Risk Factors Associated with Coronavirus Disease 2019 (COVID-19) Symptoms and Potential Vertical Transmission During Pregnancy: A Retrospective Cohort Study

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Abstract

Objective: The COVID-19 pandemic is of special concern for pregnant women. A growing body of evidence suggests the virus can have a deleterious impact upon outcomes related to birth and newborn health. There is a paucity of published research demonstrating the factors that influence disease severity among those who are pregnant, while a growing body of evidence demonstrates that vertical transmission occurs. Our study investigated the impact of maternal characteristics upon COVID-19 outcomes, as well as whether disease severity impacted pregnancy outcomes.

Methods: We conducted a retrospective cohort study of pregnant women with COVID-19 who were admitted to two public hospitals in our state between April-August, 2020. Pregnancy outcomes and clinical, laboratory, and placental data were collected.

Results: Thirty-four pregnant women tested positive for SARS-CoV-2. Among them, 55% (19/34) were symptomatic. Of those who were symptomatic, 68% (13/19) presented with fever and cough. Those with symptoms had a statistically significant higher pregestational mean BMI compared with asymptomatic women (35.7±7.9 vs 26.7±6.9, *P*=0.004). Screening of biochemical records demonstrated that symptomatic women had lower potassium levels compared with those who were asymptomatic (median: 3.70 mEq/L vs 4.30 mEq/L, *P*=0.009). High BMI (42.4 kg/m^2) and low potassium levels (3.0 mEq/L) were observed in the only case of postpartum mortality among the symptomatic women. We did not observe any influence of maternal COVID-19 severity on placental histopathology/infant health or evidence of vertical transmission, regardless of preterm status or duration of fetal exposure.

Conclusion: High pregestational BMI and lower potassium levels were associated with the presence of COVID-19 symptoms among pregnant women.

Background

As the global impact of coronavirus disease 2019 (COVID-19) has grown, so has our understanding of the plethora of presenting symptoms. Known symptoms now include anosmia, myalgia, and gastrointestinal symptoms in addition to respiratory symptoms of fever, dry cough, and dyspnea.[1–3] It is also established that older age, underlying medical conditions (immunosuppression, hypertension and diabetes), and race/ethnicity (Black, Hispanic and Asian) increase risk of severe disease.[4–6] The impact of COVID-19 and associated risk factors on pregnancy and newborn health remains less certain.

Published research demonstrates an increased risk of premature labor and worse pregnancy outcomes in women infected with SARS CoV-2.[7,8] Most often, they show no clinical symptoms and absence of transmission of infection to the newborn.[1,9] However, a recent case series reported seven maternal deaths following severe COVID-19 infection.[10] With recent implementation of aggressive COVID-19 testing, several reports have emerged associating factors such as pregestational BMI, lymphocyte count, heart rate, and respiratory rate with disease symptoms in SARS CoV-2-infected pregnant women.[11–14] Another study demonstrated an increased risk of preterm delivery in symptomatic women, suggesting a need to identify

high-risk pregnant women.[15] One of the potential reasons for the increased risk could be damage to placental tissue.[16]

Our study sought to investigate the impact of maternal demographic, clinical and biochemical characteristics on disease severity in pregnant women infected with SARS-Cov-2. We further investigated the influence of disease severity on pregnancy outcomes, vertical transmission of infection, histopathological evaluation of the placenta, and outcomes of the newborn.

Materials And Methods

Study design and study population

During the first-wave peak of COVID-19 infections in the US, testing for COVID-19 became universal for all pregnancy admissions from April 2020 in Illinois, USA. We conducted a retrospective cohort study between April 1 and August 15, 2020 that included all consecutive pregnant women who were admitted at any gestational age and had laboratory-confirmed COVID-19. Admissions were from two Chicago maternity hospitals— John H. Stroger, Jr. Hospital of Cook County and AMITA St. Mary's and Elizabeth Hospital. Our study was possible because of the April 2020 implementation of universal COVID-19 testing for all pregnant women admitted to hospitals in Illinois. We followed the World Health Organization (WHO) guidelines for diagnosis, which define positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal or pharyngeal swabs as laboratory-confirmed SARS-CoV-2.[17] Patients with lack of data on symptoms and an inconsiderable number of other clinical characteristics, including risk factors and maternal and perinatal outcomes, were excluded. We further included their newborns in the study, who were also tested for SARS-CoV-2 infection using throat swabs.

Ethical approval and data collection

The study's protocol was expeditiously approved by the institutional research ethics committees associated with John H. Stroger, Jr. Hospital of Cook County (approval number: 20–098) and AMITA Health Saints Mary and Elizabeth Medical Center (approval number: 2021-0193-02). The requirement of informed consent was waived due to the retrospective study design.

The following demographic and baseline maternal data were collected: age, race and ethnicity, anthropometric characteristics (e.g., BMI), lifestyle habits including substance abuse, comorbidities including pregestational obesity, hypertension, and gestational diabetes; whether the patient received antepartum therapy including hydroxychloroquine treatment. All participants underwent clinical evaluation of presenting signs and symptoms, detailed laboratory assessment of blood and urine samples, and radiologic chest assessment, if needed.

Maternal blood sample assessment included hemoglobin, blood cell counts, inflammatory markers (e.g., C-reactive protein [CRP]), serum concentration of electrolytes (sodium, potassium, calcium, and chloride), liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), and renal function

(blood urea nitrogen [BUN] and creatinine). Data on pregnancy outcomes (including mode of delivery, gestational age (GA), and preeclampsia), and neonatal outcomes (including symptoms, APGAR scores, and birth weight) were recorded. A preterm birth or premature birth was defined as one occurring at < 37 weeks. We used specific cut-off values to define blood dyscrasias for pregnant women according to their trimester: leukopenia as white cell count < 5.9 x 10^9/L, neutropenia as neutrophil count < 3.9 x 10^9/L, and lymphopenia as lymphocyte count < 1.0 x 10^9/L [18] for the third trimester.

