Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

Study team:

Dr. Dina El Demellawy
Division of Pathology, CHEO
401 Smyth Rd, Ottawa, Ontario
K1H 8L1
613-737-7600 ext. 3846
deldemellawy@cheo.on.ca

Research Coordinator:
Irina Oltean
401 Smyth Rd, Ottawa, Ontario
K1H 8L1
613-737-7600 ext. 3475
IOltean@cheo.on.ca

Rational

1. Background Information and Scientific Rationale

1.1 Background Information

Coronavirus disease 2019 (COVID-19; formerly known as 2019 Novel Coronavirus, 2019-nCoV) is an infectious disease caused by the recently discovered strain of coronavirus (SARS-COV-2 virus) following an outbreak in Wuhan City, Hubei Province, China, in December 2019. The exact origin of the virus is unknown (1). Current literature supports that coronaviruses compose a large family of RNA viruses, which may cause illness in humans or animals. Coronaviruses form part of the Coronaviridae family including causative viruses such as Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS) (2).

On January 30, 2020, The World Health Organization declared the SARS-COV-2 outbreak a Public Health Emergency of International Concern. On March 11, 2020, the World Health Organization characterized SARS-COV-2 as a pandemic reflecting its worldwide spread (3). The method of transmission for Coronavirus Disease 2019 is via small respiratory droplets transferred from person to person, particularly due to secretions from the nose or mouth which are spread when a person with SARS-COV-2 coughs or exhales (4). People without the disease can acquire the infection by touching surfaces contaminated by SARS-COV-2, then touching mucous membranes found in the face such as the eyes, nose, or mouth. The infection can also be acquired by breathing in the respiratory droplets from someone with SARS-COV-2 who coughs outwards or exhales these droplets.

As for vertical transmission (e.g., between mothers and their newborns), reports are very limited and inconclusive (5–7). Perinatal 2019-nCoV infection may not have adverse effects on newborns, like problems such as fetal distress, premature labor, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and even death in contrast to SARS and MERS (8). However, analysis of additional cases is necessary to elucidate the truth behind the impact of perinatal 2019-nCoV. Overall, vertical transmission of 2019-nCoV has yet to be confirmed (9).

Despite this, the placenta remains a superior example of a pregnancy diary. In other words, it is crucial to study the potential for vertical transmission of perinatal 2019-nCoV. Currently, there are few emerging studies

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

suggesting that neonates with mother's who test positive for SARS-COV-2 are subjected to premature labour. However, the clinical characteristics of SARS-COV-2 pneumonia in pregnant women were similar to those reported for non-pregnant adult patients who developed SARS-COV-2 pneumonia as well. Findings from this small group of cases suggest that there is currently no evidence for intrauterine infection caused by vertical transmission in women who develop SARS-COV-2 pneumonia in late pregnancy (5). As well, no severe adverse pregnancy outcomes have been found in three cases of pregnancy (10). The pathological results suggests that there are no morphological changes related to infection in these three placentas. Therefore, there is no evidence for intrauterine vertical transmission of 2019-nCoV among three women infected with 2019-nCoV in their late pregnancy. Yet, more evidence needs to be generated in this field before making any definitive conclusions.

Rationale

Data on the role of the SARS-COV-2 in various placental lesions (e.g., preeclampsia, abnormal placentation, intrauterine growth restriction (IUGR), and disruption of the chorionic membrane) has yet to be explored; as such, our study aims to fill this gap and generate greater evidence to help inform clinicians during the management of pregnancies complicated by SARS-COV-2.

1.2 Potential Risks and Benefits

There are no significant risks associated with this study apart from the risk to confidentiality, which will be protected by our compliance with all CHEO privacy policies.

The information gathered may help provide a basis for providing a tailored approach to the management of pregnancies complicated by SARS-COV-2 as well as anticipating and monitoring subsequent pregnancies.

