Background: In the setting of the novel 2019 coronavirus outbreak, the World Health Organization and Centers for Disease Control have identified pregnant women and children <1 year as high risk for severe
illness from SARS-CoV-2. Although there was no considerable evidence supporting vertical transmission of SARS-CoV or MERS-CoV\(^1-4\), the increased transmissibility of SARS-CoV2 compared to the aforementioned again raises important questions regarding possible vertical transmission, either via intrauterine infection, perinatal infection via exposure to maternal blood or to vaginal secretions in the birth canal, or postnatal acquisition via breastmilk or close contact with the mother. Additionally, clinical presentation and outcomes of infants born to mothers infected with SARS-CoV-2 are currently not well understood.

**What has been previously described?**
Outcome data and nasopharyngeal qRT-PCR testing of infants born to mothers with COVID-19 pneumonia are limited to case series from China:

- **On Feb 10, 2020**, an article in *Translational Pediatrics* described ten infants born to women with COVID-19 pneumonia in China, with a range of poor outcomes including intrauterine distress (6/10), poor pediatric critical illness scores (6/10), fever (2/10), and thrombocytopenia (2/10)\(^5\). One death was reported in this group of infants. However, there was no control group in this study, so it is unknown if the rates of poor outcomes were similar in infants without exposure to COVID-19 during the same time period. Additionally, all neonates tested in this study had negative pharyngeal qRT-PCR swab specimens for SARS-CoV-2, making it less clear if poor outcomes were due to COVID-19 exposure or if they were associated with the effects of the maternal COVID-19 infection. Serology testing was not conducted as it was not available at the time. Therefore, it was unclear if outcomes were directly tied to a vertical transmission of SARS-CoV-2 infection.

- **In an article published in *Lancet*** on **March 7, 2020**, 9 women with confirmed SARS-CoV-2 infection (via pharyngeal qRT-PCR) in the 3rd trimester of pregnancy were reported to have delivered 9 healthy full-term infants\(^6\). All infants in this group who were tested for SARS-CoV-2 (n = 6) via qRT-PCR from amniotic fluid, cord blood, throat swabs, and breastmilk samples of mother-infant pairs, were negative. Three sets of the 9 mother-infant pairs did not have samples collected due to two mothers delivering at night (precluding sample acquisition) and 1 mother diagnosed with COVID-19 infection after delivery. The major conclusion from this study was that there was no evidence of vertical transmission of SARS-CoV-2 from women infected in the 3rd trimester of pregnancy. Again, serology was not tested at this time, and notably, qRT-PCR testing was not collected from samples of vaginal mucosa to determine if transmission via vaginal delivery might occur later (though all infants were delivered via cesarean in this study).
  
  - Interestingly, the *Lancet* article’s discussion section highlighted a case report from Feb 6, 2020 of a neonate who tested positive for SARS-CoV-2 via pharyngeal qRT-PCR at 36 hours after birth to a pregnant woman with COVID-19 pneumonia, prompting the theoretical concern for intrauterine infection. However, as the sample was collected on day of life 2, there are theoretical concerns that postnatal infection may also have played a role. There were no details as to the level of post-natal exposure and route of delivery reported in this case.

**What is New?**
On **March 26, 2020**, three letters were published in *JAMA* highlighting new concerns for vertical transmission of SARS-CoV-2 to neonates via newly available serologic testing combined with continued qRT-PCR surveillance.

Summary: This case series out of Wuhan, China, reports 6 infants born via cesarean section Feb 16-March 6, 2020 to mothers diagnosed with (mild) pneumonia due to confirmed COVID-19 infection in the 3rd trimester. All the infants did well during C-section delivery (APGAR 8-10 at 1 & 5 min of life), and none were symptomatic as of March 8, 2020, at 2 to 14 days of age. Throat swabs and blood samples collected at birth were negative for SARS-CoV-2 via qRT-PCR in all six infants. However, 2/6 infants had elevated SARS-CoV-2 IgM and IgG at birth, and 3/6 additional infants had elevated IgG at birth. Interleukin-6 was elevated in all infants despite a lack of clinical symptoms.

- In a newsletter from the manufacturer (Shenzhen YHLO biotech), the sensitivity and specificity of the antibody assays is reported as 88.2 % and 99.0 % for IgM and 97.8 % and 97.9 % for IgG (data not formally published).

What this article adds: Though none of the infants had positive qRT-PCR testing for SARS-CoV-2 from throat or blood samples, and all were asymptomatic, 5/6 had positive IgG, which likely represents passive transfer from mother, and interestingly, 2/6 had positive IgM at birth, raising the concern for vertical transmission.

