

COVID-19 in Pregnancy and Possible Mother-to-Child SARS-CoV-2 Viral Transmission

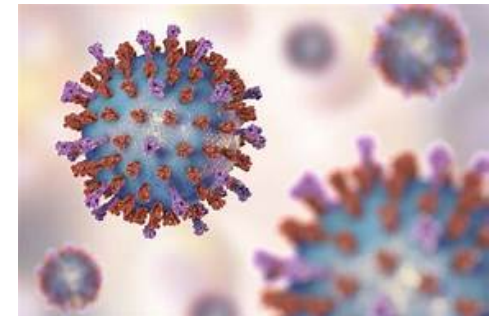
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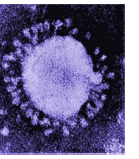
PRELIMINARY

Data Still Continue to be Preliminary, Some of Poor Quality, and Change Almost Daily





Are Pregnant Women More Likely to Acquire SARS-CoV-2?



- Most overall population studies **do not provide pregnancy status** for females.
- While initial data from CDC did not suggest higher prevalence in pregnant women (*CDC COVID-19 Response Team. MMWR. 2020 Mar 31*), some more recent data is of concern.
- In a study of universal pre-procedural SARS-CoV-2 rtPCR tests before all surgeries or deliveries in 5,543 persons in St. Louis hospital May-July 2020, positivity rates were higher in Ob than Surgical unit patients (*Kelly JC et al. Am J Obstet Gynecol. 2020 Sep 21:S0002-9378(20)31102-9*).

	Ob Unit (N=532)	Surgical Unit (N=5,011)	Adjusted* OR
Asx SARS-CoV-2 +	25 (4.7%)	14 (0.3%)	4.7 (2.3-10.6)

*Adjusted for age, race

- CDC recently reported 9% of reproductive-aged women (8,207/91,412) with lab-proven SARS-CoV-2 between Jan-June were pregnant; this was higher than expected, as CDC estimates ~5% of women aged 15-44 years are pregnant at a given point in time (*Ellington S et al. MMWR 2020 Jun;69:769-75*).
- Data are currently insufficient** to draw conclusions pregnancy status and susceptibility to SARS-CoV-2 infection.

Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

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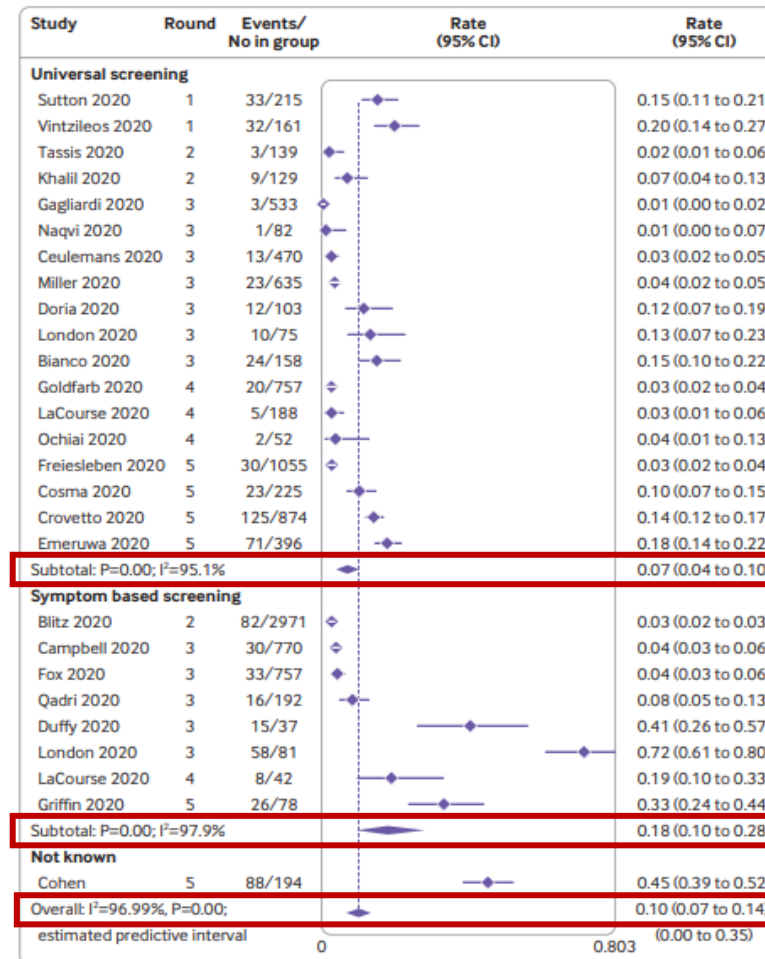
Prevalence of SARS-CoV-2 Infection in Pregnant Women, by Sampling Strategy

Allotey J et al. *BMJ*. 2020 Sep 1;370:m3320

- Systematic review; prevalence of positive SARS-CoV-2 rtPCR in 26 studies including 11,432 pregnant women attending or admitted to hospital

→ Overall 10% prevalence SARS-CoV-2 infection in pregnant women hospitalized in pandemic locales

→ Infection prevalence rates >15 % were all from US, except 1 study from France.

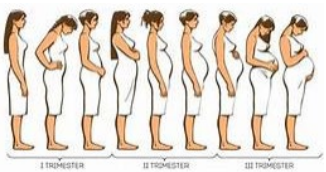


Universal screening: rtPCR of all pregnant women presenting at labor/delivery.

- Prevalence 7% (95% CI 4-10%)

Symptom-based: rtPCR only if symptoms of infection or history of close contact to individual with infection.

