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

Keywords: COVID-19, Neonatal outcome, Placental infarctions, Fetal hypoxia, vertical transmission

Posted Date: September 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-71847/v1>

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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 insufficiency 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 conflicting evidences across the globe. The dilemma about transplacental transmission of coronaviridae is not exclusive to the current outbreak. To our knowledge, nine studies^{1–10} 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. Gagnieur et al⁶ 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,^{11,12} 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 conflicting 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 placentae 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 report⁸¹.

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.^{84–86} 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.⁸⁷

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

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors

Authors' contributions

AA, LE, MA, MT contributed to the conception and design of the work

RF, RE, DH, DK, YO, SA³, MI¹, MI² contribute significantly to the acquisition of data

HA, HI, AN, GA, IG, LM, MS, MH, ME, NE, NA, NS, RD, RS, RR, SA¹, SI, SA², SK, SP contributed to the analysis and interpretation of data

R.M contributed to the drafting and revision of the manuscript

All authors have approved the submitted version

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:

MI¹: Marina Ibrahim, MI²: Monica Ibrahim. SA¹: Sadra Albala, SA²: Sama Ahmed, SA³: Sara Abohashish

Acknowledgements

To our families who are bearing the weight of our sacrifice of time to our patients. If our families were not understanding to the depth of our struggle, we would have never been able to keep the same level of dedication to our patients. To our students that we involve in each step of our researches to make them flourish in this field and take the lead the soonest the possible.

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Tables

Table1: Reported cases of vertical transmission, clinical manifestations and placental abnormalities in SARS-1, HKCoV and MERS

Abbreviations: HKCoV: Hong Kong Coronaviridae, MERS: Middle East Respiratory Syndrome, NEC: Necrotizing enterocolitis, RDS: Respiratory Distress Syndrome, SARS: Severe acute respiratory syndrome .

Paper	Wong et al ³	Robertson et al ¹⁰	Yudin et al ⁴	Stockman et al ⁵	Gagneur et al ⁶	Shek et al ⁸	Li et al ⁷	Jeong et al ¹	Payne et al ²	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 1: RDS	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 ³⁸	Australia
Kirtsman et al. ³⁰	Canada
Fan et al. ⁴¹	China
Chen et al. ²⁵	China
Li et al. ⁴⁰	China
Lee et al. ⁴⁹	China
Xiaotong et al. ⁴⁴	China
Kang et al. ³¹	China
Lu et al. ³³	China
Liao et al. ²⁸	China
Buonsenso et al. ³²	China
Khan et al. ³⁴	China
Dong et al. ⁴⁹	China
Xiong et al. ⁴⁵	China
Liu et al. ⁴⁶	China
Chen et al. ⁷⁷	China
Yu et al. ²⁹	China
Zeng et al. ⁷⁸	China
Chen, Liao and Shao ⁷⁷	China
Liu et al. ²⁷	China
Zhu et al. ⁸⁰	China
Chen et al. ³⁹	China
Chen et al. ⁸³	China
Nie et al. ³⁷	China
Khan et al. ¹⁴	China
Qianchenga et al. ²⁶	China

Wu et al. ⁵⁹	China
Yang et al. ⁶⁷	China
Liu et al. ⁷⁹	China
Zhang et al. ⁸⁸	China
Yue et al. ⁵⁰	China
Yang et al. ⁶⁷	China
Lin et al. ⁸⁹	China
Yin et al. ⁵³	China
Yang et al ⁹⁰	China
Zheng et al ⁶⁸	China
Wu et al ⁶⁵	China
Dumpa et al ⁷¹	China
Chen et al ¹⁷	China
Vivanti et al ⁶³	France
Kayem et al ⁵⁸	France
Zambrano et al. ⁴²	Honduras
Ng et al ⁷⁶	Honk Kong
Karami et al. ³⁶	Iran
Hantoushzadeh et al. ¹⁵	Iran
Ferrazzi et al. ¹⁸	Italia
Ferraiolo et al ⁷⁴	Italy
Salvatori et al ⁶⁴	Italy
Alzamora et al. ²⁴	Peru
González et al. ²²	Spain
Nyholm et al ⁶⁰	Sweden
Baud et al. ²⁰	Switzerland
Masmejan et al ⁷²	Switzerland

Kalafat et al. ³⁵	Turkey
Govind et al ⁵⁷	UK
Knight et al ⁵⁶	UK
Breslin et al. ²³	USA
Shanes et al. ⁵⁵	USA
Iqbal et al. ⁴³	USA
Hillary et al ⁷³	USA
Hong et al ⁶²	USA
Sisman et al ⁶⁶	USA
Easterlin et al ⁶¹	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//%)
<i>Asymptomatic (219/12%)</i> <i>Respiratory manifestations:</i> -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%) -Rhinorrhoea (20/1%) -Chest pain (2/0.1%) <i>GIT manifestations:</i> -Diarrhea (78/4.4%) -Abdominal pain (2/0.1%) -Vomiting (41/2.2%) <i>CNS manifestations:</i> -Limb Asthenia (1/0.05%) -Anosmia (180) -Lethargy (76/4.3%) -Dysgeusia (1/0.05%) -Headache (60/3.3%) <i>Others:</i> - Fever (951/53%) -Myalgia & joint pain (56/3%) -Back pain (2/0.1%) -Tachycardia (1/0.05%) -Tachypnea (1/0.05%)	<i>Asymptomatic (11/24%)</i> <i>Respiratory manifestations (8/17%)</i> -Pneumonia (4/8%) -Intubated (2/4%) - Ventilated (1/2%) -Cough (1/2%) <i>CNS manifestations (3/7%)</i> -Irritability (1/2%) -Axial hypertonia and opisthotonus (1/2%) -Neonatal encephalopathy (1/2%) <i>Feeding disorders and GERD (7/15%)</i> <i>Evidence of Intrauterine fetal asphyxia: (9/20%)</i> -Fetal distress (3/7%) -Meconium-stained liquor (3/7%) - Suboptimal cardiotocography (3/7%) <i>Others: (6/13%)</i> -Myocardial dysfunction/Cardiogenic Shock (2/4%) -Hypoglycaemia (1/2%) -Fever (2/4%) -Diarrhea (1/2%) Not reported (14/31%)	<i>Less than 12 hours (19 /42%)</i> <i><24 hours and >12 hrs (7 /16%)</i> <i>After 24 hrs (5 /11%)</i> <i>Not reported (14/31%)</i>	<i>Not reported</i> (26 /57.8%) <i>Preterm and IUGR (3/7%)</i> 24 W (1/2.2%) 34 W (1/2.2%) 35 W (1/2.2%) <i>Full Term (16/35%)</i> 36 W (4/8.9%) 37 W (2/4.4%) 38 W (6 /13.3%) 39 W (2/4.4%) 40 W (2/4.4%)	<i>1st trimester</i> (46/3%) <i>2nd trimester</i> (273/16%) <i>3rd trimester</i> (1313/73%) <i>Not reported</i> (155/8%)
<i>There is overlap of manifestations</i>		<i>Total: 45 COVID-19 positive neonates</i>		<i>Total: 1787 COVID-19 Mother</i>

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 microthrombosis)	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
Funisitis	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.