2. Study Objectives

We have designed a systematic review to:

1. Compare neonatal preterm outcomes preterm (36 weeks and less gestational age) versus term (37+ weeks);
2. Compare viral load to neonatal outcome;
3. Examine C-section versus vaginal delivery and associated fetal or neonatal outcomes for mothers with COVID-19;
4. Investigate ethnicity in COVID-19 positive cases (e.g., Asian, Caucasian versus other ethnicities and neonatal outcomes);
5. Determine if there is a relationship between maternal age and fetal or neonatal outcome;
6. Placental pathology and COVID-19 symptoms or viral load or fetal/neonatal outcome and maternal outcome;
7. Assess the impact of SARS-COV-2 (i.e., presence of fetal distress, premature labor, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and death) in cases of preeclampsia, abnormal placentation, intrauterine growth restriction (IUGR), and disruption of the chorionic membrane using placental samples; and
8. Differentiate the severity of SARS-COV-2 symptoms in cases of preeclampsia, abnormal placentation, intrauterine growth restriction (IUGR), and disruption of the chorionic membrane to explain differences (if any) depending on the status of these conditions

Methodology:

Search strategy:

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

Our study will identify case series, case reports, or case-control studies of mothers and/or neonates who exhibit SARS-COV-2 symptoms in addition to preeclampsia, abnormal placentation, IUGR, or chorionic membrane disruptions. Preliminary key search terms, which may be subject to change upon review from our librarian, include: COVID-19 OR SARS-COV-2 AND placental lesions OR placenta AND neonates in addition to the aforementioned health conditions. We will perform a comprehensive search of literature available from December 2019 onwards. An information specialist will search for eligible studies in: Medline Embase, CINAHL, Google Scholar and WHO database of COVID-19 articles. Alerts will be set in MEDLINE and Google Scholar to monitor emerging studies and the investigators will use this to determine when full search updates are needed. There will be no language restrictions.

Population: Pregnant women and/or neonates who test positive for COVID-19.

Condition: COVID-19 validated by positive antibody testing or viral testing using Polymerase Chain Reaction (PCR)

Comparator(s)/control: Pregnant women and/or neonates who do not have COVID-19 (are otherwise healthy).

Exclusion: literature reviews, systematic reviews, editorials, letters to the editor, conference abstracts, and commentaries.

Primary outcome(s): The potential impact or correlation of COVID-19-related signs and symptoms and placental pathology or absence of an association as well as healthy versus complicated neonatal outcome(s).

Secondary outcome: Mortality versus survival.

Experimental Plan

Data Management

Records will be downloaded into Reference Manager for duplicate removal and exported to insightScope for screening. Data abstraction will be performed using REDCap for study details and methodology. A second stage using piloted spreadsheets will be used to obtain outcome data.

Selection process

Screening will be performed in two steps (title and abstract, full text) against inclusion criteria by two independent reviewers. Consensus and/or resolution of conflicts will be performed by a third reviewer, where necessary.

Data collection process

A test set of 50 citations will be used to evaluate the inclusion/exclusion criteria. The test set will be created by a member of the investigative team and verified by a second member. All reviewers who contribute to screening will first perform the test set, and must achieve a sensitivity of $\geq 80\%$ before they are given access to the full set of study records. Reviewers who do not achieve $\geq 80\%$ sensitivity will be provided with additional training and repeat a second test set. If $\geq 80\%$ sensitivity is achieved on the repeat test set, the reviewer will be given to access to the full set of study records.

Data will be abstracted onto REDCap forms by two independent reviewers in duplicate. Consensus and/or resolution of conflicts will be performed by a third reviewer, where necessary. The data abstraction form will be piloted by at least two members of the investigative team against a total of five eligible studies.