- Prevalence 18% (95% CI 10-28%)

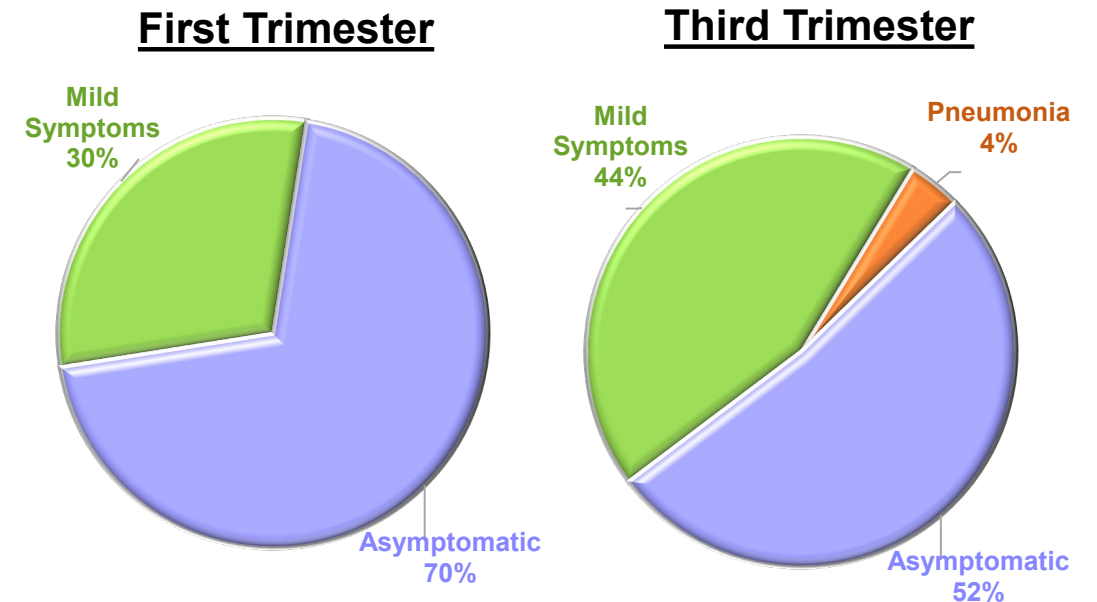


Prevalence of SARS-CoV-2 Antibody by Gestational Age

Crovetto F et al. Lancet. 2020 Aug;396:530-1

- Evaluated SARS-CoV-2-specific IgG/IgM/IgA in 372 pregnant women consecutively attending first trimester screening (10-16 wk GA) or 502 in third trimester (delivery) at 3 hospitals in Barcelona Spain Apr 14-May 5 2020.
- 125/874 (14%) were sero-positive.

	1 st T (N=372)	3 rd T (N=502)	P value
SARS-CoV-2 antibody +	54 (15%)	71 (14%)	NS
Asymptomatic	38 (70%)	37 (52%)	0.012
Hospitalization	0	7 (10%)	0.019

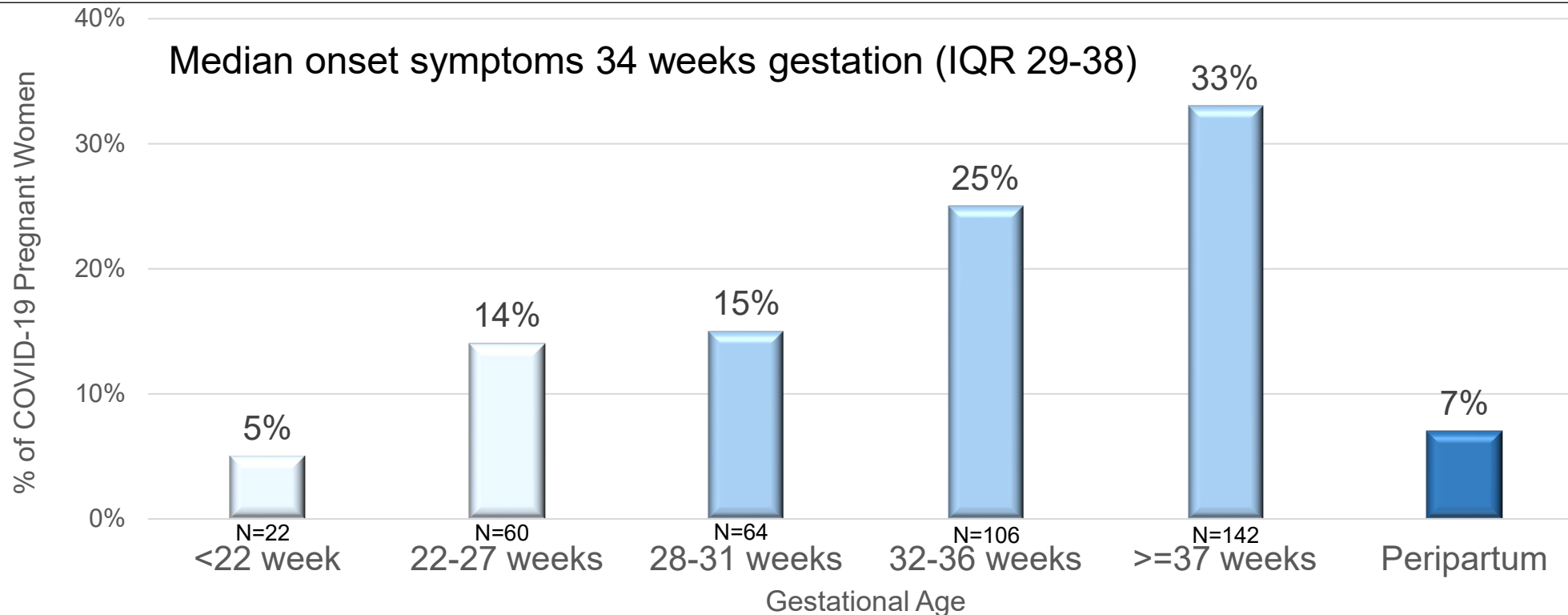


→ Symptomatic infection and hospitalization were more significantly more frequent in women with positive SARS-CoV-2 serology in 3rd trimester compared to 1st.



Most Women Have Symptom Onset in Third Trimester: 424 Pregnant Women Hospitalized with COVID-19, UK

The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group, BMJ in press



- Majority (73%) presented in 3rd trimester (21% were early 3rd, 28-31 weeks).
- 7% didn't have symptoms until in labor or immediately postpartum.
- 161 still pregnant after recovery.



As Seen in Overall Population, Disproportionate Rate of SARS-CoV-2 Infection Among Pregnant Women of Color

- Universal SARS-CoV-2 rtPCR testing of pregnant women delivering in Chicago; 7.7% + (Sakowicz A. *Am J Ob Gyn MFM*. 2020 Aug;100198)

Maternal characteristic	SARS-CoV-2 status		P value
	SARS-CoV-2 negative (n=1317)	SARS-CoV-2 positive (n=101)	
Race (n=1417)			<.001
Asian	104 (7.9)	3 (3.0)	
Black or African American	141 (10.7)	28 (28.0)	
White	772 (58.6)	23 (23.0)	
Other or unknown	300 (22.8)	46 (46.0)	
Latina ethnicity (n=1341)	244 (19.7)	53 (53.5)	<.001

→ Compared to women with negative result, rtPCR positive women more likely Black or Latina

- SARS-CoV-2 seroprevalence in 1,293 pregnant women delivering in Philadelphia; 6.2% IgG/IgM + (Flannery DD. *Sci Immunol*. 2020;5:eabd5709).

