

# **COVID-19 & Pregnancy**

# A Rapid Synthesis of Reported Cases (up to April 30, 2020)

May 7, 2020

# Ashley Raeside, Christine Wang & Chelsea Elwood

#### **Reproductive Infectious Diseases Program**

https://ridprogram.med.ubc.ca/cancovid-preg/

Department of Obstetrics and Gynaecology Faculty of Medicine University of British Columbia Vancouver, Canada

## Background

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, was first identified in Wuhan, China in December 2019<sup>1</sup>. The WHO situation report on May 1, 2020 reported 3,175,207 cases, and at least 224,172 deaths worldwide for COVID-19<sup>2</sup>.

Pregnancy is associated with adaptations to cardiorespiratory, hematologic, and immune function, among other physiologic changes. Pregnant individuals therefore represent a population worthy of focused evaluation during this pandemic, to determine the impact of COVID-19 on patients, their pregnancies, and their infants.

During the 2009 H1N1 pandemic, pregnant individuals appeared to have higher risk for infection-related adverse outcomes, such as severe illness, ICU admission and death, compared to the general population<sup>3</sup>. So far with COVID-19, larger case series have observed that pregnant individuals who become infected with SARS-CoV-2 do not tend to experience more severe disease compared to the general population<sup>4,5</sup>.

The available literature on COVID-19 in pregnancy has been evolving rapidly. Researchers from mainland China contributed the majority of early and more detailed reports to date, but published cases from Europe, Iran and the Americas are also on the rise.

There are challenges with the current body of literature that make it difficult to interpret collectively, as many publications often re-report the same cases without referencing so explicitly. This type of reporting makes it difficult to determine the true prevalence of COVID-affected pregnancies. Other challenges include the wide variability of indicators used to describe COVID-19 in pregnancy, and the lack of coordinated data surveillance, synthesis and reporting by defined jurisdictions. These issues may hinder risk assessment by care providers and policy makers, limiting their ability to apply the available information to the management of pregnant patients.

The ad-hoc reporting, lack of stated inclusion criteria, and ambiguous redundancy among cases makes it challenging to discern the true prevalence of adverse conditions that may be associated with COVID-19 in pregnancy. We are all seeking data to improve patient care and pregnancy outcomes. The observed reporting trends are somewhat understandable, given the heightened demands for all stakeholders during this pandemic. However, these challenges emphasize the importance for applying critical appraisal skills to the available literature, including evaluating data quality, and considering its generalizability to different patient populations.

The current report aims to synthesize information on COVID-affected pregnancies from across the published literature, with the hope of achieving the following objectives.

# Objectives Determine how many COVID-affected pregnancies reported across the literature to date are likely to be unique. Describe basic pregnancy outcomes for these COVID-affected pregnancies worldwide. Describe reports of adverse maternal, obstetrical, fetal and neonatal outcomes for COVID-affected pregnancies worldwide.

# **Methods**

# Search Strategy

We conducted a comprehensive literature search using PubMed and OVID Medline. The date range for the search was December 8, 2019 to April 30, 2020 inclusive. We used a combination of search terms which are described in <u>Appendix 1</u>.

We cross-referenced the list of reports we developed against *"COVID & Pregnancy: Primary Sources"*, a comprehensive list of emerging case literature maintained by Thornton et al<sup>6</sup>. We were grateful to also receive a few additional publications directly from colleagues. These were included when eligible, and not previously identified.

We evaluated clinical reports (case reports, case series, and cohort studies), as well as governmental reports based on national surveillance data. We did not actively search for non-English publications, but when these were encountered we included them if adequate translation could be facilitated. Ethics review was not sought for this study given that the analysis relied on already published data.

# **Evaluation Approach**

Two reviewers (AR and CW) independently screened the reports identified through the above-described search strategy. The goal was to identify all potentially eligible cases of

COVID-associated pregnancies contained within the reports, and review any corresponding data available about each case.

Inclusion criteria for cases included:

- Patient pregnant, or recently pregnant (within 6 weeks postpartum)
- Lab-confirmed diagnosis of COVID-19 via nasopharyngeal or throat swab for SARS-CoV-2
- Diagnostic criteria for the COVID-19 case not specified, but the case was contained within an official government report based on surveillance data
- Case determined to be likely unique, relative to other included cases in the review

Exclusion criteria for cases included:

- COVID-19 diagnosis made based on radiographic and/or clinical features alone, without a confirmatory nasopharyngeal or throat swab for SARS-CoV-2
- Case determined to be a possible duplicate of a case already included in the review

When the reviewers differed in opinion about the eligibility of a case, these differences were resolved through discussion and re-evaluation of the case, and those other cases which represented potential duplicates. Potentially redundant cases were identified by comparing all available information (e.g. reported admission date, hospital, maternal age, gestational age at admission and/or delivery, presenting symptoms and timing of symptom onset, mode of delivery, singleton versus twin pregnancy, neonatal apgars, neonatal birth weight, adverse maternal, fetal or neonatal outcomes, vertical transmission testing data). If the available information could not demonstrate the cases being compared to be distinct from one another, then only one case was counted amongst the potential overlaps.

#### Data Analysis

Data analysis was done by AR with assistance from CW. A database was created to aggregate eligible cases and their associated data. A variety of indicators were collected for, when the data was available. The database is available upon request.

The indicators for this review included: case country, pregnancy outcome, singleton versus multiple pregnancy, delivery mode, gestational age at delivery, birth weight, maternal death, maternal ICU admission, maternal mechanical ventilation, neonatal death, intrauterine fetal demise or stillbirth, serious birth asphyxia, neonatal nasopharyngeal or throat swab for SARS-CoV-2, neonatal SARS-CoV-2 antibody IgM positivity, and testing results for SARS-CoV-2 in cord blood, breast milk, vaginal secretions, placenta, or amniotic fluid.

When two or more publications presented potentially the same case or cases based on the above described comparative analysis, cases were only counted once. Supplementary case information was only extracted from whichever publication provided the more complete and detailed summary of the case for the indicators above.

# Results

#### 1. Description of Included Reports

Overall, 77 relevant publications were identified<sup>4,5,7-81</sup>. These publications provided a combination of eligible and ineligible cases, on the basis of our case-level <u>inclusion and</u> <u>exclusion criteria</u>.