Data Items and Outcomes

From all of the studies included in this review, the following information will be obtained: citation details (title of the article and the year of publication); study details including study design; location of the study and its sample size; patient demographics including age, gender and ethnicity, disease details, associated anomalies,

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

syndromic conditions, infections, gestational age, pathology of organs and/or placenta. Additional outcomes to be extracted include: follow up duration, ultrasound imaging results, pregnancy management strategies, and patient survival. We will be prioritizing neonatal endpoints and placental pathology results to identify if there is any relationship between COVID-19 symptoms and characteristics of the placenta, which will help guide future practice and management of pregnancies complicated by placental pathological conditions that are potentially exacerbated by COVID-19. Understanding the impact of COVID-19 on neonatal endpoints can aid in identifying optimal treatment methods to prevent adverse clinical outcomes.

Data will be sought for the following outcomes:

1) Demographic and Health Behaviours

- Maternal age
- Parity
- Spontaneous pregnancy or artificial reproductive treatment
- Gestational age
- Pre-pregnancy BMI (underweight, normal, overweight, obese)
- Maternal smoking
- Cannabis use in pregnancy
- Previous history of abruption
- Chronic hypertension, gestational hypertension, or preeclampsia
- Preterm Premature Rupture of Membrane (PPROM)
- Illicit Drug use
- Other medical conditions (such as pregestational diabetes, Gestational Diabetes, Thrombophilia)
- Birth weight
- Sex
- Mode of delivery
- Signs and symptoms of COVID-19 including presentation and progress
- Treatment given

The primary endpoints include:

1) Neonatal outcomes

- APGAR 1/5/10
- APGAR ≤ 5 at 10 min Y/N/not done
- Cord pH (art or venous) ≤ 7.0 Y/N/not done
- Cord pH $7.1 < 7.16$ Y/N/not done
- BD ≥ 16 on cord gas or neonatal gas within 1h of birth Y/N/not done
- BD 10-15.9 on cord gas or neonatal gas within 1 h of birth Y/N/not done
- Peak lactate first 24 hours
- Onset of first suspected seizure (minutes)
- Timing/evolution of encephalopathy (how to ask)
- SARNAT at presentation none/mild/mod/severe
- Worse SARNAT none/mild/mod/severe
- aEEG with discontinuous pattern or burst suppression Y/N/not done
- F/U evidence death, cognitive delay or CP Y/N/not done
- Admission to NICU Y/N
- CPR (chest compressions and/or epinephrine) in delivery room Y/N
- ≥ 10 m consecutive minutes of PPV at birth Y/N

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

- Elevated transaminases/increasing after birth Y/N/not done
- Cardiac depression (need for inotropes) Y/N
- Evidence ARF (Cr peak)
- Mortality still birth or neonatal death

2) Placental pathology

Retroplacental clot(s); and its location and size relative to the disc measures and weights

- Retroplacental hematoma
- Blood clot in container size and weight
- Fibrin deposition
- Compressed villi
- Infarction, location, number, size, % and relation to abruption
- Hemosiderin-laden histiocytes
- Hemosiderin in decidua
- Chorioamnionitis
- Funisitis
- Acute deciduitis
- Meconium stained membranes
- Villous stromal hemorrhage
- Villous edema
- Chronic deciduitis with plasma cells
- Decidual necrosis
- Decidual vasculopathy
- Placental infarctions including % of disc involvement and size, number and location
- Villous maldevelopment (delayed or accelerated maturation)
- Hemosiderin deposition in chorionic plate
- Intervillous thrombus
- Intravillous hemorrhage
- Chronic villitis.
- State fresh vs formal
- Disc dimensions
- Umbilical cord insertion
- Membranes retromembranous hematoma
- Circumvallate or circummarginate
- Parenchymal consolidation
- Localized lesions
- Other

Additional outcomes:

1) Maternal imaging

- Presence of hematoma/clot
- Other pathology, placenta or uterus
- COVID-19 induced changes in other organs

2) Fetal imaging

- Signal changes/damage central nervous system and other systems estimated timing of injury
- Congenital anomalies

