COVID-19 during pregnancy should we really worry from vertical transmission or rather from fetal hypoxia and placental insufficiency?  
A systematic review and meta-analysis

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Systematic Review

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Abstract

Background:
COVID-19 is the largest outbreak to strike humanity. The wide scale of fatalities and morbidities lead to a concurrent pandemic of uncertainty in scientific evidence. Conflicting evidences are released on daily basis about the neonatal outcomes of COVID-19 positive mothers. The aim of this study was to use the relevant case reports and series to determine the percentage of newborns who test positive in COVID-19 positive mothers. Secondary outcomes included examining laboratory and placental abnormalities among fetus-mother pairs.

Methods:
Systematic review was performed on all studies reporting primary data on fetus-mother pairs with COVID-19. Data bases were searched for studies that met our inclusion and exclusion criteria.

Results:
Final screening revealed 66 studies, from which the primary data of 1787 mother-infant pairs was obtained. Only 2.8% of mother infant pairs were tested positive, and this finding is identical to percentages reported in former coronaviridae outbreaks. Whereas, 20% manifested with intrauterine hypoxia alongside placental abnormalities suggestive of heavy placental vaso-occlusive involvement.

Conclusions:
These findings suggest that while vertical transmission is unlikely, there appears to be an underlying risk of placental insuicency due to the prothrombotic tendency observed in COVID-19 infection. Guidelines for proper prophylactic anticoagulation in COVID positive mothers need to be established.

Background
COVID-19 (Coronavirus disease 2019), which has been declared a pandemic in March 2020, has caused an unprecedented uncertainty within the scientific community. Contradictory scientific evidences are released almost every day, on every aspect of the pandemic from its pathogenesis, to the methods of transmission, and to the possible compassionate use of medications to combat it. Transplacental transmission of COVID-19, is one of the topics that have raised conficting evidences across the globe. The dilemma about transplacental transmission of coronaviridae is not exclusive to the current outbreak. To our knowledge, nine studies from SARS-1 (Severe Acute Respiratory syndrome) and HKCoV (Hong Kong Coronavirus) and MERS (Middle East Respiratory syndrome) outbreaks were reported; ranging from case reports to retrospective case reviews, comprising 71 mother-infant pairs. Table 1 summarizes the findings of the nine studies. Two cases only have shown vertical transmission, a remarkable finding was the strong evidence in those reports of intrauterine fetal hypoxia possibly due to placental damage or even direct evidence of placental infarctions. Gagneuer et al reported two cases of still birth that was preceded by fetal heart deceleration, whereas, Wong et al and Jeong et al demonstrated placental infarction in three cases. The vascular tropism of COVID-19 has recently gained so much interest, and many of its multi-organ manifestations has been attributed to its endothelial tropism. Such endothelial tropism is accounted for by the high load of Angiotensin Converting Enzyme 2 (ACE2) and Furin, which are important viral checkpoints, in the endothelium. Placenta is a vascular organ, whereby Furin play an important role in its differentiation, moreover, ACE2 and Angiotensin 1-7 are heavily expressed in the placenta, making the placenta an important target for the vascular tropic effect of COVID-19. As mentioned earlier, the number of conficting evidences regarding vertical transmission of COVID-19 and the effect of maternal COVID-19 on newborns and their placenta, renders systematic review of the clustered cases available of utmost importance to build stronger evidence the neonatal outcomes of COVID-19. The primary outcome parameter of this systematic review is the percentage of newborns testing positive to COVID-19 mothers, while secondary outcome parameters included the assessment of laboratory abnormalities among COVID-19 mothers, and the placental abnormalities encountered in COVID-19 mothers.

Methods
This systematic review has been conducted in agreement with the guidelines of the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).13

Data Search
A computer run has been performed EMBASE, Medline and the Cochrane Central Register (From 1st November 2019 to 1st of August 2020). The following terms were included in the search: “COVID-19” OR “SARS-CoV-2” (Severe Acute Respiratory syndrome Coronaviridae 2) AND “Pregnancy” AND “Perinatal”.
Study Selection criteria

Population: Pregnant women

Intervention: COVID-19

Comparison: No comparison has been a purpose of the study

Outcome: Neonatal infection by COVID-19, placental abnormalities, laboratory abnormalities in the newborn.

