



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Vertical transmission of SARS-CoV-2: consider the denominator



OBJECTIVE: More than 82,000 pregnant women in the United States have tested positive for SARS-CoV-2.¹ Published estimates of the incidence of vertical transmission—the passage of SARS-CoV-2 from the mother to her infant during pregnancy or childbirth—range from 1% to 3%, but these reports may be limited in their methodology.^{2–4} To date, the largest systematic review and meta-analysis reports a pooled estimate of 3.2%² and includes data from cohort studies and case series published early in the pandemic, when reports on outcomes of newborns with SARS-CoV-2 infection were urgently needed to guide clinical management and potentially overrepresented. Here, we provided additional data on vertical transmission from a multicenter cohort of pregnant women with SARS-CoV-2 infection.

STUDY DESIGN: Women with a positive nasopharyngeal polymerase chain reaction (PCR) for SARS-CoV-2 during pregnancy who delivered from March 22, 2020, to December 20, 2020, at 1 of 3 hospitals in Boston, MA—Massachusetts General Hospital (MGH), Brigham and Women's Hospital (BWH), and Beth Israel Deaconess Medical Center (BIDMC)—were included. These hospitals perform approximately 15,000 deliveries per year, accounting for approximately 75% of annual deliveries in Boston. The Mass General Brigham and BIDMC Institutional Review Boards approved this study. Some of the participants included in this study of vertical transmission have been included in previous studies describing different outcomes. Inpatient universal testing protocols for SARS-CoV-2 were in place in early April 2020 (MGH or BWH) or May 2020 (BIDMC). Outpatient testing was performed by clinical indication, that is, a known exposure or symptoms. Consistent with the American Academy of Pediatrics (AAP) guidelines released on April 2, 2020,⁵ neonatal testing by nasopharyngeal PCR was performed at 24 hours of life only in newborns of mothers with SARS-CoV-2 infection who were considered infectious at the time of delivery and at 48 hours or later at the discretion of the provider or infection control.

RESULTS: There was no case of SARS-CoV-2 infection identified in 369 newborns born to 354 women who tested positive for SARS-CoV-2 during pregnancy. Of the 369 delivered newborns, 159 newborns (43%) were tested at least once for SARS-CoV-2 during the delivery hospitalization, with 149 newborns (94%) receiving a test at 24 hours of life. Of the 354 women infected with SARS-CoV-2 during pregnancy included in this cohort, 140

(40%) delivered within 14 days from diagnosis of SARS-CoV-2 infection. The median interval from maternal diagnosis of SARS-CoV-2 infection to delivery was 29 days (interquartile range, 2–108). Asymptomatic or mild disease was noted in 259 women (73%). The [Table](#) depicts maternal and neonatal characteristics.

CONCLUSION: We identified no case of vertical transmission in our cohort, which includes a large proportion of women with asymptomatic or mild disease. Newborns were tested per hospital infection control policies (eg, not tested if born to convalescent mothers). Although vertical transmission does occur, data from our centers suggest that the incidence of SARS-CoV-2 vertical transmission, as detected via neonatal nasopharyngeal swab, is likely lower than the 1% to 3% estimated incidence in previous reports.^{2–4} The challenge in selecting the denominator for calculating the incidence of vertical transmission is illustrated by the Centers for Disease Control and Prevention (CDC) report on 2869 newborns of women with SARS-CoV-2 infection during pregnancy.⁴ Test results were available on 610 newborns—only 21% of the cohort—of which 16 (2.6%) tested positive for SARS-CoV-2. More than 60% of newborns without testing information were delivered >10 days from maternal infection. These newborns either were not tested or had a negative result, which is not mandated to be reported to the state, unlike a positive result. If all newborns born to women with SARS-CoV-2 infection during pregnancy were included in the denominator, the incidence of identified vertical transmission would be 0.6% (16 of 2869), not 2.6%. Consensus on how to define, detect, and report vertical transmission of SARS-CoV-2 is lacking. Although both the AAP and CDC recommend testing all infants born to mothers with active SARS-CoV-2 infection at the time of delivery, the optimal strategy for evaluating vertical transmission in the setting of early (first- and second-trimester) pregnancy infections is not known. Although nasopharyngeal PCR-based testing of infants born to convalescent women is likely to be low yield, sampling the fetal compartment during maternal SARS-CoV-2 infection to assess for transmission could incur risk without a clear benefit. Estimates of the incidence of vertical transmission that exclude untested newborns should be interpreted with caution, as untested newborns cannot demonstrate their presumed SARS-CoV-2—negative status. We assert that the appropriate denominator to estimate the incidence of vertical transmission includes all newborns of women with SARS-CoV-2 infection during pregnancy. ■

