there were no assessments of placentas in these studies for the presence of SARS-CoV-2 infection. However, neonatal swabs were negative for the virus **[36, 37]**. Similar pathological changes were seen in another study involving five SARS-CoV-2 positive pregnant women but the placentas were negative for the virus on direct testing for SARS-CoV-2 **[38].** Chronic intervillositis was also seen in the pathological examination of the placentas of two women where the neonates were positive for SARS-CoV2 by nasopharyngeal swab testing **[39].** Examination showed severe chronic villitis in another case where there was a stillbirth at term but direct tests of fetal tissues and placenta did not show infection with the virus **[40].**

iv. Other samples

Various other samples were tested for SARS-CoV-2 by different studies. Anal swab, rectal swab, or fecal sample was positive in 9.6% of neonates in our study. The stool sample was positive in two of the studies on Day 2 and Day 7 of life **[35, 41].** The urine sample was tested in only 3 studies without any positive results **[42- 44].** Breast milk was tested by RT-PCR in 10 of the studies with a pooled positive rate of 5.3% (3 out of 56) **[35, 45- 53]**. In one of the studies, the breast milk sample was positive in 4 consecutive days coinciding with the maternal symptoms in one woman but it was negative in milk samples of another woman. Both the babies were positive by the nasopharyngeal swab test and were symptomatic **[52].** A vaginal swab was tested in 23 women with one positive result (4.3%) **[29].** Since IgM cannot cross the placenta, elevated IgM levels in the neonate indicate possible congenital infection, as seen in some of the neonates in this review **[54, 55]**. However, the assay of IgM for the detection of infection has significant false-positive results.

2. Perinatal outcome-

Search results:

Out of 73 records selected for full-text review, a total of 60 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. 31 studies qualified as case series/cohort and 29 studies contained 4 or fewer cases in our review **(Figure-2)**. No randomized control trials were available until the time of the search.

Systematic Review:

2.1 Fetal Outcomes:

i. Fetal complications in SARS-CoV-2 +ve pregnant women

In our review, a total of 30 studies reported any fetal effects excluding all pregnancy losses or intrauterine fetal deaths (IUFD) **[Table no-4].** The most commonly reported effect was fetal distress in 36 out of 1311 pregnancies (2.74%). In addition to fetal distress, some studies have reported non-reassuring or pathological cardiotocography (CTG) (11 out of 1311; 0.83 %), and some have mentioned meconium-stained amniotic fluid (3 out of 1311; 0.22%), both findings can also be considered as evidence of fetal distress **[29, 56- 62]**. In another study involving 262 deliveries, the fetal compromise was seen in 37 fetuses and an emergency caesarean section (CS) was done in 9 of them **[23].** Thus, the cumulative chance of fetal distress in pregnant women with a positive test for SARS-CoV-2 is 6.63%.

Premature rupture of membrane (PROM) was reported in 42 pregnancies from 13 studies and Preterm PROM was reported in (PPROM) in 14 pregnancies **[24, 41, 42, 45, 50, 57, 60, 63-70].** Intrauterine growth restriction (IUGR) was reported in 12 fetuses in 5 studies **[24, 63, 65, 71, 72].** The highest number of IUGR fetuses was reported in 6 out of 10 fetuses in another study **[71]**. Besides, small for gestational age was reported in another study in 2 out of 10 fetuses **[57].** Chorioamnionitis was reported only in one study involving 3 fetuses **[5].**

Table-4: Fetal outcome- Supplimental material

ii. Mode of delivery

Mode of delivery was available for a total of 1311 out of which 8 were twin pregnancies. 761 (60%) delivered by CS 506 (40%) by VD out of 1267 pregnancies in case series. In case reports, out of 44 deliveries, 25 were CS (56.8%) and 19 (43.2%) were VD bringing the percentage of CS to 59.9% and VD to 40.1% in the pooled data. **[Table no-5].** Few studies in our data compared the CS in the SARS-CoV-2 positive pregnant women to negative controls comprising 122 CS in the positive group out of 233 and 650 CS in the control group out of 1562 in the pooled data. ODDs Ratio (OR) for CS in SARS-CoV-2 positive mothers is 1.5421 [95% CI- 1.1701 to 2.0324] and P = 0.0021. which is statistically significant **[26, 60, 66, 73].**

CS was the only mode of delivery in the majority of early published case reports as in the early days of the pandemic, elective CS delivery was the mode preferred by most of the countries for maternal indications **[29, 30, 35, 44, 45, 48, 49, 51, 54, 55, 64, 74-84].** As the pandemic progressed, favorable outcomes were reported from vaginal delivery by many studies **[50, 62, 72, 85- 87].** It was also demonstrated that the chances of the virus being present in the vaginal fluid is very remote. In the later and larger case series, CS deliveries were only done for obstetrical indications **[26].** In a study involving 134 deliveries, there were 67 CS and 67 vaginal deliveries. The rate of CS was not statistically different in women with positive SARS-CoV-2 as compared to negative pregnancies **[26].** In yet another study, there were significantly higher rates of CS deliveries in cases (14 out of 16) as compared to the control group (57 out of 121) ($p < 0.001$) but there was no

difference in the groups with regards to chronic illnesses or pregnancy complications **[66].** However, when done for maternal COVID-19 indications, the rate of cesarean was found to increase with the severity of the disease **[25]**. In another study, out of 41 CS deliveries, 12 were for COVID-19 symptoms without other obstetrical indications [4 with severe symptoms and 8 with mild/moderate symptoms] **[65].**

In the largest study in the UK, the CS delivery was seen in 156 women and vaginal birth was seen in 106 women from a total of 262 births. The indications of CS were maternal compromise (27%), fetal compromise (24%), failed induction of labor or failure to progress (19%), other obstetric reasons (16%), prior CS (10%), and maternal request (4%) **[23]**. Maternal COVID -19 related conditions were predominant indications in another larger study reporting CS for COVID-19 pneumonia in (33 out of 85), previous CS (16 out of 85), fetal distress (9 out of 85), and failure to progress in 5 out of 85 patients **[24]**. Many other studies similarly reported maternal condition requiring delivery as the commonest indication for CS **[25, 28, 81]**.

Table-5: Perinatal outcome (Pooled data)- Supplimental material

iii. Preterm Delivery

In our study, the outcome of preterm delivery was reported in a total of 43 studies involving 1318 fetuses out of which 330 out of 1273 neonates in the case series and cohort (25.9%) and 19 out of 45 neonates in the case reports (42.2%) were delivered preterm. The pooled Preterm birth was seen in 26.4% of total births **[Table no- 5].** However, the majority of them were elective deliveries to improve maternal respiratory conditions related to COVID-19. Spontaneous preterm delivery was only seen in 1.8% of neonates. The other indications included the preterm pre-labor rupture of membranes. In a substantial number of studies, data regarding the indications were not found. Few studies in our data compared the preterm delivery in the SARS-CoV-2 positive pregnant women to negative controls comprising of 52 preterm deliveries in the positive group out of 220 and 267 preterm deliveries in the control group out of 1520 in the pooled data. ODDs Ratio (OR) for preterm delivery in SARS-CoV-2 positive mothers is 1.4526 [95% CI- 1.0360 to 2.0366] and p = 0.0304 **[26, 60, 66].**

In a study involving 134 deliveries in COVID -19 patients, preterm delivery was reported in 38 pregnancies with positive SARS-CoV-2 and 239 out of 836 SARS-CoV-2 negative deliveries, which was not significantly different **[26]**. A similar report was seen in another study where 4 preterm deliveries were seen out of 17 SARS-CoV-2 confirmed group as compared to 7 out of 121 in the control group **[66]**. In another study, out of a total of 25 preterm deliveries, iatrogenic preterm delivery was done in 12 and 13 were spontaneous preterm deliveries **[65].**

Furthermore, comparing the outcomes of COVID-19 pregnancies with different disease severity involving 181 pregnant women, preterm delivery was seen in 13 out of 123 (10.6%), 14 out of 29 (48.3%), and 23 out of 29 (79.3%) in women with non-severe,

oxygen-requiring, and critical COVID-19, respectively. Delivery before 32 weeks was highest in 48.3% of women in the critical COVID-19 group. In severe disease, urgent delivery is required to stabilize the maternal condition, even when it results in iatrogenic preterm delivery **[25]**.

iv. Birth weight

In our review, birth weight was missing in many studies and only the mean weight of the babies was mentioned in some of the series. IUGR was reported in 4 studies in 11 babies **[24, 63, 71, 72].** Also, SGA was found in 2 studies in 5 babies **[41, 57].** A maximum of 6 babies had IUGR in one study but they were described as mild **[71].**

v. Miscarriage and stillbirth

Stillbirth was seen in 13 fetuses in 8 studies in our review and seven were second-trimester miscarriages **[23, 25, 26, 31, 40, 60, 69, 75] [Table no-5].** 3 intrauterine deaths were observed in one of the studies which reported maternal deaths due to COVID-19 **[75].** Similarly, we found 15 spontaneous miscarriages, and 4 induced miscarriages reported in 5 studies **[23, 25, 26, 46, 68].** Induced miscarriages were done on maternal request in both studies **[46, 68].** Among the spontaneous miscarriages, 6 were seen in 141 pregnancies in one study and 5 in 181 pregnancies in another study **[25, 26].** In one of the studies, there were 3 stillbirths. However, the causes of these 3 stillbirths reported, were not related to COVID-19 in the mother **[23].**

2.2 Neonatal Outcomes:

Table-6: Neonatal outcome- Supplimental material

i. Neonatal symptoms

The most common neonatal symptoms were respiratory problems reported as respiratory distress, shortness of breath, respiratory difficulty, dyspnea, and breathing problems **[28, 41, 52, 57- 59, 65, 70, 76, 78, 81, 82, 84].** Respiratory distress was the most common symptom reported in 14 neonates but the test for SARS-CoV-2 was positive in only 4 neonates and negative in 8 **[28, 41, 59, 65, 81, 82, 84].** Pneumonia was seen in 5 neonates who were positive for SARS-CoV-2 and 4 neonates who were negative **[41, 48, 61, 64, 75].** Although usually respiratory symptoms are seen more in preterm babies due to pulmonary immaturity, in a single case report there were no neonatal complications in a SARS-CoV-2 positive mother who delivered a preterm baby at 29 weeks 5 days by emergency CS for maternal indications **[88].**

Diffuse bilateral granular and hazy opacities in chest radiograph and thickened lungs on x-ray were found in two neonates but the neonatal test for SARS-Cov-2 was negative in both of them **[51, 84].** In another SARS-CoV-2 +ve, newborn chest X-ray was consistent

with pulmonary infection, 53 hours after birth **[68].** In another study, neonatal symptoms are extensively described. The most common first clinical symptom in the neonates of SARS-CoV-2 Positive women was shortness of breath (n=6), followed by gastrointestinal symptoms like feeding intolerance, bloating, refusing milk, and gastric bleeding (n=4). Other symptoms included fever, rapid heart rate, and vomiting. Chest radiographic abnormalities included infections (n=4), neonatal respiratory distress syndrome (n=2), and pneumothorax (n=1). Another preterm baby suffered from frequent oxygenation fluctuations and thrombocytopenia and was cured 15 days later **[57].** It was reported in yet another study that most of the complications in neonates were a result of prematurity (often iatrogenic) rather than SARS–CoV-2 infection **[41].** Other presentations in SARS-CoV-2 positive neonates included fever, cyanosis, lethargy, irritability, poor feeding, axial hypertonia, opisthotonus, and feeding difficulties **[29, 39, 41].**

ii. APGAR Score

In our review, a total of 9 studies have reported a low APGAR score among babies born to SARS-CoV-2 positive mothers **[26, 28, 29, 41, 61, 78, 82-84].** Seven of the neonates were very preterm or preterm and were SARS-CoV-2 negative. The APGAR score in these is likely to be due to pulmonary immaturity **[26, 28, 29, 78, 82-84].** Two other babies were term deliveries and tested positive for SARS-CoV-2 **[41, 61].** However, another study reported low APGAR scores of 0–3 in 2 babies of COVID positive mothers and 15 babies in COVID negative mothers, indicating no statistically significant difference **[26].**

iii. ICU admissions

Admission to the neonatal ICU was done for various reasons. The majority of admissions were for observation and isolation. Neonates admitted due to complications of prematurity constitute another higher portion of the neonates. In a study, out of a total of 24 ICU admissions, it was found that 16 babies were admitted due to low birth weight, 2 for low APGAR score, and 6 others for other uncommon reasons like ABO incompatibility **[26].** In another study, it was found that rates of admission to ICU increased with the severity of the disease in the mother **[25].** In our review, ICU admissions for suspected or confirmed neonatal sepsis was reported in 6 neonates out of which Enterobacter and Respiratory syncytial virus was found in 2 neonates.The culture was negative for 4 others **[35,41,51,52,59,70].**

iv. Neonatal death

Neonatal death was reported among 7 neonates in 5 studies **[23-25, 57, 75]**. It was unclear whether COVID-19 in mothers contributed to the deaths in 2 neonates in one of the studies **[23].** In another study, neonatal death occurred in a preterm baby on the 9th day of life who was admitted with shortness of breath and moaning and later developed

refractory shock, multiple organ failure and disseminated intravascular coagulation (DIC) **[57]**. The calculated neonatal death rate is 5.47 per 1000 live births. **[Table-6]**

3. Congenital anomaly:

We could not find any studies describing structural anomalies in the fetus associated with COVID-19. Due to an evolving pandemic, the teratogenicity of the virus has not yet been explored adequately. However, in a few of the studies, the findings of anomaly scans during pregnancy were included and they did not show any difference between fetuses of SARS-CoV-2 positive and negative women **[46, 57].** In two case reports, a multicystic dysplastic kidney was detected by antenatal ultrasound in one and after delivery in the other **[36, 59].** In another study bilateral gliosis of the deep white periventricular and subcortical matter was detected in an 11 days old neonate born to SARS-CoV-2 positive mother by magnetic resonance imaging **[29].** However, these cannot be attributed to SARS-CoV-2. Furthermore, autopsy finding in a stillborn baby born to COVID-19 mother did not show any abnormality in another report **[40].**

DISCUSSION AND CONCLUSION

We wanted to analyze the published evidence on the fetal perspective of COVID-19 infection concerning mother to child transmission, perinatal outcome, and congenital anomalies through a systematic review.

The present available data do not provide a clear conclusion into the fetal outcomes and its clinical implications. Few other reviews have explored the evidence of vertical transmission. There is varied positivity rate of different samples. The positivity of NP swab in this study is 3.67% which is in accordance with other reviews reporting 3.2% (22/936), 2% (9/493), and 3.48% (3/86), respectively **[89- 91].** In a couple of other reviews,however, the NP samples were negative [(0/113) and (0/9)] **[92, 93].** No evidence of vertical transmission was found in other reviews **[2, 94, 95].**

The placental sample was positive in our review in 11.7% of pregnancies. It is similar to the review by Kotlyar reporting 9.7% (3/31) sample positivity **[89]**. The placenta was extensively studied in another review where it was shown that there is a low likelihood of placental infection and vertical transmission of SARS-CoV-2 since the receptors and proteases, are only minimally expressed by the human placenta throughout pregnancy **[96]**. Placenta was also negative for 54 samples in another review **[90]**.

Amniotic fluid collected before the rupture of membranes was positive in 6.8% of pregnancies in our review, in contrast to the review by Kotlyar (0/51) and Ashraf (1/16) **[89, 91].**

The serological analysis was found in some studies within our review showing IgM positive results at birth indicating possible congenital transmission. Using the criteria by shah et al, we found that there is confirmed congenital transmission in 5 live-born neonates and 2 DCDA twins expelled at 24 weeks **[14]**. Similarly, the possible congenital

transmission was found in 5 neonates and probable in 2 neonates. These analyses were not reported in earlier reviews involving more than 1300 pregnancies in total.

The chance for CS is more in women with COVID-19 and in most instances for maternal indications. Preterm delivery is also high (26.4%) most commonly due to adverse maternal condition, although spontaneous preterm labor is low (1.8%). This is in accordance with another systematic review with regards to the indication but they found a trend towards spontaneous preterm labour **[97].** In contrast, an earlier review reported 6.4% of preterm deliveries as spontaneous **[98].**

Fetal distress (6.63%) was the most common complication seen in the fetus followed by PROM and PPROM (4.27%) in our review. Similar findings were seen in other reviews **[91, 94].** One earlier review did not report any fetal complications **[92].** PPROM was reported in 14 pregnancies in our review. While PROM and PPROM are unlikely to contribute to mother to child transmission as the SARS-CoV-2 has not been positive in the vaginal swab, PPROM is a significant cause of preterm labor. Through our review, it was not possible to ascertain whether COVID-19 in mothers increases the risk for PROM. IUGR was reported in 12 fetuses in 5 studies (0.9%)**.** IUGR can be multifactorial and need to be analyzed with the presence of maternal risk factors. SARS-CoV-2 has not been associated with IUGR and it was not possible to ascertain whether COVID-19 in mother increases the risk for IUGR in our study.

The rates of stillbirth and neonatal death in our study were 9.9 and 5.46 respectively. In another study, it was found that stillbirth was significantly higher during the pandemic compared to the non-pandemic period due to reasons non-associated with COVID-19 (difference, 6.93 [95% CI,1.83-12.0] per 1000 births; P= .01) **[99].** So it is unlikely that the stillbirth and neonatal death rate are increased in COVID-19 mothers. The symptoms when present in the infected neonates were most often mild and neonatal outcomes were found to be good **[100, 101].** There is no reported teratogenicity or congenital anomalies associated with SARS-CoV-2 infection.

The outcome so far is favorable for the fetus despite the risks to the mother for ICU admissions and mechanical ventilation seen in other studies **[3].** Maternal outcomes were not explored in this study. There is no significant increase in preterm birth but there is a significantly increased risk of CS in mothers with COVID-19.

Though the fetal perspective seems good in the case of maternal COVID-19, it will be reasonable to consider these findings with caution. Prospective studies and randomized control trials were missing from the evidence due to the recent nature of the infection. Therefore, larger and better quality studies are required to address the knowledge gaps and to reach at a definite guideline for management.

Strengths and Limitations of the study

There are many strengths to this study. The studies included in the review contained only confirmed maternal cases by RT-PCR and not the suspected cases or clinically diagnosed cases. The studies contained the results of neonatal testing. Studies included in this review were from countries across the world and not restricted to a specific region, making the findings from the study globally applicable. The case series/cohorts were chosen only when the total number of cases was more than 4. Moreover, various aspects of vertical transmission as well as fetal and neonatal outcomes were analyzed from the chosen studies.

Nonetheless, there are many limitations to our study. Only a limited number of available case series and cohorts were included in this review as high-quality evidence involving a higher number of subjects is lacking dues to the new kind of infection and still evolving nature of the pandemic. Almost all of the reports are retrospective reviews showing incomplete data with significant heterogeneity within the included studies with a chance of selection or recall bias. Different types of samples were used for the diagnosis of SARS-CoV-2 in different studies. Though nasopharyngeal swab was used for diagnosis in most studies, there were different types of kits used. Again the same kit may have different sensitivity and specificity in different types of samples. Universal testing of pregnant women was not done in many studies, resulting in missing fetal and perinatal effects in asymptomatic women. As maternal outcomes were not studied, the effects of the severity of maternal disease on the fetal outcomes could not be looked into.

Future Implications:

Whether there is an intrauterine infection of the fetus with respect to SARS-CoV-2 needs to be studied. What are the effects of intrauterine infection, whether there is different susceptibility at different stages of pregnancy, and whether susceptibility depends on disease severity in the mother, needs to be explored. Follow up studies are required to see long term effects of neonatal infection with SARS-CoV-2.