Cumulatively, these 77 publications contained 1,206 cases of pregnant or recently pregnant patients labeled as having COVID-19 infection. By evaluating case level data, we determined that 598 of the initial 1,206 cases are likely unique, lab-confirmed COVID-19 infections, in pregnant or recently pregnant patients, and therefore eligible for inclusion. Of the remaining cases, 550 were excluded for being potential duplicates, and 58 cases were excluded for not meeting diagnostic criteria. Eligible cases originated from 16 countries, with the greatest number from the United States (n=175, 29.3%). See **Table 1**, for more details.

<b>Table 1.</b> Unique Cases ofCOVID-affected pregnancyreported, by country.	(n)	(%)
United States	175	29.3%
China	151	25.3%
Netherlands	138	23.1%
UK	55	9.2%
Italy	42	7.0%
France	14	2.3%
Iran	10	1.7%
Singapore	3	0.5%
Spain	2	0.3%
Turkey	1	0.2%
Switzerland	1	0.2%
Sweden	1	0.2%
Peru	1	0.2%
Korea	1	0.2%
India	1	0.2%
Honduras	1	0.2%
Canada	1	0.2%
TOTALS	598	100.0%

#### 2. General Pregnancy Outcomes

Of the 598 eligible cases of COVID-19 infections associated with pregnancy, 44.5% (n=266) delivered during the studies. Another 27.6% (n=165) did not deliver during the studies, and no pregnancy outcome was reported for 27.9% (n=167) of the cases.

Among the 27.6% of patients who did not deliver during the study, this is a heterogeneous category of patients. Some continued with their pregnancy beyond the study period (including patients in the first, second, and third trimesters). A few had early pregnancy terminations in the first trimester. The remainder were mainly recent postpartum patients who represented for diagnosis and care of COVID-19 infection.

#### 3. Delivered Infants

Of the 266 deliveries which occurred across the studies, 76.7% (n=204) specified whether the delivery was for a singleton or a multiple birth. 98.5% (n=201) were singleton deliveries, and 1.5% (n=3) were twin deliveries. There were no higher order multiple births reported. Those deliveries which did not specify singleton or multiple birth were assumed to be singletons, for the purpose of enabling a count of the minimum number of infants delivered across the eligible cases.

In total, there were a minimum of 269 infants delivered for the cases included in this review (201 infants from singleton deliveries, 6 infants from twin deliveries, and 62 infants from unspecified deliveries assumed to be singleton for the purpose of providing a total minimum neonate count) (**Figure 1**).

**Figure 1.** Minimum number of neonates delivered from COVID-19 affected pregnancies across the published literature up to April 30, 2020. 

#### 4. Gestational Age at Delivery

Whether a delivery occurred at term compared to preterm was reported for 70.3% of deliveries (n=187). Among these 68.4% (n=128) were born at term (37 weeks estimated gestational age and above), and 31.6% (n=59) were born preterm (before 37 weeks estimated gestational age) (**Figure 2**).

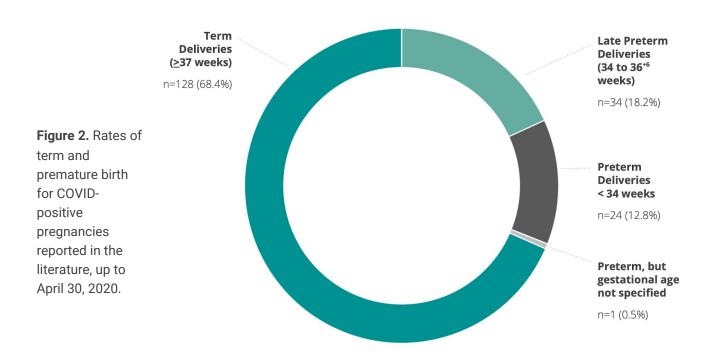
#### 5. Mode of Delivery

Of the 266 deliveries, mode of delivery was reported for 78.6% of these (n=209). Caesarean sections were almost twice as common as vaginal deliveries among the deliveries where mode was reported (**Figure 3**).

#### 6. Birth Weight

Birth weight was not routinely reported by the studies we evaluated. Only 29.0% (n=78) of infants had this information provided. Among these, 80.8% (n=63) had a birth weight above 2500 grams, and 19.2% (n=15) had low birth weight (less than 2500 grams).

In a majority of cases of low birth weight infants (93.3%, or 14 of 15), the pregnancies were affected by other potential causes of low birth weight, such as prematurity, twin pregnancy, and/or preeclampsia.



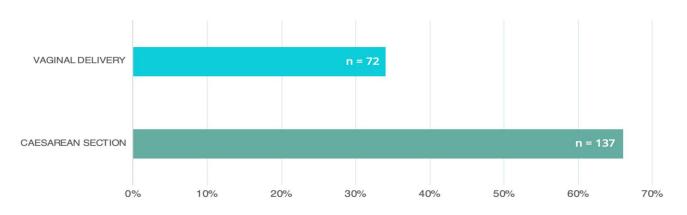


Figure 3. Mode of delivery for COVID-positive pregnancies reported in the literature.

# 7. Vertical Transmission

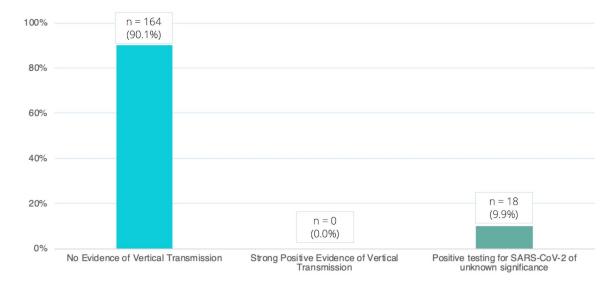
#### SUMMARY

Overall, 68.4% (n=182) of cases reported testing of some kind to evaluate for vertical transmission (which encompases in utero, during delivery or horizontal postpartum). 90.1% (n=164) of cases with testing showed no evidence of vertical transmission. Zero cases provided definitive evidence to support vertical transmission. 9.9% (n=18) had some kind of positive or uncertain test results. **Figure 4** shows a breakdown of cases with testing, and **Figure 5** provides more detail on cases with positive or uncertain results, where vertical transmission cannot be ruled out.

