Strategies to support the COVID-19 response in LMICs
A virtual seminar series
COVID-19 Risks to Maternal and Neonatal Health

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Disclosures

• I have no relevant conflicts of interest
• I receive research support from the National Institutes of Health (K23HD100594)
Objectives

• Review epidemiology of COVID-19 in pregnancy and associated outcomes in pregnant women and neonates

• Provide an overview of recommendations for management of neonates with perinatal COVID-19 exposure

• Describe clinical characteristics and outcomes in young infants with community-onset COVID-19

• Identify resources for data and guidelines on COVID-19 in pregnant women, neonates, and infants
Perinatal COVID-19: Maternal and Neonatal Outcomes

A review of the literature on COVID-19 in pregnancy and associated maternal and neonatal outcomes
SARS and MERS in pregnancy

• SARS and MERS-CoV with limited data on pregnancy
  • SARS
    • Mechanical ventilation 3x more likely among pregnant women than in non-pregnant women
    • Case fatality rate 25%
    • Other complications included spontaneous abortion with first trimester infection, preterm delivery
  • MERS-CoV
    • 13 case reports; 2 with fetal demise, 2 with preterm delivery
    • Case fatality rate 23%
    • No documented vertical transmission of SARS or MERS-CoV

• What is the risk to pregnant women and neonates with perinatal COVID-19?
COVID-19: What is the risk to pregnant women and neonates?

• What is the prevalence of COVID-19 among pregnant women?
• Are pregnant women at increased risk of infection compared to non-pregnant adults? Of severe disease?
• What is the case fatality rate in pregnant women?
• Is there an increased risk of adverse pregnancy outcomes, including miscarriage, stillbirth, and preterm delivery?
• What is the risk of early pregnancy infection to the developing fetus?
• What is the risk of vertical transmission to the neonate?
• Are preterm neonates more likely to be infected or have more severe disease?
COVID-19: What is the risk to pregnant women and neonates?

• What is the postnatal transmission risk from mother to baby in absence of separation? In absence of PPE/distancing? Does maternal symptom severity matter?

• Is breast milk infectious?

• Among infected neonates, what is the spectrum of clinical disease? Are there long-term effects of infection in infancy?

• Can maternal COVID-19 cause an inflammatory response in the neonate that manifests clinically, in absence of confirmed neonatal infection?

• What is the role of serologic testing? In mother? In neonate?

• Does fecal-oral transmission and persistent viral shedding play a major role?
Methods

• Literature review of studies published through May 15, 2020, on COVID-19 in pregnancy and maternal and neonatal outcomes

• Data sources: Medline, Embase, Google Scholar

• Limited to peer-reviewed studies for which full text could be retrieved

• Confirmed duplicate/overlapping publications were excluded except to provide additional case details
Methods

• Maternal outcomes
  • Gestational age/trimester at presentation
  • Clinical presentation
  • Adverse pregnancy outcomes
  • ICU admission
  • Mechanical ventilation
  • Death

• Neonatal outcomes
  • Gestational age, sex, mode of delivery, birth weight, APGAR scores
  • Separation from mother, NICU admission, breastfeeding
  • Clinical course
  • Laboratory parameters and chest imaging
  • SARS-CoV-2 testing results
  • Disposition
Results

• 99 studies were identified
• 705 women with laboratory-confirmed SARS-CoV-2 infection during pregnancy
• 520 neonates with perinatal exposure
• Greatest number of publications (n=41) and cases in pregnancy (n=286) were from China
Epidemiology of COVID-19 in pregnancy

• Few studies provided population-based estimates of prevalence in pregnancy

• Lombardy, Italy: 42 pregnant women over 3 week period, ~0.6% of deliveries (symptom-based testing)

• New York City academic centers: 15.4% prevalence over 2 week period after instituting universal testing

• London maternity hospital: 7.0% prevalence (universal testing)
Maternal clinical presentation

- Ranges from asymptomatic to critically ill
- Concern for asymptomatic presentation raised by Breslin et al. in case series of 7 women, 2 of whom were asymptomatic on L&D admission but had intra- and postpartum onset of symptoms; both critically ill requiring ICU admission
- Sutton et al. reported that 87.9% of women who tested positive on L&D presentation were asymptomatic, though 10.3% became febrile during admission
### Maternal clinical presentation and pregnancy outcomes