We also performed the gross and histopathological evaluation of placentas according to the Amsterdam consensus statement guidelines.[19]

We assessed the effect of length of duration of fetal exposure to maternal SARS-CoV-2 and the possibility of increased risk of vertical transmission, morbidity, and mortality specifically among preterm infants (< 37 weeks of gestation). We sub-analyzed women who were infected prior to 37 weeks of gestation, focusing on evidence of SARS-CoV-2 infection among preterm infants born to these women, including positive RT-PCR testing and any clinical signs/symptoms attributable to infection.

We further performed laboratory assessment of blood samples taken from the newborns and followed up both mother and infant until six weeks after delivery. We defined the infant's specific blood dyscrasias according to their age of life: leukopenia as white cell count < 13.0 x 10^9/L for term infants at 1–12 hours of life and < 9.0 x 10^9/L for preterm infants at birth; neutropenia as neutrophil count < 6.0 x 10^9/L for term infants at 1–12 hours of life and < 6.0 x 10^9/L for preterm infants at birth; and lymphopenia as lymphocyte count < 2.0 x 10^9/L for both term infants at 1–12 hours of life and preterm infants at birth.[21] Evidence of vertical transmission was further evaluated for the presence of SARS-CoV-2 according to CDC guidelines.[22] As, and when, appropriate we evaluated infants for immunoglobulin [Ig] G and IgM levels.

All the data collected was curated using a customized data collection form, and two study investigators (JM and BP) independently reviewed the data collection forms for any errors. The data was locked and secured appropriately according to rules and principles laid down in the Health Insurance Portability and Accountability Act *of 1996 (*HIPAA). The data collected from both sites was synchronized and any inaccuracies were verified with the concerned representative of the specific center.

Study Outcome

Study outcome
The patients were further classified into two groups: symptomatic and asymptomatic, according to the existence of any of known signs and symptoms of COVID-19 infection.

Statistical Analyses

Statistical analyses were conducted using STATA/IC 16 (Stata-Corp LP, TX, SA) and SAS 9.4 (SAS Institute, Inc., Cary, NC). Continuous variables were expressed as mean and standard deviation (SD) for normally

distributed data, median and range for non-normally distributed data, and categorical variables as frequency and percentage. The continuous variables were compared between symptomatic and asymptomatic individuals using a t-test or Mann-Whitney-U test and categorical variables were compared using the Pearson chi-square test or Fisher's-exact test, as appropriate. We calculated the unadjusted odds ratio (OR) using the simple logistic regression model. A p-value of < 0.05 was considered statistically significant.

Results

A total of 37 pregnant women with COVID-19 were admitted to the study centers during the study period. One patient was excluded for lack of information on the existence of symptoms, while two were excluded due to lack of data related to maternal and perinatal outcomes. In total, 34 women were included in the study–19 were symptomatic (55%) for COVID-19 (Fig. 1).

Baseline characteristics of pregnant women

The baseline characteristics of the study population are shown in Table 1. Among the 19 symptomatic patients, fever (n = 13; 68%), cough (n = 8; 42%), and myalgia (n = 5; 26%) were the most commonly observed symptoms (Fig. 2). In consent with their distribution, fever, cough, and myalgia was the most frequently observed combination of coexisting symptoms, seen in three patients (15.79%; data not shown). The average age of women in our study population was 26. The largest proportion were of Hispanic ancestry (44%), followed by non-Hispanic Black (38%). The distribution of age and ethnicity did not differ significantly between symptomatic and asymptomatic patients.

Table 1
Clinical and Demographic Characteristics of Pregnant Women with COVID-19 by Symptom Status

Characteristics	Asymptomatic (N = 15)		Symptomatic (N = 19)		*P*
	n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
Age at diagnosis	15	24.93 (5.09)	19	27.32 (5.96)	0.227
Gravidity					
> 1	9	60.00	15	78.95	0.276
Parity					
> 1	5	33.33	8	42.11	0.601
GA at diagnosis (weeks)	15	39.00 (26.20–41.00)	18	35.90 (24.00–41.00)	0.173
GA at delivery (weeks)	14	39.05 (27.00-41.40)	19	39.10 (37.10–41.20)	1.000
Diagnosis to delivery interval (weeks)	14	0.05 (0.00-1.80)	19	2.10 (0.00–15.00)	0.035
Ethnicity					
Hispanic	7	46.67	8	42.11	1.000
Non-Hispanic black	6	40.00	7	36.84	
Non-Hispanic white	0	0.00	1	5.26	
Other	2	13.33	3	15.79	
Complications during pregnancy					
Pre-pregnancy BMI (kg/m2)	14	26.79 (6.92)	14	35.71 (7.91)	0.004
Obesity (BMI > 30)	0	0.00	5	26.32	0.032
GBS positive	4	26.67	7	36.84	0.715
HIV positive	0	0.0	2	10.53	0.492
Preeclampsia	2	13.33	2	10.53	1.000
HTN	1	6.67	5	26.32	0.196

BMI: Body mass index, GA: Gestational age, GBS: Group B Streptococcus, HIV: Human immunodeficiency virus, HSV: Herpes

simplex virus, HTN: Hypertension, SD: Standard deviation.

Characteristics	Asymptomatic (N = 15)		Symptomatic (N = 19)		*P*
	n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
Cholestasis	0	0.00	2	10.53	0.492
Chorioamnionitis	0	0.00	3	15.79	0.244
Anemia	0	0.00	1	5.26	1.000
Gestational diabetes	0	0.00	2	10.53	0.492
Substance abuse	1	6.67	2	10.53	1.000
Depression	0	0.00	1	5.26	1.000
History of syphilis	1	6.67	0	0.00	0.441
History of HSV	0	0.00	1	5.26	1.000
Oligohydramnios	0	0.00	1	5.26	1.000
Relevant Antepartum therapy					
Flu vaccination in pregnancy	3	20.00	9	47.37	0.097
History of Malaria medication	1	6.25	0	0.00	NA
Antiviral	0	0.00	0	0.00	NA
Hydroxychloroquine	0	0.00	1	5.26	NA
Betamethasone	2	13.33	0	0.00	0.187
Labor and delivery					
Mode of delivery					
Vaginal delivery	11	73.33	14	73.68	1.000
Cesarean delivery	4	26.67	5	26.32	
Multiplicity of birth					
Twins (n, %)	2	13.33	0	0.00	0.187
Disposition/ Recovery					
Postpartum death, n (%)	0	0.00	1	5.26	1.000

BMI: Body mass index, GA: Gestational age, GBS: Group B Streptococcus, HIV: Human immunodeficiency virus, HSV: Herpes

simplex virus, HTN: Hypertension, SD: Standard deviation.

