COLLEGE of AMERICAN PATHOLOGISTS

ARCHIVES
of Pathology & Laboratory Medicine

EARLY ONLINE RELEASE

This article was posted on the *Archives* Web site as an Early Online Release. Note: Due to the extremely time sensitive nature of the content of this article, it has not been copyedited or formatted per journal style. Changes or corrections may be made to this article when it appears in a future print issue of the *Archives*. Early Online Release articles are citable by using the Digital Object Identifier (DOI), a unique number given to every article.

The DOI for this manuscript is doi: 10.5858/arpa.2020-0901-SA

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.

© 2020 College of American Pathologists

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

Corresponding author:

David A. Schwartz, MD, MS Hyg

Department of Pathology

Medical College of Georgia, Augusta University

1950 Grace Arbor Court

Atlanta, GA 30329

Email: davidalanschwartz@gmail.com

The author has no relevant financial interest in the products or companies described in this article.

Abstract

The emergence of a novel coronavirus, termed SARS-CoV-2, and the potentially life-threating respiratory disease that it can produce, COVID-19, has rapidly spread across the globe creating a massive public health problem. Previous epidemics of many emerging viral infections have typically resulted in poor obstetrical outcomes including maternal morbidity and mortality, maternal-fetal transmission of the virus, and perinatal infections and death. This communication reviews the effects of two previous coronavirus infections - severe acute respiratory syndrome (SARS) caused by SARS-CoV and Middle East respiratory syndrome (MERS) caused by MERS-CoV - on pregnancy outcomes. In addition, it analyzes literature describing 38 pregnant women with COVID-19 and their newborns in China to assess the effects of SARS-CoV-2 on the mothers and infants including clinical, laboratory and virologic data, and the transmissibility of the virus from mother to fetus. This analysis reveals that unlike coronavirus infections of pregnant women caused by SARS and MERS, in these 38 pregnant women COVID-19 did not lead to maternal deaths. Importantly, and similar to pregnancies with SARS and MERS, there were no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to their fetuses. All neonatal specimens tested, including in some cases placentas, were negative by rt-PCR for SARS-CoV-2. At this point in the global pandemic of COVID-19 infection there is no evidence that SARS-CoV-2 undergoes intrauterine or transplacental transmission from infected pregnant women to their fetuses. Analysis of additional cases is necessary to determine if this remains true.

(*Arch Pathol Lab Med*. doi: 10.5858/arpa.2020-0901-SA)

Introduction

The emergence of the novel coronavirus infection that occurred in Wuhan China in December 2019 has resulted in an epidemic that has rapidly expanded to become one of the most significant public health threats in recent times.[1-5] This newly emergent coronavirus was isolated in China in early January 2020, initially referred to as 2019-nCoV and subsequently termed SARS-CoV-2 – the disease it produces has been termed COVID-19.[6] Since then it has become an increasingly widespread and important cause of respiratory infection which can progress to severe pneumonia and, in a small number of cases, death. Since its initial identification in Wuhan, Hubei province, China, COVID-19 has now been reported from all continents except for Antarctica, affecting 125,048 persons in 118 countries and resulting in 4613 deaths as of March 12, 2020.[7] COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020.[8]

There has been a rapid increase in knowledge of the genetic, virologic, epidemiologic and clinical aspects of this emerging agent – the 7th coronavirus identified to cause human infection.[9] Recently the initial description of the pulmonary pathology that occurs from fatal COVID-19 has been described.[10]

An important question that remains unanswered is whether SARS-CoV-2 can be transmitted from a pregnant woman to her fetus, a process termed vertical transmission, and to determine the mechanism(s) if it does occur.[9,11-17] Not only is this a significant public health issue, but also represents an obstetrical management issue in determining the care received by pregnant women. The question is especially relevant given the recent history of vertical maternal-fetal transmission of such emerging viral infections as the Zika virus, Ebola virus, Marburg virus and other agents which can threaten the health and survival of an infected mother and fetus.[18-21]

Previous Experiences with Coronavirus Infections During Pregnancy

Pregnancy increases the risk of adverse obstetrical and neonatal outcomes from many respiratory viral infections. The physiologic and immunologic changes that occur as a normal component

of pregnancy can have systemic effects that increase the risk for complications from respiratory infections. Changes in the cardiovascular and respiratory systems, including increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity, as well as the development of immunologic adaptations that allow a mother to tolerate an antigenically distinctive fetus, increase the risk for pregnant women to develop severe respiratory disease.[22] Outcomes data from multiple studies of influenza have demonstrated an increased risk of maternal morbidity and mortality when compared with non-pregnant women.[22,23] This association has also been previously demonstrated to occur when pregnant women became infected with either of two pathogenic coronavirus infections – severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[9]

Severe acute respiratory syndrome (SARS)