Characteristics	Total (n = 1293)	Seropositive* (n = 80)
Race/ethnicity, n (%) [†]		
Black/non-Hispanic	537	52 (9.7)
White/non-Hispanic	447	9 (2.0)
Hispanic/Latino	125	13 (10.4)
Asian	106	1 (0.9)
Other/unknown [‡]	78	5 (6.4)

→ Higher rates SARS-CoV-2 sero-positivity in Hispanic and Black women (10%) vs White (2%)

- National cohort of 427 pregnant women admitted to hospital with SARS-CoV-2 in the UK (Knight M. *BMJ*. 2020;369:m210)

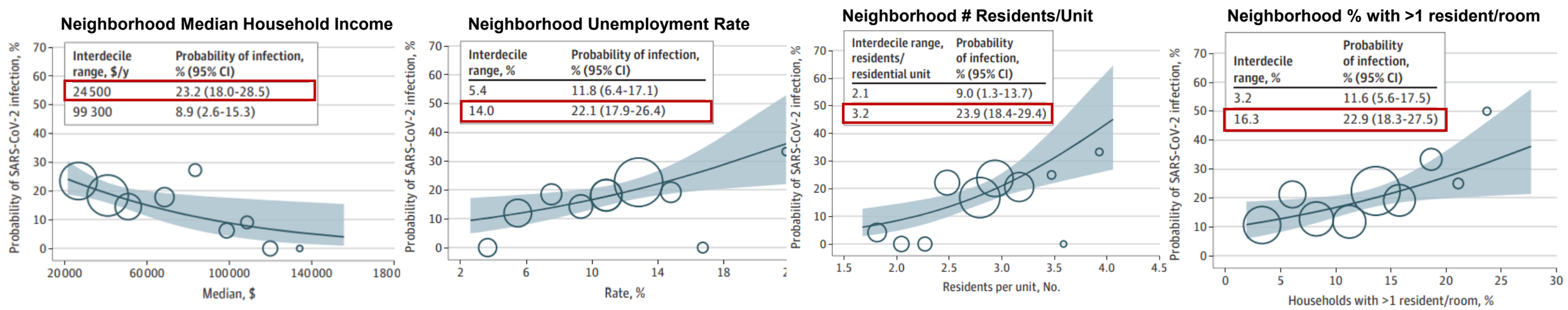
Characteristic	No (%) [*] of women (n=427)
Black or other minority ethnic group (all)	233 (56)
Asian	103 (25)
Black	90 (22)
Chinese/other	30 (7)
Mixed	10 (2)

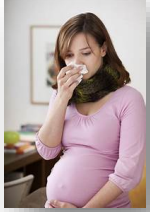
→ 56% of pregnant women admitted to hospital with SARS-CoV-2 were from Black or ethnic minority groups

Importance of Sociodemographic Factors in SARS-CoV-2 Infection: Evaluation of Factors for Infection in Pregnant Women, New York City

Emeruwa UN et al. JAMA. 2020 Jul;324:390-2

- Cross-sectional evaluation of 434 NYC pregnant women delivering at 2 NYC hospitals doing universal SARS-CoV-2 viral screening; 71 (18%) tested positive.
- Able to link 396 of those tested (91%) to SES and demographic data; probability of infection associated with:



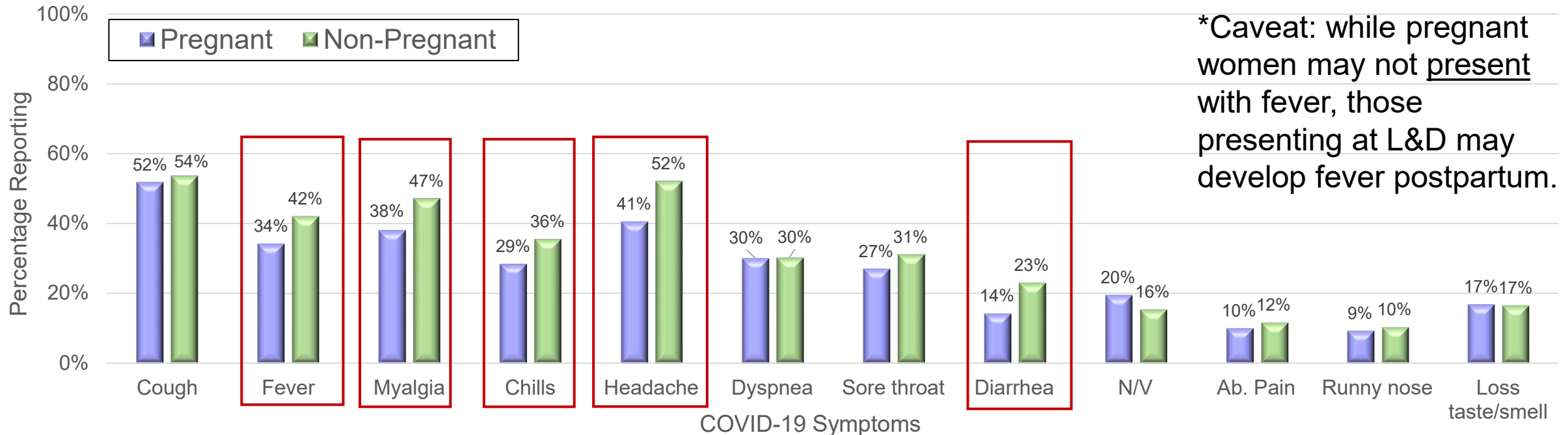


Do Symptoms Differ in Pregnant vs Non-Pregnant Women with COVID-19?



Ellington S et al. *MMWR*. 2020 Jun;69:769-75

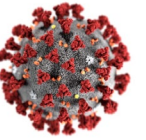
- CDC compared COVID-19 disease among 8,207 pregnant and 83,205 non-pregnant women of reproductive age in US with positive SARS-CoV-2 rtPCR reported January 22-June 7 2020.