Obesity (n = 5; 26.32%), gestational diabetes (n = 2; 10.53%), and hypertension (n = 5; 26.32%) were the most commonly occurring comorbid conditions. All three were overrepresented in symptomatic patients. We also observed that the symptomatic women had significantly higher pregestational BMI compared to asymptomatic women (35.71 vs 26.79, $P = 0.004$; Fig. 3A). Two of our symptomatic patients were also positive for HIV. Another three symptomatic women were diagnosed with chorioamnionitis. A comparatively large proportion of symptomatic women in our cohort had received the flu vaccination in the recent past (47.37% of symptomatic women vs 20.00% of asymptomatic women). We further observed that every third patient in our enrolled population was a Group B streptococcus (GBS) carrier; however, we failed to detect any influence of GBS status on the absence or presence of symptoms. Our cohort also had two women with a history with substance abuse, one symptomatic and one asymptomatic. We also detected syphilis in one of the asymptomatic patients.

Laboratory characteristics of pregnant women

Initial evaluation of laboratory characteristics of the study population are shown in Table 2. Hematological analyses suggested significantly elevated basophil counts in symptomatic, compared with asymptomatic, women ($P = 0.035$). However, we failed to observe any significant difference in blood dyscrasias, including leukopenia, neutropenia, and lymphopenia. No differences in kidney or liver function were observed. Symptomatic women had significantly lower potassium levels compared to asymptomatic women (median: 3.70 mEq/L [range 3.00-4.60] vs median 4.30 mEq/L [range 3.70–6.20]; $P = 0.009$; Fig. 3B). Three women, all of them symptomatic, showed evidence of secondary infection, with positive cell (n = 1) and urine (n = 2) cultures.

Table 2
Laboratory Characteristics of Pregnant Women with COVID-19 by Symptom Status

Characteristics	Normal range	Asymptomatic (N = 15)		Symptomatic (N = 19)		*P*
		n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
	Hematological profile					
Blood group						
A	nd	4	26.67	5	26.32	0.928
AB	nd	1	6.67	0	0.00	
B	nd	1	6.67	2	10.53	
O	nd	9	60.00	12	63.16	
Rhesus status						
Negative	nd	0	0.00	2	10.53	0.492
Positive	nd	15	100	17	89.47	
Hct (%)	34.9–44.3* 34.7–45.1**	15	34.00 (24.60–40.40)	17	33.90 (27.00-40.70)	0.940
Leukocyte count (K/uL)	4.4–10.6* 4.0–11.0**	15	8.80(4.40–14.20)	16	9.70 (4.50–12.20)	0.621
Leukopenia[a]						
Yes	nd	2	13.33	5	31.25	0.394

* CCHHS normal values, **AMITA Saint Mary's normal values

ALP: alkaline phosphate, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Ca: calcium, Hb: hemoglobin, Hct: Hematocrit, INR: international normalized ratio, K: potassium, Na: sodium, PT: prothrombin time, SD: standard definition

[a] Leucocyte count < 5.9 x 10^9 cells/L.

[b] Lymphocyte count < 10^9 cells/L.

[c] Neutrophil count < 3.9 x 10^9 cells/L.

Characteristics	Normal range		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
		n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
Lymphocyte count (K/uL)	1.2–3.4* 0.6–3.4**	10	16.75 (9.50–31.00)	9	15.40 (5.00–33.00)	0.902
Lymphopenia[b]						
Yes	nd	0	0.00	0	0.00	NA
Basophil count (K/uL)	0-0.1* 0-0.2**	10	0.05 (0.00-0.40)	9	0.30 (0.00–5.00)	0.035
Neutrophil count (K/uL)	2.2–6.9* 1.7–7.7**	10	72.70 (40.40–86.10)	7	72.80 (65.60–79.00)	1.000
Neutropenia[c]						
Yes	nd	0	0.00	0	0.00	NA
Platelet count (K/uL)	161–369* 150–450**	14	216.00 (93.00-377.00)	16	209.50 (113.00-290.00)	0.950
	Blood biochemistry profile					
ALT (U/L)	5-35* 0–50**	5	12.00 (6.00–20.00)	13	12.00 (7.00–39.00)	0.519
AST (U/L)	0-40* 0–40**	5	20.00 (19.00–28.00)	13	17.00 (12.00–35.00)	0.236

* CCHHS normal values, **AMITA Saint Mary's normal values

ALP: alkaline phosphate, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Ca: calcium, Hb: hemoglobin, Hct: Hematocrit, INR: international normalized ratio, K: potassium, Na: sodium, PT: prothrombin time, SD: standard definition

[a] Leucocyte count < 5.9 x 10^9 cells/L.

[b] Lymphocyte count < 10^9 cells/L.

[c] Neutrophil count < 3.9 x 10^9 cells/L.