Cite this article as: Shook LL, , et al. Vertical transmission of SARS-CoV-2: consider the denominator. *Am J Obstet Gynecol MFM* 2021;3:100386.

TABLE

Characteristics of pregnant women testing positive for SARS-CoV-2 and frequency of newborn SARS-CoV-2 testing

Characteristic	All (N=354)	MGH (n=144)	BWH (n=130)	BIDMC (n=80)
Maternal disease severity^a				
Asymptomatic	66 (19)	31 (22)	22 (17)	13 (16)
Mild	192 (54)	76 (53)	75 (58)	41 (51)
Moderate	59 (17)	22 (15)	23 (18)	14 (18)
Severe	25 (7)	11 (8)	7 (5)	7 (8)
Critical	12 (3)	4 (3)	3 (2)	5 (6)
GA at diagnosis in completed weeks	32 (22–38)	32 (23–38)	33 (23–37)	32 (19–36)
GA at diagnosis by trimester				
First	37 (10)	12 (8)	16 (12)	9 (11)
Second	92 (26)	38 (26)	29 (22)	25 (31)
Third	225 (64)	94 (65)	85 (65)	46 (58)
GA at delivery in completed weeks	39 (37–39)	39 (38–39)	39 (37–39)	38 (37–39)
Mode of delivery				
Vaginal delivery	221 (62)	89 (62)	83 (64)	49 (61)
Cesarean delivery	133 (38)	55 (38)	47 (36)	31 (39)
Preterm birth (<37 wk) ^b	53 (15)	18 (13)	18 (14)	17 (21)
Days from first positive test to delivery	29 (2–108)	33 (2–101)	27 (2–106)	26 (3–113)
Women delivering <14 d from date of diagnosis	140 (40)	56 (39)	49 (38)	33 (41)
Total newborns, n	369	150	135	84
Positive for SARS-CoV-2 ^c	0 (0)	0 (0)	0 (0)	0 (0)
Negative for SARS-CoV-2 ^c	159 (43)	69 (46)	60 (44)	30 (36)
Not tested for SARS-CoV-2 ^c	210 (57)	81 (54)	75 (56)	54 (64)
Incidence of vertical transmission, % (95% CI) ^d	0 (0.0–1.0)	0 (0.0–2.4)	0 (0.0–2.7)	0 (0.0–4.3)
Newborns tested for SARS-CoV-2^c after birth, n				
Tested at 24 h only	105 (66)	49 (71)	38 (63)	18 (60)
Tested at 24 h and 48 h–72 h	31 (20)	15 (22)	4 (7)	12 (40)
Tested at 24 h and 4 d–14 d	13 (8)	4 (6)	9 (15)	0 (0)
Tested at other time points	10 (6)	1 (1)	9 (15)	0 (0)

Data are presented as number (percentage) or median (interquartile range), unless otherwise indicated.

BIDMC, Beth Israel Deaconess Medical Center; BWH, Brigham and Women’s Hospital; CI, confidence interval; GA, gestational age; MGH, Massachusetts General Hospital.