Observational epidemiological studies and case reports addressing the clinical conditions of Mother–fetus pairs. Primary data of patients over 18 years old were considered eligible. Manuscripts that contained only data from pregnant women, or only fetuses, or that did not address the period of delivery, such as puerperium, were disregarded. All data from eligible studies were extracted by 2 independent investigators according to a standard protocol.

Statistical Analysis:

Each of the maternal manifestations, neonatal manifestations, placental microscopic and macroscopic changes and laboratory changes in COVID-19 positive newborns was quantified and expressed as number (n) and percentages.

Results

The literature search identified initially 114 studies, of which 44 studies were excluded, 20 were excluded as they did not tackle the primary outcome parameter of the study. While 24 studies were excluded due to repetition. Total number of studies included was 66 studies, comprising 1787 Mother-infant pair.14–80

The studies included were listed in Table 2, by alphabetical order of the country of origin.

Table 3 summarizes the clinical manifestations of included COVID-19 positive mothers and the subsequent percentage of positive newborns. Out of 1787 mother-infant pairs, only 49 tested positive (2.8%), which is surprisingly identical to the percentage of neonates affected in the reported cases series during the previous three outbreaks caused by Coronaviridae, 2/71 (2.8%) (Table 1). Most of the affected neonates were asymptomatic (24%). The commonest array of manifestations was those suggestive of intrauterine hypoxia (20%). The sampling time was not reported in 31% of cases which is a non-negligible number putting a huge risk of reporting bias. 42% of positive newborn were tested in the first 12 hours after delivery while the remainder 27 % of cases were tested after 12 hours, raising suspicion of possible postnatal infection.

Table 4 outlines the placental abnormalities in COVID-19 positive mothers. Placental infarction, an evidence of vascular compromise of the villi, was observed in a significant number of abnormal placentae (44%). A lower percentage of positive swabs was retrieved from abnormal placentae accounting for 37% of all abnormal placentae, and 5% of all examined placentae. A closer percentage of placental infarctions was observed in placenta examined from the previous outbreak.

Table 5 shows the laboratory abnormalities in COVID-19 positive neonates, the commonest laboratory abnormality in affected neonates is Lymphopenia encountered in 20% of cases.

Discussion

Vertical transmission of COVID-19 follows the same pattern of uncertainty as almost everything concerning COVID-19. New evidences being unraveled everyday make meta-analysis the only possible solution to reach consensus about points of dilemma.

This report is by far the largest systematic review to be implemented in this context, not only regarding the number of mother-infant pairs, but also the targeted outcome parameters. The largest report preceding us is De Sousa et al report.81

Our study confirmed the previous impression from the former outbreaks by CoV that transplacental transmission is very unlikely occurring in 2.8% of all positive mothers. A report by Wang and colleagues82 suggested that viremia is reported to occur in less than 1% of cases. However, this finding seems to hugely underestimate the burden of viremia in Coronaviridae infections. An old report by Chen et al83 during first SARS outbreak showed that RNA of SARS-CoV can be detected in up to 50% of blood samples and can last up to one week.

The commonest laboratory finding in affected neonates was Lymphopenia. This finding goes in agreement with the same pattern of hematologic abnormalities encountered in adult patients. The Programmed cell death receptor 1 secreted from macrophages in the lung environment as well as from resident T cells leads finally to T cell exhaustion with subsequent Lymphopenia encountered affected patients.
The most intriguing finding uncovered in our series is the strong evidence pointing towards placental damage with subsequent intrauterine hypoxia of the fetus. This finding was supported at several stages in our study. As mentioned earlier, 20% of all infants in whom manifestations have been reported have showed evidence of intrauterine hypoxia. Seven percent of all patients were born preterm due to evidence of fetal deceleration that necessitated pregnancy termination. Histopathological changes of placenta offered a strong reason for the observed neonatal manifestations. Placental changes were more prevalent than COVID-19 positive neonates, 46 vs. 45 respectively, out of which 44% showed evidence of ischemia. Placental changes encountered seemed to mirror the timeline at which infection was detected in COVID-19 positive mothers. 3% of mothers were infected in the 1st trimester, while defective proliferation and formation of villi was observed in a similar percentage of cases.

