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Assessment of SARS-CoV-2 serostatus and hypertensive disorders of pregnancy



OBJECTIVE: COVID-19, the disease caused by SARS-CoV-2, has been associated with hypertensive disorders of pregnancy (HDP).^{1,2} The link is biologically plausible given that COVID-19 results in endothelial injury and multiorgan inflammation.³ However, clinical polymerase chain reaction (PCR) testing underestimates viral exposure.⁴ We tested the hypothesis that exposure to SARS-CoV-2 is associated with HDP, using SARS-CoV-2 antibodies and PCR testing as evidence of infection.

STUDY DESIGN: This was a prospective cohort study of patients with singleton pregnancy at 2 hospitals in Philadelphia, Pennsylvania, between April 13, 2020 and December 31, 2020. The institutional review board of the University of Pennsylvania approved this study with a waiver of consent.

This was a discarded specimen study limited to patients with residual sera from routine syphilis testing. Seropositivity was defined as detectable immunoglobulin (Ig)G and/or IgM

TABLE
Baseline characteristics and pregnancy outcomes by SARS-CoV-2 exposure

Characteristic	Seronegative N = 5624	Seropositive N = 568	P
Age at delivery, y	31 (27–35)	28 (24–32)	<.001
Race/ethnicity			<.001
White/Non-Hispanic	2161 (38.4)	59 (10.4)	
Black/Non-Hispanic	2344 (41.7)	377 (66.4)	
Asian	412 (7.3)	13 (2.3)	
Hispanic	451 (8.0)	104 (18.3)	
Other/not reported	256 (4.6)	15 (2.6)	
Nulliparous	2556 (45.5)	193 (34.0)	<.001
Prepregnancy BMI ≥30.0 ^a	1533 (27.3)	225 (39.6)	<.001
Diabetes mellitus ^b	509 (9.1)	52 (9.2)	.93
Chronic hypertension	341 (6.1)	39 (6.9)	.45
Gestational age at delivery, wk	39.3 (38.3, 40.0)	39.1 (37.9, 39.9)	.04
Outcome	Seronegative N = 5624	Seropositive N = 568	aRR (95% CI)
HDP, n (%)	1433 (25.5)	147 (25.9)	0.93 (0.80–1.08)
Chronic hypertension with superimposed preeclampsia	108 (1.9)	8 (1.4)	0.53 (0.24–1.15)
Preeclampsia with severe features	253 (4.5)	24 (4.2)	0.88 (0.59–1.32)
Gestational hypertension/preeclampsia without severe features	1072 (19.1)	115 (20.2)	0.98 (0.82–1.16)

Data are presented as number (percentage) or median (interquartile range).

aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; HDP, hypertensive disorder of pregnancy.

^a Prepregnancy BMI missing for 66 patients (8 seropositive and 58 seronegative); ^b Either gestational or pregestational diabetes mellitus.

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antibodies to the receptor-binding domain of the SARS-CoV-2 spike protein, measured by enzyme-linked immunosorbent assay as previously described.⁵ We abstracted nasopharyngeal PCR results obtained at any time during pregnancy, including a universal opt-out test at birth admission, and assessed clinical symptoms at that time point from medical records. The primary outcome was HDP as defined by the International Classification of Diseases-Tenth Revision (ICD-10) diagnosis codes from the birth admission.⁵ Adjusted relative risks (RRs) were calculated by Poisson regression with robust error variances. A sensitivity analysis to assess the association of serostatus with preeclampsia was performed using data from 1 hospital where urine protein assessment was routinely performed.

RESULTS: SARS-CoV-2 serology testing was performed for 6192 of 6680 (92.7%) pregnant patients, and 568 (9.2%) patients were seropositive (Supplemental Figure). There were several baseline characteristics that differed by serostatus (Table). Seropositive patients were no more likely to be diagnosed with HDP (adjusted RR, 0.93; 95% confidence interval [CI], 0.80–1.08) compared with seronegative patients. There were no differences in severity of HDP by serostatus, nor in risk of HDP by severity of COVID-19 (Supplemental Table). There was no association in sensitivity analysis (n=3324) between seropositivity and preeclampsia (RR, 0.91; 95% CI, 0.60–1.38). PCR testing was positive for 37.1% of seropositive patients vs 1.1% of seronegative patients. SARS-CoV-2 infection by PCR was also not associated with HDP (adjusted RR, 0.99; 95% CI, 0.80–1.22). Risk of HDP did not vary by timing of infection by trimester between patients with positive and negative PCR results (Supplemental Table).

CONCLUSION: In a cohort with a relatively high incidence of HDP, we found no association between SARS-CoV-2 infection and HDP. We assessed serologic response to SARS-CoV-2 in the early period of the pandemic in the United States and before widespread availability of vaccination. Seropositivity in this study is thus highly likely to be related to SARS-CoV-2 infection during pregnancy. Only 2% of the seropositive patients were moderately or critically ill, limiting our conclusions about severity of infection and HDP. Misclassification of the outcome by use of ICD-10 codes is possible, although accuracy of codes in medical records was previously assessed.⁵ Given the high likelihood of misclassification of SARS-CoV-2 exposure based on PCR alone, prospective studies including serial PCR and symptom assessment are needed to further elucidate the relationship between timing of infection and obstetrical risks. ■

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Trends in public- and industry-funded uterine cancer clinical trials and disability-adjusted life years from 2007 to 2019



OBJECTIVE: In 2022, for the first time, uterine cancer (UC) will not only be the most common gynecologic cancer in the United States, but it may also match ovarian cancer in gross mortality.¹ This is in part owing to a lack of treatment advances in UC.¹ Gynecologic cancer trials suffer from low accrual² and receive significantly less public funding relative to societal burden than most other cancers receive.³ Most studies that have investigated cancer funding patterns utilize the federal funding data. In this study, we identified the trends in the number of open public- and industry-funded endometrial cancer trials relative to UC's disease burden.