- Symptomatic pregnant and nonpregnant women with COVID-19 reported similar frequencies cough (>50%) and dyspnea (30%), but pregnant women less frequently reported fever, muscle aches, chills, headache and diarrhea.



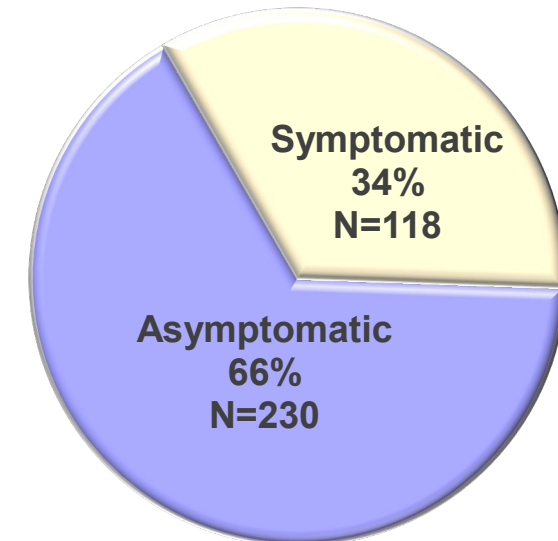
Universal Screening for SARS-CoV-2:



Majority of Infected Pregnant Women Are Asymptomatic

Author	Country	Total n	% + rtPCR	% Asymptomatic
Sutton	US (NY)	214	15.4% (n=33)	73.3% (n=29)
Vintzileos	US (NY)	161	19.9% (n=32)	65.6% (n=21)
Campbell	US (CT)	770	3.9% (n=30)	73.3% (n=22)
Goldfarb	US (Boston)	757	2.6% (n=20)	45% (n=9)
LaCourse	US (Seattle)	188	2.7% (n=5)	20% (n=1)
Buckley	US (NY)	160	17.9% (n=5)	100% (n=5)
Blitz	US (NY)	375	17.1% (n=64)	70.3% (n=45)
Ferrazzi	Italy (Milan)	1566	3.1% (n=49)	55.1% (n=27)
Miller	US (Chicago)	635	3.6% (n=23)	43.5% (n=10)
Berkowitz	US (Ohio)	492	2.0% (n=10)	70% (n=7)
Fassett	US (CA)	3923	0.4% (n=17)	100% (n=17)
Khalil	UK (London)	129	7.0% (n=9)	88.9% (n=8)
Doria	Portugal (North)	103	11.7% (n=12)	91.6% (n=11)
Ochiai	Japan (Tokyo)	52	3.8% (n=2)	100% (n=2)
Diaz-Corvillon	Chile (Santiago)	583	6.4% (n=37)	43% (n=16)

- 15 papers reporting on universal nasopharyngeal SARS-CoV-2 rtPCR testing of 10,108 women presenting in labor in hospitals in midst of COVID-19 pandemic
- 348 (3.4%) were positive on SARS-CoV-2 rtPCR.



Sutton et al., *N Engl J Med* 2020; 382:2163-2164
 Vintzileos et al., *Am J Obstet Gynecol* 2020;223:284-6
 Campbell KH et al., *JAMA* 2020;323:2520-2.
 Goldfarb et al., *Inf Contr Hosp Epidemiol.* 2020;41:1095-6
 LaCourse SM et al. *Clin Infect Dis.* 2020 May 30;ciaa675
 Buckley A et al. *Am J Obstet Gynecol MFM.* 2020 Aug;2:100147
 Blitz MJ et al. *Am J Obstet Gyencol MFM.* 2020;2:100169

Ferrazzi E et al., *J Matern Fetal Neonatal Med.* 2020 Jul 13;1-3
 Miller ES et al. *Obstet Gynecol.* 2020;136:232-4.
 Berkowitz KM et al. *Am J Obstet Gynecol.* 2020 Jul:S0002-9378(20)30729-8
 Fassett MJ et al. *Am J Perinatol.* 2020;37:1110-4
 Khalil A et al. *Am J Obstet Gynecol.* 2020;223:296-7
 Doria M et al. *Eur J Obstet Gyn Repro Bio.* 2020;250:261-2
 Ochiai D et al. *Int J Gyn Obstet.* 2020;150:268-9.
 Diaz-Corvillon P et al. *PLoSOne.* 2020;15:e0239887

Risk Factors for Hospitalization with COVID-19 in Pregnancy

The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group (UKOSS). BMJ 2020 Jun 8;369:m2107

- Population-based surveillance system, including all 194 maternity units in the UK.
- Between March 1 – April 14, 2020, 86,293 pregnant women admitted to maternity units; 427 (5%) had confirmed SARS-CoV-2 infection.

Estimated incidence hospitalization with SARS-CoV-2 in pregnancy in different population subgroups

	Incidence/1000 pregnant women	Adjusted Odds Ratio (95% CI)
Black	28.4 black vs 3.5 white	8.1 (6.2-10.5)
Age ≥ 35 years	8.8 age ≥ 35 yr vs 3.9 age 20-34 yr	2.3 (1.8-2.7)
BMI 25-<30 - overweight	6.8 BMI 25-30 vs 3.5 BMI <25	2.0 (1.5-2.5)
BMI >30 - obese	8.7 BMI ≥ 30 vs 3.5 BMI <25	2.5 (2.0-3.2)



Are Pregnant Women With COVID-19 Disease More Likely to be Admitted to Hospital?



- Early data from systematic reviews and CDC reports suggested pregnant women had similar COVID-19 disease course as nonpregnant adults (*Huntley B JF et al. Obstet Gynecol. 2020;136:303-12; CDC COVID-19 Response Team. MMWR. 2020 Apr;69:382-6*)



- However, are all non-pregnant adults the correct comparison group?

- Significant relation of age with disease severity: outcomes of COVID-19 patients reported in US broken down by age (*Garg S et al. MMWR 2020 Ap 8*):
 - Lower rates hospitalization, ICU admission, mortality in 20-44 yr (childbearing) age group.
- More recent studies demonstrated increased rate of hospitalizations, ICU care, and mechanical ventilation, but not death, in pregnant women vs age-matched nonpregnant controls.