The SARS epidemic occurred from November 2002 to July 2003, affecting greater than 8000 persons in 26 countries and resulting in 774 fatalities.[24] The causative agent, a coronavirus termed SARS-CoV, was transmitted through close person-person contact, respiratory droplets, environmental contamination, and potentially sewage.[9,25] There were 12 pregnant women reported who developed SARS during the epidemic, of whom 3 died during pregnancy (case fatality rate of 25%).[9] Miscarriages during the 1st trimester occurred in 4/7 women. Two of 5 women in the 2nd and 3rd trimester had a neonate with intrauterine growth restriction (IUGR). In addition, 4/5 pregnancies resulted in preterm birth – 1 spontaneous and 3 induction deliveries that were performed for maternal conditions.[26] Vertical transmission of the SARS-CoV virus did not occur in any of the infants; however, the clinical outcomes of pregnant women with SARS were worse than those occurring in infected women who were not pregnant.[9,26-29]

Middle East respiratory syndrome (MERS)

MERS is another coronavirus infection that causes potentially severe respiratory disease. It was first reported from Saudi Arabia in 2012, after which it spread to over 27 countries both within and

outside of the Arabian Peninsula.[9,30] MERS-CoV has been identified in camels, which have been suggested as the primary source of human infections, as well as in bats, but more research is needed to understand the role that these and other animals may play in transmission. MERS-CoV is characterized by sporadic zoonotic transmission events as well as spread between infected patients and close contacts (i.e., intra-familial transmission). Outbreaks of MERS in health care settings are characteristic of MERS, and which result from poor infection control and preventative measures.[30,31]

MERS-CoV infection has been reported from 11 pregnant women, where it has been associated with a variety of adverse clinical outcomes among 10 (91%) of them. These outcomes have included maternal deaths, premature delivery, intensive care treatment for newborns, and perinatal death. There have been no confirmed cases of vertical transmission of MERS-CoV.[9]

Current clinical features and obstetrical outcomes of pregnant women with COVID-19

There has been a total of 38 pregnant women reported with COVID-19 originating from the epicenter of the pandemic in China.[13-17] All women were in the 3rd trimester of pregnancy, and included 37 women whose SARS-CoV-2 positivity was confirmed by rt-PCR. These pregnancies resulted in 39 infants (one set of twins); detailed clinical information, obstetrical outcomes and SARS-CoV-2 status were available for 30 neonates.

Zhongnan Hospital of Wuhan University, Wuhan, China

Nine pregnant women with COVID-19 have been described in a retrospective review of medical records by Chen et al. (Table 1).[13] The women were tested for SARS-CoV-2 using rt-PCR kits recommended by the Chinese Center for Disease Control and Prevention (BioGerm, Shanghai, China). Samples were tested simultaneously using rt-PCR at the of Clinical Laboratory of Zhongnan Hospital and State Key Laboratory of Virology/Institute of Medical Virology, School of Basic Medical Sciences, Wuhan University. Positive confirmatory cases of SARS-CoV-2 infection were reported when a positive test

result from either laboratory was obtained. The mothers varied in age between 26 and 40 years of age, had documented exposure to the novel coronavirus and were in the 3rd trimester of pregnancy when they developed COVID-19 infection. Although none of the women had a preexisting chronic condition such as diabetes, cardiovascular disease or hypertension, 3 women had co-morbid conditions that developed during their pregnancy – influenza (Case 1), gestational hypertension occurring since 27 weeks gestation (Case 3), and preeclampsia developing at 31 weeks gestation (Case 4). Seven women were febrile upon admission; additional findings included cough (4/9), myalgia (3/9), sore throat (2/9) malaise (2/9), gastrointestinal symptoms (1/9) and shortness of breath (1/9). Laboratory findings included elevated C-reactive protein (6/9), lymphopenia (5/9), and increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST)(3/9). Chest CT scans were abnormal in 8 of the 9 women, demonstrating lungs with patchy ground-glass shadows. Four women had preterm labor, but none occurring prior to 36 weeks gestation. Cases 5 and 8 had fetal distress, and cases 7 and 9 had premature rupture of membranes (PROM). None of the women developed severe pneumonia, and there were no maternal deaths.

All 9 women underwent cesarean sections. Two of the 4 preterm infants were delivered at 36 weeks 2 days and weighed less than 2500 grams (Cases 4 and 7) – one of the newborn infants (Case 4) had a birthweight of 1880 grams and was delivered to a mother with preeclampsia. All of the infants had good Apgar scores.

The presence of SARS-CoV-2 was evaluated in 6 of the 9 cases from amniotic fluid, breastmilk, umbilical cord blood and neonatal throat swabs - all tests were negative. The specific cases that were tested was not specified. All of the 6 neonatal samples tested were negative for SARS-CoV-2.

Tongji Hospital of Tongji Medical College, Huazhong University, Wuhan, China

Liu et al. reported 3 pregnant women from the Tongji Hospital who became infected with SARS-CoV-2 during the 3rd trimester.[14] These 3 women were among a total of 17 pregnant women admitted to

the Obstetrics Ward during the study period - a COVID-19 prevalence of approximately 18 percent. The women's ages ranged from 30 to 34 years (Table 2). COVID-19 testing was performed using the rt-PCR assay with a SARS-CoV-2 ORF1ab/N gene detection kit (Shanghai Huirui Biotechnology Co.,Ltd, Shanghai, China), a product based on the recommendation of the National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention.

