Vertical Transmission of SARS-CoV-2

An update

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Disclosures

None

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CAUTION

The data presented here is most likely already outdated.

(April 21, 2020)

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

English language, PubMed (LitCovid)

"Covid-19", "SARS-CoV-2", "pregnancy", "newborn"

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

We currently lack data for 1st and 2nd trimester infections

Country	# Papers	# Cases
China	28*	317
USA	6	81
Italy	2	43
S. Korea	2	2
Iran	2	2
Australia	1	1
Spain	1	1
Honduras	1	1
Sweden	1	1
Turkey	1	1
Peru	1	1
TOTAL	**44**	**451**

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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

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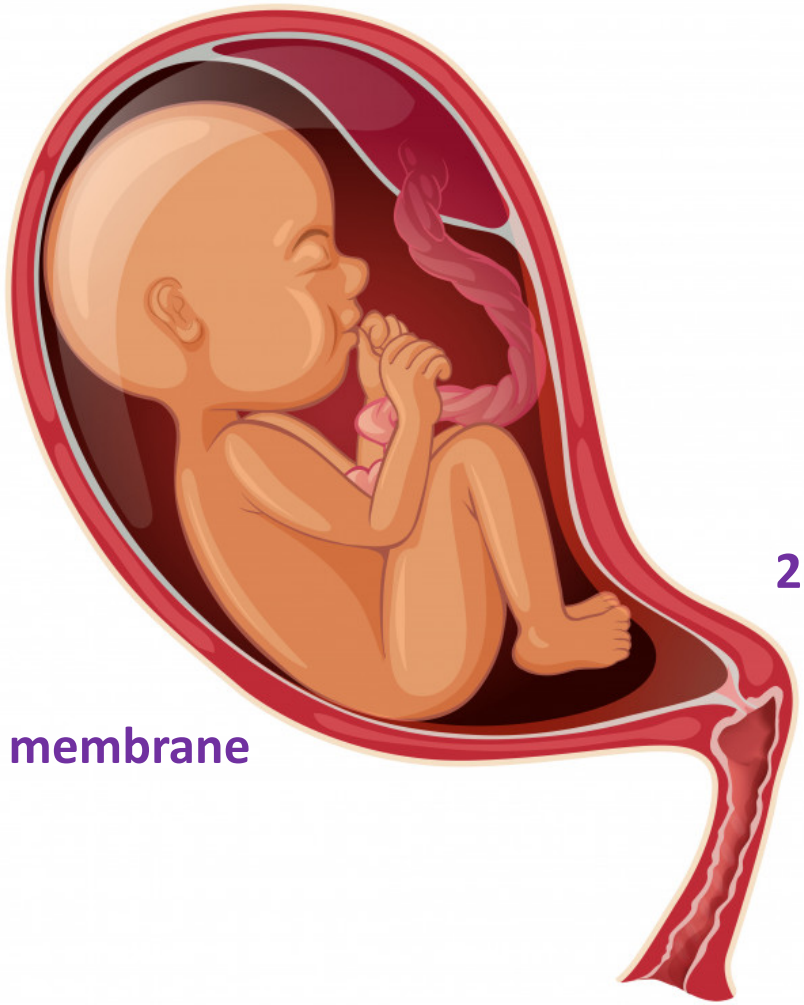
Routes of Vertical Transmission