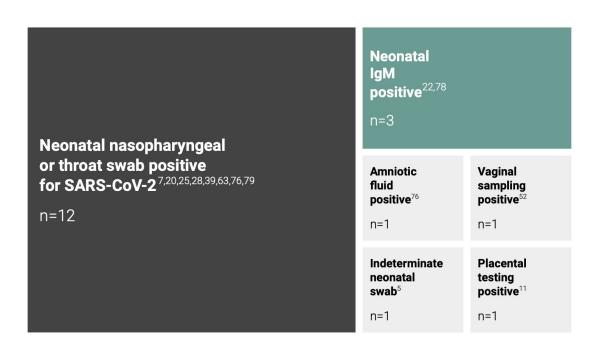
#### NEONATAL TESTING

Overall, 65.1% (n=175) of neonates received a nasopharyngeal or throat swab to test for SARS-CoV-2, one or more times after delivery. Among these, 92.6% (n=162) of neonates had all negative nasopharyngeal or throat swabs. There was one swabbed neonate (0.6%) with an indeterminate swab treated as a presumptive negative, and that infant continued to be clinically well when followed<sup>5</sup>. 6.9% (n=12) of swabbed neonates had one or more positive nasopharyngeal or throat swabs for SARS-CoV-2. The timing of these tests relative to birth was highly variable. In addition to consideration for vertical transmission, most authors caution that transmission may have occurred postnatally via typical droplet or contact routes.

Three neonates had an elevated SARS-CoV-2 IgM level at birth<sup>22,78</sup>. Serologic testing for SARS-CoV-2 was rare among infants across the studies with only 3.3% (n=9) of infants reportedly having been tested this way. The question is raised in both of these studies as to whether positive IgM for SARS-CoV-2 in a neonate at birth is evidence to support vertical transmission, but IgM assays are also known to produce false positive results<sup>85</sup>.



**Figure 4.** A summary of vertical transmission testing results for deliveries where the pregnancies were affected by COVID-19 infection.



**Figure 5.** A breakdown of positive or indeterminate test results, for cases where vertical transmission cannot be ruled out. (There are 19 results described here for 18 cases. In one case there was both a positive neonatal nasopharyngeal swab and amniotic fluid test result.)

#### OTHER TESTING

Overall, 7.1% (n=19) and 6.4% (n=14) of deliveries had testing of umbilical cord blood and breast milk respectively. All these tests were negative. 7.1% (n=19) of deliveries had amniotic fluid tested for SARS-CoV-2, and one case tested positive as shown in **Figure 5**. 4.5% (n=12) of deliveries had placental testing for SARS-CoV-2, and one case tested positive as shown in **Figure 5**. Somewhere between 4.1 to 6.8% (n=11 to 18) of deliveries had vaginal secretions tested for SARS-CoV-2, and one case tested positive. This case was mentioned in the Netherlands surveillance report<sup>52</sup>. The number ranges given above are a consequence of the denominator not being clear for the number of pregnant patients in the Dutch cohort receiving vaginal sampling for SARS-CoV-2.

#### 8. Adverse Maternal Outcomes

#### **OVERVIEW**

Overall, serious adverse outcomes for patients with COVID-affected pregnancies were rare in the studies reviewed. The overall rates of adverse outcomes reported across the published literature may be higher than the true rates of these outcomes among all COVID-affected pregnancies. For many publications, it was clear that a severe or critical outcome was what prompted a case's inclusion for a report, or case series. For example, the surveillance report by Publique Santé France<sup>54</sup> was a summary report about ICU admissions across France for all COVID-19 cases. For this reason, all pregnant cases mentioned in this report have a serious outcome, but that was the reason for their inclusion in the report. Among 2,806 ICU admissions for COVID-19, only 13 were associated with pregnancy<sup>54</sup>.

The UK report<sup>60</sup> was another critical care summary. All 47 pregnant patients mentioned were therefore admitted to ICU and 21 of these received mechanical ventilation. It would not be appropriate to assume that these complications are indicative of most COVID-19 infections among pregnant patients in the UK, given the focused inclusion of these cases.

#### CRITICAL CARE

Overall there were 49 reported cases of mechanical ventilation among the 598 cases of pregnancy-associated COVID-19 we considered eligible for inclusion<sup>7,20,27-29,32,33,35,37,41,49,52,55,60,64,70,76</sup>. In total there were 106 reported cases of ICU admission among the 598 cases in our review<sup>5,7,14,20,25,27-29,32-33,35,37,41,49,52,54-55,60,64,70,76</sup>. Two cases were reported of patients who required extracorporeal membrane oxygenation (ECMO)<sup>49,70</sup>.

#### MATERNAL DEATHS

There were 8 reported deaths reported among COVID-positive patients who were pregnant or recently pregnant (1.3% of 598 cases reviewed). All of these reported deaths occurred in Iran<sup>28,35,76</sup>. All original case data reported so far out of Iran has focused on critically ill pregnant patients, most of whom have had serious maternal, fetal and/or neonatal outcomes. We do not yet have a good understanding of how to contextualize these case reports against the broader pregnant population in Iran, to understand how prevalent these critical cases are.

Amorim et al.<sup>8</sup> published a paper describing nine deaths among patients with a COVID-affected pregnancy, including 5 from Brazil, 2 from Mexico, and 2 from Iran. However some of these were based solely on media reports, and for others we were unable to trace back to an original record of the case. Some were also lacking information to demonstrate a confirmed COVID-19 diagnosis, another one of our inclusion criteria. However, we mention the study here given the severity of the reported outcomes, and because perhaps more detailed case reports will be forthcoming.

#### OTHER ADVERSE MATERNAL OUTCOMES

Two other uncommon adverse outcomes were reported in the literature.