Limitations: Small sample size (n =6), women were infected in the 3rd trimester of pregnancy only, therefore outcomes for mother or infant if infection occurs in 1st or 2nd trimester remain unknown. This study did not examine cord blood, amniotic fluid, placental histopathology, vaginal secretions, or breast milk. The duration of illness and the level of viremia present in mothers at time of delivery were also not examined in this paper. Furthermore, the data on the antibody assay used in the study cannot be verified as it is not formally published. However, if these results are verified, they suggest that maternal pneumonia in the third trimester of gestation may result in SARS-CoV-2 viremia and potential exposure to the fetus sufficient to elicit an antibody response, without clinical manifestations of disease at birth.


Summary: This case report describes one mother with confirmed COVID-19 infection (via nasopharyngeal swab qRT-PCR) who delivered a healthy, asymptomatic term infant via cesarean section on Feb 22, 2020 in Wuhan, China. APGAR scores at 1 & 5 min of life were 9 & 10, and the infant developed no post-natal infections or complications. At 2 hrs age, infant serum was collected, and SARS-CoV-2 IgG and IgM were both elevated in the infant (as well as mother). Infant qRT-PCR testing from nasopharyngeal swabs remained negative through first 2 weeks of life, and at 2 weeks of life, IgG and IgM were both down-trending (though remained elevated compared to baseline). Maternal vaginal secretions at birth and breastmilk samples 3 weeks after delivery were negative via qRT-PCR for SARS-CoV-2.

- In this study, the antibody tests have published sensitivity and specificity values of 70.2 % and 96.2 % for IgM and 96.1 % and 92.4 % for IgG, respectively (in-house test at Renmin Hospital of Wuhan University, Chin J Lab Med, 2020,43:Epub ahead of print. DOI: 10.3760/cma.j.cn114452-20200223-00109).

What this article adds: Despite persistently negative qRT-PCR testing, an infant born to a mother with acute SARS-CoV-2 pneumonia demonstrated elevated IgM in serum. Given antibody IgM usually takes 3-7 days after exposure, an elevated IgM at 2 hrs of life might suggest in utero acquisition (supported by negative maternal vaginal qRT-PCR testing).
Limitations: Single case report. Amniotic fluid and placenta testing again were not conducted. Infection in mother occurred in the 3rd trimester, but the like the prior letter, the authors did not examine level of viremia in mothers prior to delivery. Again, this case suggests that in utero exposure to SARS-CoV-2 occurred and resulted in fetal antibody responses, without clinical manifestations of infection in the newborn.


Summary: In this case report from Wuhan, China, among 33 infants born to mothers with COVID-19 pneumonia, 3 infants tested positive for SARS-CoV-2 via nasopharyngeal swab qRT-PCR testing at 2 and 4 days of life and were negative by day 7 of life. Serology testing was not conducted in this study. One of these three infants was immediately quarantined from mother after delivery, but two were admitted to the NICU and had an unknown degree of exposure to the mother around the time of birth. Two of the 3 positive infants were born at full-term and one was born prematurely at 31 weeks and had complications related to prematurity, including bacterial sepsis. All three infants eventually had good outcomes, though the infant born prematurely at 31 weeks required mechanical ventilator support. Of the 30 exposed infants with negative qRT-PCR testing, 3 had transient respiratory distress and shortness of breath.

What this article adds: This is the first official report to describe newborns testing positive for SARS-CoV-2 via nasopharyngeal qRT-PCR testing in the first few weeks of life. In this report, congenital infection as a possible route of infection was not evaluated, and the possibility of post-natal exposure and infection exists given that infants were evaluated after 48 hrs from delivery, at 2 and 4 days of life, due to the presence of respiratory symptoms. Again, all infants were born to mothers with mild COVID-19 infection in the third trimester of gestation and ultimately did well; the one premature infant’s need for mechanical ventilation and other complications were thought to be related to respiratory distress syndrome due to prematurity and not due to SARS-CoV-2 pneumonia.

Limitations: Small sample size, did not look at serology, focused on infections that occurred in the 3rd trimester of pregnancy, with good outcomes in the mothers. In this report, the degree of exposure between mother and infant after birth was not reported in two of the three cases who tested positive (strict quarantine was not mentioned, unlike the first positive infant).

In Summary:
These articles highlight the potential risk of neonatal infection in mothers with COVID-19 disease in the third trimester of gestation. The possibility of true congenital infection is raised with the use of serological testing at birth in two case reports, and the effects of perinatal infection of infants born to mothers with COVID-19 infection in the 3rd trimester of pregnancy are assessed in a larger case series. Limitations of these studies include small sample sizes, assessment of maternal infection only in the 3rd trimester of pregnancy, evaluation limited to pregnant women with mild illness (none with ARDS), and lack of evaluation to support the possible mechanism of transmission from mother to infants, such as maternal viremia or presence of virus in maternal vaginal secretions at delivery, or respiratory tract after delivery.