AUTHORSHIP STATEMENT

Manuscript title: **COVID-19 in pregnancy; The fetal perspective- a systematic review**

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the BMJ Pediatrics-open access.

Authorship contributions

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PRISMA 2009 Flow Diagram- Mother to child transmission

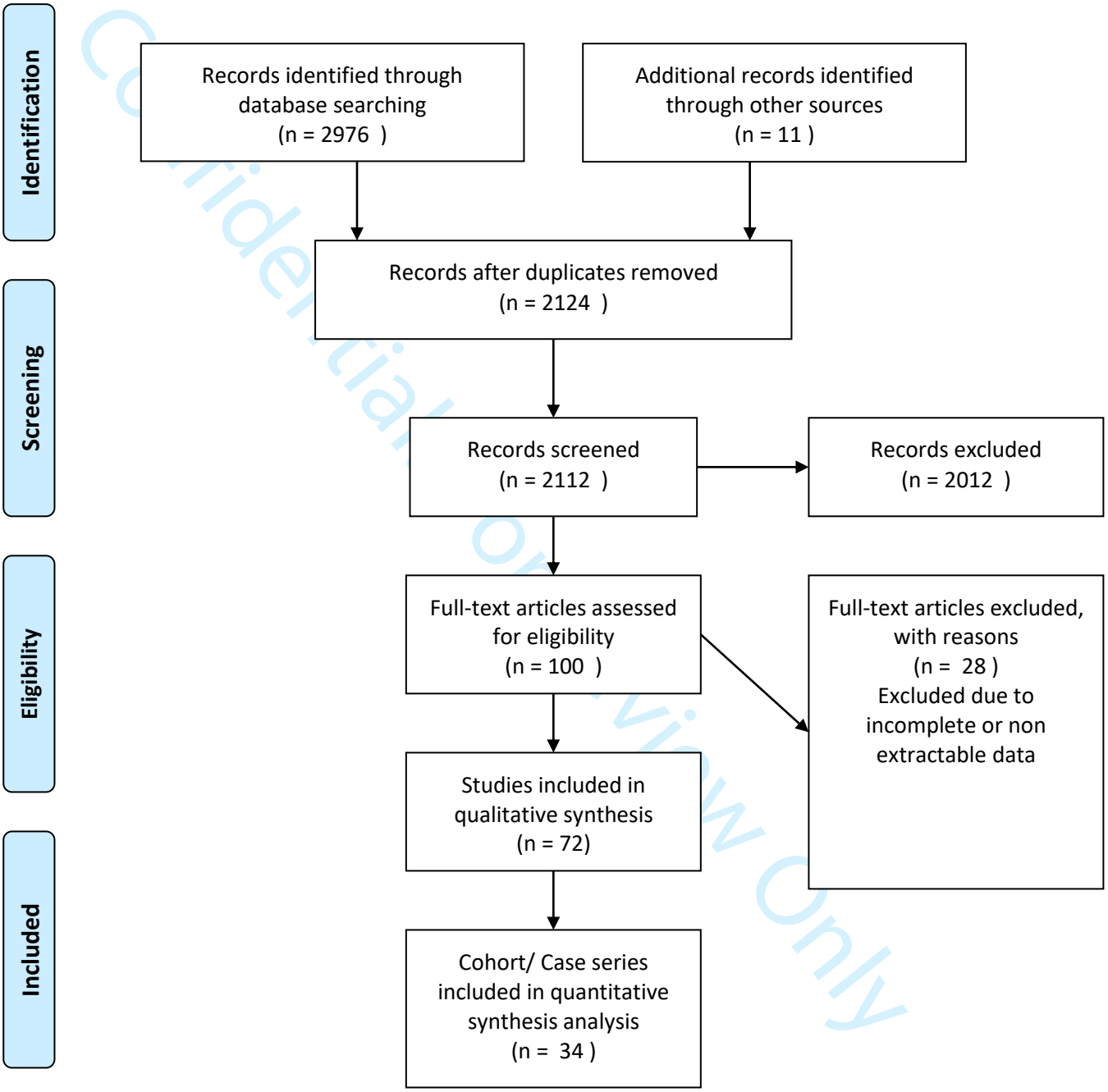

Figure-2 PRISMA 2009 Flow Diagram- Perinatal outcome

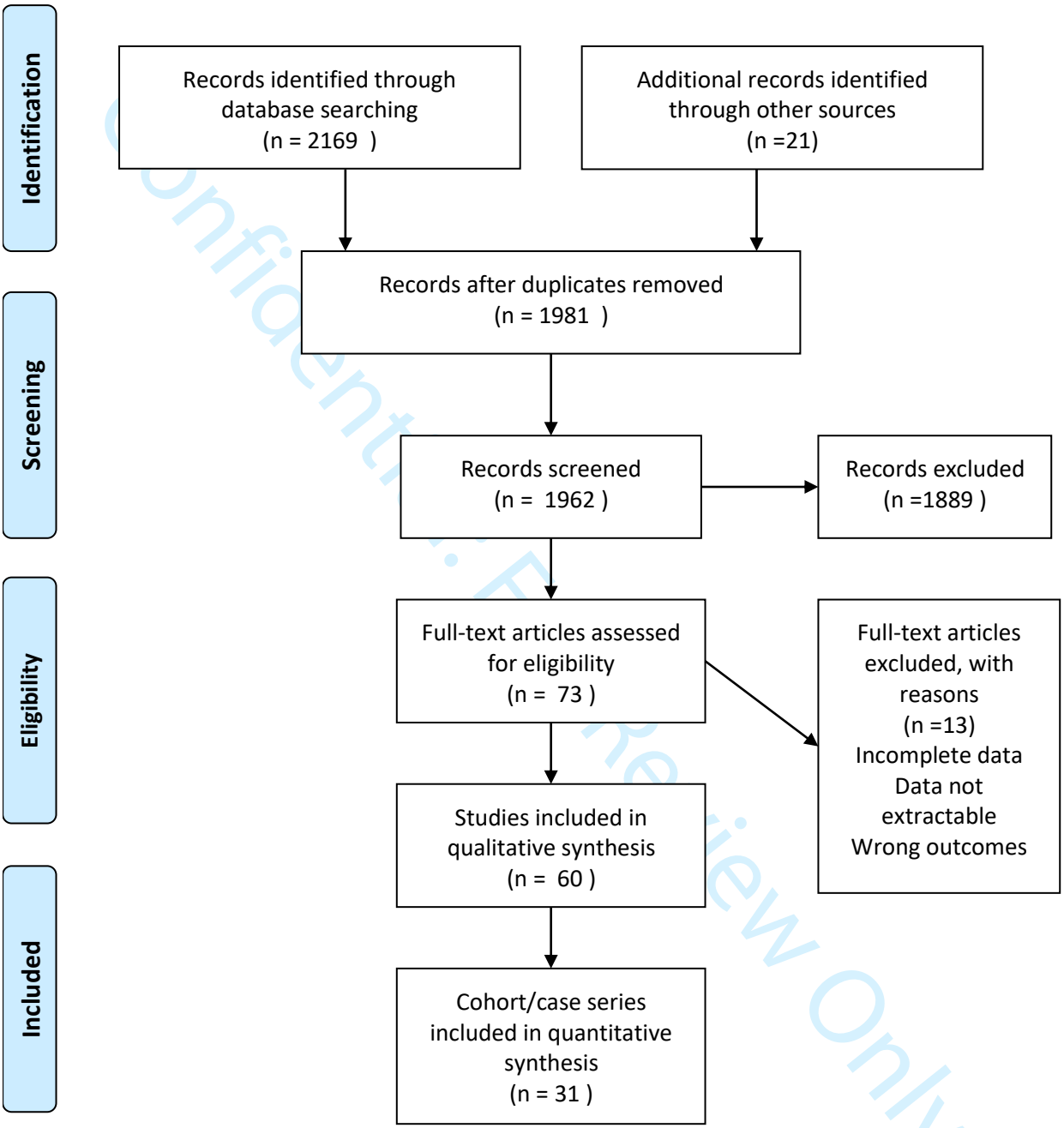

Table-1 (a): Analysis of the studies [Case series/ Cohort]

Serial number	Author (reference)	Number of pregnancies	Country	Outcomes included	Selection Contains diagnosed COVID-19 in Pregnancy	Comparability Data on pregnant women and fetus available	Outcome; Assessment and reporting	Evidence of mother to child transmission	Perinatal Outcome
1.	Chen H et al (45)	9	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
2.	Zeng H et al (54)	6	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
3.	Zhu H et al (57)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
4.	Zhang I et al (102)	61	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
5.	Penfield CA et al (103)	11	China	Placental, membrane and neonatal samples	****		**	√	
6.	Liu Y et al (69)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
7.	Khan S et al (64)	17	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
8.	Zeng L et al (41)	33	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
9.	Qianch eng X et al (107)	23	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
10.	Yang P et al (81)	7	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
11.	Yang H et al (73)	55	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	*	*	√	√

12.	Wu Y et al (47)	13	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	*	*	√	
13.	Yan J et al (24)	116	China	pregnancy and neonatal outcomes	****	**	***		√
14.	Li N et al (66)	16	China	Symptoms, maternal outcomes, neonatal outcomes	****	**	***		√
15.	Cao D et al (67)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
16.	Yin M et al (46)	31	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
17.	Hu X et al (42)	7	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
18.	Nie R et al (68)	33	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
19.	Patane L et al (39)	22	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
20.	Ferrazzi E et al (28)	42	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
21.	Savasi V et al (109)	77	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
22.	Mulvey J et al (38)	5	US	Placental characteristics	***			√	
23.	Vintzileos W et al (113)	32	US	Symptoms, maternal characteristics, Test results	***	*	***	√	
24.	Breslin N et al (59)	18	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
25.	Baergen R et al (37)	20	US	Maternal characteristics, maternal outcomes, Placental characteristics	***			√	

26.	William s R et al (63)	64	US	Maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
27.	Shanes E et al (36)	16	US	Symptoms, maternal characteristics, Placental pathology, pregnancy and neonatal outcomes	****	**	***	√	√
28.	Breslin N et al (114)	7	US	Symptoms, maternal characteristics, test result	**	**	**	√	
29.	London V et al (27)	68	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
30.	Lokken E et al (40)	46	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***		√
31.	Qadri F et al (115)	16	US	Maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	-**		√
32.	Prabhu M et al (60)	70	US	Symptoms, obstetric and neonatal outcomes, and placental pathology	****	**	***	√	√
33.	Romag ano M et al (82)	7	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	*		√
34.	Govind A et al (61)	9	UK	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
35.	Knight M et al (23)	427	UK	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
36.	Sentilhe s, et al (116)	38	France	Symptoms, maternal outcomes, neonatal outcomes	****	**	***	√	√
37.	Kayem G et al (25)	617	France	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
38.	Nayak A et al (26)	141	India	Symptoms, maternal outcomes, neonatal outcomes	****	**	***		√
39.	Hantou shzade h et al (75)	7	Iran	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√

40.	Perez O et al (65)	82	Spain	Symptoms, maternal characteristics, pregnancy outcomes	****	**	**	√	√
41.	Doria M et al (48)	10	Portugal	Symptoms, maternal characteristics, pregnancy outcomes	****	**	*		√

Table-1 (b): Analysis of the studies [Case reports]

Serial number	Author (reference)	Number of pregnancies	Country	Outcomes included	Selection Contains diagnosed COVID-19 in Pregnancy	Comparability Data on pregnant women and fetus available	Outcome; Assessment and reporting	Evidence of vertical transmission	Perinatal Outcome
1.	Alzamora et al (78)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
2.	Li Y et al (44)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
3.	Dong L et al (55)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
4.	Liao X et al (106)	1	China	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
5.	Wang X et al (77)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
6.	Huang J et al (86)	1	China	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
7.	Xiong X et al (50)	1	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
8.	Wang S et al (51)	1	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
9.	Song L et al (49)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
10.	Fan C et al (48)	2	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√

11.	Chen Y et al (58)	4	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
12.	Peng Z et al(43)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
13.	Liu W et al (56)	3	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
14.	Chen S et al (104)	3	China	Symptoms, laboratory parameters, pregnancy outcomes, samples	****	**	***	√	√
15.	Khan S et al (85)	3	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
16.	Yu N et al (108)	2	China	Symptoms, maternal characteristics, amniotic fluid in mid pregnancy	****	*	*	√	
17.	Schnettler W et al (110)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcome	****	**	**	√	
18.	Blauvelt C et al (84)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
19.	Iqbal S et al (105)	1	US	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
20.	Algorroba et al (34)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcome	***	*	*	√	
21.	Hosier H et al(32)	1	US	Symptoms, maternal characteristics, test result	****	**	**	√	
22.	Sisman J et al (70)	1	US	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
23.	Kalafat E et al (79)	1	Turkey	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
24.	Kirtsman M et al (35)	1	Canada	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√

25.	Lyra J et al (74)	1	Portugal	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
26.	Buonsenso et al (53)	4	Italy	Symptoms, maternal findings, test results	****	*	**	√	
27.	Perrone S et al (72)	4	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
28.	Buonsenso D et al (112)	2	Italy	Maternal characteristics, Samples for detection	****	**	*	√	
29.	Groß R et al (52)	2	Germany	Symptoms, maternal findings, test results	****	*	*	√	
30.	Cooke W et al (83)	2	UK	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	-**		√
31.	Pulinx B et al (31)	2	Belgium	Symptoms, maternal characteristics, laboratory parameters, second trimester miscarriage	****	*	*	√	
32.	Lee D et al (80)	1	Korea	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
33.	Gidlöf S et al (76)	2	Sweden	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
34.	Baud D et al (33)	1	Switzerland	Symptoms, maternal characteristics, laboratory parameters, second trimester miscarriage	****	*	*	√	
35.	Zamaniyan M et al (30)	1	Iran	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
36.	Zambrano L et al (87)	1	Central America	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
37.	Vivanti A et al (29)	1	France	Symptoms, maternal outcomes, neonatal outcomes	****	**	***	√	√
38.	Lowe B et al (62)	1	Australia	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√

39.	Kulkarni et al (117)	1	India	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√

Selection-* *Representativeness of the patients *Ascertained exposure to SARS-CoV-2 *Ascertained outcome- Symptoms of COVID-19 in the mother * Ruling out other causes- Test result of mother positive [****-Contains all 4 components; ***-Contains first 3 out of 4 components; **-Contains first 2 out of 4 components;*- Contains first 1 out of 4 components]*
Comparability- *Data on both mother and fetus available [**- Both maternal and fetal data available; *- Only maternal data available]*
Outcome- * *Evidence of mother to fetal/neonatal transmission, * Evidence of Fetal outcome, *Evidence of neonatal outcome [***-Contains all 3 components; **- Contains first 2 out of 3 components;*- Contains first 1 out of 3 components]*
√- *Included in analysis of mother to fetal/neonatal transmission or included in analysis of perinatal outcome or both*

Table -2 Studies and type of samples

	Author (reference)	Number of neonates tested	Specimen tested	Results- neonatal and others	Positive/ Total tested
1.	Chen H et al (45)	6	NP, AF, Cord blood, BM	Negative	
2.	Cao et al (67)	5	NP	Negative	
3.	Hu X et al (42)	7	NP, Urine, AF	NP +ve at 36 hours, others negative	1/7
4.	Zhu H et al (57)	10	NP	Negative [Within 72 hours (8); Between D7-D9 (2)]	
5.	Zhang I et al (102)	10	NP	Negative	
6.	Penfield C et al (103)	11	NP, Placental and membrane	NP- Negative (D1 and D5) Placenta and membrane +ve	3/11
7.	Knight M et al (23)	262	NP (n=244) ,Blood or aspirate	+ve at <12 hours +ve at >12 hours	6/244 6/244
8.	Kayem G et al (25)	181	NP	+ve	2/181
9.	Nayak A et al (26)	134	NP (n=131)	+ve on D1 -ve on D5	3/131
10.	Yan J et al (24)	86	NP (n=86); Cord blood (n=10),AF (n=10)	Negative	
11.	Khan S et al (64)	17	NP	+ve within 24 hours	2/17
12.	Zeng L et al (41)	33	NP , anal swab	Both +ve D2 and D4, negative on D6	3/33
13.	Breslin N et al (59)	18	NP	Negative	
14.	Breslin N et al (114)	7	NP	Negative	
15.	Qiancheng X et al (107)	23	NP	Negative	
16.	Prabhu M et al (60)	71	NP	Negative at 24 hours	
17.	Shanes E et al (36)	16	NP , Placenta	Negative	
18.	Savasi V et al (109)	57	NP	+ve	4/57
19.	London V et al (27)	48	NP	Negative	
20.	William R et al (63)	33	NP	Negative at 24 hours, +ve at 48 hours	1/33

21.	Perez O et al (65)	82	NP	NP +ve at birth and negative at 48 hours (3); NP negative at birth but +ve at D10 (2)	5/82
22.	Nie R et al (68)	26	NP, Cord blood, Placenta	NP +ve at 36 hours Negative - All other samples, NP (D4, D8,D15)	1/26
23.	Yin M et al (46)	17	NP (n=17), BM (n=14), AF (n=2), placenta (n=2), Anal swab (n=5)	Negative	
24.	Yang P et al(81)	7	NP , Cord blood, AF	Negative	
25.	Yang H et al (73)	55	NP	Negative	
26.	Wu Y et al (47)	5	NP , Anal swab, BM	Negative, BM +ve	1/5
27.	Patane L et al (39)	22	NP , Placenta	NP +ve , Placenta- Chronic intervillitis, PCR +ve in placenta	2/22
28.	Ferrazzi E et al (28)	42	NP	NP +ve on D1,D3(2) NP equivocal at birth but +ve on D3(1)	3/42
29.	Govind A et al (61)	9	NP , Placenta, AF	NP +ve	1/9
30.	Vintzileos W et al (113)	29	NP	Negative	
31.	Baergen R et al (37)	21	NP	Negative	
32.	Zeng H et al (54)	6	NP Neonatal blood	NP negative; Elevated IgM and IgG (2); Elevated IgG ,normal IgM (3)	Cytokine IL-6 elevated in all infants
33.	Liu Y et al (69)	10	Fetal blood	Negative	
34.	Mulvey J et al (38)	5	Placenta	Negative	
35.	Hantoushzadeh et al (75)	4	NP	Negative at D1; +ve at D7	1/4
36.	Buonsenso et al (53)	2	NP,AF, Placenta, Cord blood, Rectal swab, BM	1st- NP Negative on D1,D4 and +ve on D15 , Placenta, AF, rectal swab- Negative, Weak IgG+ve, IgM negative 2nd - Placenta, Breast milk- +ve but cord blood negative in neonate with NP negative result	1/2
37.	Fan C et al (48)	2	NP, AF, Cord blood, BM, Placenta , Vaginal swab	Negative	
38.	Liu W et al (56)	3	NP, Cord blood, Neonatal whole blood	Negative (D2)	
39.	Lowe B et al (62)	1	NP	Negative	
40.	Chen S et al (104)	3	NP, Placenta	Negative	
41.	Chen Y et al (58)	4	NP	Negative	
42.	Gidlöf S et al (76)	2	NP	Negative (34 hours and 4.5 days)	
43.	Khan S et al (85)	3	NP	Negative	
44.	Schnettler W et al (110)	1	NP, AF	AF Negative, NP negative on D1,D2	