Juusela et al.<sup>32</sup> reported two cases of acute cardiomyopathy (CMO) at their hospital in New Jersey, USA. Both patients had moderately reduced left ventricular ejection fractions and global hypokinesis. One patient was admitted to ICU when this happened on the same day, following delivery. Intubation and mechanical ventilation was initiated for respiratory failure. She required cardiopulmonary resuscitation (CPR) for pulseless electrical activity, and had return of spontaneous circulation within five minutes of CPR. At the time of publication, one week later the patient remained intubated and ventilated in the ICU. The second case of CMO in a COVID-infected pregnant patient was less severe and did not require mechanical ventilation. She developed a supraventricular tachycardia managed with oral beta blockers. The authors conclude that CMO in their patients may be attributed to COVID-19 infection as this complication has been observed among non-pregnant critically ill patients<sup>82,83</sup>.

Vlachodimitropoulou Koumoutsea et al.<sup>62</sup> reported two cases of rapidly progressive coagulopathy in the context of COVID-19 infection during pregnancy. The first case<sup>62</sup> was a pregnant patient in Toronto, Canada with a history of familial neutropenia, stable in adulthood. This patient had typical respiratory symptoms and a lab-confirmed diagnosis of COVID-19. Over 48 hours she had rapidly declining platelets and fibrinogen with a corresponding elevation in APTT. Given her history, superimposed bacterial sepsis was considered although respiratory parameters were stable. Preeclampsia was considered but thought to be less likely as blood pressures were normal. She was delivered late preterm by Caesarean section before her coagulopathy precluded neuraxial anesthetic. The delivery was complicated by 1.5 litre blood loss and required uterine artery ligation, B-Lynch sutures and uterotonics to manage hemorrhage. Her coagulation parameters began to improve after surgery, and she was discharged clinically well four days later.

The second case<sup>62</sup> was a pregnant patient in Clamart, France with a history of asthma and elevated BMI. She presented with mild respiratory symptoms and fever and had a lab-confirmed diagnosis of COVID-19. She was stable but experienced rapid worsening of thrombocytopenia, APTT, as well transaminitis. There was no hypertension or proteinuria to suggest preeclampsia. A non-reassuring fetal heart rate was noted, and together with the progressive coagulopathy this prompted an emergency Caesarean delivery under general anesthetic. She received fibrinogen and tranexamic acid before delivery and no postpartum hemorrhage was noted. Her coagulopathy began resolving immediately postpartum and she was discharged five days after delivery. Key considerations in both of these cases were differentiating the presentations from preeclampsia, planning prophylactic anticoagulation for potentially increased venous thromboembolism risk, and the authors provide a good review of which coagulation parameters provided the best prognostic information for these patients.

## 9. Adverse Fetal or Neonatal Outcomes

#### OVERVIEW

Overall, serious adverse outcomes such as birth asphyxia, stillbirth, and neonatal death were rare among all neonates in the studies reviewed.

The rates of these outcomes reported in the literature are likely higher than the true prevalence of these complications among COVID-affected pregnancies, because the presence of an adverse fetal or neonatal outcome was often what prompted inclusion of a case in a series or report. This is a similar trend to what was observed for adverse maternal outcomes, as described in the <u>previous section</u>.

Except in cases of serious maternal compromise or death, the other adverse neonatal outcomes observed among the cases may not necessarily be attributed to maternal SARS-CoV-2 exposure in the more common mild to moderate cases.

Prematurity seems to be the most common adverse outcome among infants born to pregnant patients with COVID-19 infection, but true prevalence and attribution has not been well established. Across the cases we included, the <u>rate of preterm birth</u> was 31.6% (n=59) of 187 deliveries. However several papers indicate that a diagnosis of COVID-19 pneumonia on its own was an indication for prompt Caesarean delivery<sup>43,70</sup>. This suggests that iatrogenic preterm birth also contributed to the rates of <u>preterm delivery</u>, as well as <u>surgical delivery</u> described by our data synthesis of the available case literature. Furthermore, as described earlier, we observed bias in reporting cases for which adverse outcomes were present.

Yan et al.<sup>70</sup> summarized pregnancy outcomes for 99 pregnant patients with COVID-19 and only reported a spontaneous preterm birth rate of 6.1% (n=6) among them. Similarly, Chen et

al.<sup>4</sup> found a spontaneous preterm birth rate of 8.8% (n=6) among 68 patients who delivered. Overall, this emphasizes the importance of wider population-level data collection to inform providers about the true prevalence of adverse outcomes such as preterm birth.

#### STILLBIRTH

Stillbirth or intrauterine fetal demise (at greater than 20 weeks estimated gestational age) were not common among COVID-infected pregnant patients reviewed by our study. These occurred among only 1.3% (n=7) of 598 cases. This rate is slightly higher than the World Health Organization's global stillbirth target of less than 1.2 per 1,000<sup>84</sup>. However, it must also be considered that many of these cases were likely selected for publication on the basis of this adverse outcome.

For one case reported by Liu et al.<sup>49</sup>, during the 34th week of pregnancy, this occurred in the context of severe maternal disease, where the pregnant patient was intubated for respiratory failure, had mutli-system organ dysfunction, and required extracorporeal membrane oxygenation (ECMO).

Another case was an intentional termination of pregnancy at 26 weeks, for a patient who was not unstable or critically unwell<sup>41</sup>.

Five cases of IUFD or stillbirth were reported from Iran<sup>28,35</sup>, and all were associated with critically unwell pregnant patients. Four of these pregnant patients unfortunately died<sup>28,35</sup>. The other was also critically unwell, requiring mechanical ventilation for at least 20 days, and was still hospitalized at the time of study completion<sup>28</sup>.

#### **BIRTH ASPHYXIA**

Most studies did not mention birth asphyxia, and those which did rarely provided their criteria for diagnosis. Overall there were only two reports of birth asphyxia (0.7% of 269 neonates).

Yan et al.<sup>70</sup> reported a case of an infant was born via emergency Caesarean section at 35<sup>+2</sup> weeks, with Apgars of 1<sup>1</sup>, 1<sup>5</sup>, and 1<sup>10</sup>. He unfortunately died at 2 hours of life. This case occurred in the context of severe maternal pneumonia, septic shock, ICU admission and mechanical ventilation.

