Vertical Transmission of SARS-CoV-2

An update

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Disclosures

None
CAUTION

The data presented here is most likely already outdated.

(April 21, 2020)
## Reports of COVID-19 in Pregnancy (as of April 21, 2020)

<table>
<thead>
<tr>
<th>Country</th>
<th># Papers</th>
<th># Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>28*</td>
<td>317</td>
</tr>
<tr>
<td>USA</td>
<td>6</td>
<td>81</td>
</tr>
<tr>
<td>Italy</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>S. Korea</td>
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<td>2</td>
</tr>
<tr>
<td>Iran</td>
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<td>2</td>
</tr>
<tr>
<td>Australia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Spain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Honduras</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Turkey</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peru</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>44</strong></td>
<td><strong>451</strong></td>
</tr>
</tbody>
</table>

- English language, PubMed (LitCovid)

* ≥15 papers with overlapping hospitals/time frames. Unclear if duplicates.

We currently lack data for 1\textsuperscript{st} and 2\textsuperscript{nd} trimester infections.
Is Vertical Transmission of SARS-CoV-2 Possible?

- Biologic feasibility of *in utero*, intrapartum, postpartum transmission
  - Evidence
    - Serologic
    - Virologic

- Proposed classification system to define true vertical transmission
Routes of Vertical Transmission

1. Placenta
2. Cervix/vagina
3. Amniotic membrane
Angiotensin-converting Enzyme 2 (ACE2): The human receptor for SARS-CoV-2

Vaduganathan et al., NEJM 2020
ACE2 expression in maternal-fetal tissue

ACE2 mRNA expression in fetal membranes and placenta at term

Marques et al., *Placenta*. 2011

ACE2 protein expression in fetal lung

Intrapartum Transmission of SARS-CoV-2

Is SARS-CoV-2 present in relevant bodily fluids?

• Vaginal fluid
  • 0/10 postmenopausal women in the ICU with severe COVID-19
  • 0/6 from pregnant women at delivery

• Stool
  • Can be PCR+ for up to 30d (Wolfel et al, *Nature* 2020)
  • Live SARS-CoV-2 has been cultured from 4 stool samples (Wang et al, *JAMA* 2020)

• Blood
  • Rarely detected (3/307 samples, Wang et al., *JAMA* 2020)
Postpartum transmission of SARS-CoV-2

- Immediate post-natal transmission in delivery room
  - Respiratory droplets
- Breastfeeding/breast milk
  - 0/17 milk samples
  - Risk from close contact during nursing
Serologic evidence

Evidence of humoral immune response to virus (exposure)
Accuracy of serologic testing still needs to be widely validated.

Test performance
Cross-reactivity
Serologic evidence for vertical transmission

Infant 1 (China-Dong)

- 37w by CD in negative pressure OR
- Separated immediately
- Infant IgM+/IgG+ @ 2hrs
- NP swabs neg x 5 (2h-16d)

Infants 2-7 (China-Zeng)

- 6 infants by CD in negative pressure OR
- Separated immediately
- 2/6 IgM+/IgG+
- 3/6 IgM-/IgG+ (all moms IgG+)
- 0/6 NP swabs PCR+
- All infants asymptomatic

Dong et al., JAMA. 2020
Zeng et al., JAMA. 2020
Serologic evidence - comments

- Neonatal IgM is too large to cross the placenta - produced *in utero*
- However, IgM and IgG assays are prone to false positives
  - Serologic assays not yet well-validated for SARS-CoV-2
- All RT-PCR in neonatal specimens were negative
- Serology alone is not considered “proof” of *in utero* transmission
Virologic Evidence

Direct detection of SARS-CoV-2 in fluids/tissues by RT-PCR.

Window of detection.

Positive PCR does not confirm infectious virus.

Need to culture virus *in vitro*
Virologic evidence for vertical transmission

Tissue samples
- 0/25 amniotic fluid
- 0/12 placenta
- 0/41 cord blood
- 0/20 neonatal gastric aspirate
- 5/44 neonatal stool
Virologic evidence for vertical transmission

Neonatal NP/OP swab

- 11/256 (4%)
  - Most tests done on DOL 2 (≤DOL 5)
  - 10/11 report immediate separation
- Serologies performed on 7 of 11, all negative

Peru: Earliest neonatal detection 16hrs after CD

Alzamora et al., Am J. Perinat. 2020
So how can we better define a *true* case of vertical transmission?
Considerations:
1. Maternal testing
2. Infant symptoms
3. Detection of virus
   • Timing
   • Blood > amniotic fluid > placenta > NP swab
4. Presence of IgM

Categories:
1. Confirmed
2. Probable
3. Possible
4. Unlikely
5. Not infected
Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates

<table>
<thead>
<tr>
<th>Category</th>
<th>Congenital</th>
<th>Neonatal Intrapartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ Infant Sx</td>
<td>No Infant Sx</td>
<td>+ Infant Sx</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>+ cord blood or + neo blood ≤12h or + amniotic fluid</td>
<td>+ cord blood or + neo blood ≤12h</td>
<td>+NP at birth and 24-48h and no other cause</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>+ NP at birth and + placenta</td>
<td>+ amniotic fluid BUT - cord blood/neo blood ≤12h</td>
<td>+NP at birth - NP 24-48h and no other cause</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>- NP at birth BUT + IgM in cord blood or +IgM neo blood ≤12h or + placenta</td>
<td>+ IgM cord blood or + placenta BUT - cord blood/neo blood ≤12h</td>
<td>- NP at birth + Other test^ and no other cause</td>
</tr>
<tr>
<td><strong>Unlikely</strong></td>
<td>- NP at birth, cord blood, neo blood ≤12h, amniotic fluid BUT no serology testing</td>
<td>- NP at birth, cord blood, neo blood ≤12h, amniotic fluid BUT no serology testing</td>
<td>- NP at birth - Other test^ and no other cause</td>
</tr>
<tr>
<td><strong>Not infected</strong></td>
<td>- NP at birth/cord blood/neo blood ≤12h/amniotic fluid and - IgM in cord or neo blood ≤12h</td>
<td>- NP at birth/cord blood/neo blood ≤12h/amniotic fluid and - IgM in cord blood</td>
<td>- NP at birth - Other test^ and other cause found</td>
</tr>
</tbody>
</table>

1. Mothers are COVID+ or suspected prenatally, within 2-3 weeks prior to birth.
2. +/- refers to RT-PCR results; NP=nasopharyngeal
^ Other tests: any of maternal vaginal/placental/cord/neonatal nasopharyngeal/skin swab at birth
Summary

- *In utero* transmission of SARS-CoV-2 is feasible.
  - ACE2 receptors are present in placenta, amniotic membranes, decidua throughout pregnancy
  - ACE2 receptors are present in fetal lung (@ 12w)
- Serologic data is suggestive, but not diagnostic of vertical transmission
- Virologic data suggestive, but still remote from birth (earliest so far 16h)
- More data is needed
  - Comprehensive infant testing at appropriate times
  - Duration of viral shedding and infectivity in different tissues
  - Time course of antibody development
  - First and second trimester infections
Thank You!

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