<table>
<thead>
<tr>
<th>Trimester (n=508)</th>
<th>Total n=705</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester, n (%)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Second trimester, n (%)</td>
<td>29 (6)</td>
</tr>
<tr>
<td>Third trimester, n (%)</td>
<td>465 (92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital course</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission, n (%)</td>
<td>88 (15)</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>60 (12)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>11 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy outcome (n=615)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivered, live birth, n (%)</td>
<td>511 (83)</td>
</tr>
<tr>
<td>Delivered, stillbirth, n (%)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Delivered, neonatal outcome not reported, n (%)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Induced abortion, n (%)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Spontaneous abortion, n (%)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Remained pregnant, n (%)</td>
<td>79 (13)</td>
</tr>
</tbody>
</table>
Pregnancy outcomes

- 448 women with reported mode of delivery
  - 337 (75%) C-section
- 100 (19%) of delivered women were reported as delivered via C-section due to maternal COVID/respiratory status
- 57 (11%) reported decreased fetal movement or non-reassuring fetal heart rate tracing
- 131 (30%) preterm deliveries
- Limited reporting of ultimate pregnancy outcome among women who remained pregnant at time of infection
# Neonatal outcomes – SARS-CoV-2 infection

## Neonatal samples

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Positive/Total (%)</th>
<th>n positive/total samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP/OP swab</td>
<td>17/229 (7)</td>
<td>17/229 (7)</td>
</tr>
<tr>
<td>Sputum</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Gastric aspirate</td>
<td>0/11</td>
<td>0/11</td>
</tr>
<tr>
<td>Stool</td>
<td>1/21 (5)</td>
<td>1/21 (5)</td>
</tr>
<tr>
<td>Urine</td>
<td>0/20</td>
<td>0/20</td>
</tr>
<tr>
<td>Blood</td>
<td>1/20 (5)</td>
<td>1/20 (5)</td>
</tr>
<tr>
<td>CSF</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Unspecified</td>
<td>4/158 (3)</td>
<td>4/158 (3)</td>
</tr>
<tr>
<td>No reported testing</td>
<td>133 (26)</td>
<td>133 (26)</td>
</tr>
</tbody>
</table>

### Neonates with at least one positive SARS-CoV-2 sample

- 21/520 (4%)
- 21/387 with reported testing (5%)

## Maternal/delivery samples

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Positive/Total (%)</th>
<th>n positive/total samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>1/37 (3)</td>
<td>1/37 (3)</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>1/42 (2)</td>
<td>1/42 (2)</td>
</tr>
<tr>
<td>Placenta</td>
<td>5/29 (17)</td>
<td>5/29 (17)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1/8 (13)</td>
<td>1/8 (13)</td>
</tr>
<tr>
<td>Cervical</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Anal/rectal swab</td>
<td>1/3 (33)</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>Stool</td>
<td>1/3 (33)</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>Urine</td>
<td>0/2</td>
<td>0/2</td>
</tr>
<tr>
<td>Blood</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Breast milk</td>
<td>2/23 (9)</td>
<td>2/23 (9)</td>
</tr>
</tbody>
</table>
Neonatal outcomes – SARS-CoV-2 IgM and IgG testing

• Limited testing in neonates
• 2 studies reported 3 neonates with elevated IgM despite negative SARS-CoV-2 PCR testing
  • Mild elevation with rapid decline
• Serologic diagnosis of congenital viral infection complicated by high rates of false positive testing
## Neonatal outcomes – clinical presentation