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

- COVID-19 induced changes in other organs

3) Fetal Topography

- Baseline Beats per minute (BPM)
 - Normal (110-160)
 - Atypical (100-110; > 160 > 30 < 80 min (rising baseline))
 - Abnormal (< 100; > 160 > 80 min (erratic baseline))
- Variability
 - Normal (Moderate minimal/absent ≤ 5 bpm < 40 min)
 - Atypical (Minimal/absent ≤ 5 bpm 40-80 min)
 - Abnormal (Minimal/absent ≤ 5 bpm; bpm > 80 min; ≥ 25 bpm > 10 min; Sinusoidal)
 - Deceleration
 - Normal (None; occasional; uncomplicated variables; early decels)
 - Atypical (Repetitive (≥ 3); uncomplicated variables; occasional late decels; single prolonged > 2 < 3 min)
 - Abnormal (Repetitive (≥ 3); complicated variables; late decels > 50% of contractions; prolonged > 3min)
 - Acceleration
 - Normal (Spontaneous or with scalp stim)
 - Atypical (Absent with scalp stim)
 - Abnormal (Usually absent)

4) Neonate imaging

- Signal changes/damage in central nervous system and its estimated timing of injury
- Congenital anomalies
- COVID-19 induced changes in other organs

5) Maternal

- Blood pressure on admission: Systolic and Diastolic (mmHg)
- Maternal Serum Markers: maternal serum alpha-fetoprotein (AFP), Human chorionic gonadotropin (HCG), pregnancy-associated plasma protein (PAPP-A), maternal serum activin A, fibronectin, thrombomodulin, d-dimer
- Ultrasound: amniotic fluid volume on last ultrasound prior to delivery
 - Oligohydramnios: no 2x2cm pocket or largest deepest pocket <2 cm or amniotic fluid index (AFI) <5cm
 - Polyhydramnios: Largest deepest pocket >8 cm or AFI > 25 cm
- Ultrasound Doppler:
 - Uterine artery Doppler Pulsatility index (PI) (with gestational age at recording)
 - Umbilical Artery Doppler PI on last US prior to delivery
 - Middle Cerebral Artery Doppler PI on last US prior to delivery
 - Middle Cerebral Artery PSV: >1.5MoM on last US prior to delivery
 - Cerebral Placenta ratio (<5th percentile) on last US prior to delivery
- Ultrasound of the Placenta and Umbilical cord on last US prior to delivery:
 - Evidence of hypoechoic to anechoic retroplacental fluid collection
 - Evidence of hematoma/clot
 - Placenta Previa
 - Velamentous cord insertion
 - Marginal cord insertion

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

- Intra-placental lesions: infarctions, fibrin deposition and chorioangiomas
 - Accessory lobe
 - Placenta imaging including location (anterior, posterior or fundal)
- Vaginal bleeding (presented with vaginal bleeding, vaginal bleeding before labor, excess bleeding in labor) and time prior to delivery first noted
- Hypertonic uterine contractions (increased tone/rigidity between contractions) and time prior to delivery first noted
- Uterine tenderness and time prior to delivery first noted
- Abdominal and/or back pain accompanied by contractions and time prior to delivery first noted
- Electronic Fetal Monitoring (EFM) Normal/Atypical/Abnormal
- Decrease fetal movement (within 48 hours prior to delivery)
- Scalp pH ≤ 7.2
- Time from neonate delivery to placental delivery
- Maternal ICU admission post delivery
- Maternal mortality

Risk of bias (quality) assessment: Observational studies will be assessed using the Ottawa-Newcastle scale. Researchers will independently perform quality assessment of publications and will compare scores in order to reach a consensus and standardize responses. When consensus cannot be reached, a third researcher will be consulted. Quality assessment will be used to inform interpretations of the data and will help identify studies whose results may be influenced by their study design.