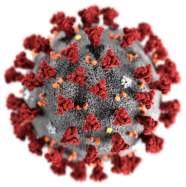
TABLE. Hospitalization, intensive care unit (ICU) admission, and case-fatality percentages for reported COVID-19 cases, by age group — United States, February 12–March 16, 2020

Age group (yrs) (no. of cases)	%*		
	Hospitalization	ICU admission	Case-fatality
0–19 (123)	1.6–2.5	0	0
20–44 (705)	14.3–20.8	2.0–4.2	0.1–0.2
45–54 (429)	21.2–28.3	5.4–10.4	0.5–0.8
55–64 (429)	20.5–30.1	4.7–11.2	1.4–2.6
65–74 (409)	28.6–43.5	8.1–18.8	2.7–4.9
75–84 (210)	30.5–58.7	10.5–31.0	4.3–10.5
>85 (144)	31.3–70.3	6.3–29.0	10.4–27.3
Total (2,449)	20.7–31.4	4.9–11.5	1.8–3.4

* Lower bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group; upper bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group with known hospitalization status, ICU admission status, or death.



More Severe COVID-19 in Pregnant vs Non-Pregnant Women of Reproductive Age: US



Ellington S et al. MMWR. 2020 Jun;69:769-75

- Compared severity of COVID-19 disease among 8,207 pregnant and 83,205 non-pregnant women of reproductive age with positive SARS-CoV-2 rtPCR reported to CDC in US January 22-June 7 2020.

Comparison of Outcomes, Pregnant vs Non-Pregnant Women with COVID-19

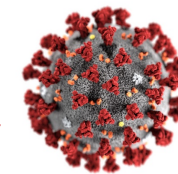
	Pregnant women (N=8,207)	Non-pregnant women (N=83,205)	Adjusted* Rate Ratio (95% CI)
Hospitalization	2,587 (31.5%)	4,840 (5.8%)	5.4 (5.1-5.6)
ICU admission	120 (1.5%)	757 (0.9%)	1.5 (1.2-1.8)
Mechanical ventilation	42 (0.5%)	225 (0.3%)	1.7 (0.1-2.4)
Death	16 (0.2%)	208 (0.2%)	0.9 (0.5-1.5)

*Adjusted for age as continuous variable, yes/no for underlying condition, and race/ethnicity; non-pregnant women are referent group.

- Older age risk factor for severity; when stratified by age, all outcomes more frequent among women aged 35-44 years than among those aged 15-34 years.



More Severe COVID-19 in Pregnant vs Non-Pregnant Women of Reproductive Age: Living Systematic Review



Allotey J et al. *BMJ*. 2020 Sept;370:m3320

- Living systematic review University Birmingham UK – identified 77 papers including 13,118 pregnant women and 83,486 non-pregnant women of reproductive age hospitalized with COVID-19.

Comparison of Outcomes, Pregnant vs Non-Pregnant Women with COVID-19

	No. Studies	Pregnant women	Non-pregnant women	Odds Ratio (95% CI)
ICU admission	4	121/8,276 (1.5%)	758/83,330 (0.9%)	1.6 (1.3-2.0)
Mechanical ventilation	4	43/8,276 (0.5%)	226/83,330 (0.3%)	1.9 (1.4-2.6)
Maternal death	4	16/8,282 (0.2%)	208/83,327 (0.2%)	0.81 (0.5-1.3)

- Older age (≥ 35 years), high body mass index and pre-existing co-morbidity (hypertension, diabetes) were risk factors for severity of COVID-19 in pregnancy.



Is Pregnancy Outcome Modified by COVID-19 Disease?

The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy

Collaborative Group (UKOSS). BMJ 2020 Jun 8;369:m2107

(see also <https://doi.org/10.1101/2020.05.08.20089268>)



- Population-based surveillance system, 427 pregnant women admitted had confirmed SARS-CoV-2 infection between March-April 2020.
- Comparison cohort from a previous study of seasonal influenza in pregnancy.
 - Control group: defined as 2 women without influenza who gave birth immediately prior to any woman hospitalized with confirmed influenza between 11/1/2017 and 10/31/2018.



Pregnancy Outcome in Women With vs Without COVID-19

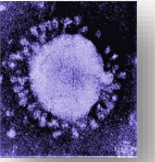
	COVID-19 cases N=427	Comparison non-COVID-19 N=694
Ongoing pregnancy	161(38%)	
Pregnancy outcome	266 (62%)	694
Pregnancy loss	4 (0.9%)	2 (0.3%)
Stillbirth	3 (0.7%)	2 (0.3%)
Had live birth	259 (265 infants)	690 (703 infants)
Mode delivery C/S	156 (60%)¹	201 (29%)
Preterm <37 weeks	66/259 (26%)²	57/690 (8%)
32-36 weeks	16%	6%
28-31 weeks	6%	1%
22-27 weeks	2%	1%
<22 weeks	2%	<1%

¹ 51% due to maternal compromise from COVID-19 (27%) or fetal concerns (24%).

² Most preterm deliveries (53/66, 80%) iatrogenic – 32 (48%) due to maternal COVID-19 disease, 9 (14%) fetal compromise, 12 (18%) other obstetric indication.



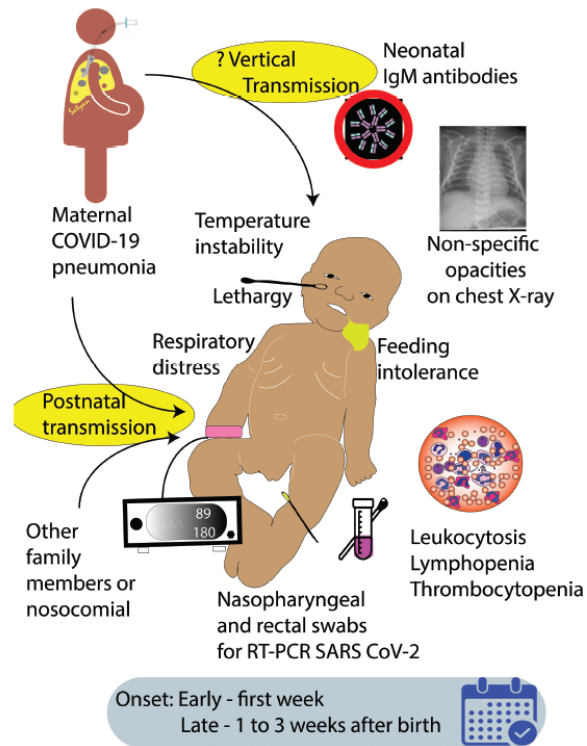
Outcomes in Infants Born to Women With vs Without COVID-19



The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group (UKOSS). BMJ 2020 Jun 8;369:m2107

- There were 265 live-born infants born to 259 pregnant women hospitalized with COVID-19 in UKOSS.
 - 67/265 infants (25%) were admitted to neonatal intensive care unit; this compared to 37/703 (5%) non-COVID births.
 - Most admissions (50/67), 75%, were due to complications prematurity, including 23 infants born at <32 weeks gestation.
 - 2 neonatal deaths, 0.8%, neither directly related to COVID-19 (due to prematurity).