1. Placenta



2. Cervix/vagina

3. Amniotic membrane

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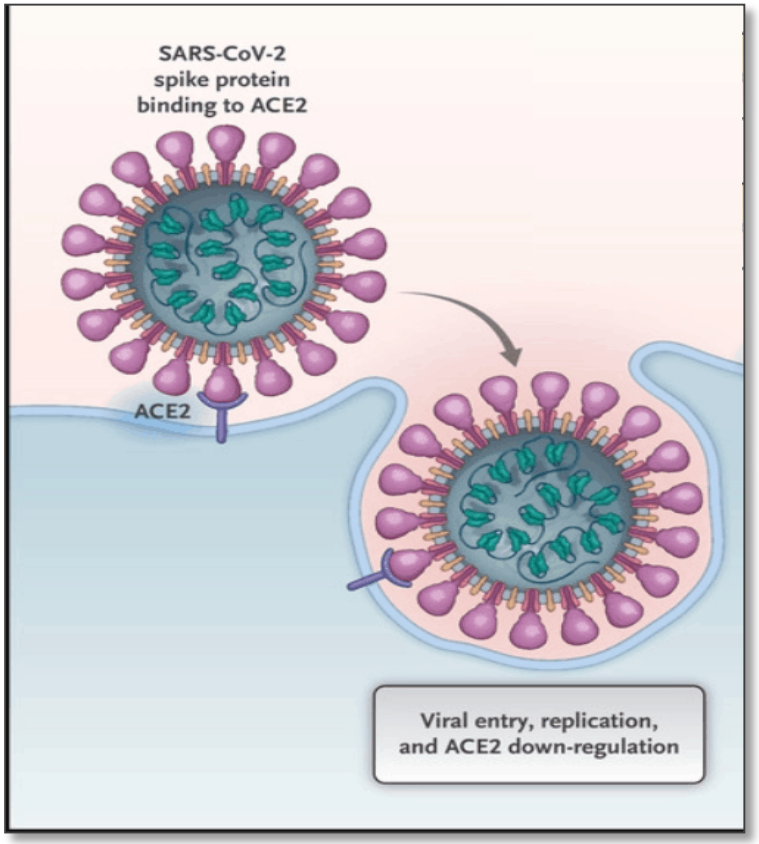
https://www.freepik.com/free-photos-vectors/baby

Angiotensin-converting Enzyme 2 (ACE2): The human receptor for SARS-CoV-2



Vaduganathan et al., *NEJM* 2020

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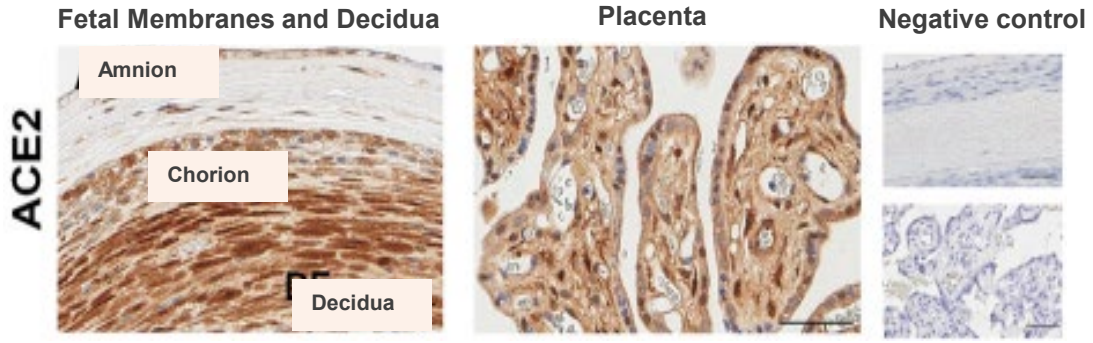
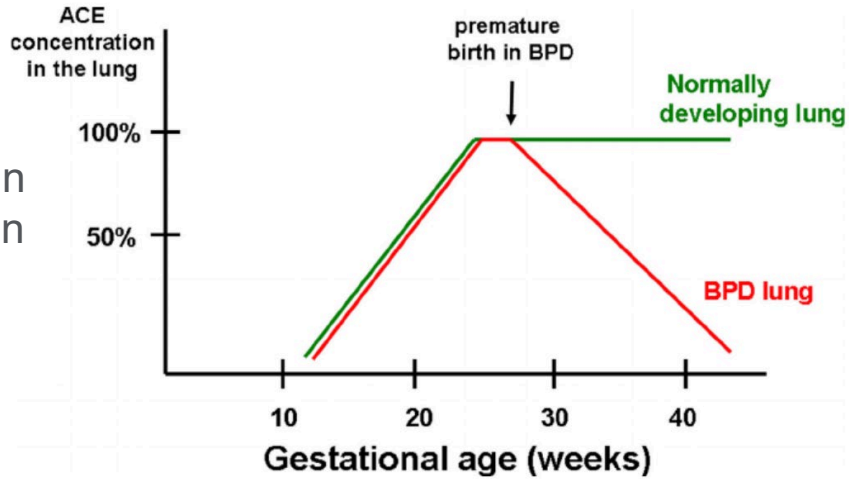
ACE2 expression in maternal-fetal tissue