Characteristics	Normal range		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
		n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
Glucose mg/dL	65–110* 70–99**	7	93.00 (49.00-301.00)	14	88.50 (70.00-144.00)	1.000
Albumin (g/dL)	3.8–5.2* 3.5–5.7**	4	2.95 (2.80–3.30)	12	3.10 (2.60–3.70)	0.760
Total bilirubin (mg/dL)	0.2–1.2* 0.0–1.0**	4	0.60 (0.40–1.60)	12	0.60 (0.30-1.00)	0.668
ALP (U/L)	20-120* 35–104**	4	198.00 (141.00-342.00)	12	147.00 (84.00-268.00)	0.163
Creatinine (mg/dL)	0.6–1.4* 0.5–1.2**	5	0.60 (0.50-1.00)	12	0.53 (0.40–0.90)	0.387
Na (mEq/L)	135-145* 133–144**	6	135.50 (132.00-140.00)	13	136.00 (128.00-139.00)	0.894
K (mEq/L)	3.5-5.0* 3.5–5.1**	7	4.30 (3.70–6.20)	13	3.70 (3.00-4.60)	0.009
Ca (mg/dL)	8.5–10.5* 8.6–10.3**	4	8.35 (7.80–8.80)	12	8.20 (7.90–9.20)	0.903

* CCHHS normal values, **AMITA Saint Mary's normal values

ALP: alkaline phosphate, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Ca: calcium, Hb: hemoglobin, Hct: Hematocrit, INR: international normalized ratio, K: potassium, Na: sodium, PT: prothrombin time, SD: standard definition

[a] Leucocyte count < 5.9 x 10^9 cells/L.

[b] Lymphocyte count < 10^9 cells/L.

[c] Neutrophil count < 3.9 x 10^9 cells/L.

Characteristics	Normal range		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
		n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
BUN (mg/dL)	8–20* 7–25**	5	5.00 (3.00–18.00)	12	5.00 (2.00–9.00)	0.631
Protein (g/dL)	6.4–8.3* 6.4–8.9**	4	5.50 (4.80-7.00)	12	5.75 (4.70–6.70)	0.670
	Coagulation profile					
PT (s)	11.9–14.1*	7	12.70 (11.30–16.00)	7	13.10 (10.70–13.50)	0.848
aPTT (s)	25.1-36.5*	7	31.70 (26.00-35.10)	6	30.45 (27.00-34.70)	0.943
INR	0.9–1.1**	7	1.00 (0.89–1.31)	7	1.01 (0.49–1.05)	0.654
Fibrinogen (mg/dL)	178–454* 163–463**	7	419.00 (283.00-674.00)	6	456.00 (354.00-542.00)	1.000
	Microbiological profile					
Blood culture						
Negative		2	100.00	4	80.00	1.000
Positive		0	0.00	1	20.00	
Urine culture						
Negative		2	100	3	60.00	1.000
Positive		0	0.00	2	4.00	

* CCHHS normal values, **AMITA Saint Mary's normal values

ALP: alkaline phosphate, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Ca: calcium, Hb: hemoglobin, Hct: Hematocrit, INR: international normalized ratio, K: potassium, Na: sodium, PT: prothrombin time, SD: standard definition

[a] Leucocyte count < 5.9 x 10^9 cells/L.

[b] Lymphocyte count < 10^9 cells/L.

[c] Neutrophil count < 3.9 x 10^9 cells/L.

Placental histopathological features

We found no association of specific histopathological placental features with signs and symptoms of COVID-19 (Table 3). However, we did observe a higher prevalence of FVM, immunological or inflammatory processes, and chorangiosis in symptomatic women compared to asymptomatic women. Fetal vascular malperfusion (n = 2; one avascular villi type and one hemorrhagic endovasculitis type) and chorangiosis (n = 4) were observed exclusively in the placentas of symptomatic patients (Fig. 4).

Table 3
Placental Pathology of Pregnant Women with COVID-19 by Symptom Status

Characteristics	Asymptomatic (N = 15)		Symptomatic (N = 19)		*P*
	n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
MVM					
No	3	25.00	6	31.58	1.000
Yes	9	75.00	13	68.42	
FVM					
No	12	100	17	89.47	0.510
Yes	0	0.00	2*	10.53	
IM processes					
No	7	58.33	7	36.84	0.242
Yes	5	41.67	12	63.16	
Chorangiosis					
No	12	100	15	78.95	0.139
Yes	0	0.00	4	21.05	
Intervillous thrombus					
No	**9**	75.00	17	89.47	0.350
Yes	3	25.00	2	10.53	
Placental weight	11	489.00 (122.87)	16	506.13 (96.44)	0.689
IM: inflammatory or immune process, FVM: fetal vascular malperfusion, MVM: maternal					
vascular malperfusion, SD: standard deviation					
*Avascular villi type (*n* = 1), hemorrhagic endovasculitis type (*n* = 1)					

Logistic regression analysis of significant maternal variables

Simple logistic regression analysis showed that the odds of severe COVID-19 increased as pregestational BMI increased and pre-delivery potassium levels decreased (Table 4). For each unit increase in pregestational BMI, the odds of being symptomatic due to SARS Cov-2 infection increased by 18% (OR: 1.18; 95% CI: 1.03–1.34), while a one-unit decrease in serum potassium levels among pregnant women before delivery increased the odds of symptomatic infection by 19.72 (OR: 19.72; 95% CI: 1.03–376.79).

Table 4
Simple Logistic Regression Model of Predictors of Symptomatic COVID-19 in Pregnant Women.

Variable	Odds ratio (OR)	95% CI
Pre-pregnancy BMI (kg/m2)	1.18	(1.03–1.34)
Potassium (mEq/L)*	19.72	(1.03-376.79)

*In the calculation of the odds ratio for potassium, negative one unit (i.e., unit = − 1) was used to calculate the increase in the odds of symptomatic infection per one unit decrease in potassium level.

Fetal and neonatal outcomes

Among 34 deliveries, there were two twin deliveries culminating in a total of 36 infants in our study population (Table 5). Mean birth weight was 3332.50g (SD = 778.37) with a median GA of 39.10 weeks (range: 27.00-41.40). The average birth weight of babies born to symptomatic women was significantly higher than that of asymptomatic women (mean: 3454.00g [SD: 521.11] vs 2885.80g [SD: 941.09], P = 0.048). We observed three premature deliveries (GA < 37 weeks), with one resulting in twin fetal demise.