The major finding that was similar in all three published letters, was that maternal and neonatal outcomes were positive. However, infants in these letters were born to women with mild COVID-19 pneumonia at time of delivery. Therefore, future studies should investigate outcomes of infants born to mother with severe disease, including pneumonia or ARDS due to SARS-CoV-2 infection.
Two of the letters claim that vertical transmission of the virus to infants must have occurred based on positive IgM antibody testing in infants at birth. However, more studies are warranted to investigate the specificity and sensitivity of these relatively new serology tests. Additionally, there was no evaluation of placenta pathology or maternal viremia to determine a biological explanation for in utero transplacental passage of virus in these patients. The third letter did not assess in utero infection but did highlight detection of the virus via qRT-PCR at 2 & 4 days of life in 3 of 33 infants born to infected mothers. Again, all infants did well, as did their mothers, and the mechanism of infection in these cases could also have been post-natal exposure to the virus (though the exact degree of postnatal exposure was not fully reported in this paper).

It is still unknown what the outcomes of pregnancy in women infected with SARS-CoV-2 in the 1st or 2nd trimester and even on the 3rd trimester of pregnancy will be, but as this pandemic evolves, more data and more studies will be published to answer these important questions. Guidance on the management of pregnant women with COVID-19 infection and their newborns is being developed by the American Academy of Pediatrics and the American College of Obstetrics and Gynecology, as current guidance from the CDC is available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html, and from the WHO at: https://www.who.int/news-room/q-a-detail/q-a-on-covid-19-pregnancy-childbirth-and-breastfeeding.

Additional References


COVID19 Literature Review Newsletter Volume #2
Infectious Diseases Fellow: Teena Xu, MD
Faculty: Jill Weatherhead, MD
April 1st, 2020

*Article published in Chinese and translated/interpreted with assistance. English abstract is available.

Methods: Open-label RCT in Shanghai, China of hospitalized adults with “common” COVID-19 (subjective fever, respiratory symptoms, radiologic pneumonia, and SpO2 >93%). Excluded patients with “serious diseases of important organs,” retinopathy, neuropsychiatric disorders. Randomized (1:1) upon
admission to receive conventional therapy alone or with HCQ (400mg daily x 5days). Endpoints: 1) viral clearance at day 7 (negative throat swab PCR x2); 2) two-week mortality; 3) adverse drug events; 4) progression to severe disease.

Results (see attached table for translated data):
a. n=30 (15 control, 15 HCQ). Comparable demographic/clinical data.
b. All patients received inhaled interferon-alpha. 73% received Umifenovir (antiviral fusion inhibitor). Lopinavir/ritonavir given to 2 patients in control arm.
c. No significant difference (p>0.05):
   - Viral clearance at day 7: n=14 (control) vs n=13 (HCQ)
   - Median time to first negative swab: 2 d vs 4 d
   - Resolution of fever: 1 d vs 1 d
   - Duration of illness (mean): 5.9 d vs 6.6 d
   - Radiologic improvement at 3 d: n=7 vs n=5
   - Adverse drug events: n=3 vs n=4
   - Progression to severe disease: n=0 vs n=1
   - Deaths: none

Discussion: In this small trial, no significant benefit was observed with the addition of HCQ for mild COVID-19 pneumonia in individuals without significant comorbidities. Results possibly confounded by use of other experimental therapies. The rapid fever resolution and virologic eradication raises concern for generalizability; control group from a prior study at the same center had longer time to defervescence (4 d) and viral clearance (7 d).

2) Gautret et al. Clinical and microbiological effect of a combination of hydroxychloroquine (HCQ) and azithromycin (AZ) in 80 COVID-19 patients with at least a six-day follow up: an observational study (Pre-print)

Background: These authors recently published a small study (n=36) suggesting decreased viral carriage at day 6 in COVID-19 patients receiving HCQ +/- AZ (70%) compared to placebo (12.5%). Internal in vitro data on HCQ + AZ synergy on SARS-CoV-2 infected cells is referenced but not published.

Methods: Prospective, observational study in Marseille, France of hospitalized adults with confirmed COVID-19 (PCR+ NP swab) treated with HCQ (200mg TID for 10 days) + AZ (500mg x1, then 250mg QD for 4 days). 6 patients also included in prior study. Main outcomes: 1) time to negative NP swab PCR (negative = PCR cycle threshold ≥ 35), 2) clinical deterioration. NP viral cultures were performed at random.