ACE2 mRNA expression in fetal membranes and placenta at term



Marques et al., *Placenta.* 2011

ACE2 protein expression in fetal lung



Castro et al., *Pediatr. Pulmon.* 2014

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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)

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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

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Serologic evidence

Evidence of humoral immune response to virus (exposure)

Accuracy of serologic testing still needs to be widely validated.

- Test performance
- Cross-reactivity

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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

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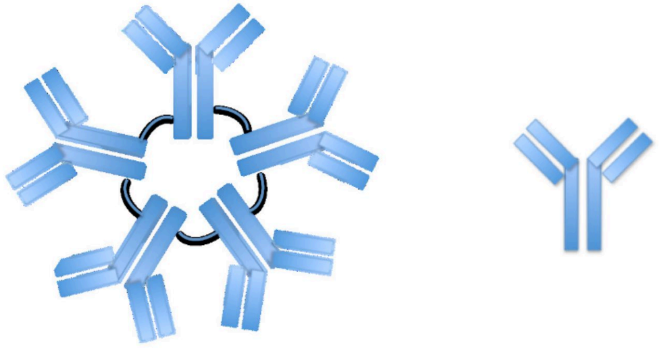
Dong et al., *JAMA.* 2020
Zeng et al., *JAMA.* 2020

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

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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*

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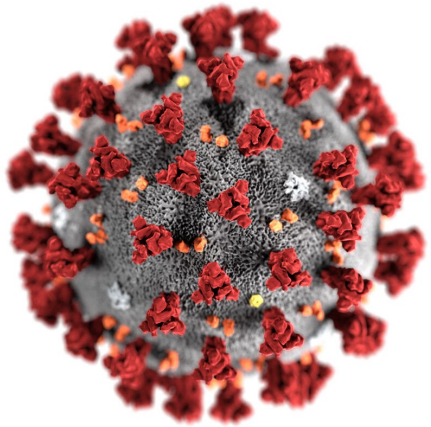
Virologic evidence for vertical transmission



Tissue samples

- 0/25 amniotic fluid
- 0/12 placenta
- 0/41 cord blood
- 0/20 neonatal gastric aspirate
- 5/44 neonatal stool

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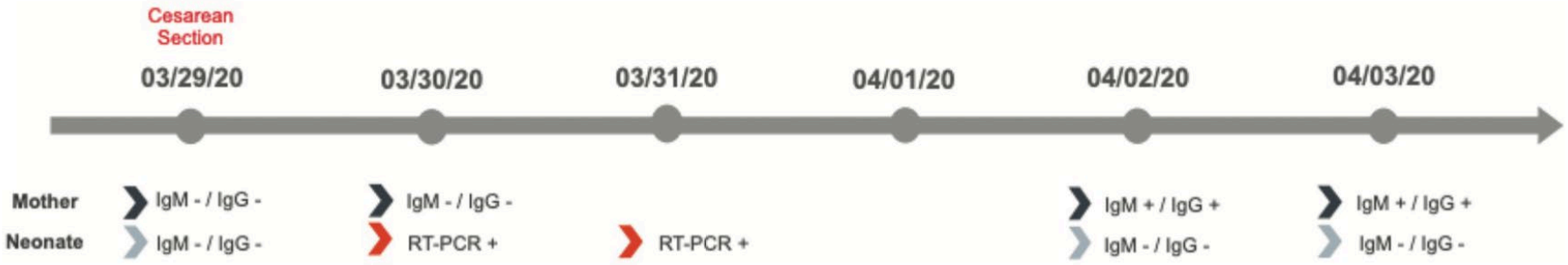
Virologic evidence for vertical transmission

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



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Alzamora et al., *Am J. Perinat.* 2020

So how can we better define a *true* case of vertical transmission?