Case 1 was a 34-year-old woman with hypothyroidism who was febrile prior to her hospital admission. She had a chest CT that showed progressively worsening bilateral pulmonary infiltrates. The mother had positive rt-PCR tests for SARS-CoV-2 from an oropharyngeal swab and feces; testing of breast milk, vaginal mucus and placenta were negative. Her 3250-gram infant was delivered at 40 weeks gestational age by cesarean section with chronic fetal distress, chorioamnionitis, meconium-stained membranes but had good Apgar scores. Specimens from the infant including whole blood, plasma serum, umbilical cord blood and an oropharyngeal swab were negative for SARS-CoV-2 by rt-PCR.

Case 2 was a 34-year-old woman with no significant obstetrical history or co-morbid conditions. She developed a fever at 37 weeks of gestation, and a CT scan of the chest revealed bilateral ground glass opacities and pulmonary consolidation, nodules in the left lower lobe and patchy consolidation in the right middle lobe. A oropharyngeal swab taken one day prior to delivery was positive for SARS-CoV-2 by rt-PCR. A 3250-gram infant was delivered by cesarean section at 38 weeks 4 days gestation with good Apgar scores. The newborn had slightly decreased muscle tone and responsiveness that had improved the day after delivery. Testing for SARS-CoV-2 from whole blood, serum, oropharyngeal swabs, urine and feces using rt-PCR were all negative for the novel coronavirus.

Case 3 was a 30-year-old woman who had developed gestational hypertension during her first pregnancy. She developed cough at 37 weeks gestation, and upon admission to the hospital had a chest CT scan that demonstrated ground glass opacities, subsolid patch and linear fibrosis in the left lung and enlarged mediastinal lymph nodes. An rt-PCR test for SARS-CoV-2 performed on an oropharyngeal swab

was positive; follow-up testing of an anal swab, vaginal mucus and breast milk were all negative. She delivered a 3670-gram infant by vaginal delivery at 39 weeks 5 days gestation with good Apgar scores. Two rt-PCR tests for SARS-CoV-2 were performed on successive days using whole blood, plasma, oropharyngeal swabs, urine and feces, and all were negative.

The mothers in this report all presented with either fever or cough accompanied by CT abnormalities during the course of their COVID-19 disease. None of the women developed severe pneumonia or died, and all 3 had successful perinatal outcomes with no evidence of intrauterine transmission of SARS-CoV-2.

Maternal and Child Health Hospital of Hubei Province, Union Hospital, Renmin Hospital, Tianmen First People's Hospital, Jingzhou Municipal Hospital and Child Health Hospital, and Pediatric Hospital affiliated with Fudan University, China

Zhu et al. described in detail the pregnancies of 9 pregnant women with COVID-19 and their 10 infants (including one set of twins) from 5 hospitals in Hubei Province (Tables 2 and 3).[15] The women ranged in age between 25 and 35 years of age, and had a 1 to 6 day interval between the onset of symptoms and delivery. All women had a chest CT revealing ground glass opacities, patchy pulmonary consolidation and blurred borders typical of viral pneumonia. Viral testing for SARS-CoV-2 nucleic acid was performed on throat swab specimens from the 9 women, and results were positive for all patients except the mother of the twins - her test was negative. She had typical clinical symptoms of COVID-19 and viral interstitial pneumonia by chest CT scan, and other diseases that could cause fever and lung infection were excluded. The local Chinese Centers for Disease Control and Prevention then registered her as a confirmed 2019-nCoV case, and she was included in the current study.

The initial symptoms among these women was fever and/or cough. Prenatal conditions included fetal distress in 6 cases, premature rupture of membranes in 3 cases (5 to 7 hours prior to the onset of labor), oligohydramnios and polyhydramnios in 1 case each, umbilical cord abnormalities in 2 cases, and

placenta previa in 1 case. Third trimester obstetrical ultrasounds were all normal. Seven of the mothers underwent cesarean sections, and 2 had vaginal deliveries. There were no cases of severe pneumonia or maternal death among the 9 women.

There were 8 singletons and 1 set of twins delivered to the mothers with COVID-19 – 4 were full-term and 6 were premature. Two newborns were small for gestational age and one was large for gestational age. The infants were evaluated for well-being using the Pediatric Critical Illness Score (PCIS), the most widely used pediatric critical illness scoring method in China. Six of the newborns had a PCIS of less than 90 – 6 infants had shortness of breath, 2 were febrile and 1 had a rapid heart rate. Gastrointestinal symptoms were present in 4 infants – these included gastric bleeding, refusal of milk, bloating and feeding intolerance. Chest radiographs revealed that 7 newborns had abnormalities at the time of admission that included infection in 4, neonatal respiratory distress syndrome in 2, and pneumothorax in 1 infant. Two infants had the onset of thrombocytopenia associated with liver dysfunction. One premature infant developed shortness of breath and fluctuations of oxygenation and decreased platelets treated with respiratory support and transfusions. There was one neonatal fatality among the cohort (Case 4) – a premature newborn developed shortness of breath, refractory shock, multiple organ failure and disseminated intravascular coagulation and died on the 9th day of life. Four neonates remained hospitalized at the time of submission of the report. Pharyngeal swab specimens were collected from 9 of the neonates between 1- and 9-days following delivery and tested for SARS-CoV-2, and all were negative.

