



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.

# Coronavirus disease 2019 infection and hypertensive disorders of pregnancy



**OBJECTIVE:** The possible connection between coronavirus disease 2019 (COVID-19) and hypertensive disorders of pregnancy (HDP) remains unclear.<sup>1</sup> Elucidating these outcomes is important both to better understand COVID-19 pathophysiology and to improve patient care in pregnant patients with COVID-19. Our objectives were to test the hypothesis that COVID-19 infection is associated with an increased risk of HDP and to examine the association

between the gestational age at COVID-19 infection and delivery and HDP risk.

**STUDY DESIGN:** This was a retrospective cohort study at Barnes-Jewish Hospital in St. Louis, which has a universal COVID-19 testing policy on admission to labor and delivery. All women admitted for delivery from June 1, 2020, to November 30, 2020, with a positive severe acute

**TABLE**  
**Maternal characteristics and pregnancy outcomes**

Characteristic	COVID-19 positive (n=83)	COVID-19 negative (n=166)	P value
Maternal age, y	26 (23–31)	28 (23–32)	.39
Gestational age, wk	39 (37–39)	39 (37–39)	.90
Black maternal race	88 (53.0)	44 (53.0)	matched
Body mass index at delivery, kg/m <sup>2</sup>	32.5±7.6	31.0±7.2	.13
Nulliparity	31 (37)	63 (38)	matched
Chronic hypertension	10 (12.1)	19 (11.5)	1.0
Pregestational diabetes	4 (4.8)	2 (1.2)	.10
Gestational diabetes	2 (2.4)	14 (8.4)	.10
History of hypertensive disorder of pregnancy	14 (16.7)	19 (11.5)	.23
Tobacco use	6 (7.2)	23 (13.9)	.12
Current substance abuse	7 (8.4)	29 (17.5)	.06
COVID-19 severity		—	
Asymptomatic	48 (57.8)	—	
Moderate	27 (32.5)	—	
Severe	7 (8.4)	—	
Mode of delivery			.37
Vaginal delivery	57 (68.7)	123 (74.0)	
Cesarean delivery	26 (31.3)	43 (26.0)	
Birthweight, g	3090 (2750–3740)	3065 (2750–3520)	.92
Small for gestational age	6 (7.2)	19 (11.5)	.30
Placental abruption	2 (2.4)	1 (0.6)	.26
Hypertensive disorder of pregnancy			.74
None	59 (71.1)	120 (72.3)	
Gestational hypertension	10 (12.1)	24 (14.5)	
Preeclampsia without severe features	3 (3.6)	7 (4.2)	
Preeclampsia with severe features	11 (13.3)	15 (9.4)	
Any hypertensive disorder of pregnancy	24 (28.9)	46 (27.7)	.84

Values are expressed as median (IQR) or number (percentage) or mean±standard deviation.

COVID-19, coronavirus disease 2019; IQR, interquartile range.

Rosenbloom. COVID-19 infection and HDP. *Am J Obstet Gynecol* 2021.

respiratory syndrome coronavirus 2 (SARS-CoV-2) test result at any time during pregnancy were compared 1:2 with randomly selected controls who had a negative SARS-CoV-2 test result and were matched for race and parity. COVID-19 was diagnosed with nasopharyngeal reverse transcription polymerase chain reaction or rapid antigen testing. HDP was diagnosed using standard criteria. Cox proportional hazards models with left truncation to account for the varying gestational age at COVID-19 diagnosis and random effects (frailty) to account for the matching design and small cluster sizes were used to examine the association between COVID-19 and HDP.<sup>2</sup> Because this was a sensitivity analysis, we also examined early (before 32 weeks' gestation) vs late COVID-19 infection and HDP development. The study was deemed exempt from review by the institutional review board.

**RESULTS:** Of 1856 births, there were 83 women (4.5%) with COVID-19 infection. There was no difference in baseline characteristics between COVID-19 infected women and controls (Table). Patients with COVID-19 infection had almost a 2-fold risk of HDP (hazard ratio [HR], 1.93; 95% confidence interval [CI], 1.13–3.31). However, COVID-19 infection was not associated with severity of HDP, and severity of COVID-19<sup>3</sup> was not associated with HDP development. Among patients with COVID-19 and HDP at delivery, the median interval from COVID-19 diagnosis to delivery was 3.8 weeks (interquartile range, 0.29–11.5). In additional analysis, early, but not late, COVID-19 infection was associated with HDP development (HR for early COVID-19, 2.17 [95% CI, 1.11–4.24]; HR for late COVID-19, 1.68 [95% CI, 0.79–3.57]).

**CONCLUSION:** Early COVID-19 infections are associated with HDP, even when accounting for differential exposure and delivery times, suggesting that COVID-19 infection may alter pregnancy physiology and increase the risk of HDP development over time. Infection closer to term is not associated with HDP, which likely reflects our high proportion of asymptomatic infections found at the time of delivery from a universal testing policy<sup>4</sup> and insufficient time to develop HDP in these cases. Furthermore, emerging evidence suggests that COVID-19 modulates placental angiotensin-converting enzyme 2 expression, which may be related to HDP development.<sup>5</sup> Our study is limited by

sampling in a single institution with a high HDP incidence. However, our results suggest that monitoring of patients with antepartum COVID-19 infection should encompass precautions for HDP development. ■

#### ACKNOWLEDGMENTS

The authors acknowledge Lori Stevenson, MSN, for performing the data collection.

Joshua I. Rosenbloom, MD, MPH  
Division of Maternal-Fetal Medicine  
Department of Obstetrics and Gynecology  
Washington University School of Medicine in St. Louis  
660 South Euclid Ave.  
St. Louis, MO 63110  
Department of Obstetrics and Gynecology  
Hadassah Medical Center and Faculty of Medicine  
Hebrew University of Jerusalem  
Jerusalem, Israel  
[rosenbloomj@wustl.edu](mailto:rosenbloomj@wustl.edu)

Nandini Raghuraman, MD, MS  
Ebony B. Carter, MD, MPH  
Jeannie C. Kelly, MD, MS  
Division of Maternal-Fetal Medicine  
Department of Obstetrics and Gynecology  
Washington University School of Medicine in St. Louis  
St. Louis, MO

The authors report no conflict of interest.

#### REFERENCES

1. Adhikari EH, Moreno W, Zofkie AC, et al. Pregnancy outcomes among women with and without severe acute respiratory syndrome coronavirus 2 infection. *JAMA Network Open* 2020;3:e2029256.
2. O'Quigley J, Stare J. Proportional hazards models with frailties and random effects. *Stat Med* 2002;21:3219–33.
3. Berlin DA, Gullick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020;383:2451–60.
4. Kelly JC, Raghuraman N, Carter EB, Palanisamy A, Stout MJ. Pre-procedural asymptomatic coronavirus disease 2019 cases in obstetrical and surgical units. *Am J Obstet Gynecol* 2021;224:114–6.
5. Jing Y, Run-Qian L, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. *Mol Hum Reprod* 2020;26:367–73.

© 2021 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2021.03.001>

## Intracervical balloon catheter for labor induction after rupture of membranes: a systematic review and meta-analysis



**OBJECTIVE:** Although unequivocal benefits to ripening exist in the setting of intact membranes, ripening remains controversial in the setting of prelabor rupture of membranes

(PROM). PROM complicates 8% of term pregnancies, which translates to approximately 270,000 births in the United States annually.<sup>1</sup> We undertook a systematic review and