45.	Blauvelt C et al (84)	1	NP, Rectal swab D2 Ig G and IgM	NP Negative on D1, D2, D14 Rectal swab negative on D2 Ig G and IgM negative (D5)	
46.	Alzamora M et al (78)	1	NP, Cord blood	Negative for IgM and IgG; NP +ve at 16 hours and 48hours	1/1
47.	Vivanti A et al (29)	1	NP, AF, Vaginal swab, NBAL, Neonatal blood and rectal swabs	NP +ve at 1hour, D3, D18; Rectal swab +ve at 1hour, D3, D18; Vaginal swab, NBAL, Neonatal blood, AF +ve,	1/1
48.	Song L et al (49)	1	NP, AF, Cord blood, BM	NP negative at D3,D7 All other negative	
49.	Zambrano L et al (87)	1	NP	Negative	
50.	Li Y et al (44)	1	NP, Neonatal Blood, feces, and urine	NP negative at birth and 48h All other negative	
51.	Dong L et al (55)	1	NP, Serum Vaginal swab	IgM level elevated NP negative at 2h,16h	1/1
52.	Baud D et al (33)	1	NP, AF, Placenta Vaginal swabs	Placenta +ve All other negative	1/1; 2nd trimester spontaneous miscarriage
53.	Wang X et al (77)	1	NP, AF, Placenta, Cord blood, gastric juice, feces	NP negative at D1, D3, D7, D9 All other negative	
54.	Huang J et al (86)	1	NP	Negative	
55.	Iqbal S et al (105)	1	NP	Negative	
56.	Kalafat E et al (79)	1	NP, Cord blood, Placenta	Negative	
57.	Lee D et al (80)	1	NP, AF, Cord blood, Placenta, neonatal serum, anal swab	Negative	
58.	Liao X et al (106)	1	NP , AF, Cord blood, Placenta	Negative	
59.	Xiong X et al (50)	1	NP, AF, BM, rectal swab	Negative	
60.	Wang S et al (51)	1	NP , Placenta, Cord blood, BM	NP +ve at 36 h Negative in all others	1/1
61.	Zamaniyan M et al (30)	1	NP, Cord blood, AF, Vaginal secretion	NP – Negative at 0 hours, +ve at D2, D4, D6 AF +ve , all others negative	1/1
62.	Kirtsman M et al (35)	1	NP, Placental, Stool, BM Neonatal plasma D4	NP +ve at D1, D2, D7 Placenta +ve Stool +ve D7, BM +ve	1/1
63.	Lyra J et al(74)	1	NP	Negative	
64.	Algorroba G et al (34)	1	NP	Negative at 0 h,D2, D7	

65.	Peng Z et al (43)	1	NP, NBAL Fluid, Sputum, Urine	Negative	
66.	Groß R et al (52)	2	BM, NP	Both NP +ve (>D7) , BM +ve (1)	2/2,1/2
67.	Perrone S et al (72)	4	NP (3),Placenta (1)	NP negative on D1, Placenta-negative	
68.	Hosier H et al (32)	1	Placenta, cord blood	Both +ve	1/1; D& E at 22 weeks
69.	Pulinx B et al (31)	2	AF, Placental	Both +ve	2/2, DCDA twin at 24 weeks
70.	Yu N et al (108)	2	AF in mid pregnancy	Negative	
71.	Kulkarni et al (117)	1	NP, Placenta, Cord stump, Neonatal blood	All +ve at 12 hours of life; Serology negative on D10 but +ve on D21	1/1
72.	Sisman J et al (70)	1	NP, Placenta	NP +ve at 24 hours, 48 hours, D14; Placenta +ve by electron microscopy	1/1

AF= Amniotic fluid; NP= Neonatal Pharyngeal/throat swab; BM= Breast milk; NBAL= Non-bronchoscopic broncho-alveolar lavage fluid; D&E- dilatation and evacuation; D1= 1st day of life,D4= 4th day of life…

Table-3 (a): Mother to child transmission-Test positive (Pooled result)

SAMPLE Tested by RT-PCR for SARS-CoV-2	**Number of studies**	**Number Tested**	**Number Positive**	**Pooled Percentage**
Neonatal Naso-pharyngeal swab	**67 [32 case series/cohort +35 case reports]**	**1388 [1335 case series/cohort+53 case reports]**	**51 [40 out of 1335 in case series/cohort+ 11 out of 53 case reports]**	**3.67% [3% in case series/cohort; 2.07% in case reports]**
Placenta ± Membranes	**22**	**111**	**13**	**11.7%**
Amniotic fluid	**19**	**58**	**4**	**6.8%**
Breast milk	**10**	**56**	**3**	**5.3%**
Cord blood/ plasma	**16**	**56**	**4**	**7.1%**
Other neonatal samples -Anal swab -Urine	 **11** **3**	 **52** **9**	 **5** **0**	**9.6%**
Neonatal serology				
IgM	**5**	**11**	**(Elevated) 3**	**27%**
IgG	**4**	**10**	**(Elevated) 6**	**60%**

Table-3 (b): Analysis of evidence of congenital/ intrapartum/ postpartum transmission

Author (reference) [samples positive/ total tested]	Samples +ve	Fetal/ Neonatal status	Alternate explanation for clinical features	Mother to child transmission (n)
Groß R et al (52) [2/2]	NP >D7	Respiratory symptoms (2), icterus (1)	Alternate explanation- excluded in 1 ; Respiratory syncytial virus +ve in 1	Neonatal infection acquired postpartum-Confirmed (1) Unlikely (1)
Buonsenso et al (53) [1/2]	1st- NP Negative on D1, D4 and +ve on D15, Placenta, AF, rectal swab- Negative, Weak IgG+ve, IgM negative 2nd - Placenta, Breast milk- +ve but cord blood negative in neonate with NP negative result	Symptoms- Absent	-	Neonatal infection acquired postpartum-Confirmed (asymptomatic) (1st) Possible congenital infection (2nd)
Vivanti A et al (29) [1/1]	NP +ve at 1hour, D3, D18; Rectal swab +ve at 1hour, D3, D18; Vaginal swab, NBAL, Neonatal blood +ve	Irritability, poor feeding, axial hypertonia and opisthotonos	Alternate explanation- excluded	Confirmed congenital infection
Kirtsman M et al (35) [1/1]	NP +ve at birth, D2, D7 Placenta (fetal side) +ve Stool +ve D7, BM +ve	Hypothermia, feeding difficulties, hypoglycemia, neutropenia	Alternate explanation- excluded	Probable congenital infection
Zamaniyan M et al (30) [1/1]	NP - negative at 0 hours, +ve at D2, D4, D6 AF before rupture of membranes +ve Cord blood and vaginal secretion - negative	Fever (1)	Alternate explanation- not identified	Confirmed congenital infection
Wang S et al (51) [1/1]	NP +ve at 36 hours Placenta, Cord blood, BM- Negative	Vomiting, lymphopenia, abnormal liver enzyme levels	Alternate explanation- excluded	Neonatal infection acquired intrapartum possible
Khan S et al (64) [2/17]	NP +ve within 24 hours	NNP	Alternate explanation- not identified	Neonatal infection acquired intrapartum- possible
Zeng L et al (41) [3/33]	NP +ve at D2, D4, negative at D6	RD (1); Cyanosis, feeding intolerance(1); Fever (2); NNP(3); Lethargy, fever(1); lethargy, fever, NNP, vomiting leukocytosis,lymphocytopenia, (1); Preterm- Neonatal RDS, NNP, lymphocytopenia (1)	Alternate explanation- excluded	Neonatal infection acquired intrapartum-possible NP not done at birth, no other samples tested
Hu X et al (42) [1/7]	NP +ve at 36 hours; fetal urine, AF are negative	Symptoms- Absent	-	Neonatal infection acquired intrapartum- Possible NP not done at birth

Knight M et al (23) [12/244]	NP +ve at <12 hours (6) NP +ve at >12 hours (6)	Neonatal encephalopathy (1)	-	Congenital infection possible(1) Other evidences lacking
Alzamora M et al (78) [1/1]	NP +ve at 16 hours and 48 hours Cord Blood IgM and Ig G negative at D1 and D5	Respiratory difficulty and cough	Alternate explanation- excluded	Neonatal infection acquired intrapartum - confirmed NP not done at birth
Hantoushzadeh et al (75) [1/4]	NP -ve on D1, +ve on D7	NNP, lymphopenia (1)	-	Neonatal infection acquired postpartum-Confirmed
William R et al (63) [1/33]	Negative at 24 hours, +ve at 48 hours	Symptoms- Absent	-	Neonatal infection acquired postpartum-Confirmed
Nayak A et al (26) [3/131]	NP +ve on D1;-ve on D5	Neonatal seizures, MAS (1)	-	Probable neonatal infection acquired intrapartum
Nie R et al (68) [1/26]	NP +ve at 36 hours, negative - D4, D8,D15; Cord blood, placenta- negative	Pulmonary infection (1)	Alternate explanation- not identified	Neonatal infection acquired intrapartum - Possible NP not done at birth
Savasi V et al (109) [4/57]	Timing of NP test could not be ascertained (early postpartum period)	-	-	-
Kayem G et al (25) [2/181]	Timing of test could not be ascertained	-	-	-
Patane L et al (39) [2/22]	1st- NP +ve at birth,>24hours, >7 days 2nd- NP negative at birth, +ve on D7 Placenta- Chronic intervillitis, PCR +ve in both placenta	Mild feeding difficulty (2)	-	Probable congenital infection (1) Possible congenital infection (1)
Ferrazzi E et al (28) [3/42]	NP +ve on D1, D3(2) NP equivocal at birth but +ve on D3(1)	Gastrointestinal symptoms, RD (2)	Alternate explanation- not identified	Neonatal infection acquired postpartum-Confirmed (1) Neonatal infection acquired intrapartum - possible(2) Other evidences lacking
Govind A et al (61) [1/9]	NP at birth	NNP (1)	Alternate explanation- excluded	Neonatal infection acquired intrapartum - confirmed? NP not done after 24 hours
Penfield C et al (103) [3/11]	NP- Negative (D1 and D5) Placenta and membrane +ve	Symptoms- Absent		Neonatal infection acquired intrapartum - Possible
Baud D et al (33) [1/1]	NP, AF, Vaginal swabs- Negative Placenta +ve	2nd trimester spontaneous miscarriage		Confirmed congenital infection
Hosier H et al (32) [1/1]	Placenta, cord blood-both +ve	D& E at 22 weeks		Confirmed congenital infection
Pulinx B et al (31) [2/2]	AF, Placenta-both +ve	DCDA twin at 24 weeks expelled		Confirmed congenital infection
Dong L et al (55) [1/1]	IgM level elevated NP negative at 2h,16h	Symptoms-absent	-	Possible congenital infection
Zeng H et al (54) [1/1]	NP negative;	Symptoms-absent	-	Possible congenital infection

	Elevated IgM and IgG (2); Elevated IgG ,normal IgM (3)			
Perez O et al (65) [5/82]	NP +ve at birth and negative at 48 hours (3); NP negative at birth but +ve at D10 (2)	RD (2) Symptoms-absent (3)	Alternate explanation- not identified (2)	Neonatal infection acquired intrapartum – Probable (2) Neonatal infection acquired intrapartum – Possible (1) Neonatal infection acquired postpartum-Confirmed (2)
Kulkarni et al (117) [1/1]	NP, placenta, Cord stump RT PCR- All +ve at 12 hours of life NP at D5 and D10 +ve	Fever, icterus, and poor feeding	Alternate explanation-excluded	Confirmed congenital infection
Sisman J et al (70) [1/1]	NP +ve at 24 hours, 48 hours, D14 Placenta +ve by electron microscopy	Fever, RD, Icterus	Alternate explanation-excluded	Confirmed congenital infection

AF= Amniotic fluid; NP= Neonatal Pharyngeal/throat swab; BM= Breast milk; NBAL= Non-bronchoscopic broncho-alveolar lavage fluid; NNP=Neonatal Pneumonia; D&E- dilatation and evacuation; RD= Respiratory distress; DCDA- Dichorionic diamniotic twin

Table-4: Fetal outcome

Serial number	Author (reference)	Number of neonates from SARS CoV-2 +ve pregnancies	Fetal complications (n)	Mode of delivery (n)	Birth weight in grams	Preterm delivery (n)	Still birth(n)	Comments
1.	Chen H et al (45)	9	FD (2) PROM (1)	CS (9)	1880-3730	Yes (2)	-	
2.	Romagano M et al (82)	7	-	CS(7)	1290-2580 (AGA)	Yes (7)		
3.	Zeng H et al (54)	6		CS (6)			-	
4.	Zhu H et al (57)	10	FD (6), PROM (3), MSA (2)	CS (7) VD (2)	SGA-2 LGA/Normal-8	Yes (6)	-	1 twin delivery
5.	Khan S et al (64)	17	PROM	CS (17)	2300–3750 <2700-3	Yes (5)	-	
6.	Zeng L et al (41)	33	PROM (3); FD (1)	VD (7); CS (26)	SGA (3) 1580-3360	Yes(4)	-	
7.	Breslin N et al (59)	18	Ab.CTG (3)	CS (8); VD (10)		Yes (1)	-	
8.	Qiancheng X et al (107)	23	-	CS (17) VD (5)	3130 (2915–3390)	Yes(1)	-	1 twin delivery
9.	Hantoushzadeh S et al (75)	5	IUFD (3)	CS (4)	1180-3200	Yes (3)	Yes (1)	1 twin delivery
10.	Perez O et al (65)	82	PROM (18) PPROM (7) IUGR (1)	VD (41) CS (41)	1450-3210	Yes (25)	-	
11.	Savasi V et al (109)	57	-	VD (34) CS (22)	3160 (840-4350)	Yes(12)	-	1 twin delivery
12.	London V et al (27)	56	DFM (1) IUFD (17 wks) (1)	CS (22) VD (33)	-	Yes(12)	-	

13.	Lokken E et al (40)	8	FD (3)	CS (3) VD (5)	-	Yes (1)	Yes(1)	
14.	Yan J et al (24)	99	FD (9); IUGR (2) PPROM (6)	CS (85) VD(14)	3108±526	Yes (21)	-	
15.	William R et al (63)	32	IUGR(2), PPROM (1)	CS (24) VD(8)	2403.3±858	Yes (19)	-	
16.	Knight M et al (23)	262	Miscarriage (4); Fetal compromise (37)	CS (156) VD (106)	-	Yes (66)	Yes (3)	
17.	Kayem G et al (25)	176	Fetal loss <21 weeks (5)	CS (87) VD (89)	-	Yes (50)	Yes (2)	
18.	Nayak A et al (26)	134	Miscarriage (6)	CS (67) VD(67)	>2500 (92) <2500 (39)	Yes (38)	Yes (3)	
19.	Prabhu M et al (60)	70	PROM and Ab.CTG (4)	CS (32) VD(38)	3060.9-3149.6	Yes (11)	Yes (1)	
20.	Li N et al (66)	17	FD(1) ; PROM (1)	CS (14) VD(2)	3078.2 ± 565.0	Yes (4)	-	1 twin delivery
21.	Cao D et al (67)	11	FD (3); PROM (4)	CS (8) VD(2)	2050-3800	Yes (4)	-	1 twin delivery
22.	Hu X et al (42)	7	PROM (1)	CS (6) VD(1)	3180-3670	-	-	
23.	Yang P et al (81)	7	-	CS(7)	2096 ± 660	Yes (4)	-	
24.	Yang H et al (73)	13	-	CS (9) VD(4)	3063.2 ± 536.4	-	-	
25.	Ferrazzi E et al (28)	42	-	CS (18) VD(24)	2730-3226	Yes(11)	-	
26.	Govind A et al (61)	9	Ab.CTG (1)	CS (8) VD(1)	1200-4300	Yes(2)	-	
27.	Nie R et al (68)	28	FD (4); IM (1); PROM (3)	VD (5); CS (22)	2988(502)	Yes (10)	-	1 twin delivery
28.	Yin M et al (46)	17	IM (3)	VD (4); CS (13)	2580-3035	Yes (5)	-	
29.	Qadri F (115)	10		CS (2) VD (8)		Yes (1)		
30.	Doria M et al (71)	10	IUGR (6)	CS (6) VD(4)	2350–3380	-	-	
31.	Liu Y et al (69)	10	FD(3), PROM (1)	CS(10)		Yes (6)	Yes(1)	
32.	Perrone S et al (72)	4	IUGR(1)	VD(4)	2290-3790	-	-	
33.	Patane L et al (39)	2	-	VD (1) CS(1)	2660, 2686	Yes(1)	-	
34.	Fan C et al (48)	2	-	CS (2)	3440-2890	Yes (1)	-	
35.	Pulinx B et al (31)	2	IUFD (1)	VD (2)		Yes (1)	Yes (1)	DCDA twins
36.	Liu W et al (56)	3	FD (1); MSA ; chorioamnionitis	CS (2) VD (1)	3250-3670	-	-	

37.	Cooke W et al (83)	2	-	CS (2)	1530,1400	Yes(2)	-	
38.	Chen Y et al (58)	4	DFM (1) Ab.CTG (1)	CS (3) VD(1)	3050-3550	-	-	
39.	Gildof S et al (76)	2	-	CS (2)	2680,2160	Yes (2)	-	
40.	Khan S et al (85)	3	-	VD (3)	2890-3750	Yes (1)	-	
41.	Zambrano L et al (87)	1	-	VD(1)	1500	Yes(1)	-	
42.	Lowe B et al (62)	1	Ab.CTG (1)	VD (1)		-	-	
43.	Blauvelt C (84)	1	-	CS(1)	1880	Yes (1)	-	
44.	Kirtsman M et al (35)	1	-	CS(1)	2930	Yes (1)	-	
45.	Lyra J et al (74)	1	-	CS(1)	3110	-	-	
46.	Li Y et al (44)	1	FD(1)	CS(1)		Yes (1)	-	
47.	Dong L et al (55)	1	-	CS(1)	3120	Yes (1)	-	
48.	Wang X et al (77)	1	FD (1)	CS(1)	1830	Yes (1)	-	
49.	Alzamora M et al (78)	1	-	CS(1)	2970	-	-	
50.	Huang J et al (86)	1	-	VD(1)		-	-	
51.	Kalafat E et al (79)	1	-	CS(1)	2790	Yes (1)	-	
52.	Xiong S et al (50)	1	PROM	VD(1)	3070	-	-	
53.	Wang S et al (51)	1	FD (1)	CS(1)	3205	-	-	
54.	Zamaniyan M et al (30)	1	-	CS(1)	2350	Yes (1)	-	
55.	Song L et al (49)	1	-	CS(1)	3630	Yes (1)	-	
56.	Lee D et al (80)	1	-	CS (1)	3130	-	-	
57.	Iqbal S et al (105)	1		VD(1)				
58.	Vivanti A et al (29)	1	Ab.CTG (1)	CS(1)	2540	Yes (1)	-	
59.	Kulkarni et al (117)	1	-	VD(1)	3200	-	-	
60.	Sisman J et al (70)	1	PROM	VD(1)	3280	Yes (1)		

FD= Fetal distress; Ab.CTG= Non-reassuring/ Pathological fetal cardio-tocography ; PROM= Pre-labor rupture of membrane ; Fetal demise= IUFD ; MSA= Meconium stained amniotic fluid; DFM= Decreased fetal movement; IM= Induced miscarriage; CS= Caesarean Section; VD= Vaginal delivery; AGA= Appropriate for gestational age; IUGR= Intrauterine growth restriction; SGA= Small for gestational age; LGA= Large for gestational age

Table-5: Perinatal outcome (Pooled data)