Results:
a. n=80, mean age 52y, 42% healthy, 92% low risk for clinical deterioration.
b. 46% URTI/asymptomatic, 15% fever, 15% hypoxia, 46% negative CT chest.
c. Mean time from symptoms to treatment was 4.9 days.
d. Day 7 NP PCR negative in 83% (n=50). 100% negative on Day 12.
e. Day 5 NP viral culture negative in 98% (n=20). 100% negative on Day 9.
f. 65/80 improved and discharged, 3 needed ICU care, 1 died.
g. All but one completed therapy.

Discussion: In this group of patients who received HCQ+AZ for mild COVID-19, viral eradication from available NP samples occurred by day 9 (culture) and day 12 (PCR). Majority of patients recovered, although clinical disease was mild in this low risk cohort. Lack of control group makes the significance of these findings impossible to interpret.
3) **Recommended reading:**

2. Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics: [https://jamanetwork.com/journals/jama/fullarticle/2763802](https://jamanetwork.com/journals/jama/fullarticle/2763802)

**COVID19 Literature Review Newsletter Volume #3**

Infectious Diseases Fellow: Melanie Goebel, MD
Faculty: Jill Weatherhead, MD
April 3rd, 2020

On 3/31, the FDA announced shortages of hydroxychloroquine and chloroquine “due to a significant surge in demand.”

**Article #1: *of note this article is getting significant press on social media and news media***

doi: [https://doi.org/10.1101/2020.03.22.20040758](https://doi.org/10.1101/2020.03.22.20040758).

- Pre-print article (not peer-reviewed)
- Background: efficacy of hydroxychloroquine (HCQ) remains unknown, with current evidence limited by small sample size and methodologic flaws
- Methods
  - Double-blind RCT, single hospital in Wuhan, China
  - Inclusion criteria: Age > 18, PCR-positive, pneumonia on CT chest, mild illness
  - Exclusions: severe illness, arrhythmias, severe liver/renal disease
  - Intervention: HCQ 200 mg bid x 5 days vs “standard treatment”
  - Outcomes: time to clinical recovery (body temp and cough measured day 1-5) and “pulmonary recovery” (repeat CT chest at day 6)
- Results
  - N=62 (31 control, 31 HCQ)
  - Body temperature recovery: of patients with fever at day 0, recovery time 3.2 days in controls (n=17) vs 2.2 days in HCQ group (n=22); P<0.05
  - Cough recovery: of patients with cough at day 0, recovery time 3.1 days in controls (n=15) vs 2.0 in HCQ group (n=22); P<0.05
  - Day 6 CT chest improved in 17/31 controls vs 25/31 HCQ; P<0.05
  - 4/31 controls vs 0/31 HCQ progressed to “severe illness”
- Limitations:
  - Blinding is questionable (no placebo)
  - Underpowered (planned sample size = 300)
- More patients in HCQ group had fever/cough at day 0
- Time of observation only 5 days
- Unclear how severe illness is defined, mortality not reported
- Clinical significance of CT chest improvement is questionable
- **Very difficult to draw any conclusions about clinical efficacy from this data given small sample size, short clinical observation time, and narrow clinical endpoints**

**Article #2**


- **Background:** Case reports from China and Washington suggest presymptomatic transmission of SARS-CoV-2
- **Methods**
  - Epidemiologic data were reviewed for 243 COVID-19 cases in Singapore from January 23–March 16
  - Containment strategy: surveillance, extensive contact tracing
  - Suspected cases (respiratory symptoms) confirmed with PCR
  - Clusters with presymptomatic transmission
    - Clear contact between source patient and secondary patient
    - No other explanations for infection
    - Source patient’s date of symptom onset occurred after date of exposure to secondary patient
- **Results**
  - 7 clusters (2-5 patients per cluster) with likely presymptomatic transmission
    - **In 4 clusters, presymptomatic transmission exposure occurred 1-3 days before the source patient developed symptoms**
    - In 3 clusters, exposure was continual (patients lived together)
  - 157/243 cases in Singapore were locally acquired
  - 10 cases within the clusters were attributed to presymptomatic transmission, accounting for 6.4% of 157 locally acquired cases
  - Proposed routes of presymptomatic transmission
    - Respiratory droplets (singing, speech)
      - Cluster B: source and secondary patients attended same singing class
      - Cluster F: source infected 2 patients who sat one row behind her in church service
    - Indirect transmission (fomites)
      - Cluster A: secondary case occupied the same seat in church that the source patients occupied earlier that day
- **Limitations**
  - Unknown source may have initiated clusters
  - Recall bias may affect symptom onset dates
  - Interviewer bias
- **Conclusion:** study provides epidemiologic evidence of presymptomatic viral shedding and transmission; contact tracing should include period before symptom onset; **social distancing is critical to public health response**
***new article out TODAY on asymptomatic and presymptomatic transmission in US. [https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e1.htm](https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e1.htm).

Other recommend articles this week:


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