Table 5
Clinical and Demographic Characteristics of Infants Born to Women with COVID-19, by Maternal Symptom Status

Characteristics		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
	n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
Weight of newborns, g	15	2885.80 (941.09)	19	3454.00 (521.11)	0.048
Premature birth (< 37 weeks)	3	21.43	0	0.00	0.067
Stillbirth*	2	13.33	0	0.00	
Sex					
Male	9	60.00	9	47.37	0.464
Female	6	40.00	10	52.63	
Apgar scores at 1 minute	15	9.00 (4.00–9.00)	19	9.00 (3.00–9.00)	0.790
Apgar scores at 5 minutes	15	9.00 (5.00–9.00)	19	9.00 (6.00–9.00)	0.724
RT PCR for SARS-Cov2					
Positive	0	0.00	0	0.00	NA
Negative	15	100.00	13	68.42	
Not done	1	0.00	6	31.58	
Initial temperature	15	36.80 (35.80–37.20)	18	36.70 (36.40–37.60)	0.971
Symptoms					
Apnea	1	7.14	0	0.00	0.424
Increased work of breathing	2	14.29	3	15.79	1.000
Desaturations	2	14.29	4	21.05	0.618
Hypoglycemia	0	0.00	1	5.26	1.000
Poor feeding	0	0.00	2	10.53	0.496

*Includes one pair of twins

NA: Not available, RDS-Respiratory distress syndrome, RT-PCR,- Reverse Transcriptase -Polymerase chain reaction, TTN-Transient tachypnea of newborn, SCN/NICU: Special Care Nursery/ Neonatal Intensive Care Unit,

GERD: gastroesophageal reflux disease.

Characteristics		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
	n	Mean (SD)/ Median (Min-Max)/ %	n	Mean (SD)/ Median (Min-Max)/ %	
Fever	1	7.14	0	0.00	0.424
Diagnosis					
Normal	9	60.00	9	50.00	0.566
RDS	2	13.33	1	5.26	0.571
Rule out sepsis	3	20.00	0	0.00	0.076
TTN	0	0.00	2	10.53	0.492
Apnea	1	6.67	0	0.00	0.441
Pneumomediastinum	0	0.00	1	5.26	1.000
Poor feeding/GERD	0	0.00	1	5.26	1.000
Hypoglycemia	0	0.00	1	5.26	1.000
Birth Injury	0	0.00	1	5.26	1.000
Disposition					
SCN/NICU visit and discharged	6	40.00	9	50.00	0.566
Nursery/Postpartum floor visit and discharged	9	60.00	9	50.00	
*Includes one pair of twins					
NA: Not available, RDS-Respiratory distress syndrome, RT-PCR,- Reverse Transcriptase -Polymerase chain reaction, TTN-Transient tachypnea of newborn, SCN/NICU: Special Care Nursery/ Neonatal Intensive Care Unit,					
GERD: gastroesophageal reflux disease.					

In contrast to the mothers, the majority of newborns were asymptomatic, with tachypnea most likely secondary to transient tachypnea observed as the most common symptom in five symptomatic newborns. Among five newborns with tachypnea, four were born to symptomatic mothers. However, all the newborns tested negative for COVID-19. We failed to detect any significant difference in method or mode of delivery between symptomatic and asymptomatic women ($P = 0.493$). Of the four caesarean deliveries performed in asymptomatic women, two were for twins in a breech presentation and two were indicated by non-reassuring fetal status.

Laboratory characteristics of newborns

We did not detect any difference in laboratory characteristics in infants of symptomatic women compared to those of asymptomatic women (Table 6). We also measured total IgM (n = 6) and total IgG (n = 7) antibodies in a limited number of infants (Table 6). Our data suggest higher levels of IgM antibodies in one infant (17.00) born to a symptomatic mother compared to four infants born to asymptomatic mothers (median: 10.00, range: 7.00–17.00), but the low sample size makes it impossible to make any meaningful clinical interpretation.

Table 6
Laboratory Characteristics of Infants Born to Women with COVID-19, by Maternal Symptom Status

Characteristics	Normal Range	Asymptomatic (N = 15)		Symptomatic (N = 19)		*P*
		n	Median (Min-Max)/ %	n	Median (Min-Max)/ %	
	Hematological profile					
Hct (%)	42–60.0* 42.0–54.0**	6	46.40 (38.70–56.40)	14	50.90 (45.20–61.80)	0.322
Leucocyte count (K/uL)	9.1–34.0* 8.0-15.4**	8	13.00 (6.90–24.80)	14	13.85 (9.10–23.70)	0.657
Leukopenia[a]						
Yes	nd	2	28.57	5	35.71	1.000
Lymphocyte count (%)	11.0-30.9* 33.7–67.6**	7	26.00 (19.00–41.00)	14	22.00 (5.00–49.00)	0.501
Lymphopenia[b]						
Yes	nd	0	0.00	0	0.00	NA

* CCHHS normal values, **AMITA Saint Marys normal values ;ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, Hct: Hematocrit, Ig: immunoglobulin, NA: not available, nd: not defined

[a] Leucocyte count < 9.0 x 10^9 cells/L for preterm infants and 13.0 x 10^9 cells/L for term infants.

[b] Lymphocyte count < 2.0 x 10^9 cells/L.

[c] Neutrophil count < 6.0 x 10^9 cells/L.