Defective formation of villi can be accounted due to the role played by an intracellular enzyme termed Furin in the genesis of placental villi. AbdelMassih outlined the important interplay between Furin, COVID-19, and the vascular endothelium; an important constituent of the human placenta.

In view of the above findings, proper hydration and prophylactic anticoagulation should be provided for COVID-19 pregnant women, especially those whose tests suggests strong prothrombotic tendency such elevated D-Dimer, or those whose abdominal ultrasound and fetal cardiotocography offer a strong evidence of placental insufficiency. The guidelines of several Obstetrics and gynecological international societies were clustered by D’Souza et al, and went in agreement with our suggestions.

**Conclusion**

The aggregated data in this systematic review are by far the largest to date regarding neonatal outcomes of COVID-19. Results suggest that vertical transmission of COVID-19 is unlikely but underlines an important and underestimated risk, which is placental insufficiency due to the prothrombotic tendency created by COVID-19. These findings should warrant all Ob/Gyn societies across the world about establishing guidelines for safe prophylactic anticoagulation in COVID-19 positive mothers.

**Abbreviations**

- **ACE2**: Angiotensin Converting Enzyme 2
- **CNS**: Central Nervous System
- **COVID-19**: Coronavirus disease 19
- **GA**: Gestational Age
- **GERD**: Gastro-oesophageal Reflux Disease
- **GIT**: Gastro-intestinal System
- **HKCoV**: Hong Kong Coronavirus
- **IUGR**: Intrauterine Growth Retardation
- **MERS**: Middle East Respiratory Syndrome
- **N**: number
- **NEC**: Necrotizing Enterocolitis
- **Ob/Gyn**: Obstetrics and Gynaecology
- **PRISMA Statement**: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
- **RDS**: Respiratory Distress Syndrome
- **SARS-1**: Severe Acute Respiratory Syndrome
- **W**: weeks

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not Applicable
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Not applicable

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The authors declare that they have no competing interests

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AA, LE, MA, MT contributed to the conception and design of the work
RF, RE, DH, DK, YO, SA\(^3\), MI\(^1\), MI\(^2\) contribute significantly to the acquisition of data
HA, HI, AN, GA, IG, LM, MS, MH, ME, NE, NA, NS, RD, RR, SA\(^1\), SI, SA\(^2\), SK, SP contributed to the analysis and interpretation of data
R.M contributed to the drafting and revision of the manuscript

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All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

NB: Due to identical initials of some authors we used superscript to define authors with identical initials as follows:
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**Tables**

Table 1: Reported cases of vertical transmission, clinical manifestations and placental abnormalities in SARS-1, HKCoV and MERS

**Abbreviations**: HKCoV: Hong Kong Coronavirus, MERS: Middle East Respiratory Syndrome, NEC: Necrotizing enterocolitis, RDS: Respiratory Distress Syndrome, SARS: Severe acute respiratory syndrome.
| Paper | Wong et al | Robertson et al | Yudin et al | Stockman et al | Gagneur et al | Shek et al | Li et al | Jeong et al | Payne et al | Totals |
|-------|------------|----------------|------------|----------------|---------------|------------|---------|-------------|------------|--------|
| Outbreak | SARS-1 | SARS-1 | SARS-1 | MERS | HKCoV/SARS | SARS-1 | SARS-1 | MERS | MERS |
| Number of Studied Mother-Infant pairs | 12 | 1 | 1 | 2 | 7 | 5 | 41 | 1 | 1 | 71 |
| Number of Neonates with vertical transmission | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2/71 (2.8%) |
| Reported Complications In Neonates (whether with positive or negative swabs) | 2: NEC | 0 | 0 | 0 | 2: Still birth with fetal deceleration | 2: NEC | 0 | 0 | 1: Still birth | RDS: 1/71 (1.4%) Still birth: 3/71 (4.2%) NEC: 4/71 (5.6%) |
| Reported Placental abnormalities | 1: Placental infarction | 0 | 0 | 0 | 0 | Not Reported | Not reported | 2: Placental infarction | 0 | 3/25 (12%) |
Table 2: References used to construct Table 3, 4, 5 about Neonatal and maternal outcome of COVID-19