The Second Affiliated Hospital and The Affiliated Infectious Hospital of Soochow University, Suzhou, China

In a case report Wang et al. described a 28-year-old pregnant woman who presented to the hospital with a fever of one-week duration (Table 3).[16] She was at 30 weeks gestation at the time of her admission and 2 throat swabs tested negative for SARS-CoV-2 using rt-PCR. Chest CT examination 2 days

later showed left-sided subpleural patchy consolidation and right-sided ground-glass opacities. A repeat rt-PCR examination of sputum performed 4 days after admission was positive for SARS-CoV-2. She was transferred to the Intensive Care Unit where she was placed in isolation. An obstetrical ultrasound revealed a normal fetus of 30 weeks gestation. On hospital day 3 decreased fetal movement was observed with absent variability of the fetal heart rate, and an emergence cesarean section was performed. A preterm male infant was delivered that weighed 1.83 kg and with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Samples were taken of placenta, amniotic fluid, umbilical cord blood, gastric juice and throat swabs of the infant - all results tested negative for SARS-CoV-2 using rt-PCR. Three days following delivery rt-PCR testing of the neonatal throat swab and stool samples were negative. Seven and 9 days after birth throat swab and rt-PCR tests from the mother and the infant remained negative for the novel coronavirus.

Renmin Hospital of Wuhan University, Wuhan and the Central Hospital of Qianjiang City, Qianjiang, China

Zhang and colleagues retrospectively examined medical records of 16 pregnant women with rt-PCR confirmed COVID-19 and their newborn infants, and compared these results with a cohort of 45 pregnant women who were not infected (translated from Simplified Chinese by DAS) – this constituted the first comparison study between women with and without SARS-CoV-2 infection during pregnancy.[17] Throughout this study testing for SARS-CoV-2 was performed using the New Coronavirus (2019) Nucleic Acid Detection Kit (Dual Fluorescence PCR) provided by Jiangsu Shuo Shi Biotechnology Co., Ltd. All women were in their 3rd trimester of pregnancy. Diagnosis of COVID-19 was based on the diagnostic criteria of the New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan (Trial Fifth Edition) issued by the National Health and Health Commission.

In the COVID-19 cohort the women varied from 24 to 34 years of age, had previously been pregnant between 1 and 4 times, and had parity varying from 0 to 1 (Table 4). The gestational age at the

time of delivery varied between 35 weeks 5 days up to 41 weeks, averaging 38.7 weeks. In the cohort of women who were not infected with SARS-CoV-2 the maternal ages varied between 24 and 40 years, had 1 to 5 previous pregnancies and parity of 0 or 1, and delivered their infants between 35 weeks 2 days and 41 weeks with an average of 37.9 weeks. The women with COVID-19 had infants weighing between 2300 and 3750 grams (average 3139 g), and the women without COVID -19 had infants weighing between 2180 and 4100g (average 3260g). There were no significant differences between the 2 cohorts in gravidity, parity, gestational age at delivery, birthweight or intraoperative blood loss. The maternal ages were significantly different – mothers in the COVID-19 cohort were younger than those in the non-COVID-19 cohort (*P*=.01).

Among the 16 women with COVID-19 there were several mothers with co-morbid obstetrical conditions – 3 women had gestational diabetes, 3 had premature rupture of membranes, 3 had preterm deliveries, 2 had scarred uterus, 2 required B-Lynch suture procedure (a form of compression suture used in obstetrics to mechanically compress an atonic uterus in the clinical setting of severe postpartum hemorrhage). There was one incident of severe preeclampsia, meconium-stained amniotic fluid, fetal distress and fetal asphyxia. Three of 16 women with COVID-19 had cough, chest tightness, shortness of breath, and diarrhea that did not improve significantly with treatment. One of these mothers had COVID-19 pneumonia – she was 35 weeks 6 days gestation with oxygen saturation of 93% accompanied by chest tightness and shortness of breath, and with decreased fetal movement and abnormal fetal heart monitoring. All of the women with COVID-19 underwent cesarean deliveries.

There were no significant differences between the groups of pregnant women with and without COVID-19 in occurrence of severe preeclampsia, gestational diabetes, premature rupture of membranes, fetal distress, meconium-stained amniotic fluid, premature delivery, neonatal asphyxia, B-Lynch suture procedure or other compression sutures. The proportion of uterine scarring in the non-

COVID-19 group was statistically higher than that in COVID-19 group (p=0.032) – this abnormality predated the development of COVID-19.

Among the cohort of 16 mothers with COVID-19 there were 10 infants for whom SARS-CoV-2 infection status was known – all were negative using rt-PCR analysis of throat swabs. Nine of these newborns were full-term and 1 was preterm (36 weeks 2 days). Three of the neonates had bacterial pneumonia based on their symptoms, laboratory testing, sputum culture, and imaging results – all of them recovered following treatment. After discharge of the newborns from the hospital, follow-up examinations demonstrated no neonatal illness or deaths.