<table>
<thead>
<tr>
<th></th>
<th>Neonates with positive SARS-CoV-2 PCR testing</th>
<th>Neonates without positive SARS-CoV-2 testing</th>
<th>All neonates n=456</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal critical illness, n/total (%)</td>
<td>5/18 (28)</td>
<td>44/362 (12)</td>
<td>49/380 (13)</td>
</tr>
<tr>
<td>Gestational age in completed weeks, median (IQR)</td>
<td>39 (33-40)</td>
<td>38 (36-38)</td>
<td>38 (35-39)</td>
</tr>
<tr>
<td>Preterm, n/total (%)</td>
<td>7/18 (39)</td>
<td>124/417 (30)</td>
<td>131/435 (30)</td>
</tr>
<tr>
<td>Birth weight in grams, median (IQR)</td>
<td>3163 (2608-3333)</td>
<td>3130 (2628-3398)</td>
<td>3130 (2615-3375)</td>
</tr>
<tr>
<td>Male sex, n/total (%)</td>
<td>9/14 (64)</td>
<td>69/108 (64)</td>
<td>78/122 (64)</td>
</tr>
<tr>
<td>Caesarean delivery, n/total (%)</td>
<td>15/20 (75)</td>
<td>306/413 (74)</td>
<td>321/433 (74)</td>
</tr>
<tr>
<td>APGAR score at 1 minute, median (IQR)</td>
<td>8 (6-9)</td>
<td>9 (8-9)</td>
<td>9 (8,9)</td>
</tr>
<tr>
<td>APGAR score at 5 minutes, median (IQR)</td>
<td>9 (9-10)</td>
<td>9 (9-10)</td>
<td>9 (9-10)</td>
</tr>
<tr>
<td>Neonatal asphyxia, n (%)</td>
<td>1/20 (5)</td>
<td>6/377 (2)</td>
<td>7/397 (2)</td>
</tr>
<tr>
<td>Separation from mother after delivery, n/total (%)</td>
<td>12/17 (71)</td>
<td>157/170 (92)</td>
<td>169/187 (90)</td>
</tr>
<tr>
<td>Breastfed, n/total (%)</td>
<td>4/12 (33)</td>
<td>15/131 (11)</td>
<td>19/143 (13)</td>
</tr>
<tr>
<td>NICU admission, n/total (%)</td>
<td>15/18 (83)</td>
<td>125/304 (41)</td>
<td>140/322 (43)</td>
</tr>
<tr>
<td>Fever, n/total (%)</td>
<td>5/15 (33)</td>
<td>4/249 (2)</td>
<td>9/264 (3)</td>
</tr>
<tr>
<td>Respiratory distress, n/total (%)</td>
<td>12/19 (63)</td>
<td>33/288 (11)</td>
<td>45/307 (15)</td>
</tr>
<tr>
<td>Abnormal chest imaging, n (%)</td>
<td>11/13 (85)</td>
<td>21/45 (47)</td>
<td>32/58 (55)</td>
</tr>
<tr>
<td>Need for PPV, n/total (%)</td>
<td>5/15 (33)</td>
<td>6/262 (2)</td>
<td>11/277 (4)</td>
</tr>
<tr>
<td>Need for mechanical ventilation, n/total (%)</td>
<td>3/16 (19)</td>
<td>7/266 (3)</td>
<td>10/282 (4)</td>
</tr>
<tr>
<td>GI symptoms, n/total (%)</td>
<td>5/14 (36)</td>
<td>10/277 (4)</td>
<td>15/291 (5)</td>
</tr>
<tr>
<td>DIC, n/total (%)</td>
<td>1/17 (6)</td>
<td>2/274 (1)</td>
<td>3/290 (1)</td>
</tr>
<tr>
<td>Lymphopenia, n/total (%)</td>
<td>1/9 (11)</td>
<td>4/88 (5)</td>
<td>5/97 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia, n/total (%)</td>
<td>1/8 (13)</td>
<td>7/60 (12)</td>
<td>8/68 (12)</td>
</tr>
<tr>
<td>Elevated aminotransferases, n/total (%)</td>
<td>4/7 (57)</td>
<td>19/64 (30)</td>
<td>23/71 (32)</td>
</tr>
<tr>
<td>Neonatal death, n (%)</td>
<td>0/21</td>
<td>6/424 (1)</td>
<td>6/445 (1)</td>
</tr>
</tbody>
</table>
Neonatal outcomes – neonates with positive SARS-CoV-2 PCR testing

- Age at first positive test: 0-8 days (most day of birth through 2 days of age)
- 3 reported as asymptomatic, 1 without description of course
- Prematurity and bacterial infection thought to contribute to clinical symptoms in several cases
- 1 neonate with asphyxia, 1 presented with encephalitic symptoms
- Kirtsman et al. reported likely in utero transmission: PCR positive – placental swab (maternal, fetal), placental tissue (parenchyma, chorion), neonatal NP day 0, 2, 7, neonatal plasma day 4, neonatal stool day 7
- Possible postnatal transmission reported in 5 cases; maternal post-delivery diagnosis in 4, possible nosocomial transmission in 1
- No deaths, but final disposition not reported in several cases
Neonatal outcomes