Strategy for data synthesis: Data to be used will be aggregate or at the level of individual participants. Tables will be used to summarize the general characteristics of the studies included. Depending on the data and the level of variation between studies, a meta-analysis will be used to synthesize data. Count and dichotomous data will be expressed as odds ratios with 95% confidence intervals, while continuous data will be expressed as a mean or standardized mean difference with 95% confidence intervals. Forest plots will be utilized to visualize the data. Statistical heterogeneity of the included studies will be assessed using the I-squared test with 95% confidence intervals, and publication bias will be determined using a funnel plot and Egger's test when possible (>10 included studies). Should there be an insufficient number of studies to allow for meta-analysis, then only a systematic review will be carried out.

Meta-bias(es)

Two independent researchers will assess the risk of bias to both selective publication and selective non-reporting using GRADE, which evaluates the different sources of reporting bias across separate domains (e.g., selective nonreporting in the 'study limitations' risk of bias domain and bias due to selective publication in the 'publication bias' domain). Publication bias will be determined using a funnel plot and Egger's test when possible (>10 included studies). We will also be assessing the presence of small ('positive') studies with for-profit interest, discrepancy in findings between published and unpublished studies, and whether search strategies were comprehensive or not (11).

Confidence in cumulative evidence

If a meta-analysis will be undertaken, the strength of the body of evidence will be assessed using GRADE. Our evidence will come from non-randomised studies and will be upgraded if there is a large magnitude of effect, evidence of a dose-response effect, and confounders are adjusted for. After the process of upgrading or downgrading is complete, each researcher will rate each outcome as high, moderate, low, or very low (12).

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

Dissemination plans: The protocol will be submitted to PROSPERO and posted as a Preprint in Open Science Framework, as will a preprint of the completed review. We intend to publish the review in a peer-reviewed journal. Results will also be disseminated through conference presentations and academic meetings or research days.

Funding sources/sponsors: This study is not funded.

Conflicts of interest: There is no conflict of interest to declare.

Impact of COVID-19 on the placental pathology of pregnant women and their infants: A Systematic Review

References

1. Coronavirus Disease 2019 (COVID-19) Testing Who to test [Internet]. 2020. p. 1–8. Available from: <https://www.publichealthontario.ca/en/laboratory-services/test-information-index/wuhan-novel-coronavirus>
2. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* [Internet]. 2020;8(4):420–2. Available from: [http://dx.doi.org/10.1016/S2213-2600\(20\)30076-X](http://dx.doi.org/10.1016/S2213-2600(20)30076-X)
3. Troyer J. Q&A on coronaviruses (COVID-19) [Internet]. 2020. p. 56. Available from: <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>
4. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Mil Med Res*. 2020;7(1):1–10.
5. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* [Internet]. 2020;395(10226):809–15. Available from: [http://dx.doi.org/10.1016/S0140-6736\(20\)30360-3](http://dx.doi.org/10.1016/S0140-6736(20)30360-3)
6. Qiao J. What are the risks of COVID-19 infection in pregnant women? *Lancet* [Internet]. 2020;395(10226):760–2. Available from: [http://dx.doi.org/10.1016/S0140-6736\(20\)30365-2](http://dx.doi.org/10.1016/S0140-6736(20)30365-2)
7. Interim Considerations for Infection Prevention and Control of Coronavirus Disease 2019 (COVID-19) in Inpatient Obstetric Healthcare Settings - ITA [Internet]. 2020. p. 331–8. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html>
8. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. *Arch Pathol Lab Med* [Internet]. 2020; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32180426>
9. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;1(9):51–60.
10. Chen S, Huang B, Luo DJ, Li X, Yang F, Zhao Y, et al. [Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases]. *Zhonghua bing li xue za zhi = Chinese J Pathol* [Internet]. 2020;49(0):E005. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32114744>
11. Page MJ, McKenzie JE, Higgins JPT. Tools for assessing risk of reporting biases in studies and syntheses of studies: A systematic review. *BMJ Open*. 2018;8(3):1–16.
12. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: Development and pilot validation. *Syst Rev*. 2014;3(1):1–9.