Conclusions

Intrauterine transmission is one of the most serious complications of viral diseases occurring during pregnancy. It can occur with maternal infection by congenitally-transmitted TORCH agents (acronym for **T**oxoplasma, **O**ther, **R**ubella, **C**ytomegalovirus, **H**erpes) which also include Zika virus and Ebola virus.[32] Maternal-fetal transmission of viral diseases (with the exception of herpes virus) is usually through the hematogenous route in which the virus circulating in the maternal blood stream enters the placenta, reaches the chorionic villous tree and fetal blood vessels, and is transmitted to the fetus. Fortunately, this mechanism of transmission has been shown not to occur with infection of pregnant women with 2 other pathogenic coronaviruses – SARS-CoV and MERS-CoV, although the clinical infections caused by these coronaviruses has resulted in severe maternal pneumonia, maternal deaths and early pregnancy losses.[12]

In this analysis of the detailed published reports of 38 pregnant women with COVID-19, of whom 37 had rt-PCR-confirmed SARS-CoV-2 infection, there were no cases of either severe pneumonia or maternal deaths. Although there were co-morbid conditions present in some of the women, some of which were obstetrical in etiology, they apparently did not result in life-threatening maternal SARS-CoV-2 disease. It is significant that these co-morbid maternal conditions, which included preeclampsia,

pregnancy-induced hypertension, uterine scarring, gestational diabetes, and uterine atony, did not appear to be risk factors for intrauterine transmission of SARS-CoV-2 to the fetus. Gestational age among these 22 mothers at the time of onset of COVID-19 varied between 30 and 40 weeks, and at least in this range did not appear to be associated with heightened risk for maternal-fetal viral transmission

Among the 30 neonates delivered to these women who underwent testing, there were no cases of rt-PCR-confirmed SARS-CoV-2 infection, despite the existence of perinatal complications in some of the infants. An interesting observation is that in those cases where placentas were tested for SARS-CoV-2, the results were negative. This lack of maternal-fetal transmission of SARS-CoV-2 is consistent with past experiences with other coronavirus infections – SARS and MERS - occurring in pregnant women.

Early in the epidemic there were two cases of neonatal SARS-CoV-19 infection reported. One was an infant diagnosed at 17 days of life having a history of close contact with 2 confirmed cases of SARS-CoV-2 infection (mother and nanny), and the other was a neonate who was found to be infected 36 hours following delivery. In both infants there was no direct evidence for vertical transmission, and because viral testing was delayed, a postpartum neonatal infection acquired through an infected contact could not be eliminated.[11,12]

A joint mission by the World Health Organization consisting of 25 national and international experts travelled to the affected regions of China between 16 and 24 February 2020.[33] They investigated 147 pregnant women (64 confirmed, 82 suspected and 1 asymptomatic with COVID-19). Among these women 8% had severe disease and 1% were critical. The joint mission concluded that pregnant women were not at higher risk for developing severe disease due to COVID-19. This report did not examine vertical transmission or neonatal outcomes.

As this global epidemic continues to expand there will be additional information available on the effects of COVID-19 on pregnant women and their infants. In the unfortunate event of mortality resulting from SARS-CoV-2 infection among pregnant women or neonates, pathological evaluation of

311 tissues together with molecular characterization of the virus would be useful in determining the
312 pathogenesis of the disease as it has in many cases of emerging infections.[34] There are currently updated
313 recommendations available on the obstetrical management of SARS-CoV-2 infection in pregnant
314 women.[35] In addition, it must be remembered that as vaccine development proceeds for COVID-19 that
315 pregnant women should be considered for inclusion in the clinical trials as well as the eventual
316 distribution of the vaccine unless the risks outweigh the potential benefits.[36]
317
318 **REFERENCES**

319 1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with
320 pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. Available from:
321 https://www.nejm.org/doi/10.1056/NEJMoa2001017 (accessed 4 March 2020).
322 2. Huang C, Wang Y, Li X, Ren, L., Zhao, J., Hu, Y., et al. Clinical features of patients infected with 2019
323 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506. doi:
324 https://doi.org/10.1016/S0140-6736(20)30183-5 Available from:
325 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext (accessed 3
326 March 2020).
327 3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. et al. Epidemiological and clinical characteristics of 99
328 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395
329 (10223):507-513. doi: https://doi.org/10.1016/S0140-6736(20)30211-7 Available from:
330 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30211-7/fulltext (accessed 1
331 March 2020).
332 4. European Centre for Disease Prevention and Control. Update: Cluster of pneumonia cases associated
333 with novel coronavirus – Wuhan, China – 2019. 14 January 2020. Available from:

https://www.ecdc.europa.eu/en/news-events/update-cluster-pneumonia-cases-associated-novel-coronavirus-wuhan-china-2019 (accessed 1 March 2020).

5. She J, Jiang J, Ye L, Hu L, Bai C, Song C. 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. *Clin Trans Med*. 2020;9:19. doi: https://doi.org/10.1186/s40169-020-00271-z. Available from: https://clintransmed.springeropen.com/articles/10.1186/s40169-020-00271-z#citeas (accessed 3 March 2020).