^a Defined by the National Institute of Health and endorsed by the Society for Maternal-Fetal Medicine; ^b Includes both iatrogenic and spontaneous preterm births; ^c By clinically available nasopharyngeal polymerase chain reaction for SARS-CoV-2; ^d Number of newborns testing positive for SARS-CoV-2 divided by number of newborns delivered to women with SARS-CoV-2 infection (all hospitals, 369; MGH, 150; BWH, 135; BIDMC, 84). The 95% CI was calculated using the exact (Clopper-Pearson) method.

Shook. Vertical transmission of SARS-CoV-2. *Am J Obstet Gynecol MFM* 2021.

Lydia L. Shook, MD
 Department of Obstetrics and Gynecology
 Massachusetts General Hospital
 55 Fruit St.
 Boston MA
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA
lshook@mgh.harvard.edu

Ai-Ris Y. Collier, MD
 Obstetrics, Gynecology, and Reproductive
 Biology
 Harvard Medical School
 Boston MA
 Department of Obstetrics and Gynecology
 Beth Israel Deaconess Medical Center
 Boston MA

Ilona T. Goldfarb, MD
 Department of Obstetrics and Gynecology
 Massachusetts General Hospital
 Boston MA
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA

Khady Diouf, MD
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA
 Department of Obstetrics and Gynecology
 Brigham and Women's Hospital
 Boston MA

Babatunde O. Akinwunmi, MD, MPH
 Department of Obstetrics and Gynecology
 Brigham and Women's Hospital
 Boston MA

Nicola Young, BA
 Department of Obstetrics and Gynecology
 Massachusetts General Hospital
 Boston MA

Alec Brown, BA
 Department of Obstetrics and Gynecology
 Beth Israel Deaconess Medical Center
 Boston MA

Michele R. Hacker, ScD, MSPH
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA
 Department of Obstetrics and Gynecology
 Beth Israel Deaconess Medical Center
 Boston MA

Anjali J. Kaimal, MD, MAS
 Department of Obstetrics and Gynecology
 Massachusetts General Hospital
 Boston MA
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA

Kathryn J. Gray, MD, PhD
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA

Department of Obstetrics and Gynecology
 Brigham and Women's Hospital
 Boston MA

Andrea G. Edlow, MD, MSc
 Department of Obstetrics and Gynecology
 Massachusetts General Hospital
 Boston MA
 Obstetrics, Gynecology, and Reproductive Biology
 Harvard Medical School
 Boston MA

The authors report no conflict of interest.

The study was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant numbers 1R01HD100022-01 and 3R01HD100022-02S2 [A.G.E.] and grant number K12HD000849 [A.Y.C.]) and the National Heart, Lung, and Blood Institute (grant number K08 HL146963-02 [K.J.G.]). A.G.E. is also supported by the Claflin Award from Massachusetts General Hospital Executive Committee on Research, and A.Y.C. is also supported by the Burroughs Wellcome Fund. M.R.H. is supported by the Harvard Catalyst, the Harvard Clinical and Translational Science Center (the National Center for Advancing Translational Sciences of the National Institutes of Health Award: award number UL1TR002541) and by financial contributions from Harvard University and its affiliated academic healthcare centers.

REFERENCES

- Centers for Disease Control and Prevention. COVID data tracker. Available at: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html. Accessed December 28, 2020.
- Kotlyar AM, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2021;224. 35–53.e3.
- Flaherman VJ, Afshar Y, Boscardin WJ, et al. Infant outcomes following maternal infection with SARS-CoV-2: first report from the PRIORITY study. *Clin Infect Dis* 2020. [Epub ahead of print].
- Woodworth KR, Olsen EO, Neelam V, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1635–40.
- The American Academy of Pediatrics. FAQs: management of infants born to mothers with suspected or confirmed COVID-19. Available at: <https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/>. Accessed January 15, 2021.

© 2021 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajogmf.2021.100386>