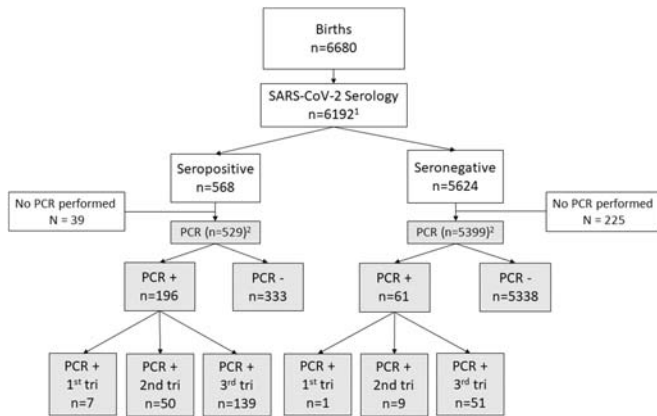
STUDY DESIGN: We queried [ClinicalTrials.gov](https://clinicaltrials.gov) to obtain the number of open endometrial cancer clinical trials that utilized public and industry funds from 2007 to 2019 in the United States. Public funders include the National Cancer Institute and other federal agencies. Industry funders represent pharmaceutical and device companies. A study is considered open if the date of first enrollment in that year begins between January 1 and December 31. The disability-adjusted life year (DALY) number incorporates the years of potential life lost owing to premature mortality and the years of productive life lost because of disability. DALY has been shown to correlate better with funding decisions than other cancer burden metrics.⁴ The DALY numbers for UC from 2007 to 2019 were retrieved from the Institute for Health Metrics and Evaluation database.⁵ The ratios of the number of open trials to DALY number per 100,000 people were generated as studies funded by public (#P/DALY) and industry (#I/DALY). Linear regression analyzed the trend lines and rates of change. This study

was considered exempt from institutional review board approval.

RESULTS: The results are presented in the [Figure](#). From 2007 to 2019, UC's DALY increased significantly ($R^2=0.981$; $P<.001$). The number of public-funded trials did not change ($R^2=0.072$; $P=.375$), but the number of industry-funded trials rose significantly ($R^2=0.604$; $P=.002$). #P/DALY showed a negative trend over the study period ($R^2=0.317$; $P=.045$), reflecting decreases in the number of public-funded studies relative to the rise in DALY. By #I/DALY, endometrial cancer experienced significant increases in industry-funded studies relative to DALY ($R^2=0.427$; $P=.015$).

CONCLUSION: The Society of Gynecologic Oncology declared a clinical trial crisis in gynecologic oncology in 2016.² The reasons were multifactorial, but a commonality was the paucity of gynecologic cancer trials. Our findings found that, whereas industry-funded clinical trials rose significantly, public-funded trials for endometrial cancer did not increase significantly to reflect the striking rise in UC's societal burden from 2007 to 2019. In fact, relative to DALY, the number of public-funded trials decreased. This suggests that public funding for UC has been disproportionately low, considering its escalating disease burden. The opposite was seen with industry-funded studies. For public funding agencies to continue to meaningfully contribute to UC advancements, greater efforts need to be made to secure funding for clinical trials that is proportionate to its high and worrisome disease burden. Future studies that will additionally evaluate the number of patients enrolled by each funding source and utilize different burden

SUPPLEMENTAL FIGURE
Study population and cohort testing results



Missingness for sera was 488 (7.3%). Those without serologic test results were older (32 vs 31 years; $P=.003$), more likely to be White/non-Hispanic ($P=.008$), and more likely to have delivered at <37 weeks' gestation (26.7% vs 8.5%; $P<.001$). PCR was missing for 264 (4.3%). Those without PCR results were younger (30 vs 31 years; $P=.007$) and more likely to be Black/non-Hispanic ($P=.008$).

PCR, polymerase chain reaction.

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SUPPLEMENTAL TABLE
Hypertensive disorders of pregnancy and COVID-19 by timing and severity of disease

COVID-19	HDP (n = 1519)	No HDP (n = 4409)	RR (95% CI)
Timing of infection			
Negative	1449 (95.4)	4222 (95.8)	Reference
Positive PCR in first trimester	1 (0.1)	7 (0.2)	0.49 (0.08–3.06)
Positive PCR in second trimester	12 (0.8)	47 (1.1)	0.80 (0.48–1.32)
Positive PCR in third trimester	57 (3.8)	133 (3.0)	1.17 (0.94–1.47)
Severity of infection ^a			
Asymptomatic	35 (70.0)	118 (64.8)	Reference
Mild	12 (24.0)	56 (30.8)	0.77 (0.43–1.39)
Moderate–critical	3 (6.0)	8 (4.4)	1.19 (0.43–3.27)

Data are presented as number (percentage).

CI, confidence interval; HDP, hypertensive disorders of pregnancy; PCR, polymerase chain reaction; RR, relative risk.

^a Determined for 232 patients with available records to determine severity of disease.

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