• 6 neonatal deaths
  • 5 in the setting of maternal critical illness
  • All preterm
    • None had positive SARS-CoV-2 PCR testing, though not all had reported testing

• Length of stay variable, in some cases driven by persistently positive testing

• Limited reporting of post-discharge follow-up; 2 neonates tested positive as outpatients, both asymptomatic and thought to be due to postnatal transmission
Summary – literature review

• Maternal clinical presentation of SARS-CoV-2 infection ranges from asymptomatic to critical illness
  • Case fatality rate significantly lower than that described with SARS and MERS-CoV

• Neonatal infection seen in 5% of neonates with reported testing, with no reported deaths among neonates with positive testing
  • Likely a mix of vertical and horizontal transmission

• Breast milk rarely tested positive; no documented transmission events related to use of breast milk

• Most common symptom in exposed neonates is respiratory distress, including in neonates with negative or no reported testing
Limitations – literature review

• Preponderance of case reports ➔ limited understanding of epidemiology, including prevalence of disease among pregnant women and neonatal infection rate

• Significant variability in reporting of clinical course

• Variable evaluation of exposed neonates, many of whom had no reported testing

• Limited capacity to determine mechanism of transmission in most neonates with positive SARS-CoV-2 PCR testing

• Very few studies with post-discharge follow-up
Notable studies published in recent months – population-based cohort study (UK)

• UK population based cohort study using national surveillance system
  • 427 pregnant women admitted with SARS-CoV-2 (laboratory confirmed and clinically diagnosed), representing a rate of 4.9 per 1000 pregnancies
  • 41 (10%) required respiratory support, 5 (1%) died
  • 266 (62%) delivered or had pregnancy loss, 196 of women (73%) gave birth at term
  • 12 (5%) neonates had positive PCR testing; 6 (50%) had positive testing within first 12 hours
  • Study is notable for high proportion (56%) of black and other minority ethnic groups among cohort

Notable studies published in recent months – case report of likely vertical transmission

• Sisman et al. reported a case of likely in utero transmission
  • Maternal infection 5 days prior to delivery
  • Vaginal delivery at 34 weeks; neonate separated from mother
  • Neonate presented with respiratory distress and fever, weaned off respiratory support by day of life 5 and discharged on day of life 21
  • Neonate with positive nasopharyngeal SARS-CoV-2 PCR testing at 24 hours, 48 hours, and 14 days; negative evaluation for other causes of clinical presentation
  • Placental pathology notable for intervillositis and villitis; immunohistochemistry for SARS-CoV-2 demonstrated cytoplasmic staining in syncytiotrophoblasts

Clinical management of neonates with perinatal COVID exposure

• Reduction of transmission risk through infection prevention and control strategies
  • Mode of delivery should be determined by obstetric indications; C-section is not indicated to reduce risk of transmission
  • Infection prevention strategies as appropriate and available to reduce transmission risk during labor and delivery
  • No contraindication for delayed cord clamping
  • Recommendations regarding post-delivery practices are variable and are partially resource-driven
    • WHO recommends against separation of mother and neonate and encourages breastfeeding; mask use and hand hygiene by mother to reduce risk of transmission
    • AAP guidelines updated July 2020 – temporary separation of mother and neonate no longer recommended unless medically necessary; PCR testing from NP/OP recommended at 24 hours and 48 hours
Community-onset COVID-19 in Young Infants

A review of the literature on community-onset COVID-19 among infants less than 3 months of age
Community-onset COVID-19 among young infants

- Systematic review of laboratory-confirmed community-onset COVID-19 among infants less than 3 months of age published through June 15, 2020
- 38 studies identified, reporting 63 infants
- Preponderance of case reports and case series; 1 cohort study identified
Clinical characteristics of young infants with COVID-19