Characteristics	Normal Range		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
		n	Median (Min-Max)/ %	n	Median (Min-Max)/ %	
Basophil count (%)	0.0-0.3* 0.1–0.8**	5	2.00 (0.00–7.00)	7	0.00 (0.00–17.00)	0.487
Monocyte count (%)	0.0–10.0* 6.7–19.9**	3	9.00 (8.00–12.00)	8	13.20 (7.00–18.00)	0.357
Neutrophil count (%)	65.9–69.1* 20.2–46.2**	7	50.00 (44.00–69.00)	14	60.50 (16.00–77.00)	0.192
Neutropenia[c]						
Yes	nd	0	0.00	0	0.00	NA
Platelet count (K/uL)	200–400* 145–262**	8	192.00 (144.00-263.00)	14	245.50 (65.00-475.00)	0.232
Eosinophils count (%)	0.3–5.2**	3	3.00 (0.00–4.00)	6	1.55 (0.00–4.00)	0.691
	Blood biochemistry profile					
CRP (mg/ dL)	< 1.0**	3	0.10 (0.07–2.09)	8	0.09 (0.01–1.50)	0.409
ALT (U/L)	5–35* 0.0–40.0**	3	10.00 (9.00–17.00)	6	13.50 (8.00–24.00)	0.519
AST (U/L)	0–40* 0–32**	2	42.50 (25.00–60.00)	5	49.00 (28.00–63.00)	0.847

* CCHHS normal values, **AMITA Saint Marys normal values ;ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, Hct: Hematocrit, Ig: immunoglobulin, NA: not available, nd: not defined

[a] Leucocyte count < 9.0 x 10^9 cells/L for preterm infants and 13.0 x 10^9 cells/L for term infants.

[b] Lymphocyte count < 2.0 x 10^9 cells/L.

[c] Neutrophil count < 6.0 x 10^9 cells/L.

Characteristics	Normal Range		Asymptomatic (N = 15)		Symptomatic (N = 19)	*P*
		n	Median (Min-Max)/ %	n	Median (Min-Max)/ %	
Creatinine (mg/dL)	0.6–1.4* 0.5–1.2**	3	0.70 (0.70–0.80)	6	0.86 (0.50–1.30)	0.693
BUN (mg/dL)	8–20* 7–25**	3	9.00 (7.00–28.00)	5	8.00 (3.00–15.00)	0.368
Blood culture						
Negative		7	100	9	100	NA
Positive		0	0.00	0	0.00	
	Immunological profile					
IgM (mg/dL)	3–13* 14–142 **	5	10.00 (7.00–17.00)	1	17.00 (17.00–17.00)	0.373
IgG (mg/dL)	74-1421*	5	724.00 (483.00-1190.00)	2	560.00 (20.00-1100.00)	0.847

* CCHHS normal values, **AMITA Saint Marys normal values ;ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, Hct: Hematocrit, Ig: immunoglobulin, NA: not available, nd: not defined

[a] Leucocyte count < 9.0×10^9 cells/L for preterm infants and 13.0×10^9 cells/L for term infants.

[b] Lymphocyte count < 2.0×10^9 cells/L.

[c] Neutrophil count < 6.0×10^9 cells/L.

Length of preterm fetal exposure and risk of vertical transmission

Fourteen of 33 pregnant women (42%) were infected prior to GA of 37 weeks, the cutoff for preterm birth (one woman had missing data on GA at the onset of infection). For the women who were diagnosed prior to 37 weeks (n = 14), the gestational age of the fetus at maternal COVID diagnosis ranged from 24 to 36.6 weeks, with the longest duration of exposure 14.5 weeks (Table 7). The average duration of fetal exposure, which is the time interval between the diagnosis of maternal COVID-19 infection and birth, was two weeks. The mean duration of fetal exposure was longer for symptomatic than asymptomatic women (2.10 weeks versus 0.05 weeks (P = 0.035). However, none of the infants tested positive for COVID-19, despite fetal prematurity and a relatively long duration of exposure. Moreover none of the infants demonstrated any signs or symptoms specific to COVID-19 .

Table 7
Neonatal outcomes and duration of fetal exposure among women infected with SARS-CoV-2 prior to 37 weeks gestation.*

S. No.	GA at maternal COVID-19 diagnosis	GA of fetus/ new-born on delivery	Duration between infection and delivery in days	COVID-19 test on the newborn (24hrs)	COVID-19 test on the newborn (48hrs)	Total IgM (mg/dL)	Total IgG (mg/dL)	Signs and symptoms exclusively attributed to COVID-19 infections
1	26.2	28	12	Negative	Negative	10	483	None
2	33.3	38.3	35	Negative	Negative	NA	NA	None
3	36.6	37.2	03	Negative	Negative	NA	NA	None
4	34.6	38	22	NA	NA	NA	NA	None
5	35.2	37.3	14	Negative	Negative	NA	NA	None
6	32.1	32.6**	05	Negative, Negative	Negative, Negative	9, 17	706, 724	None
7	33.1	39.6	60	Negative	Negative	NA	NA	None
8	28.4	39.4	76	NA	NA	NA	NA	None
9	36.6	37.1	02	Negative	Negative	NA	< 20	None
10	32.6	40	50	Negative	Negative	NA	NA	None
11	24	38.5	102	NA	NA	NA	NA	None
12	28	39.3	80	NA	NA	NA	NA	None
13	32	39.5	53	NA	NA	NA	NA	None

*Among 14 women infected prior to 37 weeks gestation, one mother had an infant with fetal demise.

**Twins; GA: gestational age, Ig: immunoglobulin, NA: not available

Discussion

To the best of our knowledge, this is the largest cohort of mother-baby dyads (SARS-Cov-2–positive women and their newborn infants) to undergo detailed clinical and biochemical investigation in the state of Illinois. In this study, high BMI and low potassium levels were associated with symptomatic disease in mothers.

About half of pregnant women in our study developed symptoms of COVID-19, which falls in the middle range of similar studies. A recent study of 70 pregnant women with SARS-CoV-2 in New York City reported that only 21% presented with symptoms,[23] while an earlier study from Wuhan, China showed 95% of pregnant women with the virus exhibited symptoms.[24]

We found that women with a higher pregestational BMI were more likely to be symptomatic, consistent with several reports showing an association between pregestational BMI with severe maternal outcomes among women with COVID-19.[11,13] An Italian study observed significantly higher pregestational BMI in 7 of 14 women showing severe symptoms,[11] and a case-series from Washington State found that the majority of pregnant women with severe infection were overweight or obese.[13]

Our finding of significantly lower potassium levels in symptomatic women is consistent with a report of lower potassium levels (< 3.5 mEq/L) in 119 patients (41%) of 290 with COVID-19 in the general population.[25] In that study, hypokalemic patients were more likely to stay longer in hospitals, with a higher rate of respiratory symptoms. COVID-19 infection promotes angiotensin-converting enzyme 2 (ACE2) depletion in affected cells, which in turn promotes vasoconstriction, leading to increased reabsorption of water and sodium.[26] These changes could lead to increased potassium excretion, specifically in symptomatic patients who may have higher viral loads.[27] Also, the contribution of respiratory alkalosis or diarrhea to low potassium levels among pregnant women with COVID-19 cannot be ruled out. Since low potassium levels could lead to life-threatening conditions, including cardiac events, our findings suggest the need to monitor serum potassium and improve care for pregnant women with COVID-19 by ensuring adequate potassium supplementation.