| Reference                  | Location |
|----------------------------|----------|
| Lowe e Bopp                | Australia|
| Kirtsman et al.            | Canada   |
| Fan et al.                 | China    |
| Chen et al.                | China    |
| Li et al.                  | China    |
| Lee et al.                 | China    |
| Xiaotong et al.            | China    |
| Kang et al.                | China    |
| Lu et al.                  | China    |
| Liao et al.                | China    |
| Buonsenso et al.           | China    |
| Khan et al.                | China    |
| Dong et al.                | China    |
| Xiong et al.               | China    |
| Liu et al.                 | China    |
| Chen et al.                | China    |
| Yu et al.                  | China    |
| Zeng et al.                | China    |
| Chen, Liao and Shao        | China    |
| Liu et al.                 | China    |
| Zhu et al.                 | China    |
| Chen et al.                | China    |
| Chen et al.                | China    |
| Nie et al.                 | China    |
| Khan et al.                | China    |
| Qianchenga et al.          | China    |
| Authors          | Country    |
|------------------|------------|
| Wu et al.        | China      |
| Yang et al.      | China      |
| Liu et al.       | China      |
| Zhang et al.     | China      |
| Yue et al.       | China      |
| Yang et al.      | China      |
| Lin et al.       | China      |
| Yin et al.       | China      |
| Yang et al.      | China      |
| Zheng et al.     | China      |
| Wu et al         | China      |
| Dumpa et al.     | China      |
| Chen et al.      | China      |
| Vivanti et al.   | France     |
| Kayem et al.     | France     |
| Zambrano et al.  | Honduras   |
| Ng et al         | Hong Kong  |
| Karami et al.    | Iran       |
| Hantoushzadeh et al. | Iran   |
| Ferrazzi et al.  | Italia     |
| Ferraiolo et al. | Italy      |
| Salvatori et al. | Italy      |
| Alzamora et al.  | Peru       |
| González et al.  | Spain      |
| Nyholm et al.    | Sweden     |
| Baud et al.      | Switzerland|
| Masmejan et al.  | Switzerland|
| Authors         | Country      |
|-----------------|--------------|
| Kalafat et al.  | Turkey       |
| Govind et al.   | UK           |
| Knight et al.   | UK           |
| Breslin et al.  | USA          |
| Shanes et al.   | USA          |
| Iqbal et al.    | USA          |
| Hillary et al.  | USA          |
| Hong et al.     | USA          |
| Sisman et al.   | USA          |
| Easterlin et al.| USA          |

Abbreviations: UK: United Kingdom, USA: United States of America

Table 3
Maternal manifestations (n/%) | New-born manifestations among COVID-19 positive cases (n/%) | Sample time (n/%) | GA (n/%) | Trimester (n/%)
---|---|---|---|---
**Asymptomatic (219/12%)**
**Respiratory manifestations:**
- Cough (934/52.2%)
- Dyspnoea (417/23.3%)
- Respiratory support needed (130/7%)
- Expectoration (1/0.05%)
- Sore throat (44/2.4%)
- Minor symptoms (124/7%)
- Critical symptoms (35/2%)
- Rhinorrhea (20/1%)
- Chest pain (2/0.1%)
**CNS manifestations:**
- Anosmia (180)
- Lethargy (76/4.3%)
- Dysgeusia (1/0.05%)
- Headache (60/3.3%)
**Others:**
- Fever (951/53%)
- Myalgia & joint pain (56/3%)
- Back pain (2/0.1%)
- Tachycardia (1/0.05%)
- Tachypnea (1/0.05%)

**Asymptomatic (11/24%)**
**Respiratory manifestations (8/17%)**
- Pneumonia (4/8%)
- Intubated (2/4%)
- Ventilated (1/2%)
- Cough (1/2%)