6. World Health Organization. Naming the coronavirus disease (COVID-2019) and the virus that causes it. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (accessed 23 February 2020).

7. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report – 52. 12 March 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/20200312-sitrep-52-covid-19.pdf?sfvrsn=e2bfc9c0_2 (accessed 13 March 2020).

8. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed 11 March 2020).

9. Schwartz DA, Graham AL. Potential maternal and infant outcomes from Coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: Lessons from SARS, MERS, and other human coronavirus infections. *Viruses*. 2020;12:194. Available from: https://www.mdpi.com/1999-4915/12/2/194 (accessed 28 February 2020).

10. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [published online ahead of print February 18, 2020]. *The Lancet Resp Med*. 2020. doi: https://doi.org/10.1016/S2213-2600(20)30076-X Available from:

https://www.thelancet.com/journals/lancet/article/PIIS2213-2600(20)30076-X/fulltext (accessed 27 February 2020).

11. Qiao J. What are the risks of COVID-19 infection in pregnant women? [Published online ahead of print February 12, 2020]. *The Lancet*. doi: https://doi.org/10.1016/S0140-6736(20)30365-2 Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30365-2/fulltext (accessed 26 February 2020).

12. Schwartz DA. COVID-19, SARS-CoV-2 and pregnancy: Does the past predict the present? *ContagionLive*. 28 February 2020. Available from: https://www.contagionlive.com/news/covid19-sarscov2-and-pregnancy-does-the-past-predict-the-present (accessed 1 March 2020).

13. 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 [Published online ahead of print February 12, 2020]. *The Lancet.* 2020. https://doi.org/10.1016/S0140-6736(20)30360-3.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30360-3/fulltext (accessed 28 February 2020).

14. Liu W, Wang Q, Zhang Q, Chen L, Chen J, Zhang B. et al. Coronavirus disease 2019 (COVID-19) during pregnancy: A case series. *Preprints* 2020;2020020373. Available from: https://www.preprints.org/manuscript/202002.0373/v1 (accessed 28 February 2020).

15. 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. doi: 10.21037/tp.2020.02.06. Available from: http://tp.amegroups.com/article/view/35919/28274 (accessed 1 March 2020).

16. Wang X, Zhou Z, Zhang J, Zhu F, Tang Y, Shen X. A Case of 2019 novel coronavirus in a pregnant woman with preterm delivery [Published online ahead of print February 28, 2020]. *Clin Infect Dis*. 2020.

381 doi: 10.1093/cid/ciaa200. Available from: https://pubmed.ncbi.nlm.nih.gov/32119083-a-case-of-2019-
382 novel-coronavirus-in-a-pregnant-woman-with-preterm-delivery/ (accessed 10 March 2020).
383 17. Zhang I, Jiang Y, Wei M, Cheng BH, Zhou XC, Li J, et al. 湖北地区新型冠状病毒肺炎流行期间孕妇的
384 妊娠结局分析 [Analysis of the Pregnancy Outcomes in Pregnant Women With COVID-19 in Hubei
385 Province]. *Zhonghua Fu Chan Ke Za Zhi* . 2020;55(0), E009. Available from:
386 http://rs.yiigle.com/yufabiao/1184338.htm (accessed and translated 12 March 2020).
387 18. Alvarado MG, Schwartz DA. Zika virus infection in pregnancy, microcephaly and maternal and fetal
388 health - What we think, what we know, and what we think we know. *Arch Pathol Lab Med*. 2017;141(1):
389 26-32. doi: 10.5858/arpa.2016-0382-RA. Available from:
390 https://www.archivesofpathology.org/doi/10.5858/arpa.2016-0382-RA (accessed 2 March 2020).
391 19. Schwartz DA. Maternal and infant death and the rVSV-ZEBOV vaccine through three recent Ebola
392 virus epidemics - West Africa, DRC Équateur and DRC Kivu: Four years of excluding pregnant and
393 lactating women and their infants from immunization. *Curr Trop Med Reports*. 2019;6(4).
394 doi.org/10.1007/s40475-019-00195-w. Available from:
395 https://link.springer.com/article/10.1007/s40475-019-00195-w
396 20. Schwartz DA., Anoko JN, Abramowitz S. Editors. *Pregnant in the Time of Ebola: Women and Their*
397 *Children in the 2013-2015 West African Epidemic.* Springer, New York and Berlin. 2019. [ISBN-13: 978-
398 3319976365] [ISBN-10: 3319976362] eBook published January 2, 2019.
399 21. Schwartz DA. Maternal filovirus infection and death from Marburg and Ravn viruses: Highly lethal to
400 pregnant women and their fetuses similar to Ebola Virus. In: *Re-Emerging Filovirus Diseases*, S.I. Okware,
401 Ed. IntechOpen. ISBN: 978-1-78985-550-0. DOI: 10.5772/intechopen.88270. Available from:
402 https://www.intechopen.com/online-first/maternal-filovirus-infection-and-death-from-marburg-and-
403 ravn-viruses-highly-lethal-to-pregnant-women

22. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol*. 2012;207(3 Suppl):S3–S8. doi:10.1016/j.ajog.2012.06.068 Available from: https://www.ajog.org/article/S0002-9378(12)00722-3/pdf (accessed 26 February 2020).