Hispanic and Non-Hispanic Black populations comprised 44% and 38% of the pregnant women in our study population, respectively. However, we did not observe an association between ethnicity or race and symptomatic infection. Our findings are in contrast to a recent study of 1,568 pregnant and postpartum women that identified Hispanic ethnicity and obesity as major risk factors for moderate and severe COVID-19.[28]

Our results also showed significantly higher basophil cell count in symptomatic patients compared with asymptomatic patients. A recent study demonstrated an association of elevated basophil levels with the IgG antibodies against SARS-CoV-2 produced by B cells during the disease's recovery phase, suggesting the possibility of heightened humoral response in symptomatic pregnant women.[29]

We did not find a statistically significant association of specific placental pathologies with COVID-19 symptom status among the women in our study, and this result is consistent with a recent report by Hecht et al.[30] However, we did observe a spectrum of histopathologies (chorangiosis and FVM) exclusively among symptomatic women, which were similar to inflammatory changes observed in placentas from a case series of fetal demise associated with maternal SARS-Cov-2 infection. [16]

Our data showed absence of perinatal transmission of COVID-19, regardless of the duration the fetus was exposed to the virus prior to delivery (Table 7). Our findings are remarkable because they underscore the distinctly different perinatal transmission dynamics of SARS-CoV-2 compared to other viruses that cause congenital infections, [20] where timing and duration of exposure may affect likelihood of transmission and/or severity of disease in the newborn, and effects may be even greater for preterm infants.[20] In our study, none of the preterm infants were affected, and even the infant exposed for over 3 months in utero did not test positive or show symptoms of COVID-19. Our results are in line with current literature showing low rates of vertical transmission and symptomatic infection among infants of women with COVID-19 during pregnancy.[31–33]

Our study has several limitations. The small sample size limits generalizability to other states and cities across US, and we may be underpowered due to missing values for several laboratory characteristics. Additionally, our retrospective data collection may contribute to ascertainment bias.

Even so, our findings have important implications for clinical management of pregnant women with COVID-19. Our study suggests this group should be closely monitored for a rapid progression of symptoms, especially women with a high pregestational BMI and/or low potassium levels. However, it remains to be seen whether low potassium levels are a cause or outcome of symptoms observed in pregnant women with COVID-19.

Declarations

Ethics approval and consent to participate

The study's protocol was expeditiously approved by the institutional research ethics committees associated with John H. Stroger, Jr. Hospital of Cook County (approval number: 20-098) and AMITA Health Saints Mary and Elizabeth Medical Center (approval number: 2021-0193-02). The institutional research ethics committees associated with John H. Stroger, Jr. Hospital of Cook County (approval number: 20-098) and AMITA Health Saints Mary and Elizabeth Medical Center (approval number: 2021-0193-02) waived the requirement of informed consent.

Guidelines

All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, with removal of identifying information.

Competing interests

The author(s) report no conflict(s) of interest.

Funding

No funding was received for this study.

Authors' contributions

Author contributions were as follows: JM—conception, design, data analysis, and first draft; BP—data collection, case follow-up, and first-draft edit; NR and KF—pathologic analysis of placentas and review/edit of related content; KM—review and substantial edit; BL and LY data collection and IRB permissions from AMITA St. Mary’s and Elizabeth Hospital.

All authors have approved the manuscript and have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