Zeng et al.<sup>79</sup> reported the second case of an infant with birth asphyxia. Delivery was via emergency Caesarean section at 31<sup>+2</sup> weeks for fetal distress, with Apgars of 3<sup>1</sup>, 4<sup>5</sup>, and 5<sup>10</sup>. This infant had neonatal respiratory distress, pneumonia confirmed by chest x-ray, *Enterobacter*-positive blood cultures, suspected sepsis, and nasopharyngeal and anal swabs positive for SARS-CoV-2 on Day 2 and 4 of life. For this baby, it is difficult to determine the attribution for his overall clinical condition given the many factors at play (prematurity, birth asphyxia, bacteremia, possible sepsis, positive COVID test results).

#### NEONATAL DEATH

Neonatal deaths were not common among COVID-infected pregnant patients reviewed by our study. We identified four neonatal deaths, occurring for 1.5% of 269 infants.

Zhu et al.<sup>81</sup> described a neonate who died at 9 days of life after developing refractory shock, multiple organ failure, and disseminated intravascular coagulation from gastrointestinal bleeding. This neonate had a negative throat swab for SARS-CoV-2 after delivery.

Yan et al.<sup>70</sup> described a neonatal death in the context of severe maternal compromise and birth asphyxia. This case has already been covered in detail, above.

Hantoushzadeh et al.<sup>28</sup> described neonatal death for two dichorionic diamniotic twins following their delivery by emergency Caesarean section at 28<sup>+2</sup> weeks. This occurred in the context of severe maternal compromise, and ultimately maternal death from COVID-19 infection.

# Summary

In our data synthesis for 77 publications on COVID-19 infection in pregnant and recently pregnant individuals, we identified 598 likely unique cases as of April 30, 2020. The cases span 16 countries worldwide, with the highest number of published cases so far from the United States and China. We determined that 266 deliveries have occurred for COVID-affected pregnancies. A majority (65.6%) of these were Caesarean sections.

Maternal and neonatal adverse outcomes were reported, but uncommon. There were 8 maternal deaths, 49 cases of maternal mechanical ventilation, and 106 maternal ICU admissions. There were 7 reports of IUFD or stillbirth, 2 cases of birth asphyxia, and 4 neonatal deaths.

The prevalence of adverse outcomes among reported cases in the literature is generally higher than expected for pregnancies not affected by COVID-19. This may be explained by an understandable reporting bias for sharing this type of case information widely with other clinicians. Future publications of national or population-level surveillance data will be more informative regarding actual prevalence of adverse outcomes in pregnancy from COVID-19.

At this time, the evidence does not suggest COVID-19 outcomes are worse for pregnant patients compared to the general non-pregnant population<sup>4,5</sup>. There are still unresolved questions around the mechanism and prevalence of various maternal and neonatal complications, as well as for whether antepartum or intrapartum vertical transmission is possible. The literature on COVID-19 in pregnancy is rapidly emerging and we are hopeful that our collective understanding will improve as more knowledge is shared.

# **REFLECTION POINTS**

- In the literature, the ad-hoc reporting, lack of stated inclusion criteria, and redundancy among cases makes it challenging to discern the true prevalence of adverse conditions that may be associated with COVID-19 in pregnancy.
- Rates of adverse maternal, obstetrical, fetal and neonatal outcomes reported in the literature are likely higher than the true prevalence of these complications among COVID-affected pregnancies, because of selection and reporting bias.

*i.e.* Presence of an adverse outcome was often what prompted inclusion of a case in a series or report. Cases where nothing happened may not have been prioritized for publication.

- Prevalence rates resulting from our data synthesis are likely not representative of, or applicable to complication rates in the wider population of COVID-affected pregnancies.
- Our priority was to synthesize and present the available published literature to date on the subject of COVID in pregnancy, with potential case redundancy removed.
- The consequence of our inclusion criteria is that they may have led to our own selection bias. We ended up more likely to include detailed case reports because they are easier to demonstrate as unique, compared to groups of cases without any distinguishing events or features. Cases we included were probably more likely to have an adverse outcome.
- Care providers and policy makers need surveillance data and studies with rigorous methodologies that guard against the selection and reporting bias observed in much of the available literature to date. Our study wasn't designed to solve, or protect against this.

# Acknowledgements

We would like to offer an acknowledgement about the land on which we live, do research and practice medicine. Here in Vancouver, we acknowledge the traditional, ancestral and unceded territories of the Coast Salish peoples: Squamish, Tsleil-Waututh and Musqueam Nations.

# Disclosures

This study did not receive any funding assistance. The authors have no financial, commercial or other conflicts of interest to disclose.

# References

Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*, 2020; 395, 565–574.

The World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 102. Accessed May 1, 2020.

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200501-covid-19-sitrep.pdf?sfvrsn=74 2f4a18\_2

- Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. Am J Obstet Gynecol, 2011; 205, 10–18.
- 3. Chen L, Li Q, Zheng D. Clinical Characteristics of Pregnant Women with COVID-19 in Wuhan, China. *N Engl J Med*, 2020; published online Apr 17, 2020. <u>https://doi.org/10.1056/NEJMc2009226</u>
- Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol, MFM, 2020; published online Apr 9, 2020. <u>https://doi.org/10.1016/j.ajogmf.2020.100118</u>
- 5. Thornton J, O'Donoghue K, Walker K. COVID & Pregnancy: Primary Sources. Last accessed April 30, 2020. https://ripe-tomato.org/2020/03/22/covid-19-in-pregnancy/
- 6. Alzamora MC, Paredes T, Caceres D, et al. Severe COVID-19 during Pregnancy and Possible Vertical Transmission. Am J Perinatol, 2020; published online Apr 18, 2020. <u>https://doi.org/10.1055/s-0040-1710050</u>
- Amorim MM, Takemoto ML, Fonseca EB. Maternal Deaths with Covid19: a different outcome from mid to low resource countries? *Am J Obstet Gynecol*, 2020; published online Apr 26, 2020. <u>https://doi.org/10.1016/j.ajog.2020.04.023</u>
- 8. Asadi L, Tabatabaei RS, Safinejad H, et al. New Coronavirus (COVID-19) Management in Pregnancy and Childbirth. Arch Clin Infect Dis, 2020, 15(COVID-19):e102938.
- Ashokka B, Loh MH, Tan CH, et al. Care of the pregnant woman with COVID-19 in labour and delivery: anesthesia, emergency cesarean delivery, differential diagnosis in the acutely ill parturient, care of the newborn, and protection of the healthcare personnel. Am J Obstet Gynecol, 2020; published online Apr 10, 2020. https://doi.org/10.1016/j.ajog.2020.04.005
- 10. Baud D, Greub G, Favre G, *et al.* Second Trimester Miscarriage in a Pregnant Woman with SARS-CoV-2 Infection. *JAMA*, 2020; published online Apr 30, 2020. <u>https://doi.org/10.1001/jama.2020.7233</u>
- 11. Breslin N, Baptiste C, Miller R, et al. COVID-19 in pregnancy: early lessons. Am J Obstet Gynecol MFM, 2020; published online Mar 27,2020. https://doi.org/10.1016/j.ajogmf.2020.100111
- 12. Browne, PC, Linfert, JB, Perez-Jorge E. Successful Treatment of Preterm Labor in Association with Acute COVID-19 Infection. *Am J Perinatol*, 2020; published online Apr 24, 2020. <u>https://doi.org/10.1055/s-0040-1709993</u>
- CDC. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 – United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep April 3, 2020. 69(13):382–386. Accessed May 1, 2020 from: <u>http://dx.doi.org/10.15585/mmwr.mm6913e2</u>
- 14. Chen H, Guo J, Wang, C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*, 2020; 395(10226): 809–815.
- Chen R, Zhang Y, Huang L, et al. Safety and efficacy of different anesthetic regimens for parturients with COVID-19 undergoing Cesarean delivery: a case series of 17 patients. Can J Anesth, 2020; published online Mar 16, 2020. <u>https://doi.org/10.1007/s12630-020-01630-7</u>
- 16. Chen S, Huang B, Luo DJ, et al. Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. *Chinese J Pathol*, 2020; 49. [Original text in Chinese]. https://doi.org/10.3760/cma.j.cn112151-20200225-00138

- 17. Chen S, Liao E, Cao D, et al. Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. J Med Virol, 2020; published online Mar 28 2020. https://doi.org/10.1002/jmv.25789
- 18. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). Front Pediatr, 2020; 8.
- 19. Diaz CA, Maestro ML, Pumarega MT, *et al.* First case of neonatal infection due to COVID-19 in Spain. *An Pediatria*, 2020; 92(4):237-238. [Original text in Spanish]
- Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalized UK patients with COVID-19 using the ISARIC WHO clinical characterisation Protocol. 2020; Preprint online Apr 28,2020. <u>https://doi.org/10.1101/2020.04.23.20076042</u>
- 21. Dong L, Tian J, He S. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA*, 2020; published online Mar 26, 2020. <u>https://doi.org/10.1001/jama.2020.4621</u>
- 22. Fan C, Lei D, Fang C, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? Clin Infect Dis, 2020; published online Mar 17, 2020. <u>https://doi.org/10.1093/cid/ciaa226</u>
- 23. Ferrazzi EM, Frigerio L, Cetin I, et al. COVID-19 Obstetrics Task Force, Lombardy, Italy: executive management summary and short report of outcome. *Int J Gynecol Obstet*, 2020; published online Apr 8, 2020. https://doi.org/10.1002/ijgo.13162
- 24. Ferrazzi EM, Frigerio L, Savasi V, et al. Vaginal delivery in SARS-CoV-2 infected pregnant women in Northern Italy: a retrospective analysis. *BJOG*, 2020; published online Apr 27, 2020. <u>https://doi.org/10.1111/1471-0528.16278</u>
- 25. Gidlof S, Savchenko J, Brune T, *et al.* COVID-19 in pregnancy with comorbidities: More liberal testing strategy is needed. *Acta Obstet Gyn Scan*, 2020; published online Apr 6, 2020. <u>https://doi.org/10.1111/AOGS.13862</u>
- 26. Gonzalez-Romero D, Ocampo Pérez J, Bautista LG, *et al.* Pregnancy and perinatal outcome of a woman with COVID-19 infection. *Rev Clin Esp*, 2020; published online Apr 17, 2020. <u>https://doi.org/10.1016/j.rce.2020.04.006</u>
- 27. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal Death due to COVID-19 Disease. Am J Obstet Gynecol, 2020; published online Apr 28, 2020. <u>https://doi.org/10.1016/j.ajog.2020.04.030</u>
- 28. Hirshberg A, Kern-Goldberger AR, Levine LD, et al. Care of critically ill pregnant patients with COVID-19: a case series. Am J Obstet Gynecol, 2020.
- Hu X, Gao J, Luo X, et al. Severe Acute respiratory Syndrome coronavirus 2 (SARS-CoV-2) Vertical transmission in neonates born to mothers with Coronavirus Disease 2019 (COVID-19) Pneumonia. Obstet Gynecol, 2020; published online Apr 24, 2020. <u>https://doi.org/10.1097/AOG.00000000003926</u>
- 30. Iqbal S, Overcash R, Mokhtari N, *et al.* An uncomplicated delivery in a patient with COVID-19 in the United States. *New Engl J Med*, 2020; published online Apr 1, 2020. <u>https://doi.org/10.1056/NEJMc2007605</u>
- 31. Juusela A, Nazir M, Gimovsky M. Two Cases of COVID-19 Related Cardiomyopathy in Pregnancy. *AJOG MFM*, 2020; published online Apr 3 2020. <u>https://doi.org/10.1016/j.ajogmf.2020.100113</u>
- 32. Kalafat E, Yaprak E, Cinar G, et al. Lung Ultrasound and computed tomographic findings in pregnant woman with COVID-19. *Ultrasound Obstet Gynecol*, 2020; published online Apr 6, 2020. <u>https://doi.org/10.1002/uog.22034</u>
- 33. Kang X, Zhang R, He H, et al. Anesthesia management in cesarean section for a patient with coronavirus disease 2019. *J Zhejiang Univ*, 2020; 49(1). [Original text in Chinese]. <u>https://doi.org/10.3785/j.issn.1008-9292.2020.03.04</u>
- Karami P, Naghavi M, Feyzi A, et al. Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. *Travel Med Infect Dis*, 2020; published online Apr 11, 2020. <u>https://doi.org/10.1016/j.tmaid.2020.101665</u>
- Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, et al. Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review. Fetal Pediatr Pathol, 2020; published online Apr 2, 2020. https://doi.org/10.1080/15513815.2020.1747120