Is There Mother to Child Transmission?



→ *Is MTCT feasible?*

→ *What data do we have to date?*



What are Requirements for *In Utero* Transmission?

- *In utero* infection requires the **pathogen to be able to *reach* and *cross* the placenta and to *infect* the fetus.**
 - Is there **viremia** to enable the virus to reach placenta?
 - Rarely – 21/587 (3.6%) samples, 8 studies; ↑ likelihood severe disease
 - Are there receptors for SARS-CoV-2 in the **placenta**?
 - ACE2 & TMPRSS2 found in placenta, late>early, but co-expression may be minimal (other proteases present and could substitute for TMPRSS2).
 - Are there receptors for SARS-CoV-2 in the **fetus** to enable infection of fetus?
 - ACE2 & TMPRSS2 in fetal lung (peak mid-gestation), heart, liver
 - Is there **placental disruption** to allow viral passage *without* placenta infection?
 - Possible due to coagulopathy – in one study, 10/20 placentas showed some evidence of vascular malperfusion or fetal vascular thrombosis.

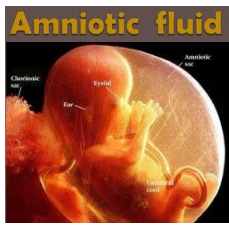


Does Finding Virus by PCR in the Placenta Always Indicate Infection of the Fetus?



Example of HIV

- CD4 receptor found in placenta and fetus, and HIV shown to be capable of infecting placental trophoblast cells, Hofbauer cells.
- However, the presence of HIV antigen in the placenta did not always correlate with infection of the infant (*Mattern CF et al. Pediatrics. 1992;89:207-9; Backe E et al. Am J Perinatol. 1994;11:326-30*).
 - 19 placentas **positive** HIV PCR: 14 uninfected, 5 infected infants
 - 48 placentas **negative** HIV PCR: 43 uninfected, 5 infected infants
- Thus, for HIV, definition of HIV infection of infant requires confirmed positive PCR **on infant blood samples**.



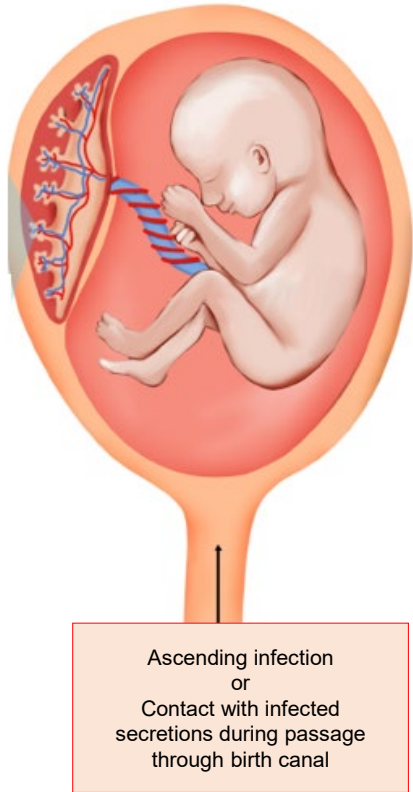
Does Finding Virus by PCR in the Amniotic Fluid Always Indicate Infection of the Fetus?

- Various viruses have been detected by PCR in amniotic fluid of low-risk pregnancies *without* evidence fetal disease:
 - Prospective study of women at *low risk* for viral infection referred for 2nd trimester genetic amniocentesis; PCR for CMV, parvovirus, adenovirus, enterovirus, HSV, RSV and EBV performed.
 - 44/686 (6.4%) samples were positive for ≥ 1 virus (adenovirus most common); pregnancy and perinatal outcomes **did not differ** between those with or without positive PCR.
 - Positive viral PCR **not associated** with elevated IL-6 cytokine levels in amniotic fluid (suggesting fetal inflammation/infection) or pregnancy loss.
- Amniotic fluid detection of virus by PCR does not necessarily mean fetal infection.

- Baschat AA et al. Prevalence viral DNA in amniotic fluid of low-risk pregnancies in the second trimester. *J Matern Fetal Neonatal Med.* 2003;13:381-4
- Wenstrom KD et al. Intrauterine viral infection at the time of second trimester genetic amniocentesis. *Obstet Gynecol.* 1998;92:420-4.
- Miller JL et al. Perinatal outcomes after second trimester detection of amniotic fluid viral genome in asymptomatic patients. *J Perinat Med.* 2009;17:140-3.

What Are Requirements for Intrapartum Transmission?

- Intrapartum transmission requires fetal/infant exposure to the pathogen during labor and delivery (**contact with infectious blood/secretions** during passage through the birth canal) and for **pathogen to infect** the newborn.
 - Is SARS-CoV-2 found in **vaginal fluids**?
 - Rarely - 2/69 pregnant women + at delivery, 15 studies
 - Is SARS-CoV-2 found in **feces**?
 - **Frequently** - >40% have fecal + PCR
 - If SARS-CoV-2 is found by PCR, is it **infectious**?
 - Unclear – in 5 studies, infectious virus found in 35% (6 of 17 patients).

