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COVID-19 Infection and Hypertensive Disorders of Pregnancy

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Objective: The possible connection between COVID-19 and hypertensive disorders of pregnancy (HDP) remains unclear (1). 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-November 30, 2020, with a positive Sars-CoV-2 test at any time during pregnancy were compared 1:2 with randomly selected controls who had a negative SARS-CoV-2 test and were matched for race and parity. COVID-19 was diagnosed with nasopharyngeal RT-PCR 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 (2). As 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 significant difference in baseline characteristics between COVID-19 infected women and controls. Patients with COVID-19 infection had almost a two-fold risk of HDP (HR 1.93 (95%CI 1.13, 3.31). However, COVID-19 infection was not associated with severity of HDP, and severity of COVID-19 (3) 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 (IQR 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).

Conclusions: 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 (4) and insufficient time to develop HDP in these cases. Furthermore, emerging evidence suggests that COVID-19 modulates placental ACE2 expression, which may be related to HDP development (5). 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.

Table: Maternal Characteristics and Pregnancy Outcomes

	COVID-19 Positive N=83	COVID-19 Negative N=166	P
Maternal age, years	26 (23, 31)	28 (23,32)	0.39
Gestational age, weeks	39 (37, 39)	39 (37, 39)	0.90
Black maternal race	88 (53.0)	44 (53.0)	matched
Body mass index at delivery, kg/m^2	32.5 ± 7.6	31.0 ± 7.2	0.13
Nulliparity	31 (37)	63 (38)	matched
Chronic Hypertension	10 (12.1)	19 (11.5)	1.0
Pre-gestational diabetes	4 (4.8)	2 (1.2)	0.10
Gestational Diabetes	2 (2.4)	14 (8.4)	0.10
History of hypertensive disorder of pregnancy	14 (16.7)	19 (11.5)	0.23
Tobacco use	6 (7.2)	23 (13.9)	0.12
Current substance abuse	7 (8.4)	29 (17.5)	0.06
COVID Severity		------	
Asymptomatic	48 (57.8)	------	
Moderate	27 (32.5)	------	
Severe	7 (8.4)	------	
Mode of delivery			0.37
Vaginal delivery	57 (68.7%)	123 (74.0%)	
Cesarean delivery	26 (31.3%)	43 (26.0%)	
Birthweight, g	3,090 (2,750, 3,740)	3,065 (2,750, 3,520)	0.92
Small for gestational age	6 (7.2)	19 (11.5)	0.30
Placental abruption	2 (2.4)	1 (0.6)	0.26
Hypertensive disorder of pregnancy			0.74
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)	0.84

Numbers are Median (IQR) or N(%) or mean ± standard deviation

References

1. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RRJ, Spong CY. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA network open. 2020;3(11):e2029256.
2. O'Quigley J, Stare J. Proportional hazards models with frailties and random effects. Stat Med. 2002 Nov 15;21(21):3219-33.
3. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. 2020;383(25):2451-60.
4. Kelly JC, Raghuraman N, Carter EB, Palanisamy A, Stout MJ. Preprocedural asymptomatic coronavirus disease 2019 cases in obstetrical and surgical units. Am J Obstet Gynecol. 2021;224(1):114-6.
5. Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, Fei C. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod. 2020;26(6):367-73.