**Respiratory manifestations (24 hrs or less):**
- Cough (1/2%)

**Respiratory manifestations (>24 hrs):**
- Pneumonia (4/8%)
- Intubated (2/4%)
- Ventilated (1/2%)

**GIT manifestations:**
- Diarrhea (78/4.4%)
- Abdominal pain (2/0.1%)
- Vomiting (41/2.2%)

**CNS manifestations:**
- Limb Asthenia (1/0.05%)
- Anosmia (180)
- Lethargy (76/4.3%)
- Dysgeusia (1/0.05%)
- Headache (60/3.3%)
**Others:**
- Myocardial dysfunction/Cardiogenic Shock (2/4%)
- Hypoglycaemia (1/2%)
- Fever (2/4%)
- Diarrhea (1/2%)

**Evidence of Intrauterine fetal asphyxia:** (9/20%)
- Fetal distress (3/7%)
- Meconium-stained liquor (3/7%)
- Suboptimal cardiotocography (3/7%)

**Feeding disorders and GERD:** (7/15%)
- Irritability (1/2%)
- Axial hypertonia and opisthotonus (1/2%)
- Neonatal encephalopathy (1/2%)

**Others:** (6/13%)
- Myocardial dysfunction/Cardiogenic Shock (2/4%)
- Hypoglycaemia (1/2%)
- Fever (2/4%)
- Diarrhea (1/2%)

There is overlap of manifestations

Total: 45 COVID-19 positive neonates
Total: 1787 COVID-19 Mother

COVID-19: Coronaviridae, CNS: Central Nervous System, GA: Gestational Age, GERD: Gastroesophageal reflux, IUGR: Intrauterine Growth retardation

Table 4: Placental abnormalities in placentae of COVID-19 positive mothers in retrieved studies
| Type of Placental Abnormalities | Number (n) | Percentage of abnormalities to Total number of abnormal placentae | Percentage of abnormalities to Total number of examined placentae |
|--------------------------------|------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| **Changes in Placental weight** |            |                                                                 |                                                                |
| Small Placenta                 | 3          | 6.7                                                             | 1.0                                                            |
| Large Placenta                 | 1          | 2.2                                                             | 0.3                                                            |
| **Microscopic Changes**        |            |                                                                 |                                                                |
| Delayed maturation of villous tree | 1          | 2.2                                                             | 0.3                                                            |
| Terminal villi (capillary congestion and focal microchlangiosis) | 1 | 2.2 | 0.3 |
| Villous agglutination          | 1          | 2.2                                                             | 0.3                                                            |
| Multiple organizing intervillous hemorrhage /thrombi | 4 | 8.9 | 1.3 |
| Chronic intervillitis          | 3          | 6.7                                                             | 1.0                                                            |
| Fusiitis                       | 1          | 2.2                                                             | 0.3                                                            |
| Infiltration with Inflammatory cells | 4 | 8.9 | 1.3 |
| Defective placental barrier    | 7          | 15.6                                                            | 2.2                                                            |
| Fibrosis/avascular villi       | 20         | 44.4                                                            | 6.3                                                            |
| Placental Swab positive for SARS CoV-2 | 17 | 37.8 | 5.4 |
| Total number of Placentae found with abnormalities | 46 | | 14.3 |
| Total Number of examined placentae | 315 | | |

Table 5: Laboratory abnormalities in COVID-19 POSITIVE NEONATES

|                                   | Number | Percentage |
|-----------------------------------|--------|------------|
| No. of neonates positive for COVID-19 | 45     | 100        |
| Leukocytosis                       | 6      | 13.3       |
| Leucopenia                         | 5      | 11.1       |
| Neutrophilia                       | 3      | 6.7        |
| Lymphopenia                        | 9      | 20.0       |
| Reticulocytosis                    | 1      | 2.2        |
| CRP                               | 2      | 4.4        |
| Elevated Prothrombin Time          | 3      | 6.7        |
| Elevated Ferritin                  | 1      | 2.2        |
| Elevated AST                       | 4      | 8.9        |
| Elevated ALT                       | 2      | 4.4        |
| Elevated Bilirubin total           | 3      | 7.7        |
| Elevated Indirect bilirubin        | 1      | 2.2        |
| Elevated IL-6                      | 3      | 6.7        |
| Elevated IL-10                     | 1      | 2.2        |

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, COVID-19: Coronavirus Disease 2019, CRP: C-Reactive protein, IL: interleukin.