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Short communication

Who said differentiating preeclampsia from COVID-19 infection was easy?

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1. Introduction

Differentiating preeclampsia from clinical imitators during pregnancy (e.g. fatty liver disease, lupus, chronic hypertension, kidney disease) has never been easy. Recent reports suggest COVID-19 infection is an additional preeclampsia imitator [1,2]. We sought to identify clinical phenotypic features with potential to discern COVID-19 from preeclampsia on clinical grounds alone.

2. Methods

From April to November 2020, 1,418 pregnant women at > 20 weeks' gestational age were screened for SARS-CoV-2 infection at University of Illinois at Chicago's Labor and Delivery Unit. Demographic and clinical data including the need for preeclampsia work-up were prospectively collected and entered into a database. To determine if COVID-19 modifies the severity of clinical symptoms triggering the need for preeclampsia workup, we designed two scores, one corroborating the clinical symptomatology (clinical severity score) and the other summing the presence or absence of abnormal laboratory test results (laboratory severity score) as previously described [3]. Pregnancy hypertensive disorders were defined using recognized clinical criteria [4]. Final diagnoses were considered confirmed if specifically documented after the work-up as preeclampsia with or without severe features, gestational hypertension or chronic hypertension and supported by the clinical rationale of the managing providers. The Institutional Review Board concluded this analysis was not human subject research.

3. Results

Within the study period 75 mothers tested SARS-CoV-2 positive for a prevalence of 5.2% (75/1418) positivity rate. Of these positive cases, 44% (33/75) had a preeclampsia work-up due to hypertension or other confounding symptomatology during their pregnancy. A preeclampsia work-up was not deemed necessary nor indicated in the remaining 56% (42/75) SARS-CoV-2 positive mothers. Contemporaneously, 334 consecutive women testing SARS-CoV-2 negative also underwent preeclampsia work-up with a frequency of work-up being 26% (343/1343) among SARS-CoV-2 negative women ($p < 0.001$ vs. SARS-CoV-2 positive women). The demographic characteristics of the patients in the groups worked-up for preeclampsia and in the COVID-19 positive patients who did not require work-up for preeclampsia are presented in Table 1. The frequency of a clinically confirmed diagnosis of preeclampsia was similar in the groups that underwent preeclampsia work-up irrespective of COVID-19 positivity. However, the frequency of a final diagnosis of gestational hypertension was lower among COVID-19 positive women with more of these women having negative work-up results. Overall, a diagnosis of COVID-19 during index pregnancy did not appear to impact on the severity of clinical symptoms triggering preeclampsia work-up, with no clinical symptom or sign being identified more often in the COVID-19 positive group (Table 2). A positive SARS-CoV-2 test result was not associated with a higher need for anti-hypertensive or magnesium therapy during pregnancy. COVID-19 infection did not significantly alter the platelet count, kidney or liver function tests and laboratory scores among the patients in this study. Results maintained when analysis was restricted to patients screened for COVID-19 infection and evaluated for preeclampsia during the same episode of care.

4. Discussion

Recent reports have raised the question whether the SARS-CoV-2 virus selectively targets the vascular endothelium and kidneys to explain the high frequency of newly diagnosed hypertension and kidney dysfunction associated with COVID-19 infection [5,6]. However, for pregnant patients any newly identified hypertension generates concern due to overlapping symptomatology with gestational hypertension and preeclampsia making differentiation between two condition impossible on clinical grounds alone. Our study demonstrates that women who are

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Table 1
Demographic and clinical characteristics of the three study groups.