FETAL OUTCOME				
OUTCOME	Number of studies	Results	Indications	
Preterm birth	43 studies [26 case series/cohort and 17 case reports]	-Preterm birth=330 out of 1273 neonates in the case series/cohort (25.9%) -Preterm birth= 19 out of 45 neonates in the case reports (42.2%)	-Iatrogenic prematurity to improve maternal COVID-19 related respiratory symptoms =153 -Spontaneous preterm labor=24 -Fetal compromise/ distress=17 -Unknown/ other = 156	Pooled Preterm birth in 26.4% of total births Spontaneous preterm birth- 1.8% of total births
Mode of delivery	59 studies [30 case series/cohort and 29 case reports]	-In case series/ cohorts, out of 1267 deliveries, CS=761 (60%) and VD=506 (40%) -In case reports, out of 44 deliveries, CS=25 (56.8%) and VD=19 (43.2%)	Maternal COVID-19 related conditions most common indication	Pooled data- CS= 786 (59.9%) VD= 525 (40.1%)
Still birth Miscarriage	Still birth=8 studies Miscarriage= 5 studies	Still birth=13 Spontaneous miscarriage= 15 Induced miscarriage=4	All induced miscarriages were due to maternal request	Stillbirth rate= 9.9
Feral complications	FD= 21 studies PROM and PPROM= 15 studies	Fetal distress (87 out of 1311 pregnancies) (6.63%) PROM and PPROM (56 out of 1311 pregnancies) (4.27%)	-	-
IUGR and SGA	IUGR-5 studies SGA-2 studies	12 fetuses had IUGR (0.9%) 5 neonates had SGA (0.38%)	-	-
NEONATAL OUTCOMES				
OUTCOME		**Results**		
Neonatal symptoms		Respiratory symptoms= 23 neonates (1.79%) Neonatal pneumonia and pulmonary infection= 14 neonates (1.1%) Fever= 12 neonates (0.9%)	Most common symptom is respiratory distress in (1.17%)	
APGAR score		Score of less than 7 at 1minute and 5 minutes= neonates	Most common reason is preterm birth	
ICU admissions		In 276 neonates (21.5%)	Most common reason was for observation and isolation (32.6 %). Prematurity is second most common reason	

		ICU admissions for suspected or confirmed neonatal sepsis was reported in 6 neonates (0.46%).	
Neonatal death	7 neonates		Neonatal death rate=5.46 per 1000 live births

FD= Fetal distress; Ab.CTG= Non-reassuring/ Pathological fetal cardio-tocography ; PROM= Pre-labor rupture of membrane ; MSA= Meconium stained amniotic fluid; IM= Induced miscarriage; CS= Caesarean Section; VD= Vaginal delivery; IUGR= Intrauterine growth restriction; SGA= Small for gestational age

Table-6: Neonatal outcome

Serial number	Author (reference)	Number of neonates	APGAR score (1 minute, 5 minute)	Neonatal symptoms (n)	Neonatal ICU admission (n)	Neonatal death	Neonatal RTPCR status
1.	Alzamora M et al (78)	1	6, 8	Respiratory difficulty Cough on D6	(1) [due to maternal sedation]	-	**+ve**
2.	Chen H et al (45)	9	8-10	-	-	-	
3.	Fan C et al (48)	2	9-10	Fever, abdominal distension, lymphopenia (1) Mild NNP, lymphopenia (1)	-	-	**Negative**
4.	Dong L et al (55)	1	9-10	-	-	-	
5.	Zeng H et al (54)	6	9-10		-	-	
6.	Liu W et al (56)	3	8-10	decreased responsiveness and decreased muscle tone	-	-	**Negative**
7.	Zhu H et al (57)	10	8-10 in all 7-8 in 1	Shortness of breath (6), vomiting (1), rash (1), Fever (3)	Yes (2)	YES (1)	**Negative**
8.	Wang X et al (77)	1	9-10	-	Yes (1)	-	
9.	Liu Y et al (69)	10	10	-	-	-	
10.	Chen Y et al (58)	4	8-9 (3) 7-8 (1)	Edema (1), Rash (2),Dyspnea and TTN (1)	Yes (2)	-	**Negative**
11.	Gidlof S et al (76)	2	9-10	Breathing problem, cyanotic attack(1)			**Negative**
12.	Huang J et al (86)	1	8-9	-	-	-	
13.	Iqbal S et al (105)	1	9	-	-	-	
14.	Lee D et al (80)	1	9-10	-	Yes (1)	-	
15.	Khan S et al (85)	3	9-10	-	-	-	
16.	Khan S et al (64)	17	9-10 (16) 7-9 (1)	NNP (5)	-	-	**2 out of 5 with pneumonia were +ve**
17.	Xiong S et al (50)	1	9-10	-	-	-	
18.	Wang S et al (51)	1	8-9	Vomiting, lymphopenia, abnormal liver enzyme levels	Yes (1)	-	**Negative**
19.	Zeng L et al (41)	33	Preterm newborn-3,4 Term - Normal	RD (4=3 -ve, 1+ve). Cyanosis, feeding intolerance (3=2-ve,1+ve) Fever in 2, NNP in 3 of the 3 +ve Lethargy, fever(1) lethargy, fever, NNP, leukocytosis, lymphocytopenia, vomiting (1)	Yes (3)	-	**+ve**

				Preterm- Neonatal RDS, NNP, lymphocytopenia (1)			
20.	Zamaniyan M et al (30)	1	8,9	Fever (1)	-	-	**+ve**
21.	Breslin N et al (59)	18	>7, >9	RD/ sepsis (1)	Yes (3)	-	**Negative**
22.	Qiancheng X et al (107)	23	10,10		-	-	
23.	Hantoushzadeh S et al (75)	5	7 (2), 9-10	NNP, lymphopenia (1)	Yes (1)	YES(2)	**Negative**
24.	Shanes E et al (36)	15	7(8),8(7); 9				
25.	Zambrano L et al (87)	1	-	-	Yes (1)	-	
26.	Perez O et al (65)	82	<5 (3)	RD (2)	Yes (19)		**+ve**
27.	Savasi V et al (109)	57	10	-	Yes(9)	-	
28.	Song L et al (49)	1	8,9	-	-	-	
29.	Lokken E et al (40)	8					
30.	Yan J et al (24)	99	9,10	Neonatal asphyxia (1)	Yes(47)	YES (1)	**Negative**
31.	William R et al (63)	32	7.9±1.7	-	Yes (21)	-	
32.	Knight M et al (23)	262		Neonatal encephalopathy (1)	Yes (67)	YES (2)	**Unclear whether symptomatic neonate was +ve**
33.	Kayem G et al (25)	181		-	Yes (37)	YES (1)	
34.	Nayak A et al (26)	131	7–10 (128) <7 (6)	Neonatal seizures (1), MAS (1)	Yes (24)		**Unclear whether symptomatic neonates were +ve**
35.	Prabhu et al (60)	73	9	-	Yes (13)	-	**Negative**
36.	Vivanti A et al (29)	1	4,7	irritability, poor feeding, axial hypertonia and opisthotonos	Yes (1)	-	**+ve**
37.	Li N et al (66)	17	9.6 ± 0.5, 10	-	-	-	
38.	Cao D et al (67)	11	8-9,10	-	-	-	
39.	Hu X et al (42)	7	7-8,8-9	-	-	-	
40.	Yang P et al (81)	7	8-9,9-10	Vomiting(1), RD (2), Moaning (2)	Yes (5)	-	**Negative**
41.	Yang H et al (73)	13	9,10	Fever(1)	-	-	
42.	Patane L et al (39)	2	9,10	Mild feeding difficulty (2)	Yes (1)	-	**+ve**
43.	Ferrazzi E et al (28)	42	<7 (2)	Gastrointestinal symptoms, RD (2)	Yes (3)	-	**+ve**
44.	Govind A et al (61)	9	<7 (2)	NNP (1)	Yes (1)	-	**+ve**
45.	Nie R et al (68)	28	8-10, 10	Pulmonary infection (1)	Yes (1)	-	**+ve**
46.	Yin M et al (46)	17	8,9	-	-	-	
47.	Doria M et al (71)	10	9,10	-	-	-	
48.	Perrone S et al (72)	4	9,10	-	-	-	
49.	Romagano M et al (82)	7	1-7,4-9	RD	Yes(7)	-	**Negative**
50.	Cooke W et al (83)	2	1-6, 3-8	Bowel perforation D6(1)	Yes(2)	-	**Negative**
51.	Lowe B et al (62)	1	9,9	-	-	-	
52.	Blauvelt C (84)	1	4,8	RD	YES(1)	-	**Negative**
53.	Kirtsman M et al (35)	1	9,9	Neutropenia, hypothermia, feeding difficulties, hypoglycemia	YES(1)	-	+ve
54.	Lyra J et al (74)	1	8,9	-	-	-	**Negative**

55.	Groß R et al (52)	2	-	Respiratory symptoms (2), icterus (1)	-	-	+ve
56.	Kulkarni et al (117)	1	6,9	Fever, icterus,and poor feeding	YES(1)	-	+ve
57.	Sisman J et al (70)	1	7,9	Fever, RD, Icterus	YES(1)	-	+ve

RD= Respiratory distress; MAS= Meconium aspiration syndrome; TTN= Transient Tachypnea of Newborn; NNP= Neonatal Pneumonia

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Title Page

Article Title- COVID-19 in pregnancy; The fetal perspective- a systematic review

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Title: COVID-19 in pregnancy; The fetal perspective- a systematic review

Abstract:

Objective: We aimed to conduct a systematic review of the available literature to determine the effects of confirmed cases of COVID-19 in pregnant women from the fetal perspective by estimation of mother to child transmission, perinatal outcome and possible teratogenicity.

Methods
Data sources: Eligible studies between November 1, 2019 and August 10, 2020 were retrieved from PubMed, Embase, LitCovid, Google Scholar, EBSCO MEDLINE, CENTRAL, CINAHL, MedRXiv, BioRXiv, and Scopus collection databases.English language case reports, case series and cohort studies of SARS-CoV-2 confirmed pregnant women with data on perinatal outcome, congenital anomalies and mother to child transmission were analysed.

Results: 38 case reports, 34 cohort and case series describing 1408 neonates were included for evidence acquisition of mother to child transmission. 29 case reports and 30 case series and cohort studies describing 1318 fetuses were included for the evaluation of perinatal outcome and congenital anomalies. A pooled proportion of 3.67% neonates had positive SARS-CoV-2 viral RNA nasopharyngeal swab results and 7.1 % had positive cord blood samples. 11.7% of the placenta, 6.8% of amniotic fluid, 9.6% of fecal and rectal swabs, and none of the urine samples were positive. The rate of preterm labor was 26.4% (OR=1.45, 95% CI- 1.03 to 2.03 with p = 0.03) and Cesarean delivery (CS) was 59.9% (OR=1.54, 95% CI- 1.17 to 2.03 with p = 0.002). The most common neonatal symptom was breathing difficulty (1.79%). Stillbirth rate was 9.9 per 1000 total births in babies born to COVID-19 mothers.

Conclusion: Chances of mother to child transmission of the SARS-CoV-2 virus is low. The perinatal outcome for the fetus is favorable. There is increased chances of CS but not preterm delivery.The stillbirth and neonatal death rates are low. There are no reported congenital anomalies in babies born to SARS CoV-2 positive mothers.

Keywords: COVID-19, SARS-CoV-2, mother to child transmission, perinatal outcome, congenital anomaly

KEY MESSAGE:

A. What is known about the subject –
Studies specifically analyzing all aspects of the fetus in SARS-CoV-2 positive mothers are not currently available. There are some systematic reviews reporting maternal outcomes, vertical transmission and neonatal outcomes involving a lesser number of pregnancies separately but aspects like fetal complications and teratogenicity are not adequately reported.

B. What this study adds –

The confirmed congenital transmission rate was found to be 9/1408 (0.63%). The risk of caesarean delivery is significantly higher in SARS-CoV-2 positive mothers but there is no significantly higher risk of prematurity. There is evidence of fetal distress, and neonatal respiratory symptoms in COVID-19 mothers but stillbirth is low.

INTRODUCTION

Novel coronavirus infection and associated coronavirus disease-2019 (COVID -19) pandemic has changed our lives forever and has compelled us to reconsider almost everything we have long taken for granted. Among the different coronaviruses severely affecting human species, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2 are significant, causing MERS, SARS, and COVID-19 respectively. SARS-CoV-2 strains show significant sequence homology to SARS-CoV and MERS-CoV **[1]**. As the pandemic evolved, there were significant advances in our knowledge about various aspects of the COVID-19 including epidemiology, clinical features, transmission, detection, and management modalities. Discoveries along the process of evolution are still contributing to our management practices.

There were concerns regarding the maternal and fetal effects since the beginning of the pandemic. The earlier evidence of COVID-19 in pregnancy pointed towards pregnancy being considered as low risk for the disease and no difference in disease behavior in pregnant and non-pregnant women was reported **[2]**. On the contrary, a newer study involving pooled data from more than 8000 women in the USA pointed towards a significantly higher rate of intensive care unit (ICU) admission [adjusted relative risk (aRR) = 1.5] and need for mechanical ventilation (aRR = 1.7) in pregnant women as compared to non-pregnant women, even when adjusted for race/ethnicity and underlying comorbid conditions **[3].** Similar findings were reported from other studies from the US and Sweden **[4-6].**

However, these studies did not specify adequately fetal effects resulting from congenital or neonatal infection in SARS-CoV-2 positive mothers and consequent perinatal outcomes. Evidence of COVID-19 specifically focusing on fetal and neonatal outcomes are lacking. Most of the reported literature have smaller studies. Previous systematic reviews focusing on the outcomes of all coronaviruses have reported a higher risk of pre-eclampsia, preterm birth, miscarriage, and perinatal death.

Through this article, we want to analyze the published evidence on the fetal perspective of COVID-19 infection concerning mother to child transmission (congenital or neonatal infection) and perinatal outcome through a systematic review. This will aid in alleviating uncertainties faced while doing patient counseling and help in subsequent management during these testing times.

METHODS

Search strategy: A systematic search of PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus electronic database was done. Medical subject handling terms (MeSH) and free text term keywords like vertical transmission, perinatal outcome, fetal, neonate, newborn, pregnancy were used in combination with COVID-19, 2019-nCoV, SARS-CoV- 2 to search for data from 1st November 2019 till 10th July 2020. Thereafter manual update was done on weekly basis till 10th August 2020. The references of relevant studies were also searched.

The keywords detail and full search strategy used in each of PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus electronic database are as follows: Both medical subject headings (MeSH) and key-words: "2019 novel coronavirus infection" OR "COVID-19" OR "COVID19" OR "coronavirus disease 2019" OR "nCoV infection" OR "2019-nCoV" OR "2019 novel coronavirus" OR "2019 coronavirus" OR "novel coronavirus" OR (2019 AND coronavirus) OR "SARS CoV-2" OR "SARS CoV2" AND "vertical transmission" OR "fetal outcome" OR "perinatal outcome" OR "neonatal outcome" OR "pregnancy" OR "congenital infection" OR "mother-to-child transmission" OR "(transmission AND vertical)" OR "(transmission AND fetomaternal) " OR "teratogenicity".

Selection criteria: The search consisted of only English language articles (original English articles and other language articles with available English translation) including case reports, case series, and letters to editors containing case information. After a thorough screening, no randomized clinical trials or cohort studies were found.

Inclusion criteria: The studies fulfilling all of the following criteria (1,2 and 3) were included for review.

1- Studies reporting pregnant women with confirmed COVID-19 who had delivered.

2- Studies containing the results of the SARS-CoV-2 test [including reverse transcriptase-polymerase chain reaction (RT-PCR) and serological tests] in both mothers and newborns samples.

3- Studies that present the out-come of vertical transmission or congenital transmission or neonatal transmission or the perinatal outcome or congenital anomaly.

Exclusion criteria: Exclusions consisted of studies in pregnant women yet to deliver, duplicated studies, review articles, articles in languages other than English where translation was not possible, studies where infection in mothers is not confirmed, or where neonatal testing was not done. Conference abstracts, expert opinions, and critical appraisals were also excluded.

Both the authors (RD, SSK) reviewed all titles independently. The potential relevance of the studies to be included for review were agreed upon by discussion. Selected titles and abstracts were further screened between studies to reject overlap of cases.

Full-text copies of the selected papers were obtained and the relevant data regarding study characteristics, evidence of vertical transmission, and perinatal outcomes were extracted by the same two reviewers independently. In the case of individual case reports, if the same patient was included in more than 1 study with similar characteristics and findings, only the report with a larger number of patients was included. As far as possible, single case reports were cross-checked with other reports from the same location and hospital. If a case series included multiple locations, the individual reports from the same centers were excluded. Similarly, if the time-frame of the reported cases matched from the same center, the characteristics were compared to decide regarding the inclusion or exclusion from the study. Finally, studies were screened by assessing selection, comparability, and exposure for inclusion into evidence acquisition of mother to child transmission (congenital or neonatal transmission) and/or perinatal outcome measures **[Table-1a,1b].**

Study Outcomes

1. Mother to child transmission-

Evidence of mother to child transmission (congenital or neonatal transmission) is indicated by positive RT-PCR status in different samples like the neonatal nasopharyngeal swab, cord blood, amniotic fluid, breast milk, and placental tissue. Transmission of infection from mother to fetus generally includes transmission through germ cells or the placenta during pregnancy, via the birth canal during labor and delivery, and the postpartum period through breastfeeding or close contact. The transfer of microorganisms during pregnancy is seen with many of the common pathogens with resultant effects ranging from asymptomatic infection, intrauterine growth restriction, intrauterine death, and structural anomalies as a sequel of infection. Some pathogens like cytomegalovirus (CMV) or Zika virus produce mild to no symptoms in the pregnant patient but can cause congenital infection with severe consequences **[7].** Viruses specifically can be transmitted to the fetus via the maternal blood when it enters the placental villus, containing the fetal blood vessels, or by direct access to the placenta from the lower genital tract by ascending infection **[8].** Again even when transferred trans-placentally during the antenatal period, the specific timing of maternal infection can have different effects on the fetus. The first-trimester infection can cause severe structural anomalies whereas second and third-trimester infections are more likely to cause functional organ abnormalities **[9].**

Several factors are contributing to the concerns of mother to child transmission in Covid-19. It is known that the SARS-COV-2 uses angiotensin-converting enzyme 2 (ACE2)

receptors for entry into the cells. ACE-2 receptors are detected in various parts of the uterus, vagina, decidual cells, and placenta **[10-13].** Recently, the case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates has been published with a categorization of infection into confirmed, probable, possible, unlikely, and not infected groups **[14]**.

Congenital infection with intrauterine fetal death/stillbirth is **[14]**-

- confirmed from fetal tissue or autopsy material if the virus is detected by PCR from fetal or placental tissue or electron microscopic detection of the viral particle in tissue or viral growth in culture from fetal or placental tissue.
- a probable infection if the virus is detected by PCR in the surface swab from the fetus or placental swab on the fetal side.
- unlikely if it is positive in the maternal side of the placenta but fetal tissues are not tested and not present if it is not detected in fetal tissue in an autopsy.

Similarly, congenital infection in live-born symptomatic neonate is **[14]**-

- confirmed when the virus is detected by PCR in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or amniotic fluid collected prior to the rupture of the membrane.
- a probable infection when there is the detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) AND placental swab from the fetal side of the placenta in a neonate born via cesarean section before rupture of membrane or placental tissue.
- possible when there are anti-SARS-CoV-2 IgM antibodies in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or placental tissue but nasopharyngeal swab test at birth is negative.
- unlikely or absent when samples are negative within 12 hours of birth (nasopharyngeal swab, umbilical cord blood, or neonatal blood) and antibody testing is not done or negative, respectively.