23. Silasi M, Cardenas I, Racicot K, Kwon J-Y, Aldo P, Mor G. Viral infections during pregnancy. *Am J Reprod Immunol*. 2015;73(3):199–213. doi: 10.1111/aji.12355 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610031/ (accessed 26 February 2020).

24. Centers for Disease Control and Prevention. CDC SARS Response Timeline. Available from: https://www.cdc.gov/about/history/sars/timeline.htm (accessed 25 February 2020).

25. Hung LS. The SARS epidemic in Hong Kong: what lessons have we learned? *J R Soc Med*. 2003;96(8): 374–378. doi: 10.1258/jrsm.96.8.374. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC539564/ (accessed 24 February 2020).

26. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol*. 2004;191(1):292-297.

27. Lam CM, Wong SF, Leung TN, et al. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. *BJOG.* 2004;111(8):771-774. Available from: https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/j.1471-0528.2004.00199.x (accessed 19 February 2020).

28. Zhang JP, Wang YH, Chen LN, Zhang R, Xie YF. Clinical analysis of pregnancy in second and third trimesters complicated severe acute respiratory syndrome. *Zhonghua Fu Chan Ke Za Zhi.* 2003;38(8):516–520.

29. Maxwell C, McGeer A, Tai KFY, Sermer M. No. 225-Management guidelines for obstetric patients and neonates born to mothers with suspected or probable severe acute respiratory syndrome (SARS). *J Obstet Gynaecol Can.* 2017;39(8):e130-e137. doi: 10.1016/j.jogc.2017.04.024. Available from: https://www.jogc.com/article/S1701-2163(17)30464-4/fulltext (accessed 28 February 2020).

428 30. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Summary
429 and literature update – as of 27 March 2014. Available from:
430 https://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_Update_27_March_2014.pdf?ua=
431 1 (accessed 27 February 2020).
432 31. Hui DS. Epidemic and emerging coronaviruses (severe acute respiratory syndrome and Middle East
433 respiratory syndrome). *Clin Chest Med*. 2017;38(1):71-86. doi: 10.1016/j.ccm.2016.11.007. Available
434 from: https://www.sciencedirect.com/science/article/pii/S0272523116301289?via%3Dihub (accessed
435 25 February 2020).
436 32. Schwartz DA. The origins and emergence of Zika virus, the newest TORCH infection: What's old is
437 new again. *Arch Pathol Lab Med*. 2017;141(1):18-25. Available from:
438 https://www.archivesofpathology.org/doi/full/10.5858/arpa.2016-0429-ED (accessed 13 March 2020).
439 33. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019
440 (COVID-19). Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-
441 mission-on-covid-19-final-report.pdf (accessed 8 March 2020).
442 34. Schwartz DA, Bryan RT, Hughes JM. Pathology and emerging infections - quo vadimus? *Am J Pathol*.
443 1995;147(6):1525-1533. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1869939/
444 (accessed 4 March 2020).
445 35. Favre G, Pomar L, Qi X, Nielsen-Saines K, Musso D, Baud D. Guidelines for pregnant women with
446 suspected SARS-CoV-2 infection [Published online ahead of print, March 3, 2020]. *The Lancet*. 2020. doi:
447 https://doi.org/10.1016/S1473-3099(20)30157-2 Available from:
448 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30157-
449 2/fulltext#.Xl9nyRMYAv4.twitter (accessed 4 March 2020).
450 36. Krubiner C, Faden RF, Karron RA. In the race for coronavirus vaccines, don't leave pregnant women
451 behind. *STAT News*. 25 February 2020. Available from:

https://www.statnews.com/2020/02/25/coronavirus-vaccine-covid-19-pregnant-women/ (accessed 1 March 2020).

Table 1. Characteristics of 7 pregnant women with COVID-19 and their infants.

Case and 1st author	**Case 1 Chen[13]**	**Case 2 Chen[13]**	**Case 3 Chen[13]**	**Case 4 Chen[13]**	**Case 5 Chen[13]**	**Case 6 Chen[13]**	**Case 7 Chen[13]**
Maternal age (years)	33	27	40	26	26	26	29
Gestational age at delivery	37wk 2d	38wk 3d	36 wk	36wk 2d	38wk 1d	36wk 3d	36wk 2d
Comorbid events	Influenza	None	Gestational hypertension	Pre-eclampsia	Fetal distress	None	PROM
Maternal rt-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Symptom-to-delivery interval	1 day	6 days	4 days	3 days	1 day	4 days	2 days
C-section or vaginal	C-s	C-s	C-s	C-s	C-s	C-s	C-s
Birthweight	2870 g	3730 g	3820 g	1880 g	2970 g	3040 g	2460 g
Apgars at 1 & 5 mins	8, 9	9, 10	9, 10	8, 9	9, 10	9, 10	9, 10
Neonatal outcome	Normal	Normal	Normal	SGA	Normal	Normal	Normal
Neonatal rt-PCR for SARS-CoV-2	According to Chen et al. there were 6 of 9 neonates tested for SARS-CoV-2 and all 6 were found to be negative by rt-PCR, but which 6 neonates that were tested was not specified						