Variables	COVID-19 positive & YES PE work-up (n = 33)	COVID-19 positive & NO PE work-up (n = 42)	COVID-19 negative & YES PE work up (n = 334)	*P* value [a]
Age, years [b]	27 [22–32]	27 [23–33]	28 [23–34]	0.252
Nulliparity [c]	19 (58)	28 (67)	153 (46)	0.301
Married or co-habitating [c]	3 (10)	4 (10)	75 (22)	0.037
Race/Ethnicity [c]				0.039
White Non-Hispanic	3 (9) *	1 (2)	29 (9) *	
Black Non-Hispanic	24 (73)	22 (52)	214 (64)	
Hispanic	6 (18)	19 (45)	73 (22)	
Asian	0 (0)	0 (0)	5 (1)	
Other	0 (0)	0 (0)	13 (4)	
BMI classification [c]				0.020
Underweight (<18.5)	0 (0) *	0 (0)	0 (0) *	
Normal (18.5–24.9)	1 (3)	7 (17)	13 (4)	
Overweight (25–29.9)	3 (9)	8 (19)	58 (17)	
Obese class I (30–34.9)	10 (30)	14 (33)	92 (28)	
Obese class II (35–39.9)	6 (18)	6 (14)	67 (20)	
Obese class III (>40)	13 (39)	7 (17)	104 (31)	
Blood type [c]				0.694
O	19 (58)	20 (48)	165 (49)	
A	11 (33)	14 (33)	95 (28)	
B	2 (6)	7 (17)	63 (19)	
AB	1 (3)	1 (2)	11 (3)	
Gestational age at test, weeks [c]				0.106
$20^{0/7}$-$27^{6/7}$	2 (6)	4 (10)	6 (2)	
$28^{0/7}$-$33^{6/7}$	2 (6)	5 (12)	28 (8)	
$34^{0/7}$-$36^{6/7}$	4 (12)	3 (7)	32 (10)	
$\geq 37^{0/7}$	25 (76)	30 (71)	268 (80)	
Co-morbidities [d]				0.385
Diabetes	6 (18)	5 (12)	51 (15)	
Chronic hypertension	10 (30)	1 (2)	75 (22)	
Renal disease	0 (0)	0 (0)	5 (1)	
Anemia [e]	18 (55)	15 (36)	210 (63)	
Two or more co-morbidities [b]	9 (27) *	1 (2)	73 (22) *	0.007

* indicates significance ($P < 0.05$) vs. COVID-19 positive & NO PE work-up group.

[a] *P* values for the comparison among the 3 groups by Kruskal-Wallis ANOVA on Ranks or Chi square tests.

[b] Data presented as median [IQR] and compared with Kruskal-Wallis ANOVA on Ranks followed by multiple comparison with Dunn's post-hoc test.

[c] Data presented as no. (%) and compared with multiple Chi square tests.

[d] Percentages do not add to 100 as 83 women had 2 or more of the listed co-morbidities.

[e] Anemia defined by hemoglobin concentration < 10.5 g/dL.

positive for COVID-19 undergo work-up for preeclampsia more frequently due to clinical uncertainty but do not seem to have a higher frequency of symptomatology or laboratory abnormalities than expected for the COVID-negative group with preeclampsia. To differentiate between newly induced COVID-19 hypertension which is likely transitory and preeclampsia and to diminish unnecessary laboratory testing and hospitalization more specific molecular markers for preeclampsia are needed.

Table 2
Clinical and laboratory variables and severity scores of the three study groups.

Variables	COVID-19 positive & YES PE work-up (n = 33)	COVID-19 positive & NO PE work-up (n = 42)	COVID-19 negative & YES PE work up (n = 334)	*P* value[a]
COVID-19 clinical variables				
COVID-19 manifestations [b]				0.675
asymptomatic	22 (66)	31 (74)	NA	
symptomatic	11 (33)	11 (26)	NA	
COVID-19 positive test result during current episode of care [c]	18 (55)	30 (71)	NA	0.204
HDP clinical variables				
Final diagnosis of preeclampsia [b]	18 (55) *	0 (0)	158 (47) *	<0.001
HDP discharge diagnoses [b]				
Preeclampsia with severe features	13 (39) *	0 (0)	102 (31) *	
Preeclampsia without severe features	5 (15)	0 (0)	56 (17)	
Gestational HTN	6 (18)	2 (5)	128 (38)	<0.001
Chronic HTN	4 (12)	1 (2)	35 (10)	
None	5 (15)	39 (93)	13 (4)	
PE work-up clinical variables				
Clinical severity score [d,e]	1 [1 –4] *	0 [0–0]	2 [1 –3] *	<0.001
Systolic blood pressure[e]	146 [134–170] *	118 [109–123]	153 [144–170] *	<0.001
Diastolic blood pressure[e]	86 [75–96] *	72 [65–79]	90 [81–97] *	<0.001
Blood pressure range [b,f]				
Severe range	12 (36) *	0 (0)	127 (38) *	
Mild range	13 (40)	2 (1)	185 (55)	<0.001
Normotensive	8 (24)	40 (91)	22 (7)	
Headache [b]	5 (15)	3 (7)	52 (16)	0.346
RUQ pain [b]	0 (0)	0 (0)	18 (5)	0.121
Nausea & vomiting [b]	0 (0)	1 (2)	6 (2)	0.704
Need for IV anti-HTN [b]	10 (30) *	0 (0)	96 (29) *	<0.001
Need for IV magnesium sulfate [b]	12 (36) *	1 (2)	118 (35) *	<0.001
PE work-up laboratory variables				
Laboratory severity score [g,e]	1 [0–1] *	0 [0–0]	0 [0–1] *	<0.001
Proteinuria [b,h]	17 (54)	NA	136 (43)	0.554
Serum creatinine > 1.1 mg/dL [b]	4 (14)	1 (6)	24 (7)	0.418
Serum creatinine, mg/dL[e]	0.68 [0.58–0.83] *	0.54 [0.52–0.68]	0.69 [0.59–0.82] *	0.013
Platelets < 100,000 mm^3 [b]	0 (0)	0 (0)	11 (3)	0.295
Platelets, cells/mm^3 [e]	216 [183–266]	199 [165–226]	195 [162–239]	0.121