- Age range 5 days - <3 months
- Male predominance (69%)
- Eight infants with significant prior medical history: extreme prematurity (n=1), congenital heart disease (n=3), cystic fibrosis (n=1), renal anomalies (n=3)
- 41 (69%) with reported contact with symptomatic or COVID-confirmed individual
- Most common symptoms: fever (73%), cough (38%), rhinitis (36%), respiratory distress (26%), poor feeding (24%), emesis (14%), diarrhea (14%)
Clinical characteristics of young infants with COVID-19

- Unusual presentations worth noting: apnea (3%), seizures (3%), elevated cardiac enzymes (5%)
- 3 neonates were asymptomatic
- Laboratory abnormalities reported included neutropenia (56%), lymphopenia (16%), thrombocytopenia (7%); elevated inflammatory markers and aminotransferases also reported
- Abnormal chest imaging: 13/28 (46%) with chest X-ray, 9/9 (100%) with chest CT
- Co-infection with another respiratory viral pathogen in 5 (8%)
SARS-CoV-2 PCR test results among infants with COVID-19

• 97% of infants with at least one positive respiratory specimen; 2 infants only tested positive from an anal swab

• Anal/stool samples positive in 8/10 (80%)

• CSF PCR positive in 1/6 (17%), blood in 1/3 (33%), and urine in 1/2 (50%)

• Han et al. reported serial quantitative PCR testing in infant who had positive testing from NP, OP, saliva, blood, urine, and stool samples
  • Gradual decline in viral load over 3 week hospital admission
Clinical course of infants with COVID-19

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=63</td>
</tr>
<tr>
<td>Hospital admission, n (%)</td>
<td>58 (92)</td>
</tr>
<tr>
<td>ICU admission, n/total (%)</td>
<td>13/61 (21)</td>
</tr>
<tr>
<td>Nasal cannula, n/total (%)</td>
<td>12/55 (22)</td>
</tr>
<tr>
<td>CPAP, n/total (%)</td>
<td>3/59 (5)</td>
</tr>
<tr>
<td>Mechanical ventilation, n/total (%)</td>
<td>2/62 (3)</td>
</tr>
<tr>
<td>Pressors, n/total (%)</td>
<td>1/59 (2)</td>
</tr>
<tr>
<td>Antibiotics, n/total (%)</td>
<td>25/39 (64)</td>
</tr>
<tr>
<td>COVID-specific treatment, n (%)</td>
<td>8/56 (14)</td>
</tr>
<tr>
<td>Length of stay in days, median (IQR)</td>
<td>3 (2, 8) (n=46)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0/63</td>
</tr>
</tbody>
</table>
Summary

• Spectrum of clinical disease ranges from asymptomatic to critical illness; most infants have mild to moderate disease and recover quickly with supportive treatment

• Male predominance

• Symptoms are non-specific and warrant high index of suspicion as well as evaluation for other etiologies, especially among neonates and young infants presenting with fever

• Neurologic and cardiac manifestations are rare but noteworthy in this age group and mirror symptoms seen in older age groups
Limitations

• Reliance on case reports
• Variable evaluation of neonates – most with respiratory samples but limited testing from GI, blood, urine, and CSF samples
• Limited post-discharge follow-up
Resources

An overview of available resources and references for COVID-19 in pregnant women, neonates, and young infants
COVID-19 resources

• Individual journal websites – COVID collections usually not behind paywall
• Review/synthesis of published literature
  • Review/synthesis of neonatal and pediatric literature: www.dontfortgetthebubbles.com
Registries for COVID in pregnancy

- International (COVI-PREG)
- United States (AAP – neonates, UCSF – pregnant women)
- United Kingdom (UKOSS)
- Ireland (ROI COVID-19)
- Netherlands (NethOSS)
- Australia (CHOPAN)
- Italy (ItOSS)
- Multiple national/regional registries for COVID in general or for maternal outcomes in general are also reporting on COVID in pregnancy
Guidelines for COVID-19 in pregnant women and for exposed neonates

• World Health Organization

• United States Centers for Disease Control and Prevention

• American Academy of Pediatrics
References – perinatal COVID-19


References – perinatal COVID-19


References – perinatal COVID-19


References – perinatal COVID-19


References – perinatal COVID-19


49. 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; published online Apr 16. doi: 10.2214/AJR.20.23247.


References – perinatal COVID-19


References – perinatal COVID-19


References – perinatal COVID-19


References – perinatal COVID-19


References – COVID-19 in young infants


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