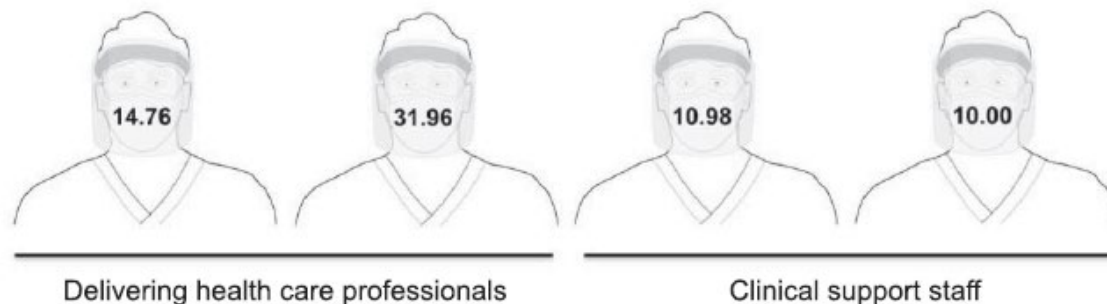


SARS-CoV-2 Environmental Contamination and Childbirth

Hermesch AC et al. *Obstet Gynecol.* 2020 Oct;136:827-9

- U. Oregon hospital collected environmental swabs from room surfaces and health care worker face-shield and air in births from 4 asymptomatic women who tested SARS-CoV-2 positive (2 vaginal, 2 cesarean deliveries).
- In baseline empty room samples, positive PCR was detected in 3/45 (7%) surface and 1/23 (4%) air samples. After delivery, this increased to 8/45 (18%) surface and 5/23 (22%) air samples, with greatest change vaginal birth.
- Post-delivery face shield samples were positive in all health care workers with vaginal birth, none with cesarean births.

SARS-CoV-2 Copy Number per Face Shield Swab (copies/mL), Vaginal Birth

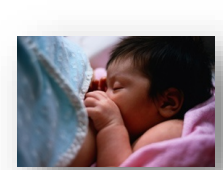




What Are Requirements for Breast Milk Transmission?

- Postnatal transmission through breastfeeding requires infant exposure to **infectious breast milk** and infant infection via **oral or gastrointestinal** route.
 - Has SARS-CoV-2 been detected by **rtPCR in breast milk**?
 - **Rarely** – 20/196 milk samples (10%) from 10/85 women (12%) positive by PCR, generally **transiently**, in 12 studies
 - If so, is the virus **infectious**?
 - **No replication-competent virus** in 1 + PCR milk sample (Chambers C et al. JAMA. 2020 Aug 20)
 - 2 cases of infants fed +PCR milk, uninfected (Buonsenso D Am J Perinatol 2020 May 2; Lugli L Pediatrics 2020)
 - 2 cases of infant fed +PCR milk, infected while breastfeeding, but mother infected postpartum, horizontal tx cannot be excluded (Grob R. Lancet 2020 May 21, Bertino E Lancet 2020)25)

Virus in milk: 3 studies cited by Lackey KA et al. *Matern Child Nutr.* 2020 May 30:e13032 [1+ in 48 samples in 32 women]; Bastug A et al. *Breastfeeding Med.* 2020 Jul 1. [3+ in 3 samples in 1 woman +d 1, 3, 4]; Grob R et al. *Lancet* 2020 May 21. [3+ in 7 samples in 1 woman +d 10, 12 13; 0 of 4 samples in 1 woman]; Buonsenso D et al. *Am J Perinatol.* 2020 May 2. [3+ of 10 samples in 1 woman +d1, 2, 4; 0 of 10 samples 1 woman]; Fenizia C et al. *COVID IAS Virtual July 2020 Track A* [1+ of 10 samples in 10 women]; Chambers C et al. *JAMA.* 2020 Aug 20 (1+ of 64 samples/18 women); Bertino E et al. *Lancet* 2020 Aug 20 preprint (1+ in 18 samples in 12 women); Lugli L et al. *Pediatrics* 2020 Aug 25 (2+/ 2 samples in 1 woman); Costa S et al. *Clin Microbio Infect* 2020 Jun 2 (3+ in 6 samples 1 woman, 0/6 in 1 woman); Zhu C et al. *J Infect* 2020;81:470-3 (2+ in 1 woman, 0 of 6 samples in 4 women)



What Are Requirements for Breast Milk Transmission?

- Has SARS-CoV-2 infection via oral/GI tract been shown? – Not yet
- Is SARS-CoV-2 **antibody** found in breast milk?
 - SARS-CoV-2-specific IgG, IgM and IgA have been detected in breast milk in several studies

Antibody in milk: Lackey KA et al. *Matern Child Nutr.* 2020 May 30:e13032; Powell RL. COVID-19 IAS Virtual July 2019 Track A; Fenizia C et al. COVID IAS Virtual July 2020 Track A; van Keulen BJ et al. *MedRxiv.*2020 Aug 18

Published Definitions of SARS-CoV-2 Mother-to-Child Transmission:

- *Shah PS et al. Acta Obstet Gynecol Scand. 2020;99:565-8:* [Complex](#)
 - Maternal and infant infection, categories (confirmed, probable, possible, unlikely, not infected)
 - 4 infant classifications (*congenital with fetal death, congenital live birth, intrapartum, postpartum*)
 - Further stratified by *symptom status* of mother and infant
 - Assumes maternal status definitive or probable and occurs “in vicinity of childbirth”
- *Blumberg DA et al. Am J Perinatol. 2020;37:769-72 :* [Simplified](#)
 - Maternal infection within 14 d of birth to 2 days after
 - No categorization – infected or not
 - Symptoms *not* part of classification
 - *Persistence* important part of classification
 - 3 classifications:
 - *In utero*
 - *Intrapartum or early postnatal (combined)*: exposure to maternal blood, vaginal secretions, and/or feces or via respiratory route or due to direct contact with infected mother or other caregivers or potential transmission through breast milk
 - *Superficial exposure (transient)*: assumes SARS-CoV-2 virus may be transiently detected for up to 24 hours after birth due to superficial contamination or transient viremia or due to neonatal resuscitation in delivery room leading to aspiration of potentially infectious secretions into infant airway (respiratory, fecal)

Living Systematic Review: Potential SARS-CoV-2 Vertical Transmission Cases

- Preliminary review (**May 28**) – 87 papers including 869 infants
- 52/869 with suspect infection (6.0%): 49 positive rtPCR on respiratory secretions, 3 infants reported with IgM found in neonatal blood.
- However, major issues in most of these papers – for example:
 - Timing of maternal infection (25% first diagnosed postpartum)
 - Type sample (“throat” vs nasopharyngeal vs not specified)
 - Timing of infant testing (many done several days after birth)
 - Lack of confirmatory testing
 - Lack of placental/amniotic fluid testing
 - Lack of serologic testing in the virologic-positive children