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SPECIAL EDITORIAL

AOGS
Acta Obstetricia et Gynecologica Scandinavica

Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates

Shah et al., *Acta Obstet Gynecol Scand.* 2020

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

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Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates

Shah et al., *Acta Obstet Gynecol Scand.* 2020

	Congenital		Neonatal Intrapartum		Postpartum
Category	+ Infant Sx	No Infant Sx	+ Infant Sx	No Infant Sx	+ Infant Sx ≥48h
Confirmed	+ cord blood *or* + neo blood ≤12h *or* + amniotic fluid	+ cord blood *or* + neo blood ≤12h	+NP at birth *and* 24-48h *and* no other cause	+NP at birth *and* 24-48h	- NP at birth +NP *or* + rectal swab ≥48h
Probable	+ NP at birth *and* + placenta	+ amniotic fluid *BUT* - cord blood/neo blood ≤12h	+NP at birth - NP 24-48h *and* no other cause		
Possible	- NP at birth *BUT* + IgM in cord blood *or* +IgM neo blood ≤12h *or* + placenta	+ IgM cord blood *or* + placenta *BUT* - cord blood/neo blood ≤12h	- NP at birth + Other test^ *and* no other cause	+NP at birth - NP 24-48h	No birth test +NP *or* + rectal swab ≥48h
Unlikely	- NP at birth, cord blood, neo blood ≤12h, amniotic fluid *BUT* no serology testing	- NP at birth, cord blood, neo blood ≤12h, amniotic fluid *BUT* no serology testing	- NP at birth - Other test^ *and* no other cause		
Not infected	- NP at birth/cord blood/neo blood ≤12h/amniotic fluid *and* - IgM in cord or neo blood ≤12h	- NP at birth/cord blood/neo blood ≤12h/amniotic fluid *and* - IgM in cord blood	- NP at birth - Other test^ *and* other cause found	- NP at birth - Other test^	+NP *or* + rectal swab ≥48h *and* other cause found

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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

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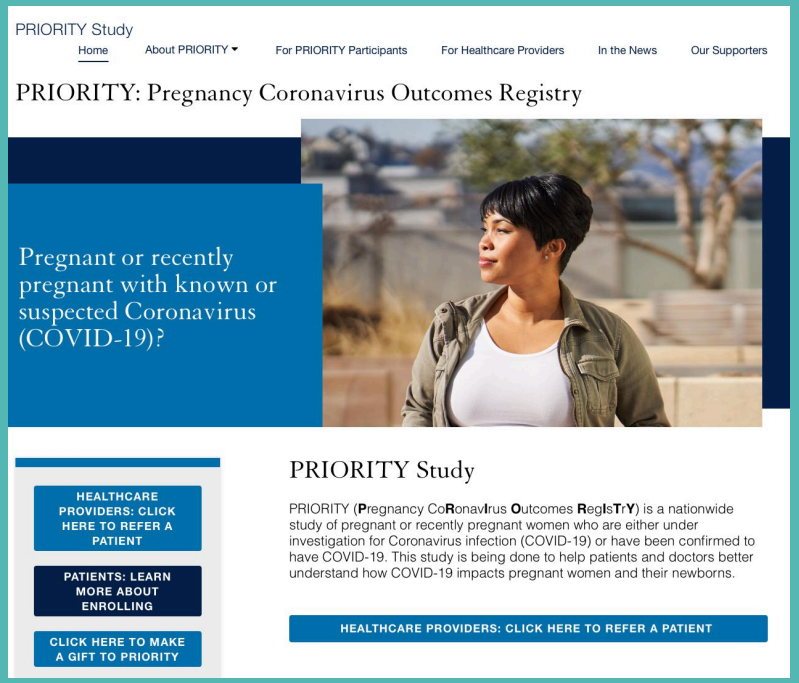
Thank You!

Questions: stephanie.gaw@ucsf.edu



https://priority.ucsf.edu/