(*continued on next page*)

Table 2 (*continued*)

Variables	COVID-19 positive & YES PE work-up (n = 33)	COVID-19 positive & NO PE work-up (n = 42)	COVID-19 negative & YES PE work up (n = 334)	*P* value[a]
AST, IU/L[e]	22 [16–32]	18 [15–22]	20 [16–27]	0.215
ALT, IU/L[e]	17 [11–29] *	10 [9–25]	12 [9–19]	0.043
Elevated LFT twice the normal [b,i]	2 (6)	0 (0)	14 (4)	0.540

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDP, hypertensive disorders of pregnancy, HTN, hypertensive; LFT, liver function tests; RUQ, right upper quadrant.

[*] indicates significance ($P < 0.05$) vs. COVID-19 positive & NO PE work-up group.

[a] *P* value for the comparison among the 3 groups by Kruskal-Wallis ANOVA on Ranks or Chi square tests.

[b] Data presented as no. (%) and compared with multiple Chi square tests.

[c] The current episode of care was defined as the same admission and < 14 days interval from SARS-CoV-2 testing result to the work-up evaluation for preeclampsia.

[d] Clinical severity score included: neurologic symptoms (0: absent, 1: present); right upper quadrant pain (0: absent, 1: present); systolic blood pressure (0: <140 mmHg, 1: 140–160 mmHg, 2: >160 mmHg); diastolic blood pressure (0: <90 mmHg, 1: 90–105 mmHg, 2: >105 mmHg); nausea and/or vomiting (0: absent, 1: present), anti-hypertensive medication need (0: absent, 1: present); magnesium sulfate need (0: absent, 1: present). The score is the sum of 0 and 1 values and ranges from 0 to 9.

[e] Data presented as median [IQR] and compared with Kruskal-Wallis ANOVA on Ranks followed by multiple comparison with Dunn's post-hoc test.

[f] Severe range: systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 110 mmHg; mild range: systolic blood pressure of 40–159 mmHg or diastolic blood pressure of 90–109 mmHg; normotensive: systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg.

[g] Laboratory severity score included: proteinuria defined as protein/creatinine ratio > 0.3 or 24-hour urine protein > 300 mg (0: absent, 1: present); abnormal liver function tests (AST: 0: 0–39 U/L, 1: >40 U/L and/or ALT: 0: 0–49 U/L, 1: >50 U/L); serum creatinine (0: <1.0 mg/dL, 1: ≥1.1 mg/dL); platelet count (0: ≥100,000/mm^3, 1: <100,000/mm^3). The score is the sum of 0 and 1 values and ranges from 0 to 4.

[h] Defined as protein-to-creatinine ratio > 0.3 or 24-hour proteinuria > 300 mg.

[i] Normal AST: 10–40 IU/L and normal ALT: 7–50 IU/L.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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