- 36. Kelly JC, Dombrowski M, O-Neil-Callahan M, *et al.* False-negative COVID-19 testing: considerations in Obstetrical Care. *AJOG MFM*, 2020; published online Apr 28, 2020. <u>https://doi.org/10.1016/j.ajogmf.2020.100130</u>
- 37. Khan S, Peng L, Siddique R, *et al.* Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. *Infect Cont Hosp Ep*, 2020; 1-3, published online Mar 19, 2020. <u>https://doi.org/10.1017/ice.2020.84</u>
- Khan S, Jun L, Nawsherwan, et al. Association of COVID-19 Infection with pregnancy outcomes in healthcare workers and general women. *Clin microbiol Infect*, 2020; published online Apr 8, 2020. <u>https://doi.org/10.1016/j.cmi.2020.03.034</u>
- Lee D, Lee J, Kim E, et al. Emergency Cesarean section on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) confirmed patient. *Korean J Anesthesiol*, 2020; published online Mar 31, 2020. <u>https://doi.org/10.4097/kja.20116</u>
- Lei D, Wang C, Li C, et al. Clinical characteristics of COVID-19 in pregnancy: analysis of nine cases Translated from Chinese]. Chin J Perinat Med, 2020; 23(03): 225-231. [Original text in Chinese] <u>https://doi.org/10.3760/cma.j.cn113903-20200216-00117</u>
- Li L, Liu D, Yang L. Follow-up information about the four pregnant patients with Coronavirus Disease (COVID-19) pneumonia who were still in the hospital at the end of our study. *Am J Roentgenol*, 2020; W1-W2, published online Apr 16, 2020. <u>https://doi.org/10.2214/AJR.20.23247</u>
- 42. Li N, Han L, Peng M, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. *Clin Infect Dis*, 2020; published online Mar 30, 2020. <u>https://doi.org/10.1093/cid/ciaa352</u>
- 43. Li Y, Zhao R, Zheng S, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. *Emerg Infect Dis*, 2020; 26(6).
- 44. Liao X, Yang H, Kong J, et al. Chest CT Findings in a Pregnant Patient with 2019 Novel Coronavirus Disease. Balk Med J, 2020; published online Mar 26, 2020. <u>https://doi.org/10.4274/balkanmedj.galenos.2020.2020.3.89</u>
- Liu D, Li L, Wu X, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) Pneumonia: a preliminary analysis. Am J Roentgenol, 2020; 1–6, published online Mar 18 2020. <u>https://doi.org/10.2214/AJR.20.23072</u>
- Liu H, Liu F, Li J, et al. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. J Infection, 2020; 80(5), e7-e13, published online Mar 21, 2020. https://doi.org/10.1016/j.jinf.2020.03.007
- 47. Liu W, Wang Q, Zhang Q, et al. Coronavirus disease 2019 (COVID-19) during pregnancy: a case series. 2020; Preprint online Feb 25, 2020. https://www.preprints.org/manuscript/202002.0373/v1
- Liu Y, Chen H, Tang K, et al. Clinical manifestations and outcome of SARS-CoV2 infection during pregnancy. J Infection, 2020; published online Mar 4, 2020. <u>https://doi.org/10.1016/j.jinf.2020.02.028</u>
- Lowe B, Bopp B. COVID-19 Vaginal Delivery A case report. Aust N Z J Obstet Gynaecol, 2020; published online Apr 15, 2020. <u>https://doi.org/10.1111/ajo.13173</u>
- Lu D, Sang L, Du S, et al. Asymptomatic COVID-19 infection in late pregnancy indicated no vertical transmission. J Med Virol, 2020; published online Apr 24, 2020. <u>https://doi.org/10.1002/jmv.25927</u>
- 51. NVOG. Update registration COVID-19 positive pregnant women in NethOSS. [Original text in Dutch]. Accessed May 1, 2020 from: <u>https://www.nvog.nl/actueel/registratie-van-covid-19-positieve-zwangeren-in-nethoss/</u>
- 52. Peng Z, Wang J, Mo Y, *et al.* Unlikely SARS-CoV-2 vertical transmission from mother to child: A case report. J Infect Public Health, 2020; 13(5): 818-820.
- 53. Santé Publique France. COVID-19 Weekly epidemiological update for April 16, 2020. [Original text in French]. Accessed May 1, 2020 from: <u>https://www.santepubliquefrance.fr/publications</u>