If a live-born neonate has no clinical features of infection, congenital infection is **[14]**-

- confirmed by detection of the virus by PCR in cord blood or neonatal blood collected within the first 12 hours of birth.
- probable if the virus is detected by PCR in amniotic fluid collected prior to rupture of the membrane but no detection in umbilical cord blood or neonatal blood collected within the first 12 hours of birth.
- possible when there is anti-SARS-CoV-2 IgM in umbilical cord blood or detection of the virus by PCR in placental tissue but PCR in umbilical cord blood, amniotic fluid, and neonatal blood (<12hours of life) is negative.

Furthermore, infection acquired intrapartum in a symptomatic neonate is confirmed if the virus is detected by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age AND alternate explanation for clinical features excluded **[14].**

Intrapartum neonatal infection in asymptomatic neonate is confirmed by detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age **[14]**.

Postpartum infection is confirmed if a neonate shows symptoms beyond 48 hours of life and the nasopharyngeal swab is positive beyond 48hours which was negative at birth**[14]**.

If a neonate is born with a specific structural sequel of an infection, intrauterine infection is a probability. The probability of infection also depends on the presence of the agent in the genital tract and time taken from exposure to detection by definitive tests to differentiate between intrapartum and postpartum infection. Furthermore, the sensitivity of RT-PCR testing is different for detecting SARS-CoV-2 in different samples. Therefore, it is rational to test samples from multiple sites to improve detection and reduce false-negative cases **[9, 15].**

2. Perinatal outcome

Perinatal outcome measures included fetal outcomes like fetal complications in SARS-CoV 2 positive pregnant women, gestational age at delivery (preterm delivery), mode of delivery, birth weight, and stillbirth. The neonatal period is defined as the time period from birth until the end of the first 28 days of life. Events in the early neonatal period (first 7 days) usually are related to the pregnancy more significantly and it is also included in the definition of the perinatal period. In this review, we have assessed the neonatal outcomes using the APGAR score at 1 minute and 5 minutes of life, neonatal symptoms, admission into neonatal intensive care unit (ICU), and neonatal death, as the parameters. An APGAR score of less than 7 at 1 minute and 5 minutes after birth in a newborn is defined as a low APGAR score in this study **[16].** Any outcome measures not explicitly mentioned were considered not to have been reported.

- Fetal distress (FD) is assessed during labor by non-reassuring or pathological cardiotocographic (CTG) findings and meconium-stained amniotic fluid **[17, 18]**. For this research, studies reporting FD, abnormal or non-re-assuring or pathological CTG, fetal compromise, meconium-stained amniotic fluid are included under FD. Other fetal complications were pre-labor rupture of membranes and preterm prelabor rupture of membranes.
- Preterm delivery is defined as delivery of a viable product of conception before 37 completed weeks of gestation.

- Delivery can be vaginal delivery (including instrumental) and by caesarean section (CS). For this research, instrumental vaginal deliveries and normal vaginal deliveries were considered together (VD).
- Both the Royal College of Obstetrics and Gynecology and the American College of Obstetricians and Gynecologists have adopted the definition of Intrauterine growth restriction (IUGR) is defined as an estimated fetal weight less than 10th percentile. The term is IUGR has been used interchangeably with Small for gestational age (SGA). SGA is a term commonly used for a neonate with birth weight less than 10 percent **[19,20].**
- For this research, stillbirth was considered as fetal death beyond 24 weeks of gestation, and stillbirth rate (SBR) is calculated as the number of stillbirths per 1000 total births.

Statistical analysis: Pooled proportions of categorical variables were calculated with percentage after obtaining the positive rates of each of the SARS-CoV-2 testing methods used, wherever applicable. Odds Ratio was calculated for the fetal outcome of preterm delivery and mode of delivery in the SARS-CoV-2 positive mothers from the pooled data (combining the studies where the control group of SARS-CoV-2 negative pregnant women was available) with 95% confidence interval and p values. The percentage of the most common variables were also calculated.

Public and patient involvement statement: This research is not “coproduced” with patients, carers or members of the public.

RESULTS

1. Mother to child transmission-

Search Results:

Out of 100 records selected for full-text review, 3 Chinese , 1 Italian , 1 Dutch and 1 Spanish studies were excluded due to nonavailability of English translation. 72 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. 38 studies were case reports containing 4 or fewer number of cases and 34 studies had 5 or more number of patients **(Figure-1).**

Since evidence from randomized control trials were not available until the time of the search, 34 studies having 5 or more number of patients were considered for qualitative analysis **[21, 22].** However, the findings from the case reports were also noted. The majority of earlier studies were from China but later studies contained cases from the rest of the world **[Table-1a,1b].**

Table-1 (a): Analysis of the studies [Case series/ Cohort] -Supplemental material

Table-1 (b): Analysis of the studies [Case reports] -Supplemental material

Systematic review:

Tests for diagnosis of SARS-CoV-2 was done in a total of 1408 neonates. The most common type of sample tested was neonatal nasopharyngeal samples (NP swab) (67 out of 72 studies) followed by the placenta, amniotic fluid, and cord blood. In the majority, samples were taken from more than one site. In a few studies, the same type of sample was repeated at different intervals (e.g., NP swab and breast milk samples) **[Table-2].**

Table -2 Studies and type of samples

Serial Number	Author (reference)	Number of neonates tested	Specimen tested	Results- neonatal and others	Positive/ Total tested
1.	Chen H et al (45)	6	NP, AF, Cord blood, BM	Negative	
2.	Cao et al (67)	5	NP	Negative	
3.	Hu X et al (42)	7	NP, Urine, AF	NP +ve at 36 hours, others negative	1/7
4.	Zhu H et al (57)	10	NP	Negative [within 72 hours (8); Between D7-D9 (2)]	
5.	Zhang I et al (102)	10	NP	Negative	
6.	Penfield C et al (103)	11	NP, Placental and membrane	NP- Negative (D1 and D5) Placenta and membrane +ve	3/11
7.	Knight M et al (23)	262	NP (n=244) ,Blood or aspirate	+ve at <12 hours +ve at >12 hours	6/244 6/244
8.	Kayem G et al (25)	181	NP	+ve	2/181
9.	Nayak A et al (26)	134	NP (n=131)	+ve on D1., -ve on D5	3/131
10.	Yan J et al (24)	86	NP (n=86); Cord blood (n=10),AF (n=10)	Negative	
11.	Khan S et al (64)	17	NP	+ve within 24 hours	2/17
12.	Zeng L et al (41)	33	NP , anal swab	Both +ve D2 and D4, negative on D6	3/33
13.	Breslin N et al (59)	18	NP	Negative	
14.	Breslin N et al (114)	7	NP	Negative	
15.	Qiancheng X et al (107)	23	NP	Negative	
16.	Prabhu M et al (60)	71	NP	Negative at 24 hours	
17.	Shanes E et al (36)	16	NP , Placenta	Negative	
18.	Savasi V et al (109)	57	NP	+ve	4/57
19.	London V et al (27)	48	NP	Negative	
20.	William R et al (63)	33	NP	Negative at 24 hours, +ve at 48 hours	1/33
21.	Perez O et al (65)	82	NP	NP +ve at birth and negative at 48 hours (3); NP negative at birth but +ve at D10 (2)	5/82
22.	Nie R et al (68)	26	NP, Cord blood, Placenta	NP +ve at 36 hours, Negative - All other samples, NP (D4,D8,D15)	1/26
23.	Yin M et al (46)	17	NP (n=17), BM (n=14), AF (n=2), placenta (n=2), Anal swab (n=5)	Negative	
24.	Yang P et al(81)	7	NP , Cord blood, AF	Negative	
25.	Yang H et al (73)	55	NP	Negative	
26.	Wu Y et al (47)	5	NP , Anal swab, BM	Negative, BM +ve	1/5
27.	Patane L et al (39)	22	NP , Placenta	NP +ve , Placenta- Chronic intervillitis, PCR +ve in placenta	2/22
28.	Ferrazzi E et al (28)	42	NP	NP +ve on D1,D3(2) NP equivocal at birth but +ve on D3(1)	3/42
29.	Govind A et al (61)	9	NP , Placenta, AF	NP +ve	1/9
30.	Vintzileos W et al (113)	29	NP	Negative	
31.	Baergen R et al (37)	21	NP	Negative	
32.	Zeng H et al (54)	6	NP Neonatal blood	NP negative; Elevated IgM and IgG (2); Elevated IgG ,normal IgM (3)	Cytokine IL-6 elevated in all infants
33.	Liu Y et al (69)	10	Fetal blood	Negative	
34.	Mulvey J et al (38)	5	Placenta	Negative	

35.	Hantoushzadeh et al (75)	4	NP	Negative at D1; +ve at D7	1/4
36.	Buonsenso et al (53)	2	NP,AF, Placenta, Cord blood, Rectal swab, BM	1st- NP Negative on D1,D4 and +ve on D15 , Placenta, AF, rectal swab-Negative, Weak IgG+ve, IgM negative 2nd - Placenta, Breast milk- +ve but cord blood negative in neonate with NP negative result	1/2
37.	Fan C et al (48)	2	NP, AF, Cord blood, BM, Placenta , Vaginal swab	Negative	
38.	Liu W et al (56)	3	NP, Cord blood, Neonatal whole blood	Negative (D2)	
39.	Lowe B et al (62)	1	NP	Negative	
40.	Chen S et al (104)	3	NP, Placenta	Negative	
41.	Chen Y et al (58)	4	NP	Negative	
42.	Gidlöf S et al (76)	2	NP	Negative (34 hours and 4.5 days)	
43.	Khan S et al (85)	3	NP	Negative	
44.	Schnettler W et al (110)	1	NP, AF	AF Negative, NP negative on D1,D2	
45.	Blauvelt C et al (84)	1	NP, Rectal swab D2 Ig G and IgM	NP Negative on D1, D2, D14 Rectal swab negative on D2 Ig G and IgM negative (D5)	
46.	Alzamora M et al (78)	1	NP, Cord blood	Negative for IgM and IgG; NP +ve at 16 hours and 48hours	1/1
47.	Vivanti A et al (29)	1	NP, AF, Vaginal swab, NBAL, Neonatal blood and rectal swabs	NP +ve at 1hour, D3, D18; Rectal swab +ve at 1hour, D3, D18; Vaginal swab, NBAL, Neonatal blood, AF +ve,	1/1
48.	Song L et al (49)	1	NP, AF, Cord blood, BM	NP negative at D3,D7 All other negative	
49.	Zambrano L et al (87)	1	NP	Negative	
50.	Li Y et al (44)	1	NP, Neonatal Blood, feces, and urine	NP negative at birth and 48h All other negative	
51.	Dong L et al (55)	1	NP, Serum Vaginal swab	IgM level elevated NP negative at 2h,16h	1/1
52.	Baud D et al (33)	1	NP, AF, Placenta Vaginal swabs	Placenta +ve All other negative	1/1; 2nd trimester spontaneous miscarriage
53.	Wang X et al (77)	1	NP, AF, Placenta, Cord blood, gastric juice, feces	NP negative at D1, D3, D7, D9 All other negative	
54.	Huang J et al (86)	1	NP	Negative	
55.	Iqbal S et al (105)	1	NP	Negative	
56.	Kalafat E et al (79)	1	NP, Cord blood, Placenta	Negative	
57.	Lee D et al (80)	1	NP, AF, Cord blood, Placenta, neonatal serum, anal swab	Negative	
58.	Liao X et al (106)	1	NP , AF, Cord blood, Placenta	Negative	
59.	Xiong X et al (50)	1	NP, AF, BM, rectal swab	Negative	
60.	Wang S et al (51)	1	NP , Placenta, Cord blood, BM	NP +ve at 36 h Negative in all others	1/1
61.	Zamaniyan M et al (30)	1	NP, Cord blood, AF, Vaginal secretion	NP – Negative at 0 hours, +ve at D2, D4, D6 AF +ve , all others negative	1/1
62.	Kirtsman M et al (35)	1	NP, Placental, Stool, BM Neonatal plasma D4	NP +ve at D1, D2, D7 Placenta +ve Stool +ve D7, BM +ve	1/1
63.	Lyra J et al(74)	1	NP	Negative	
64.	Algorroba G et al (34)	1	NP	Negative at 0 h,D2, D7	
65.	Peng Z et al (43)	1	NP, NBAL Fluid, Sputum, Urine	Negative	
66.	Groß R et al (52)	2	BM, NP	Both NP +ve (>D7) , BM +ve (1)	2/2,1/2
67.	Perrone S et al (72)	4	NP (3),Placenta (1)	NP negative on D1, Placenta-negative	
68.	Hosier H et al (32)	1	Placenta, cord blood	Both +ve	1/1; D& E at 22 weeks
69.	Pulinx B et al (31)	2	AF, Placental	Both +ve	2/2, DCDA twin at 24 weeks
70.	Yu N et al (108)	2	AF in mid pregnancy	Negative	
71.	Kulkarni et al (117)	1	NP, Placenta, Cord stump, Neonatal blood	All +ve at 12 hours of life; Serology negative on D10 but +ve on D21	1/1

72.	Sisman J et al (70)	1	NP, Placenta	NP +ve at 24 hours, 48 hours, D14; Placenta +ve by electron microscopy	1/1

AF= Amniotic fluid; NP= Neonatal Pharyngeal/throat swab; BM= Breast milk; NBAL= Non-bronchoscopic broncho-alveolar lavage fluid; D&E- dilatation and evacuation; D1= 1st day of life,D4= 4th day of life.

i. Neonatal Nasopharyngeal swab

In our review, a total of 1388 neonates born to mothers with COVID-19 infection were tested by NP swabs. 51 neonates were found positive by the RT-PCR test constituting 3.67% of total pooled samples. **[Table-3a].**

Table-3 (a): Mother to child transmission-Test positive (Pooled result) - Supplimental material

SAMPLE Tested by RT-PCR for SARS-CoV-2	Number of studies	Number Tested	Number Positive	Pooled Percentage
Neonatal Naso-pharyngeal swab	67 [32 case series/cohort +35 case reports]	1388 [1335 case series/cohort+53 case reports]	51 [40 out of 1335 in case series/cohort+ 11 out of 53 case reports]	3.67% [3% in case series/cohort; 2.07% in case reports]
Placenta ± Membranes	22	111	13	11.7%
Amniotic fluid	19	58	4	6.8%
Breast milk	10	56	3	5.3%
Cord blood/ plasma	16	56	4	7.1%
Other neonatal samples -Anal swab -Urine	 11 3	 52 9	 5 0	9.6%
Neonatal serology				
IgM	5	11	(Elevated) 3	27%
IgG	4	10	(Elevated) 6	60%

The largest cohort study from the UK involved 427 pregnant women with COVID-19. 244 out of the 262 neonates were tested by NP swab. 6 of the neonates were positive for SARS-CoV-2 within 12 hours of birth and 6 more were positive after 12 hours of birth (12 out of 244; 4.9%) **[23].** Studies involving 181 women and 116 women in China showed 2 positive neonates out of 181 (2 out of 181; 1.1%) and no positive cases for SARS-CoV-2 in the other study **[24, 25].** An analysis of 141 women from a hospital in India showed that 3 of the 131 neonates were tested positive for SARS-CoV-2 by NP swab **[26].** In another study in a New York Hospital, 48 neonates born to 55 women were all tested negative on Day 0 of life **[27].** However, One Italian study found three infants positive by NP swab out of 42 tested within 48 hours after birth **[28].**

One recent case report revealed that RT-PCR was positive for SARS-CoV-2 in all of the samples for amniotic fluid, vaginal swab, blood, and non-bronchoscopic bronchoalveolar lavage fluid as well as NP swab and rectal swabs collected at 1 hour of life, and then repeated at 3 days and 18 days suggesting a trans-placental transmission **[29].**

As stated earlier NP swab positivity at different neonatal ages plays an important role in confirming or ruling out the viral transmission from a SARS-CoV-2 positive mother.
On further analysis of the positive samples, the congenital infection was confirmed in 5 live-born neonates, possible in 5 neonates, and probable in 2 neonates. Neonatal infection acquired intrapartum was confirmed in 2 neonates, probable in 5 neonates, and possible in 14 neonates. Similarly, neonatal infection acquired postpartum was confirmed in 7 neonates and infection was unlikely in 1 neonate **[Table-3b].**

Table-3 (b): Analysis of evidence of congenital/ intrapartum/ postpartum transmission

Author (reference) [samples positive/ total tested]	Samples +ve	Fetal/ Neonatal status	Alternate explanation for clinical features	Mother to child transmission (n)
Groß R et al (52) [2/2]	NP >D7	Respiratory symptoms (2), icterus (1)	Alternate explanation-excluded in 1 ; Respiratory syncytial virus +ve in 1	Neonatal infection acquired postpartum-Confirmed (1) Unlikely (1)
Buonsenso et al (53) [1/2]	1st- NP Negative on D1, D4 and +ve on D15, Placenta, AF, rectal swab-Negative, Weak IgG+ve, IgM negative 2nd - Placenta, Breast milk-+ve but cord blood negative in neonate with NP negative result	Symptoms- Absent	-	Neonatal infection acquired postpartum-Confirmed (asymptomatic) (1st) Possible congenital infection (2nd)
Vivanti A et al (29) [1/1]	NP +ve at 1hour, D3, D18; Rectal swab +ve at 1hour, D3, D18; Vaginal swab, NBAL, Neonatal blood +ve	Irritability, poor feeding, axial hypertonia and opisthotonos	Alternate explanation-excluded	Confirmed congenital infection
Kirtsman M et al (35) [1/1]	NP +ve at birth, D2, D7 Placenta (fetal side) +ve Stool +ve D7, BM +ve	Hypothermia, feeding difficulties, hypoglycemia, neutropenia	Alternate explanation-excluded	Probable congenital infection
Zamaniyan M et al (30) [1/1]	NP - negative at 0 hours, +ve at D2, D4, D6 AF before rupture of membranes +ve Cord blood and vaginal secretion - negative	Fever (1)	Alternate explanation-not identified	Confirmed congenital infection
Wang S et al (51) [1/1]	NP +ve at 36 hours Placenta, Cord blood, BM-Negative	Vomiting, lymphopenia, abnormal liver enzyme levels	Alternate explanation-excluded	Neonatal infection acquired intrapartum possible
Khan S et al (64) [2/17]	NP +ve within 24 hours	NNP	Alternate explanation-not identified	Neonatal infection acquired intrapartum- possible
Zeng L et al (41) [3/33]	NP +ve at D2, D4, negative at D6	RD (1); Cyanosis, feeding intolerance(1); Fever (2); NNP(3); Lethargy, fever(1); lethargy, fever, NNP, vomiting leukocytosis,lymphocytopenia, (1); Preterm- Neonatal RDS, NNP, lymphocytopenia (1)	Alternate explanation-excluded	Neonatal infection acquired intrapartum-possible NP not done at birth, no other samples tested
Hu X et al (42) [1/7]	NP +ve at 36 hours; fetal urine, AF are negative	Symptoms- Absent	-	Neonatal infection acquired intrapartum- Possible NP not done at birth
Knight M et al (23) [12/244]	NP +ve at <12 hours (6) NP +ve at >12 hours (6)	Neonatal encephalopathy (1)	-	Congenital infection possible(1) Other evidences lacking
Alzamora M et al (78) [1/1]	NP +ve at 16 hours and 48 hours	Respiratory difficulty and cough	Alternate explanation-excluded	Neonatal infection acquired intrapartum - confirmed NP not done at birth