Infant SARS-CoV-2 Testing

862 infants born to mothers with COVID-19 tested

13 (25%)
born to mother diagnosed **Postpartum**

- **Likely horizontal given maternal contact**

52 (6.0%)
suspected infection

Timing of specimen

39 (75%)
born to mother diagnosed **Antepartum**
(32 caesarean 7 vaginal)

- **Vaginal delivery could result in infant contamination or intrapartum transmission, so only 32 possible**

29 first + NP rtPCR age >24 hr

- **Cannot rule out intrapartum or horizontal transmission**

20 first NP rtPCR test age <24 hr

- **10 negative 1st test**, positive later tests
- **10 positive 1st test**, but no repeat test 9

8 first + NP rtPCR age ≤12 hr (3 studies)¹

- 5 caesarean, 3 vaginal delivery
- No testing of cord/neonatal blood, amniotic fluid or placenta
- 1 IgM **negative**
- Only 1 had repeat test, **negative at 36 hr**
- No symptoms

3 IgM antibodies age ~12 hr (2 studies)²

- 3 caesarean delivery
- rtPCR infant respiratory tests **negative**; 1 had multiple repeat tests negative, 2 no repeat
- No symptoms

¹ Knight M. *BMJ*. 2020;369:m2107

Carosso A. *Eur J Ob Gyn Repro Bio*. 2020;250:246-9
Liu W. *Front Med*. 2020 Apr 13

² Zeng H. *JAMA* 2020 Mar 26

Dong L. *JAMA* 2020 Mar 26

SARS-CoV-2 Detection in Other Tissue Samples

Placenta

6 positive (4 studies) ¹
/ 56 tested

- 1 was 2nd trimester miscarriage; amniotic fluid, cord blood, fetal tissue rtPCR **negative**
- Remaining 5 cases: all infant NP tests **negative**; no infant symptoms

Amniotic fluid

1 positive (1 study) ²
/ 62 tested

Possible?

- Infant fever at birth, treated antibiotics (maternal death 9 d PP)
- Vaginal fluid, cord blood **negative**; no placenta or IgM testing
- Infant birth NP specimen **negative**, although **positive** at 24 hr, 8 d

Cord blood

1 positive (1 study) ³
/ 65 tested

Possible?

- Infant no symptoms
- Placenta also positive and maternal breast milk positive but infant birth and 3 repeat NP samples **all negative**

¹ Buonsenso D. Am J Perinatol. 2020
Penfiled Am J Obstet Gynecol. 2020
Algarroba Am J Obstet Gynecol. 2020
Baud D. JAMA. 2020

² Zamaniyan M et al. Prenatal Diagn. 2020

³ Buonsenso D. Am J Perinatol. 2020

What Do These Data Tell Us About SARS-CoV-2 Mother-to-Child Transmission?

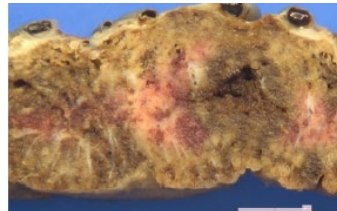


- Most studies have not obtained appropriate specimens at appropriate times or confirmed persistence of virus.
 - 59% reporting virus in respiratory specimens were obtained in infants age ≥ 1 day, and horizontal transmission cannot be ruled out.
- Virologic data consistent with *in utero* infection in only 2 of 52 possible cases to date:
 - One positive amniotic fluid - but negative birth infant blood and initial NP sample
 - One positive cord blood and placenta - but multiple negative infant samples
 - Of 8 with positive infant specimens near birth, in those tested was not persistent or IgM was negative
 - None with IgM positive near birth had positive infant specimens

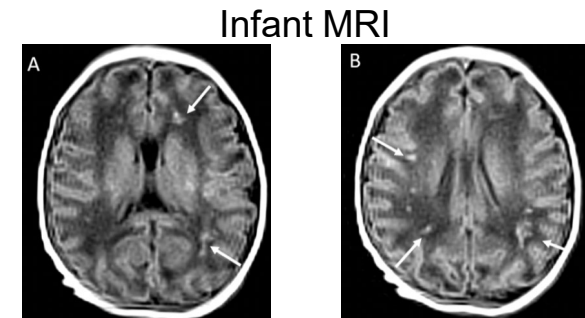
Very Recent Case of Apparent Well-Documented *In Utero* Infection

Vivanti A et al. Nat Commun. 2020 Jul 14;11:3572

- Mother 23 yrs, 35.2 wk GA, 2 days **moderate-severe illness** with lymphopenia, thrombocytopenia, elevated CRP and ferritin; SARS-CoV-2 detected in **blood**, NP and vaginal swab.
- Emergency CS: **amniotic fluid** (prior ROM) and **placenta positive** for SARS-CoV-2 PCR; **placenta path fibrin deposition and infarction**.
- Infant needed active resuscitation, extubated at 6 hours.
 - Before extubation, **blood and BAL fluid positive** SARS-CoV-2 PCR
 - **NP and rectal swab positive** PCR at 1 hour, 3 and 18 d PP.
- **Day 2 neurologic symptoms**, CSF sterile but 300 WBC; MRI at 11 days bilateral gliosis of deep white periventricular and subcortical matter (arrows).
- Discharged improved at 18 days.

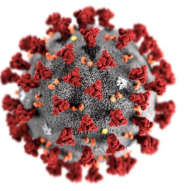


Placenta with infarction





Summary – COVID-19 in Pregnancy



- Many questions remain regarding pregnancy and COVID 19.
- Inconclusive data on whether pregnant women more likely to become infected.
- Pregnant women may be more likely to have severe disease; severe disease more common with obesity or underlying conditions.
- Severe COVID-19 in pregnancy may be associated with preterm delivery, but likely due to maternal disease/fetal distress; NICU admission appears more likely due to prematurity than infant infection.
- Effects on the embryo/fetus unclear.
 - Few reports of 1st trimester infection, so effects of early infection unknown.
 - Transplacental infection rare.
- Peripartum (intrapartum/early perinatal) can occur but uncommon, and no proven cases of breast milk transmission.
- In general, SARS-CoV-2-exposed infants appear to do well.

Thank You For Your Attention!