- Schnettler WT, Al Ahwel Y, Suhag A. Severe ARDS in COVID-19 infected pregnancy: obstetric and intensive care considerations. AJOG MFM, 2020; published online Apr 14, 2020. <u>https://doi.org/10.1016/j.ajogmf.2020.100120</u>
- Sharma KA, Kumari R, Kachhawa G, et al. Management of the first patient with confirmed COVID-19 in pregnancy in India: From guidelines to frontlines. Int J Gynecol Obstet, 2020; published online Apr 23, 2020. <u>https://doi.org/10.1002/IJG0.13179</u>
- Song L, Xiao W, Ling K, et al. Anesthetic Management for Emergent Cesarean Delivery in a Parturient with Recent Diagnosis of Coronavirus Disease 2019 (COVID-19): A Case Report. *Transl perioper & Pain Med*, 2020; 7(3): 234-237.
- 57. Sutton D, Fuchs K, D'Alton M, et al. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *New Engl J Med*, 2020; published online Apr 13, 2020. <u>https://doi.org/10.1056/NEJMc2009316</u>
- 58. Tekbali A, Grünebaum A, Saraya A, et al. Pregnant versus non-pregnant SARS-CoV-2 and COVID-19 Hospital Admissions: The first 4 weeks in New York. Am J Obstet Gynecol, 2020; published online Apr 15, 2020. https://doi.org/10.1016/j.ajog.2020.04.012
- 59. ICNARC. ICNARC report on COVID-19 in critical care May 1, 2020. Accessed May 1, 2020 from: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports
- Vintzileos WS, Muscat J, Hoffmann E. et al. Screening all pregnant women admitted to Labor and Delivery for the virus responsible for COVID-19. Am J Obstet Gynecol, 2020; published online Apr 26, 2020. <u>https://doi.org/10.1016/j.ajog.2020.04.024</u>
- 61. Vlachodimitropoulou Koumoutsea E, Vivanti AJ, Shehata N, et al. COVID19 and acute coagulopathy in pregnancy. J Thromb Haemost, 2020; published online Apr 17, 2020. https://doi.org/10.1111/jth.14856
- 62. Wang S, Guo L, Chen L, et al. A case report of neonatal COVID-19 in China. *Clin Infect Dis*, 2020; published online Mar 12, 2020. <u>https://doi.org/10.1093/cid/ciaa225</u>
- 63. Wang X, Zhou Z, Zhang J, et al. A case of 2019 novel coronavirus in a pregnant woman with preterm delivery. *Clin Infect Dis*, 2020; published online Feb 28, 2020. <u>https://doi.org/10.1093/cid/ciaa200</u>
- 64. Wen R. Sun Y, Zing QS. A patient with SARS-CoV-2 infection during pregnancy in Qingdao, China. *J Microbiol Immunol*, 2020; published online Mar 10, 2020. <u>https://doi.org/10.1016/j.jmii.2020.03.004</u>
- 65. Wu C, Yang W, Qu X, et al. Clinical Manifestation and Laboratory Characteristics of SARS-CoV-2 Infection in Pregnant Women. *Virol Sin*, 2020; published online Apr 20, 2020. <u>https://doi.org/10.1007/s12250-020-00227-0</u>
- 66. Wu X, Sun R, Chen J, et al. Radiological findings and clinical characteristics of pregnant women with COVID-19 pneumonia. Int J Gynecol Obstet, 2020; published online Apr 8, 2020. <u>https://doi.org/10.1002/ijgo.13165</u>
- 67. Xia H, Zhao S, Wu Z, et al. Emergency caesarean delivery in a patient with confirmed coronavirus disease 2019 under spinal anesthesia. Br J Anaesth, 2020; 124(5):E216-E218.
- 68. Xiong, X, Wei, H, Zhang Z, et al. Vaginal Delivery Report of a Healthy Neonate born to a convalescent Mother with COVID-19. J Med Virol, 2020; published online Apr 10, 2020. <u>https://doi.org/10.1002/jmv.25857</u>
- 69. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: A report based on 116 cases. Am J Obstet Gynecol, 2020; published online Apr 23, 2020. <u>https://doi.org/10.1016/J.AJOG.2020.04.014</u>
- 70. Yang H, Sun G, Tang F, et al. Clinical Features and Outcomes of Pregnant Women suspected of Coronavirus Disease 2019. *J Infection*, 2020; published online Apr 12, 2020. <u>https://doi.org/10.1016/j.jinf.2020.04.003</u>
- 71. Yang P, Wang X, Liu P, et al. Clinical characteristics and risk assessment of newborns born to mothers with COVID-19. *J Clin Virol*, 2020; 127. <u>https://doi.org/10.1016/j.jcv.2020.104356</u>
- Yin MZ, Zhang L, Deng G, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection during pregnancy in China: A retrospective Cohort Study. Preprint online Apr 11, 2020. <u>https://doi.org/10.1101/2020.04.07.20053744</u>

- Yu N, Kang Q, Xiong Z, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-center descriptive study. Lancet Infect Dis, 2020; published online Mar 24, 2020. <u>https://doi.org/10.1016/S1473-3099(20)30176-6</u>
- 74. Yu, N, Li, W, Kang Q, et al. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. *Lancet Infect Dis*, 2020; published online Apr 22, 2020. <u>https://doi.org/10.1016/S1473-3099(20)30320-0</u>
- 75. Zamaniyan M, Ebadi A, Mir SA, *et al.* Preterm delivery in pregnant women with critical COVID-19 pneumonia and vertical transmission. *Prenat Diagn*, 2020; published online Apr 17, 2020. <u>https://doi.org/10.1002/pd.5713</u>
- 76. Zambrano LI, Fuentes-Barahona IC, Bejarano-Torres DA. *et al*. A pregnant woman with COVID-19 in Central America. *Travel Med Infect Dis*, 2020; published online Mar 25, 2020. <u>https://doi.org/10.1016/j.tmaid.2020.101639</u>
- 77. Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA, 2020; published online Mar 26, 2020. https://doi.org/10.1001/jama.2020.4861
- Zeng L, Xia S, Yuan W, et al. Neonatal early onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr, 2020; published online Mar 26, 2020. <u>https://doi.org/10.1001/jamapediatrics.2020.0878</u>
- 79. Zhang L, Yan W, Min W, *et al.* Analysis of pregnancy outcomes of pregnant women during the epidemic of new coronavirus pneumonia in Hubei. *Chin J Obstet Gynecol*, 2020; 55. [Original text in Chinese]. https://doi.org/10.3760/cma.j.cn112141-20200218-00111
- 80. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*, 2020; 9(1): 51-60.
- Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol, 2020; published online March 27, 2020. <u>https://doi.org/10.1001/jamacardio.2020.1017</u>
- 82. Arentz M, Yim E, Klaff L, *et al.* Characteristics and Outcomes of 21 Critically III Patients With COVID-19 in Washington State. *JAMA*, 2020; published online March 19, 2020. <u>https://doi.org/10.1001/jama.2020.4326</u>
- 83. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet*, 2016; 387(10018): 587-603.
- 84. Woods CR. False-Positive Results for Immunoglobulin M Serologic Results: Explanations and Examples. J Pediat Inf Dis Soc, 2013; 2(1): 87-90.

# **Appendix 1 - Database Search Strategy**

(((((((COVID-19[Title/Abstract]) OR coronavirus[Title/Abstract]) OR Acute Respiratory Distress Syndrome[Title/Abstract]) OR RDS[Title/Abstract]) OR SARS-CoV-2[Title/Abstract]) OR severe acute respiratory syndrome coronavirus 2[Title/Abstract]) OR SARs[Title/Abstract])) AND (((((((Pregnancy[Title/Abstract]) OR Pregnant women[Title/Abstract]) OR Pregnant [Title/Abstract]) OR Labour[Title/Abstract]) OR Labor[Title/Abstract]) OR Obstetrics[Title/Abstract]) OR Female[Title/Abstract].)