	Cord Blood IgM and Ig G negative at D1 and D5			
Hantoushzadeh et al (75) [1/4]	NP -ve on D1, +ve on D7	NNP, lymphopenia (1)	-	Neonatal infection acquired postpartum-Confirmed
William R et al (63) [1/33]	Negative at 24 hours, +ve at 48 hours	Symptoms- Absent	-	Neonatal infection acquired postpartum-Confirmed
Nayak A et al (26) [3/131]	NP +ve on D1;-ve on D5	Neonatal seizures, MAS (1)	-	Probable neonatal infection acquired intrapartum
Nie R et al (68) [1/26]	NP +ve at 36 hours, negative - D4, D8,D15; Cord blood, placenta-negative	Pulmonary infection (1)	Alternate explanation-not identified	Neonatal infection acquired intrapartum - Possible NP not done at birth
Savasi V et al (109) [4/57]	Timing of NP test could not be ascertained (early postpartum period)	-	-	-
Kayem G et al (25) [2/181]	Timing of test could not be ascertained	-	-	-
Patane L et al (39) [2/22]	1st- NP +ve at birth,>24hours, >7 days 2nd- NP negative at birth, +ve on D7 Placenta- Chronic intervillitis, PCR +ve in both placenta	Mild feeding difficulty (2)	-	Probable congenital infection (1) Possible congenital infection (1)
Ferrazzi E et al (28) [3/42]	NP +ve on D1, D3(2) NP equivocal at birth but +ve on D3(1)	Gastrointestinal symptoms, RD (2)	Alternate explanation-not identified	Neonatal infection acquired postpartum-Confirmed (1) Neonatal infection acquired intrapartum - possible(2) Other evidences lacking
Govind A et al (61) [1/9]	NP at birth	NNP (1)	Alternate explanation-excluded	Neonatal infection acquired intrapartum - confirmed? NP not done after 24 hours
Penfield C et al (103) [3/11]	NP- Negative (D1 and D5) Placenta and membrane +ve	Symptoms- Absent		Neonatal infection acquired intrapartum - Possible
Baud D et al (33) [1/1]	NP, AF, Vaginal swabs-Negative Placenta +ve	2nd trimester spontaneous miscarriage		Confirmed congenital infection
Hosier H et al (32) [1/1]	Placenta, cord blood-both +ve	D& E at 22 weeks		Confirmed congenital infection
Pulinx B et al (31) [2/2]	AF, Placenta-both +ve	DCDA twin at 24 weeks expelled		Confirmed congenital infection
Dong L et al (55) [1/1]	IgM level elevated NP negative at 2h,16h	Symptoms-absent	-	Possible congenital infection
Zeng H et al (54) [1/1]	NP negative; Elevated IgM and IgG (2); Elevated IgG ,normal IgM (3)	Symptoms-absent	-	Possible congenital infection
Perez O et al (65) [5/82]	NP +ve at birth and negative at 48 hours (3); NP negative at birth but +ve at D10 (2)	RD (2) Symptoms-absent (3)	Alternate explanation-not identified (2)	Neonatal infection acquired intrapartum – Probable (2) Neonatal infection acquired intrapartum – Possible (1) Neonatal infection acquired postpartum-Confirmed (2)
Kulkarni et al (117) [1/1]	NP, placenta, Cord stump RT PCR- All +ve at 12 hours of life NP at D5 and D10 +ve	Fever, icterus, and poor feeding	Alternate explanation-excluded	Confirmed congenital infection
Sisman J et al (70) [1/1]	NP +ve at 24 hours, 48 hours, D14 Placenta +ve by electron microscopy	Fever, RD, Icterus	Alternate explanation-excluded	Confirmed congenital infection

AF= Amniotic fluid; NP= Neonatal Pharyngeal/throat swab; BM= Breast milk; NBAL= Non-bronchoscopic broncho-alveolar lavage fluid; NNP=Neonatal Pneumonia; D&E- dilatation and evacuation; RD= Respiratory distress; DCDA- Dichorionic diamniotic twin

However, in a larger study, out of 12 neonates with positive NP result [6 within 12 hours of life and 6 at more than 12 hours of life], further analysis was not possible due to lack of followup swab results and unavailability of test results of other maternal samples like placenta and amniotic fluid **[23].**

ii. Amniotic fluid

In our review, 58 samples of amniotic fluid were tested in 19 studies with a positive result in 4 samples **[29, 30, 31]**. Congenital infection is confirmed in 2 of the studies in live-born neonates **[29, 30].** Congenital infection is also confirmed in a dichorionic, diamniotic (DCDA) twin expelled at 24 weeks by positive amniotic fluid result **[31].**

iii. Placenta

A total of 22 studies were identified in our review where the placenta was examined for the presence of SARS-CoV-2 or related pathological changes. A total of 111 placental samples were tested and 13 were found positive for SARS-CoV-2. PCR for SARS-CoV-2 RNA was positive from the placenta in two case reports where there were spontaneous miscarriage and dilatation and curettage respectively confirming a congenital infection **[32, 33].** In one of them, the umbilical cord was also positive for the virus, but the fetal organs were tested negative. The virus was confirmed to be localized mostly in the syncytiotrophoblastic cells of the placenta by immunohistochemistry for the SARS-CoV-2 spike protein as well as electron microscopy and it was identical to the typically locally isolated virus **[32].** In another study, electron microscopy showed the presence of the virus in the fetal side of the placenta. The virions were present in the mesenchymal core of the terminal villus and were demonstrated to be invading a syncytiotrophoblast and a microvillus. However, the neonate delivered at 28 weeks in this pregnancy was tested negative for the virus **[34].**

Evidence of probable mother to child transmission was obtained in another case where the newborn was found positive for the virus by nasopharyngeal swab, plasma, and stool samples along with the placenta **[35].** Similarly, confirmed congenital transmission of the virus was demonstrated by another study where SARS-CoV-2 was detected in amniotic fluid aspirated before the rupture of the membranes, vaginal swab, neonatal blood, bronchoalveolar lavage fluid, and neonatal swabs on repeated occasions at 1 hour, 3rd day and 18th day of life. The trophoblastic cells showed SARS-CoV-2 N protein on immunostaining **[29].**

Placental pathological examination showed an array of changes including vascular malperfusion, fibrin deposition, and chronic villitis, intervillositis, and villous infarctions in our review. Two of these studies showed vascular malperfusion in 10 out of 20 placentas and 12 out of 15 placentas respectively but there were no assessments of placentas in these studies for the presence of SARS-CoV-2 infection. However, neonatal swabs were negative for the virus **[36, 37]**. Similar pathological changes were seen in another study involving five SARS-CoV-2 positive pregnant women but the placentas were negative for the virus on direct testing for SARS-CoV-2 **[38].** Chronic intervillositis was also seen in the pathological examination of the placentas of two women where the neonates were positive for SARS-CoV2 by nasopharyngeal swab testing **[39].** Examination showed

severe chronic villitis in another case where there was a stillbirth at term but direct tests of fetal tissues and placenta did not show infection with the virus **[40].**

iv. Other samples

Various other samples were tested for SARS-CoV-2 by different studies. Anal swab, rectal swab, or fecal sample was positive in 9.6% of neonates in our study. The stool sample was positive in two of the studies on Day 2 and Day 7 of life **[35, 41].** The urine sample was tested in only 3 studies without any positive results **[42- 44].** Breast milk was tested by RT-PCR in 10 of the studies with a pooled positive rate of 5.3% (3 out of 56) **[35, 45- 53]**. In one of the studies, the breast milk sample was positive in 4 consecutive days coinciding with the maternal symptoms in one woman but it was negative in milk samples of another woman. Both the babies were positive by the nasopharyngeal swab test and were symptomatic **[52].** A vaginal swab was tested in 23 women with one positive result (4.3%) **[29].** Since IgM cannot cross the placenta, elevated IgM levels in the neonate indicate possible congenital infection, as seen in some of the neonates in this review **[54, 55]**. However, the assay of IgM for the detection of infection has significant false-positive results.

2. Perinatal outcome-

Search results:

Out of 73 records selected for full-text review,1 Chinese and 1 Spanish study were excluded due to unavailability of English translation. a total of 60 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. 31 studies qualified as case series/cohort and 29 studies contained 4 or fewer cases in our review **(Figure-2)**. No randomized control trials were available until the time of the search.

Systematic Review:

2.1 Fetal Outcomes:

i. Fetal complications in SARS-CoV-2 +ve pregnant women

In our review, a total of 30 studies reported any fetal effects excluding all pregnancy losses or intrauterine fetal deaths (IUFD) **[Table no-4].** The most commonly reported effect was fetal distress in 36 out of 1311 pregnancies (2.74%). In addition to fetal distress, some studies have reported non-reassuring or pathological cardiotocography (CTG) (11 out of 1311; 0.83 %), and some have mentioned meconium-stained amniotic fluid (3 out of 1311; 0.22%), both findings can also be considered as evidence of fetal distress **[29, 56- 62]**. In another study involving 262 deliveries, the fetal compromise was seen in 37 fetuses and an emergency caesarean section (CS) was done in 9 of them **[23].**

Thus, the cumulative chance of fetal distress in pregnant women with a positive test for SARS-CoV-2 is 6.63%.

Premature rupture of membrane (PROM) was reported in 42 pregnancies from 13 studies and Preterm PROM was reported in (PPROM) in 14 pregnancies **[24, 41, 42, 45, 50, 57, 60, 63-70].** Intrauterine growth restriction (IUGR) was reported in 12 fetuses in 5 studies **[24, 63, 65, 71, 72].** The highest number of IUGR fetuses was reported in 6 out of 10 fetuses in another study **[71]**. Besides, small for gestational age was reported in another study in 2 out of 10 fetuses **[57].** Chorioamnionitis was reported only in one study involving 3 fetuses **[5].**

Table-4: Fetal outcome

Serial number	Author (reference)	Number of neonates from SARS CoV-2 +ve pregnancies	Fetal complications (n)	Mode of delivery (n)	Birth weight in grams	Preterm delivery (n)	Still birth(n)	Comments
1.	Chen H et al (45)	9	FD (2) PROM (1)	CS (9)	1880-3730	Yes (2)	-	
2.	Romagano M et al (82)	7	-	CS(7)	1290-2580 (AGA)	Yes (7)		
3.	Zeng H et al (54)	6		CS (6)			-	
4.	Zhu H et al (57)	10	FD (6), PROM (3), MSA (2)	CS (7) VD (2)	SGA-2 LGA/Normal-8	Yes (6)	-	1 twin delivery
5.	Khan S et al (64)	17	PROM	CS (17)	2300–3750 <2700-3	Yes (5)	-	
6.	Zeng L et al (41)	33	PROM (3); FD (1)	VD (7); CS (26)	SGA (3) 1580-3360	Yes(4)	-	
7.	Breslin N et al (59)	18	Ab.CTG (3)	CS (8); VD (10)		Yes (1)	-	
8.	Qiancheng X et al (107)	23	-	CS (17) VD (5)	3130 (2915–3390)	Yes(1)	-	1 twin delivery
9.	Hantoushzadeh S et al (75)	5	IUFD (3)	CS (4)	1180-3200	Yes (3)	Yes (1)	1 twin delivery
10.	Perez O et al (65)	82	PROM (18) PPROM (7) IUGR (1)	VD (41) CS (41)	1450-3210	Yes (25)	-	
11.	Savasi V et al (109)	57	-	VD (34) CS (22)	3160 (840-4350)	Yes(12)	-	1 twin delivery
12.	London V et al (27)	56	DFM (1) IUFD (17 wks) (1)	CS (22) VD (33)	-	Yes(12)	-	
13.	Lokken E et al (40)	8	FD (3)	CS (3) VD (5)	-	Yes (1)	Yes(1)	
14.	Yan J et al (24)	99	FD (9); IUGR (2) PPROM (6)	CS (85) VD(14)	3108±526	Yes (21)	-	
15.	William R et al (63)	32	IUGR(2), PPROM (1)	CS (24) VD(8)	2403.3±858	Yes (19)	-	
16.	Knight M et al (23)	262	Miscarriage (4); Fetal compromise (37)	CS (156) VD (106)	-	Yes (66)	Yes (3)	
17.	Kayem G et al (25)	176	Fetal loss <21 weeks (5)	CS (87) VD (89)	-	Yes (50)	Yes (2)	
18.	Nayak A et al (26)	134	Miscarriage (6)	CS (67) VD(67)	>2500 (92) <2500 (39)	Yes (38)	Yes (3)	
19.	Prabhu M et al (60)	70	PROM and Ab.CTG (4)	CS (32) VD(38)	3060.9-3149.6	Yes (11)	Yes (1)	
20.	Li N et al (66)	17	FD(1) ; PROM (1)	CS (14) VD(2)	3078.2 ± 565.0	Yes (4)	-	1 twin delivery
21.	Cao D et al (67)	11	FD (3); PROM (4)	CS (8) VD(2)	2050-3800	Yes (4)	-	1 twin delivery

22.	Hu X et al (42)	7	PROM (1)	CS (6) VD(1)	3180-3670	-	-	
23.	Yang P et al (81)	7	-	CS(7)	2096 ± 660	Yes (4)	-	
24.	Yang H et al (73)	13	-	CS (9) VD(4)	3063.2 ± 536.4	-	-	
25.	Ferrazzi E et al (28)	42	-	CS (18) VD(24)	2730-3226	Yes(11)	-	
26.	Govind A et al (61)	9	Ab.CTG (1)	CS (8) VD(1)	1200-4300	Yes(2)	-	
27.	Nie R et al (68)	28	FD (4); IM (1); PROM (3)	VD (5); CS (22)	2988(502)	Yes (10)	-	1 twin delivery
28.	Yin M et al (46)	17	IM (3)	VD (4); CS (13)	2580-3035	Yes (5)	-	
29.	Qadri F (115)	10		CS (2) VD (8)		Yes (1)		
30.	Doria M et al (71)	10	IUGR (6)	CS (6) VD(4)	2350–3380	-	-	
31.	Liu Y et al (69)	10	FD(3), PROM (1)	CS(10)		Yes (6)	Yes(1)	
32.	Perrone S et al (72)	4	IUGR(1)	VD(4)	2290-3790	-	-	
33.	Patane L et al (39)	2	-	VD (1) CS(1)	2660, 2686	Yes(1)	-	
34.	Fan C et al (48)	2	-	CS (2)	3440-2890	Yes (1)	-	
35.	Pulinx B et al (31)	2	IUFD (1)	VD (2)		Yes (1)	Yes (1)	DCDA twins
36.	Liu W et al (56)	3	FD (1); MSA ; chorioamnionitis	CS (2) VD (1)	3250-3670	-	-	
37.	Cooke W et al (83)	2	-	CS (2)	1530,1400	Yes(2)	-	
38.	Chen Y et al (58)	4	DFM (1) Ab.CTG (1)	CS (3) VD(1)	3050-3550	-	-	
39.	Gildof S et al (76)	2	-	CS (2)	2680,2160	Yes (2)	-	
40.	Khan S et al (85)	3	-	VD (3)	2890-3750	Yes (1)	-	
41.	Zambrano L et al (87)	1	-	VD(1)	1500	Yes(1)	-	
42.	Lowe B et al (62)	1	Ab.CTG (1)	VD (1)		-	-	
43.	Blauvelt C (84)	1	-	CS(1)	1880	Yes (1)	-	
44.	Kirtsman M et al (35)	1	-	CS(1)	2930	Yes (1)	-	
45.	Lyra J et al (74)	1	-	CS(1)	3110	-	-	
46.	Li Y et al (44)	1	FD(1)	CS(1)		Yes (1)	-	
47.	Dong L et al (55)	1	-	CS(1)	3120	Yes (1)	-	
48.	Wang X et al (77)	1	FD (1)	CS(1)	1830	Yes (1)	-	
49.	Alzamora M et al (78)	1	-	CS(1)	2970	-	-	
50.	Huang J et al (86)	1	-	VD(1)		-	-	
51.	Kalafat E et al (79)	1	-	CS(1)	2790	Yes (1)	-	
52.	Xiong S et al (50)	1	PROM	VD(1)	3070	-	-	
53.	Wang S et al (51)	1	FD (1)	CS(1)	3205	-	-	
54.	Zamaniyan M et al (30)	1	-	CS(1)	2350	Yes (1)	-	
55.	Song L et al (49)	1	-	CS(1)	3630	Yes (1)	-	
56.	Lee D et al (80)	1	-	CS (1)	3130	-	-	
57.	Iqbal S et al (105)	1		VD(1)				
58.	Vivanti A et al (29)	1	Ab.CTG (1)	CS(1)	2540	Yes (1)	-	
59.	Kulkarni et al (117)	1	-	VD(1)	3200	-	-	
60.	Sisman J et al (70)	1	PROM	VD(1)	3280	Yes (1)		

FD= Fetal distress; Ab.CTG= Non-reassuring/ Pathological fetal cardio-tocography ; PROM= Pre-labor rupture of membrane ; Fetal demise= IUFD ; MSA= Meconium stained amniotic fluid; DFM= Decreased fetal movement; IM= Induced miscarriage; CS= Caesarean Section; VD= Vaginal delivery; AGA= Appropriate for gestational age; IUGR= Intrauterine growth restriction; SGA= Small for gestational age; LGA= Large for gestational age

ii. Mode of delivery

Mode of delivery was available for a total of 1311 out of which 8 were twin pregnancies. 761 (60%) delivered by CS 506 (40%) by VD out of 1267 pregnancies in case series. In case reports, out of 44 deliveries, 25 were CS (56.8%) and 19 (43.2%) were VD bringing the percentage of CS to 59.9% and VD to 40.1% in the pooled data. **[Table no-5].** Few

studies in our data compared the CS in the SARS-CoV-2 positive pregnant women to negative controls comprising 122 CS in the positive group out of 233 and 650 CS in the control group out of 1562 in the pooled data. ODDs Ratio (OR) for CS in SARS-CoV-2 positive mothers is 1.5421 [95% CI- 1.1701 to 2.0324] and P = 0.0021. which is statistically significant **[26, 60, 66, 73].**

CS was the only mode of delivery in the majority of early published case reports as in the early days of the pandemic, elective CS delivery was the mode preferred by most of the countries for maternal indications **[29, 30, 35, 44, 45, 48, 49, 51, 54, 55, 64, 74-84].** As the pandemic progressed, favorable outcomes were reported from vaginal delivery by many studies **[50, 62, 72, 85- 87].** It was also demonstrated that the chances of the virus being present in the vaginal fluid is very remote. In the later and larger case series, CS deliveries were only done for obstetrical indications **[26].** In a study involving 134 deliveries, there were 67 CS and 67 vaginal deliveries. The rate of CS was not statistically different in women with positive SARS-CoV-2 as compared to negative pregnancies **[26].** In yet another study, there were significantly higher rates of CS deliveries in cases (14 out of 16) as compared to the control group (57 out of 121) ($p < 0.001$) but there was no difference in the groups with regards to chronic illnesses or pregnancy complications **[66].** However, when done for maternal COVID-19 indications, the rate of cesarean was found to increase with the severity of the disease **[25]**. In another study, out of 41 CS deliveries, 12 were for COVID-19 symptoms without other obstetrical indications [4 with severe symptoms and 8 with mild/moderate symptoms] **[65].**

In the largest study in the UK, the CS delivery was seen in 156 women and vaginal birth was seen in 106 women from a total of 262 births. The indications of CS were maternal compromise (27%), fetal compromise (24%), failed induction of labor or failure to progress (19%), other obstetric reasons (16%), prior CS (10%), and maternal request (4%) **[23]**. Maternal COVID -19 related conditions were predominant indications in another larger study reporting CS for COVID-19 pneumonia in (33 out of 85), previous CS (16 out of 85), fetal distress (9 out of 85), and failure to progress in 5 out of 85 patients **[24]**. Many other studies similarly reported maternal condition requiring delivery as the commonest indication for CS **[25, 28, 81]**.