Abbreviations: SGA – small for gestational age; PROM – premature rupture of membranes

Table 2. Characteristics of additional 7 pregnant women with COVID-19 and their infants

Case and 1st author	**Case 8 Chen[13]**	**Case 9 Chen[13]**	**Case 1 Liu[14]**	**Case 2 Liu[14]**	**Case 3 Liu[14]**	**Case 1 Zhu[15]**	**Case 2 Zhu[15]**
Maternal age (years)	28	34	34	34	30	25	35
Gestational age at delivery	38wk	39wk 4d	40wk	38wk 4d	39wk 5d	38wk 4d	33w 6d
Comorbid events	Fetal distress	PROM	Hypothyroid	Placenta acreta	Gestational diabetes	Fetal distress, oligo	Scarred uterus
Maternal rt-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Symptom-to-delivery interval	2 days	7 days	~1 day	~7 days	~13 days	< 1 day	< 1day
C-section or vaginal	C-s	C-s	C-s	C-s	Vaginal	C-s	C-s
Birthweight	2800 g	3530 g	3250 g	3250 g	3670 g	2,450g	2,050 g
Apgars at 1 &5 mins	9, 10	8, 10	8, 9	8, 9	8, 9	9, 10	9, 10
Neonatal outcome	Normal	Normal	Normal	Normal	Normal	SGA	SOB
Neonatal rt-PCR for SARS-CoV-2	See Table 1	See Table 1	Negative	Negative	Negative	Negative	Negative

Abbreviations: PROM – premature rupture of membranes; oligo-oligohydramnios; SGA-small for gestational age; SOB-shortness of breath

Table 3. Characteristics of additional 8 pregnant women with COVID-19 and their 9 infants including one set of twins

Case and 1st author	**Case 3 Zhu[15]**	**Case 4 Zhu[15]**	**Case 5 Zhu[15]**	**Case 6 Zhu[15]**	**Case 7 Zhu[15]**	**Case 8 Zhu[15]**	**Case 9 Zhu[15]**	**Case 10 Zhu[15]**
Maternal age (years)	35	30	30	30	30	29		34
Gestational age at delivery	34w 2d	34wk 5d	39w	37w	34w 6d	31w		39w
Comorbid events	Fetal distress	Vaginal bleeding, fetal distress	Cholecystitis	Placenta previa, fetal distress poly	Fetal distress	Twins, fetal distress, viral pneumonia c/w with COVID-19		None
Maternal rt-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive	Negative		Positive
Symptom-to-delivery interval	2 days after delivery	3 days after delivery	6 days before delivery	4 days before delivery	4 days before delivery	3 days before delivery		1 day after delivery
C-section or vaginal	Vaginal	C-s	C-s	C-s	C/s	Vaginal twin		C-s
Birthweight	2350 g	2200 g	3030 g	3800 g	2300 g	1520 g	1720 g	2810 g
Apgars at 1 & 5 mins	8, 9	8, 8	8, 9	7, 8	9, 10	9, 10	9, 10	10, 10
Neonatal outcome	SOB	Multiple organ failure, shock, gastric bleeding, DIC, death	Diffuse scattered rashes, edema, facial skin lesions	LGA, in hospital	SOB, fever, GI bleeding DIC	SOB, in hospital	SOB, in hospital	SGA, SOB, cyanosis, in hospital
Neonatal rt-PCR for SARS-CoV-2	Neg	Neg	Not performed	Neg	Neg	Neg	Neg	Neg

Abbreviations: LGA – large for gestational age; poly-polyhydramnios; SGA-small for gestational age; SOB-shortness of breath; DIC-disseminated intravascular coagulation; c/w – consistent with

Table 4. Characteristics of an additional 17 pregnant women with COVID-19 and their infants

Case and 1st author	**Case 1 Wang[16]**	**Cases 1 to 16 Zhang et al.[17]**
Maternal age (years)	35	Varies from 24 to 34 years with mean of 29.3 ± 2.9
Gestational age at delivery	31 w	Varies from 35 weeks 5 days up to 41 weeks with mean of 38.7 ± 1.4
Comorbid events	Fetal distress	Gestational diabetes (3), PROM (3), preterm delivery (3), uterine scarring (2), B-Lynch/compression suture procedure (2), severe preeclampsia (1), fetal distress (1), fetal asphyxia (1), meconium staining (1), COVID-19 pneumonia (1)
Maternal rt-PCR for SARS-CoV-2	Positive	Positive in all 16 women
Symptom-to-delivery interval	13 days before delivery	Not stated
C-section or vaginal	C-s	C-s in all 16 women
Birthweight	1830 g	Varies from 2300 to 3750 grams with mean of 3139 g ± 437
Apgars at 1 & 5 mins	9, 10	Not stated
Neonatal outcome	Normal	Bacterial pneumonia in 3 neonates, 1 preterm infant
Neonatal rt-PCR for SARS-CoV-2	Neg	Viral testing results available for 10 of 16 neonates, all of whom were negative for infection

Abbreviations: PROM – premature rupture of membranes