Table-5: Perinatal outcome (Pooled data)

FETAL OUTCOME				
Outcome	**Number of studies**	**Results**	**Indications**	**Remarks**
Preterm birth	43 studies [26 case series/cohort and 17 case reports]	-Preterm birth=330 out of 1273 neonates in the case series/cohort (25.9%) -Preterm birth= 19 out of 45 neonates in the case reports (42.2%)	-Iatrogenic prematurity to improve maternal COVID-19 related respiratory symptoms =153 -Spontaneous preterm labor=24 -Fetal compromise/ distress=17	Pooled Preterm birth in 26.4% of total births Spontaneous preterm birth- 1.8% of total births

			-Unknown/ other = 156	
Mode of delivery	59 studies [30 case series/cohort and 29 case reports]	-In case series/ cohorts, out of 1267 deliveries, CS=761 (60%) and VD=506 (40%) -In case reports, out of 44 deliveries, CS=25 (56.8%) and VD=19 (43.2%)	Maternal COVID-19 related conditions most common indication	Pooled data- CS= 786 (59.9%) VD= 525 (40.1%)
Still birth Miscarriage	Still birth=8 studies Miscarriage= 5 studies	Still birth=13 Spontaneous miscarriage= 15 Induced miscarriage=4	All induced miscarriages were due to maternal request	Stillbirth rate= 9.9
Feral complications	FD= 21 studies PROM and PPROM= 15 studies	Fetal distress (87 out of 1311 pregnancies) (6.63%) PROM and PPROM (56 out of 1311 pregnancies) (4.27%)	-	-
IUGR and SGA	IUGR-5 studies SGA-2 studies	12 fetuses had IUGR (0.9%) 5 neonates had SGA (0.38%)	-	-
NEONATAL OUTCOMES				
OUTCOME		**Results**		
Neonatal symptoms		Respiratory symptoms= 23 neonates (1.79%) Neonatal pneumonia and pulmonary infection= 14 neonates (1.1%) Fever= 12 neonates (0.9%)	Most common symptom is respiratory distress in (1.17%)	
APGAR score		Score of less than 7 at 1minute and 5 minutes= neonates	Most common reason is preterm birth	
ICU admissions		In 276 neonates (21.5%)	Most common reason was for observation and isolation (32.6 %). Prematurity is second most common reason ICU admissions for suspected or confirmed neonatal sepsis was reported in 6 neonates (0.46%).	
Neonatal death		7 neonates		Neonatal death rate=5.46 per 1000 live births

FD= Fetal distress; Ab.CTG= Non-reassuring/ Pathological fetal cardio-tocography ; PROM= Pre-labor rupture of membrane ; MSA= Meconium stained amniotic fluid; IM= Induced miscarriage; CS= Caesarean Section; VD= Vaginal delivery; IUGR= Intrauterine growth restriction; SGA= Small for gestational age

iii. Preterm Delivery

In our study, the outcome of preterm delivery was reported in a total of 43 studies involving 1318 fetuses out of which 330 out of 1273 neonates in the case series and cohort (25.9%) and 19 out of 45 neonates in the case reports (42.2%) were delivered preterm. The pooled Preterm birth was seen in 26.4% of total births **[Table no- 5].** However, the majority of them were elective deliveries to improve maternal respiratory conditions related to COVID-19. Spontaneous preterm delivery was only seen in 1.8% of neonates. The other indications included the preterm pre-labor rupture of membranes. In a substantial number of studies, data regarding the indications were not found. Few studies in our data compared the preterm delivery in the SARS-CoV-2 positive pregnant women to negative controls comprising of 52 preterm deliveries in the positive group out of 220 and 267 preterm deliveries in the control group out of 1520 in the pooled data. ODDs Ratio (OR) for preterm delivery in SARS-CoV-2 positive mothers is 1.4526 [95% CI- 1.0360 to 2.0366] and p = 0.0304 **[26, 60, 66].**

In a study involving 134 deliveries in COVID -19 patients, preterm delivery was reported in 38 pregnancies with positive SARS-CoV-2 and 239 out of 836 SARS-CoV-2 negative deliveries, which was not significantly different **[26]**. A similar report was seen in another study where 4 preterm deliveries were seen out of 17 SARS-CoV-2 confirmed group as compared to 7 out of 121 in the control group **[66]**. In another study, out of a total of 25 preterm deliveries, iatrogenic preterm delivery was done in 12 and 13 were spontaneous preterm deliveries **[65].**

Furthermore, comparing the outcomes of COVID-19 pregnancies with different disease severity involving 181 pregnant women, preterm delivery was seen in 13 out of 123 (10.6%), 14 out of 29 (48.3%), and 23 out of 29 (79.3%) in women with non-severe, oxygen-requiring, and critical COVID-19, respectively. Delivery before 32 weeks was highest in 48.3% of women in the critical COVID-19 group. In severe disease, urgent delivery is required to stabilize the maternal condition, even when it results in iatrogenic preterm delivery **[25]**.

iv. Birth weight

In our review, birth weight was missing in many studies and only the mean weight of the babies was mentioned in some of the series. IUGR was reported in 4 studies in 11 babies **[24, 63, 71, 72].** Also, SGA was found in 2 studies in 5 babies **[41, 57].** A maximum of 6 babies had IUGR in one study but they were described as mild **[71].**

v. Miscarriage and stillbirth

Stillbirth was seen in 13 fetuses in 8 studies in our review and seven were second-trimester miscarriages **[23, 25, 26, 31, 40, 60, 69, 75] [Table no-5].** 3 intrauterine deaths were observed in one of the studies which reported maternal deaths due to COVID-19 **[75].** Similarly, we found 15 spontaneous miscarriages, and 4 induced miscarriages reported in 5 studies **[23, 25, 26, 46, 68].** Induced miscarriages were done on maternal request in both studies **[46, 68].** Among the spontaneous miscarriages, 6 were seen in

141 pregnancies in one study and 5 in 181 pregnancies in another study **[25, 26].** In one of the studies, there were 3 stillbirths. However, the causes of these 3 stillbirths reported, were not related to COVID-19 in the mother **[23].**

2.2 Neonatal Outcomes:

Table-6: Neonatal outcome

Serial number	Author (reference)	Number of neonates	APGAR score (1 minute, 5 minute)	Neonatal symptoms (n)	Neonatal ICU admission (n)	Neonatal death	Neonatal RTPCR status
1.	Alzamora M et al (78)	1	6, 8	Respiratory difficulty Cough on D6	(1) [due to maternal sedation]	-	**+ve**
2.	Chen H et al (45)	9	8-10	-	-	-	
3.	Fan C et al (48)	2	9-10	Fever, abdominal distension, lymphopenia (1) Mild NNP, lymphopenia (1)	-	-	**Negative**
4.	Dong L et al (55)	1	9-10	-	-	-	
5.	Zeng H et al (54)	6	9-10		-	-	
6.	Liu W et al (56)	3	8-10	decreased responsiveness and decreased muscle tone	-	-	**Negative**
7.	Zhu H et al (57)	10	8-10 in all 7-8 in 1	Shortness of breath (6), vomiting (1), rash (1), Fever (3)	Yes (2)	YES (1)	**Negative**
8.	Wang X et al (77)	1	9-10	-	Yes (1)	-	
9.	Liu Y et al (69)	10	10	-	-	-	
10.	Chen Y et al (58)	4	8-9 (3) 7-8 (1)	Edema (1), Rash (2),Dyspnea and TTN (1)	Yes (2)	-	**Negative**
11.	Gidlof S et al (76)	2	9-10	Breathing problem, cyanotic attack(1)			**Negative**
12.	Huang J et al (86)	1	8-9	-	-	-	
13.	Iqbal S et al (105)	1	9	-	-	-	
14.	Lee D et al (80)	1	9-10	-	Yes (1)	-	
15.	Khan S et al (85)	3	9-10	-	-	-	
16.	Khan S et al (64)	17	9-10 (16) 7-9 (1)	NNP (5)	-	-	**2 out of 5 with pneumonia were +ve**
17.	Xiong S et al (50)	1	9-10	-	-	-	
18.	Wang S et al (51)	1	8-9	Vomiting, lymphopenia, abnormal liver enzyme levels	Yes (1)	-	**Negative**
19.	Zeng L et al (41)	33	Preterm newborn-3,4 Term - Normal	RD (4=3 -ve, 1+ve). Cyanosis, feeding intolerance (3=2-ve,1+ve) Fever in 2, NNP in 3 of the 3 +ve Lethargy, fever(1) lethargy, fever, NNP, leukocytosis, lymphocytopenia, vomiting (1) Preterm- Neonatal RDS, NNP, lymphocytopenia (1)	Yes (3)	-	**+ve**
20.	Zamaniyan M et al (30)	1	8,9	Fever (1)	-	-	**+ve**
21.	Breslin N et al (59)	18	>7, >9	RD/ sepsis (1)	Yes (3)	-	**Negative**
22.	Qiancheng X et al (107)	23	10,10		-	-	
23.	Hantoushzadeh S et al (75)	5	7 (2), 9-10	NNP, lymphopenia (1)	Yes (1)	YES(2)	**Negative**
24.	Shanes E et al (36)	15	7(8),8(7); 9				

25.	Zambrano L et al (87)	1	-	-	Yes (1)	-	
26.	Perez O et al (65)	82	<5 (3)	RD (2)	Yes (19)		**+ve**
27.	Savasi V et al (109)	57	10	-	Yes(9)	-	
28.	Song L et al (49)	1	8,9	-	-	-	
29.	Lokken E et al (40)	8					
30.	Yan J et al (24)	99	9,10	Neonatal asphyxia (1)	Yes(47)	YES (1)	**Negative**
31.	William R et al (63)	32	7.9±1.7	-	Yes (21)	-	
32.	Knight M et al (23)	262		Neonatal encephalopathy (1)	Yes (67)	YES (2)	**Unclear whether symptomatic neonate was +ve**
33.	Kayem G et al (25)	181		-	Yes (37)	YES (1)	
34.	Nayak A et al (26)	131	7–10 (128) <7 (6)	Neonatal seizures (1), MAS (1)	Yes (24)		**Unclear whether symptomatic neonates were +ve**
35.	Prabhu et al (60)	73	9	-	Yes (13)	-	**Negative**
36.	Vivanti A et al (29)	1	4,7	irritability, poor feeding, axial hypertonia and opisthotonos	Yes (1)	-	**+ve**
37.	Li N et al (66)	17	9.6 ± 0.5, 10	-	-	-	
38.	Cao D et al (67)	11	8-9,10	-	-	-	
39.	Hu X et al (42)	7	7-8,8-9	-	-	-	
40.	Yang P et al (81)	7	8-9,9-10	Vomiting(1), RD (2), Moaning (2)	Yes (5)	-	**Negative**
41.	Yang H et al (73)	13	9,10	Fever(1)	-	-	
42.	Patane L et al (39)	2	9,10	Mild feeding difficulty (2)	Yes (1)	-	**+ve**
43.	Ferrazzi E et al (28)	42	<7 (2)	Gastrointestinal symptoms, RD (2)	Yes (3)	-	**+ve**
44.	Govind A et al (61)	9	<7 (2)	NNP (1)	Yes (1)	-	**+ve**
45.	Nie R et al (68)	28	8-10, 10	Pulmonary infection (1)	Yes (1)	-	**+ve**
46.	Yin M et al (46)	17	8,9	-	-	-	
47.	Doria M et al (71)	10	9,10	-	-	-	
48.	Perrone S et al (72)	4	9,10	-	-	-	
49.	Romagano M et al (82)	7	1-7,4-9	RD	Yes(7)	-	**Negative**
50.	Cooke W et al (83)	2	1-6, 3-8	Bowel perforation D6(1)	Yes(2)	-	**Negative**
51.	Lowe B et al (62)	1	9,9	-	-	-	
52.	Blauvelt C (84)	1	4,8	RD	YES(1)	-	**Negative**
53.	Kirtsman M et al (35)	1	9,9	Neutropenia, hypothermia, feeding difficulties, hypoglycemia	YES(1)	-	+ve
54.	Lyra J et al (74)	1	8,9	-	-	-	**Negative**
55.	Groß R et al (52)	2	-	Respiratory symptoms (2), icterus (1)	-	-	+ve
56.	Kulkarni et al (117)	1	6,9	Fever, icterus,and poor feeding	YES(1)	-	+ve
57.	Sisman J et al (70)	1	7,9	Fever, RD, Icterus	YES(1)	-	+ve

RD= Respiratory distress; MAS= Meconium aspiration syndrome; TTN= Transient Tachypnea of Newborn; NNP= Neonatal Pneumonia

i. Neonatal symptoms

The most common neonatal symptoms were respiratory problems reported as respiratory distress, shortness of breath, respiratory difficulty, dyspnea, and breathing problems **[28, 41, 52, 57- 59, 65, 70, 76, 78, 81, 82, 84].** Respiratory distress was the most common symptom reported in 14 neonates but the test for SARS-CoV-2 was positive in only 4 neonates and negative in 8 **[28, 41, 59, 65, 81, 82, 84].** Pneumonia was seen in 5 neonates who were positive for SARS-CoV-2 and 4 neonates who were negative **[41, 48, 61, 64, 75].** Although usually respiratory symptoms are seen more in preterm babies due

to pulmonary immaturity, in a single case report there were no neonatal complications in a SARS-CoV-2 positive mother who delivered a preterm baby at 29 weeks 5 days by emergency CS for maternal indications **[88].**

Diffuse bilateral granular and hazy opacities in chest radiograph and thickened lungs on x-ray were found in two neonates but the neonatal test for SARS-Cov-2 was negative in both of them **[51, 84].** In another SARS-CoV-2 +ve, newborn chest X-ray was consistent with pulmonary infection, 53 hours after birth **[68].** In another study, neonatal symptoms are extensively described. The most common first clinical symptom in the neonates of SARS-CoV-2 Positive women was shortness of breath (n=6), followed by gastrointestinal symptoms like feeding intolerance, bloating, refusing milk, and gastric bleeding (n=4). Other symptoms included fever, rapid heart rate, and vomiting. Chest radiographic abnormalities included infections (n=4), neonatal respiratory distress syndrome (n=2), and pneumothorax (n=1). Another preterm baby suffered from frequent oxygenation fluctuations and thrombocytopenia and was cured 15 days later **[57].** It was reported in yet another study that most of the complications in neonates were a result of prematurity (often iatrogenic) rather than SARS–CoV-2 infection **[41].** Other presentations in SARS-CoV-2 positive neonates included fever, cyanosis, lethargy, irritability, poor feeding, axial hypertonia, opisthotonus, and feeding difficulties **[29, 39, 41].**

ii. APGAR Score

In our review, a total of 9 studies have reported a low APGAR score among babies born to SARS-CoV-2 positive mothers **[26, 28, 29, 41, 61, 78, 82-84].** Seven of the neonates were very preterm or preterm and were SARS-CoV-2 negative. The APGAR score in these is likely to be due to pulmonary immaturity **[26, 28, 29, 78, 82-84].** Two other babies were term deliveries and tested positive for SARS-CoV-2 **[41, 61].** However, another study reported low APGAR scores of 0–3 in 2 babies of COVID positive mothers and 15 babies in COVID negative mothers, indicating no statistically significant difference **[26].**

iii. ICU admissions

Admission to the neonatal ICU was done for various reasons. The majority of admissions were for observation and isolation. Neonates admitted due to complications of prematurity constitute another higher portion of the neonates. In a study, out of a total of 24 ICU admissions, it was found that 16 babies were admitted due to low birth weight, 2 for low APGAR score, and 6 others for other uncommon reasons like ABO incompatibility **[26].** In another study, it was found that rates of admission to ICU increased with the severity of the disease in the mother **[25].** In our review, ICU admissions for suspected or confirmed neonatal sepsis was reported in 6 neonates out of which Enterobacter and Respiratory syncytial virus was found in 2 neonates.The culture was negative for 4 others **[35,41,51,52,59,70].**

iv. Neonatal death

Neonatal death was reported among 7 neonates in 5 studies **[23-25, 57, 75]**. It was unclear whether COVID-19 in mothers contributed to the deaths in 2 neonates in one of the studies **[23].** In another study, neonatal death occurred in a preterm baby on the 9th day of life who was admitted with shortness of breath and moaning and later developed refractory shock, multiple organ failure and disseminated intravascular coagulation (DIC) **[57]**. The calculated neonatal death rate is 5.47 per 1000 live births. **[Table-6]**

3. Congenital anomaly:

We could not find any studies describing structural anomalies in the fetus associated with COVID-19. Due to an evolving pandemic, the teratogenicity of the virus has not yet been explored adequately. However, in a few of the studies, the findings of anomaly scans during pregnancy were included and they did not show any difference between fetuses of SARS-CoV-2 positive and negative women **[46, 57].** In two case reports, a multicystic dysplastic kidney was detected by antenatal ultrasound in one and after delivery in the other **[36, 59].** In another study bilateral gliosis of the deep white periventricular and subcortical matter was detected in an 11 days old neonate born to SARS-CoV-2 positive mother by magnetic resonance imaging **[29].** However, these cannot be attributed to SARS-CoV-2. Furthermore, autopsy finding in a stillborn baby born to COVID-19 mother did not show any abnormality in another report **[40].**

DISCUSSION AND CONCLUSION

We wanted to analyze the published evidence on the fetal perspective of COVID-19 infection concerning mother to child transmission, perinatal outcome, and congenital anomalies through a systematic review.

The present available data do not provide a clear conclusion into the fetal outcomes and its clinical implications. Few other reviews have explored the evidence of vertical transmission. There is varied positivity rate of different samples. The positivity of NP swab in this study is 3.67% which is in accordance with other reviews reporting 3.2% (22/936), 2% (9/493), and 3.48% (3/86), respectively **[89- 91].** In a couple of other reviews,however, the NP samples were negative [(0/113) and (0/9)] **[92, 93].** No evidence of vertical transmission was found in other reviews **[2, 94, 95].**

The placental sample was positive in our review in 11.7% of pregnancies. It is similar to the review by Kotlyar reporting 9.7% (3/31) sample positivity **[89]**. The placenta was extensively studied in another review where it was shown that there is a low likelihood of placental infection and vertical transmission of SARS-CoV-2 since the receptors and proteases, are only minimally expressed by the human placenta throughout pregnancy **[96]**. Placenta was also negative for 54 samples in another review **[90]**.

Amniotic fluid collected before the rupture of membranes was positive in 6.8% of pregnancies in our review, in contrast to the review by Kotlyar (0/51) and Ashraf (1/16) **[89, 91].**

The serological analysis was found in some studies within our review showing IgM positive results at birth indicating possible congenital transmission. Using the criteria by shah et al, we found that there is confirmed congenital transmission in 5 live-born neonates and 2 DCDA twins expelled at 24 weeks **[14]**. Similarly, the possible congenital transmission was found in 5 neonates and probable in 2 neonates. These analyses were not reported in earlier reviews involving more than 1300 pregnancies in total.

The chance for CS is more in women with COVID-19 and in most instances for maternal indications. Preterm delivery is also high (26.4%) most commonly due to adverse maternal condition, although spontaneous preterm labor is low (1.8%). This is in accordance with another systematic review with regards to the indication but they found a trend towards spontaneous preterm labour **[97].** In contrast, an earlier review reported 6.4% of preterm deliveries as spontaneous **[98].**

Fetal distress (6.63%) was the most common complication seen in the fetus followed by PROM and PPROM (4.27%) in our review. Similar findings were seen in other reviews **[91, 94].** One earlier review did not report any fetal complications **[92].** PPROM was reported in 14 pregnancies in our review. While PROM and PPROM are unlikely to contribute to mother to child transmission as the SARS-CoV-2 has not been positive in the vaginal swab, PPROM is a significant cause of preterm labor. Through our review, it was not possible to ascertain whether COVID-19 in mothers increases the risk for PROM. IUGR was reported in 12 fetuses in 5 studies (0.9%). IUGR can be multifactorial and need to be analyzed with the presence of maternal risk factors. SARS-CoV-2 has not been associated with IUGR and it was not possible to ascertain whether COVID-19 in mother increases the risk for IUGR in our study.

The rates of stillbirth and neonatal death in our study were 9.9 and 5.46 respectively. In another study, it was found that stillbirth was significantly higher during the pandemic compared to the non-pandemic period due to reasons non-associated with COVID-19 (difference, 6.93 [95% CI,1.83-12.0] per 1000 births; P= .01) **[99].** So it is unlikely that the stillbirth and neonatal death rate are increased in COVID-19 mothers. The symptoms when present in the infected neonates were most often mild and neonatal outcomes were found to be good **[100, 101].** There is no reported teratogenicity or congenital anomalies associated with SARS-CoV-2 infection.

The outcome so far is favorable for the fetus despite the risks to the mother for ICU admissions and mechanical ventilation seen in other studies **[3].** Maternal outcomes were not explored in this study. There is no significant increase in preterm birth but there is a significantly increased risk of CS in mothers with COVID-19.

Though the fetal perspective seems good in the case of maternal COVID-19, it will be reasonable to consider these findings with caution. Prospective studies and randomized

control trials were missing from the evidence due to the recent nature of the infection. Therefore, larger and better quality studies are required to address the knowledge gaps and to reach at a definite guideline for management.

Strengths and Limitations of the study

There are many strengths to this study. The studies included in the review contained only confirmed maternal cases by RT-PCR and not the suspected cases or clinically diagnosed cases. The studies contained the results of neonatal testing. Studies included in this review were from countries across the world and not restricted to a specific region, making the findings from the study globally applicable. The case series/cohorts were chosen only when the total number of cases was more than 4. Moreover, various aspects of vertical transmission as well as fetal and neonatal outcomes were analyzed from the chosen studies.

Nonetheless, there are many limitations to our study. Only a limited number of available case series and cohorts were included in this review as high-quality evidence involving a higher number of subjects is lacking dues to the new kind of infection and still evolving nature of the pandemic. In our review, studies in languages other than English were excluded due to unavailability of English translation.Almost all of the reports are retrospective reviews showing incomplete data with significant heterogeneity within the included studies with a chance of selection or recall bias. Different types of samples were used for the diagnosis of SARS-CoV-2 in different studies. Though nasopharyngeal swab was used for diagnosis in most studies, there were different types of kits used. Again the same kit may have different sensitivity and specificity in different types of samples. Universal testing of pregnant women was not done in many studies, resulting in missing fetal and perinatal effects in asymptomatic women. As maternal outcomes were not studied, the effects of the severity of maternal disease on the fetal outcomes could not be looked into.

Future Implications:

Whether there is an intrauterine infection of the fetus with respect to SARS-CoV-2 needs to be studied. What are the effects of intrauterine infection, whether there is different susceptibility at different stages of pregnancy, and whether susceptibility depends on disease severity in the mother, needs to be explored. Follow up studies are required to see long term effects of neonatal infection with SARS-CoV-2.

AUTHORSHIP STATEMENT

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the BMJ Pediatrics-open access.

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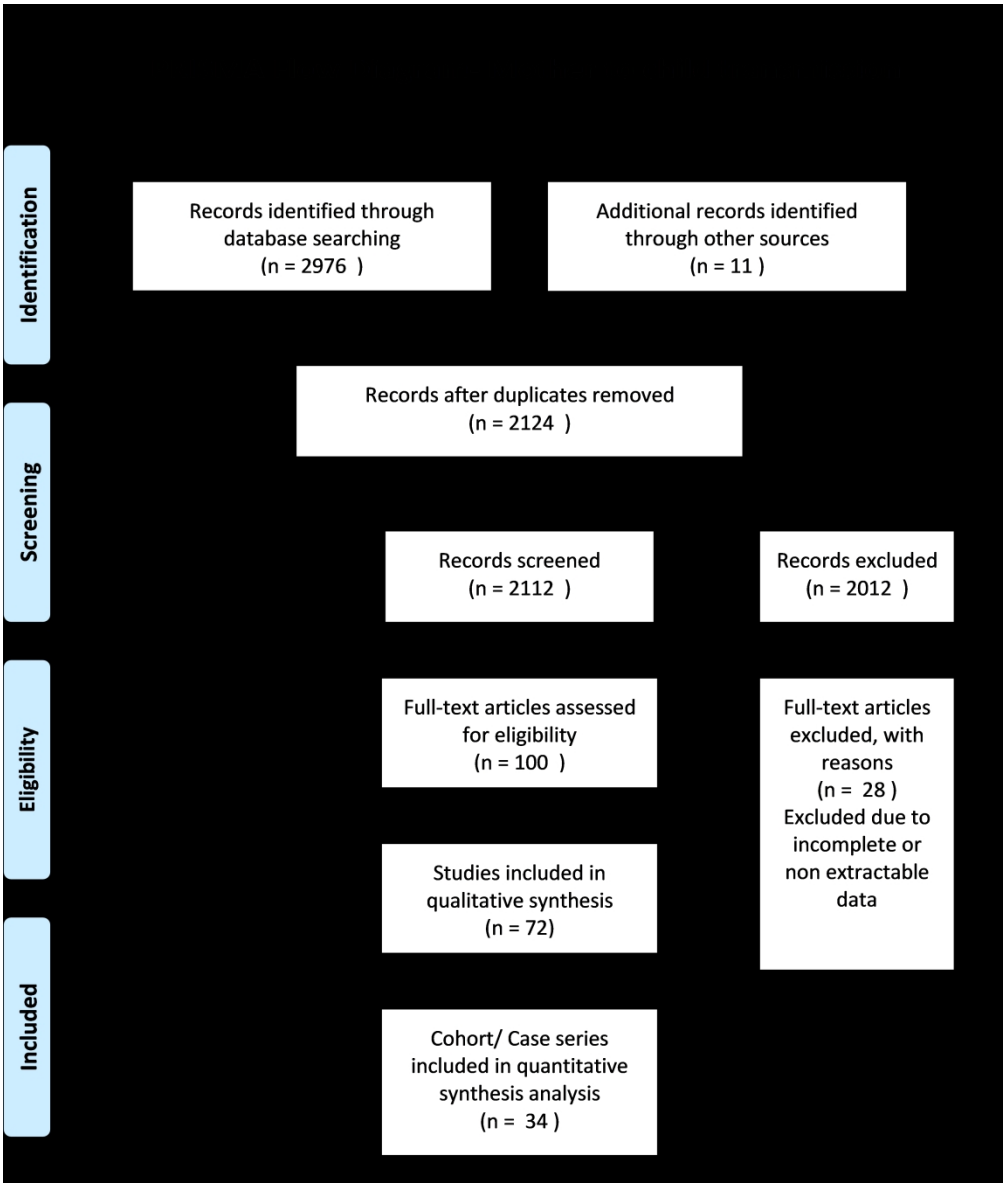
Identification
Records identified through database searching (n = 2976)
Additional records identified through other sources (n = 11)
Screening
Records after duplicates removed (n = 2124)
Records screened (n = 2112)
Records excluded (n = 2012)
Eligibility
Full-text articles assessed for eligibility (n = 100)
Full-text articles excluded, with reasons (n = 28) Excluded due to incomplete or non extractable data
Included
Studies included in qualitative synthesis (n = 72)
Cohort/ Case series included in quantitative synthesis analysis (n = 34)

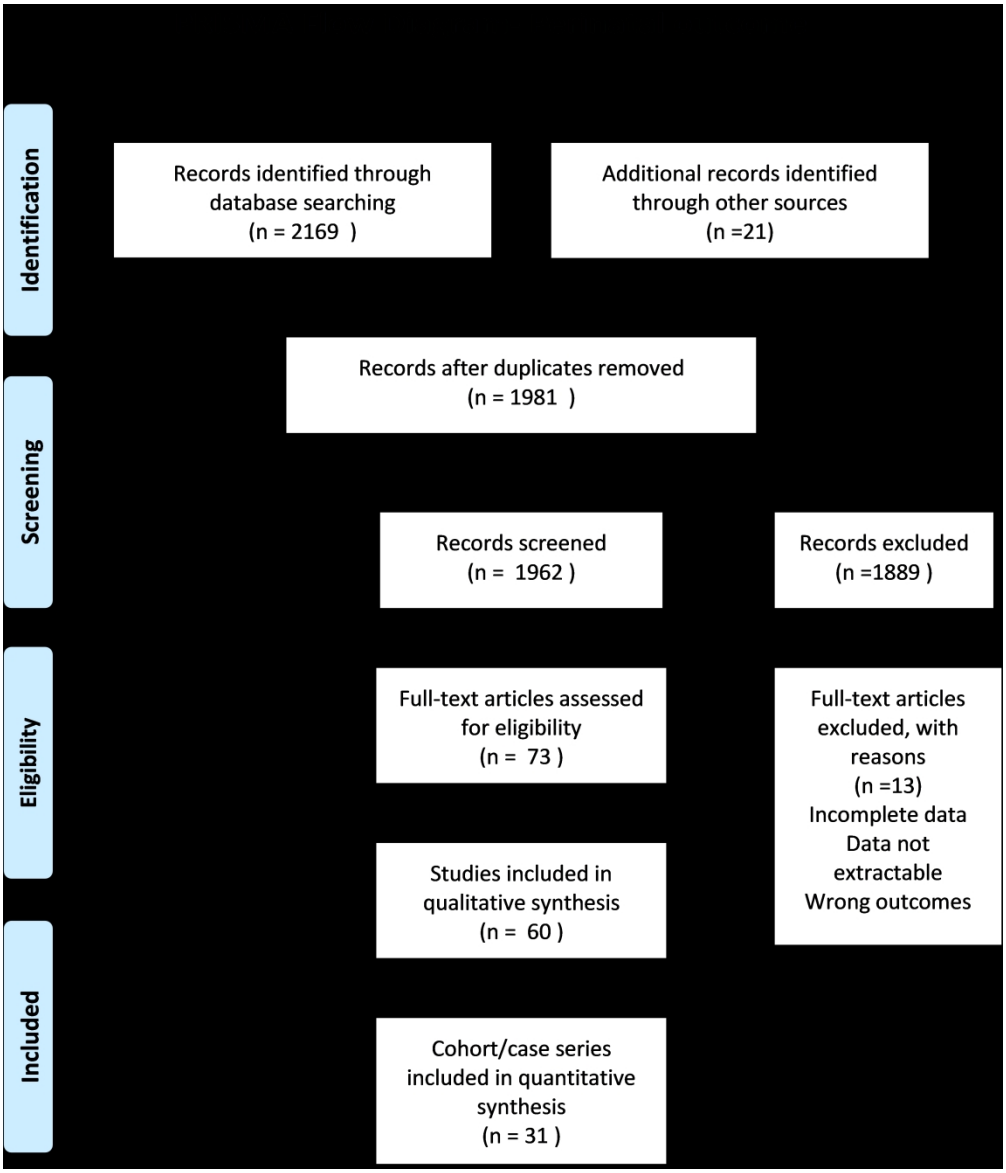
Identification
Records identified through database searching (n = 2169)
Additional records identified through other sources (n =21)
Screening
Records after duplicates removed (n = 1981)
Records screened (n = 1962)
Records excluded (n =1889)
Eligibility
Full-text articles assessed for eligibility (n = 73)
Full-text articles excluded, with reasons (n =13) Incomplete data Data not extractable Wrong outcomes
Included
Studies included in qualitative synthesis (n = 60)
Cohort/case series included in quantitative synthesis (n = 31)

Table-1 (a): Analysis of the studies [Case series/ Cohort]

Serial number	Author (reference)	Number of pregnancies	Country	Outcomes included	Selection Contains diagnosed COVID-19 in Pregnancy	Comparability Data on pregnant women and fetus available	Outcome; Assessment and reporting	Evidence of mother to child transmission	Perinatal Outcome
1.	Chen H et al (45)	9	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
2.	Zeng H et al (54)	6	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
3.	Zhu H et al (57)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
4.	Zhang I et al (102)	61	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
5.	Penfield CA et al (103)	11	China	Placental, membrane and neonatal samples	****		**	√	
6.	Liu Y et al (69)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
7.	Khan S et al (64)	17	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
8.	Zeng L et al (41)	33	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
9.	Qianch eng X et al (107)	23	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
10.	Yang P et al (81)	7	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
11.	Yang H et al (73)	55	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	*	*	√	√

12.	Wu Y et al (47)	13	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	*	*	√	
13.	Yan J et al (24)	116	China	pregnancy and neonatal outcomes	****	**	***		√
14.	Li N et al (66)	16	China	Symptoms, maternal outcomes, neonatal outcomes	****	**	***		√
15.	Cao D et al (67)	10	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
16.	Yin M et al (46)	31	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
17.	Hu X et al (42)	7	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
18.	Nie R et al (68)	33	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***	√	√
19.	Patane L et al (39)	22	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
20.	Ferrazzi E et al (28)	42	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
21.	Savasi V et al (109)	77	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
22.	Mulvey J et al (38)	5	US	Placental characteristics	***			√	
23.	Vintzileos W et al (113)	32	US	Symptoms, maternal characteristics, Test results	***	*	***	√	
24.	Breslin N et al (59)	18	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
25.	Baergen R et al (37)	20	US	Maternal characteristics, maternal outcomes, Placental characteristics	***			√	

26.	William s R et al (63)	64	US	Maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
27.	Shanes E et al (36)	16	US	Symptoms, maternal characteristics, Placental pathology, pregnancy and neonatal outcomes	****	**	***	√	√
28.	Breslin N et al (114)	7	US	Symptoms, maternal characteristics, test result	**	**	**	√	
29.	London V et al (27)	68	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
30.	Lokken E et al (40)	46	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	***		√
31.	Qadri F et al (115)	16	US	Maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	-**		√
32.	Prabhu M et al (60)	70	US	Symptoms, obstetric and neonatal outcomes, and placental pathology	****	**	***	√	√
33.	Romag ano M et al (82)	7	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcomes	****	**	*		√
34.	Govind A et al (61)	9	UK	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
35.	Knight M et al (23)	427	UK	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
36.	Sentilhe s, et al (116)	38	France	Symptoms, maternal outcomes, neonatal outcomes	****	**	***	√	√
37.	Kayem G et al (25)	617	France	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
38.	Nayak A et al (26)	141	India	Symptoms, maternal outcomes, neonatal outcomes	****	**	***		√
39.	Hantou shzade h et al (75)	7	Iran	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√

40.	Perez O et al (65)	82	Spain	Symptoms, maternal characteristics, pregnancy outcomes	****	**	**	√	√
41.	Doria M et al (48)	10	Portugal	Symptoms, maternal characteristics, pregnancy outcomes	****	**	*		√

Table-1 (b): Analysis of the studies [Case reports]

Serial number	Author (reference)	Number of pregnancies	Country	Outcomes included	Selection Contains diagnosed COVID-19 in Pregnancy	Comparability Data on pregnant women and fetus available	Outcome; Assessment and reporting	Evidence of vertical transmission	Perinatal Outcome
1.	Alzamora et al (78)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
2.	Li Y et al (44)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
3.	Dong L et al (55)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
4.	Liao X et al (106)	1	China	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
5.	Wang X et al (77)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
6.	Huang J et al (86)	1	China	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
7.	Xiong X et al (50)	1	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
8.	Wang S et al (51)	1	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
9.	Song L et al (49)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
10.	Fan C et al (48)	2	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√

11.	Chen Y et al (58)	4	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
12.	Peng Z et al(43)	1	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
13.	Liu W et al (56)	3	China	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
14.	Chen S et al (104)	3	China	Symptoms, laboratory parameters, pregnancy outcomes, samples	****	**	***	√	√
15.	Khan S et al (85)	3	China	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
16.	Yu N et al (108)	2	China	Symptoms, maternal characteristics, amniotic fluid in mid pregnancy	****	*	*	√	
17.	Schnettler W et al (110)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcome	****	**	**	√	
18.	Blauvelt C et al (84)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
19.	Iqbal S et al (105)	1	US	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
20.	Algorroba et al (34)	1	US	Symptoms, maternal characteristics, laboratory parameters, pregnancy outcome	***	*	*	√	
21.	Hosier H et al(32)	1	US	Symptoms, maternal characteristics, test result	****	**	**	√	
22.	Sisman J et al (70)	1	US	Symptoms, maternal characteristics, pregnancy outcomes	****	**	***	√	√
23.	Kalafat E et al (79)	1	Turkey	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
24.	Kirtsman M et al (35)	1	Canada	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√

25.	Lyra J et al (74)	1	Portugal	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
26.	Buonsenso et al (53)	4	Italy	Symptoms, maternal findings, test results	****	*	**	√	
27.	Perrone S et al (72)	4	Italy	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
28.	Buonsenso D et al (112)	2	Italy	Maternal characteristics, Samples for detection	****	**	*	√	
29.	Groß R et al (52)	2	Germany	Symptoms, maternal findings, test results	****	*	*	√	
30.	Cooke W et al (83)	2	UK	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	-**		√
31.	Pulinx B et al (31)	2	Belgium	Symptoms, maternal characteristics, laboratory parameters, second trimester miscarriage	****	*	*	√	
32.	Lee D et al (80)	1	Korea	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
33.	Gidlöf S et al (76)	2	Sweden	Symptoms, maternal characteristics, pregnancy and neonatal outcomes	****	**	***	√	√
34.	Baud D et al (33)	1	Switzerland	Symptoms, maternal characteristics, laboratory parameters, second trimester miscarriage	****	*	*	√	
35.	Zamaniyan M et al (30)	1	Iran	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcomes	****	**	***	√	√
36.	Zambrano L et al (87)	1	Central America	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√
37.	Vivanti A et al (29)	1	France	Symptoms, maternal outcomes, neonatal outcomes	****	**	***	√	√
38.	Lowe B et al (62)	1	Australia	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√

39.	Kulkarni et al (117)	1	India	Symptoms, maternal characteristics, laboratory parameters, pregnancy and neonatal outcome	****	**	***	√	√

Selection-* *Representativeness of the patients *Ascertained exposure to SARS-CoV-2 *Ascertained outcome- Symptoms of COVID-19 in the mother * Ruling out other causes- Test result of mother positive [********-Contains all 4 components; *******-Contains first 3 out of 4 components; ******-Contains first 2 out of 4 components;*****- Contains first 1 out of 4 components]*

Comparability- *Data on both mother and fetus available [******- Both maternal and fetal data available; *****- Only maternal data available]*

Outcome- * *Evidence of mother to fetal/neonatal transmission, * Evidence of Fetal outcome, *Evidence of neonatal outcome [*******-Contains all 3 components; ******- Contains first 2 out of 3 components;*****- Contains first 1 out of 3 components]*

√**-** *Included in analysis of mother to fetal/neonatal transmission or included in analysis of perinatal outcome or both*