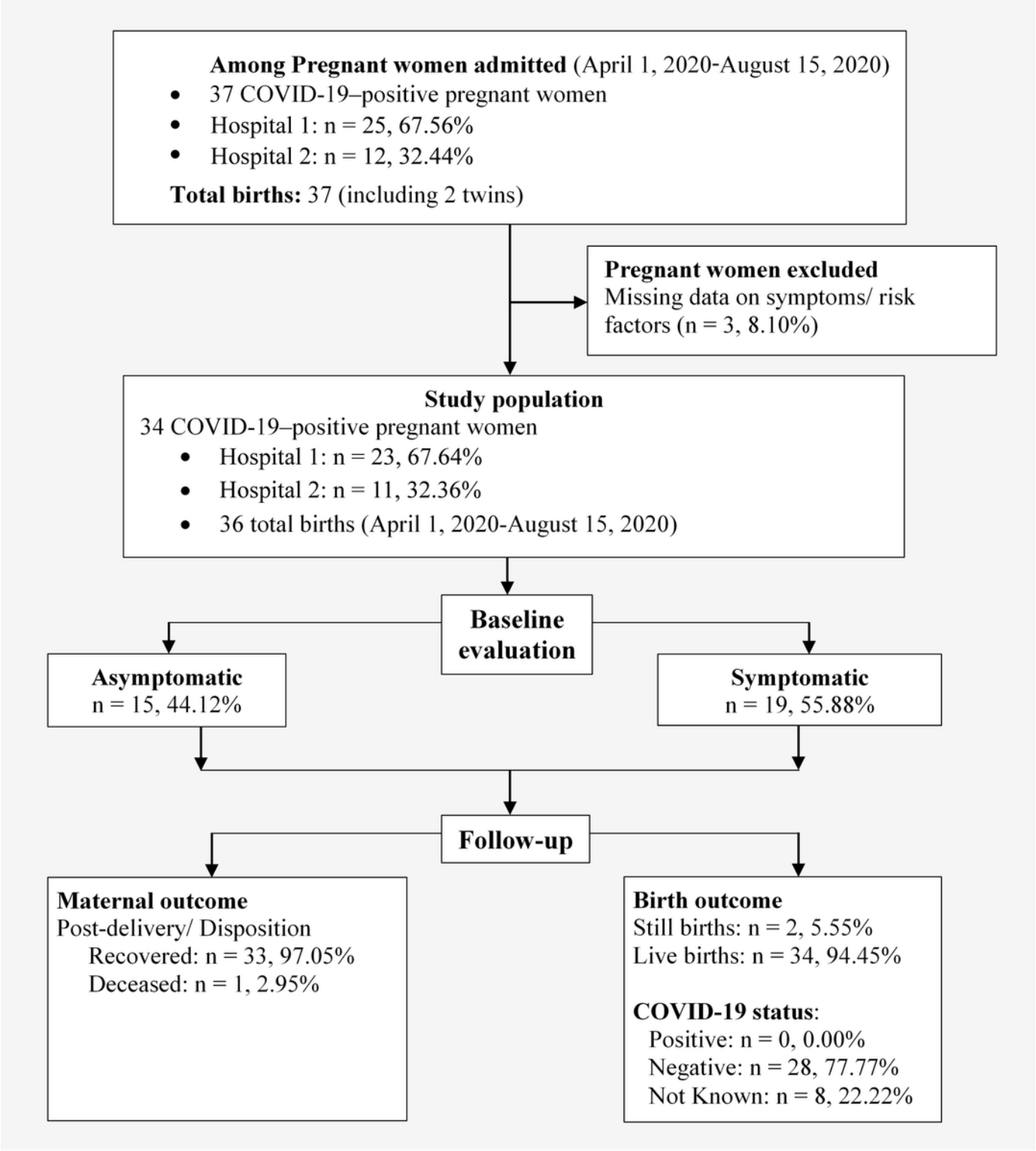

Figure 1

Flowchart of the study population selection and maternal and infant outcomes. Hospital 1 is John H Stoger, Jr Hospital of Cook County; Hospital 2 is Amita St. Mary's and Elizabeth Hospital.

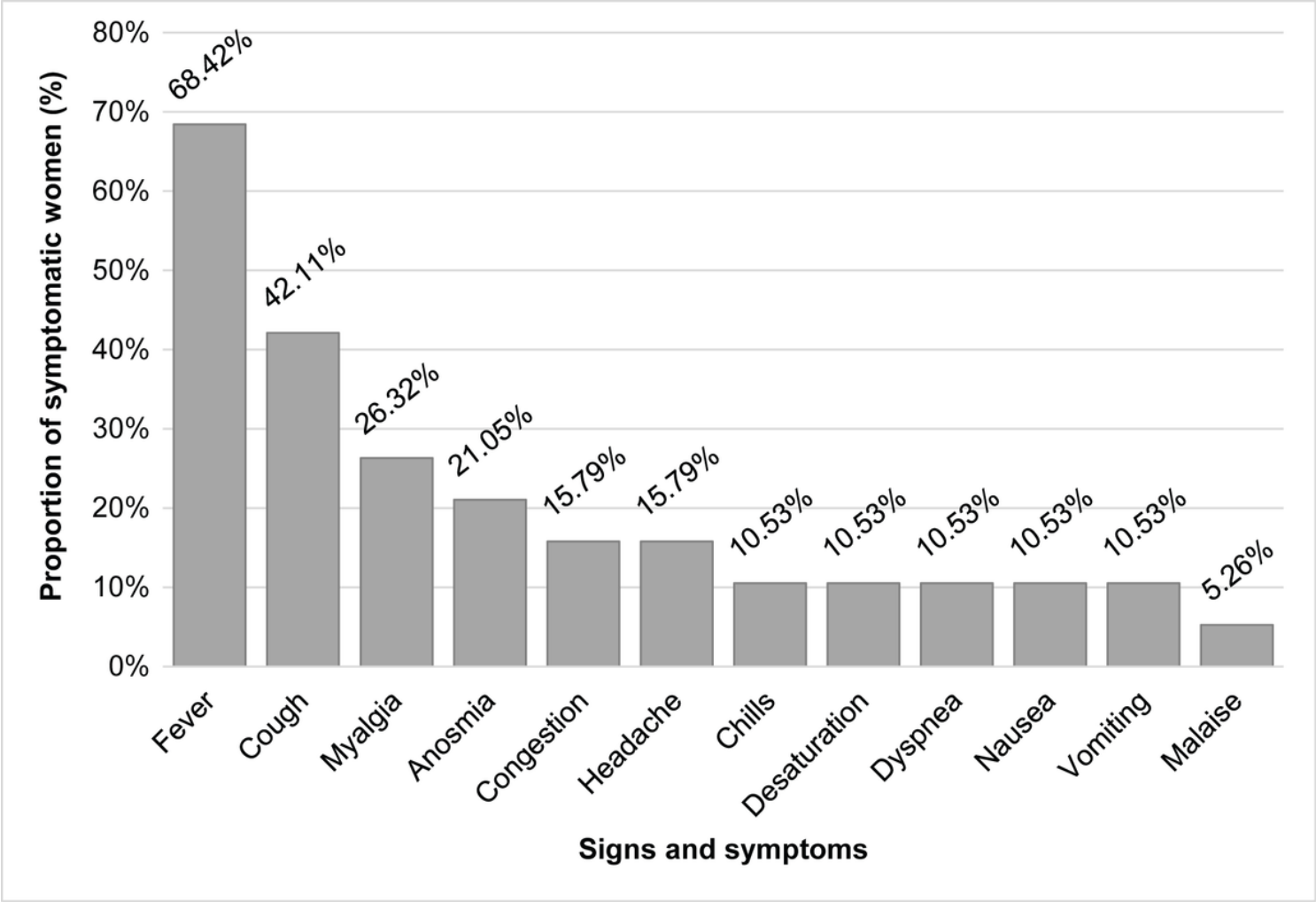

Figure 2

Distribution of symptoms, secondary to COVID-19 infection, among symptomatic pregnant women.

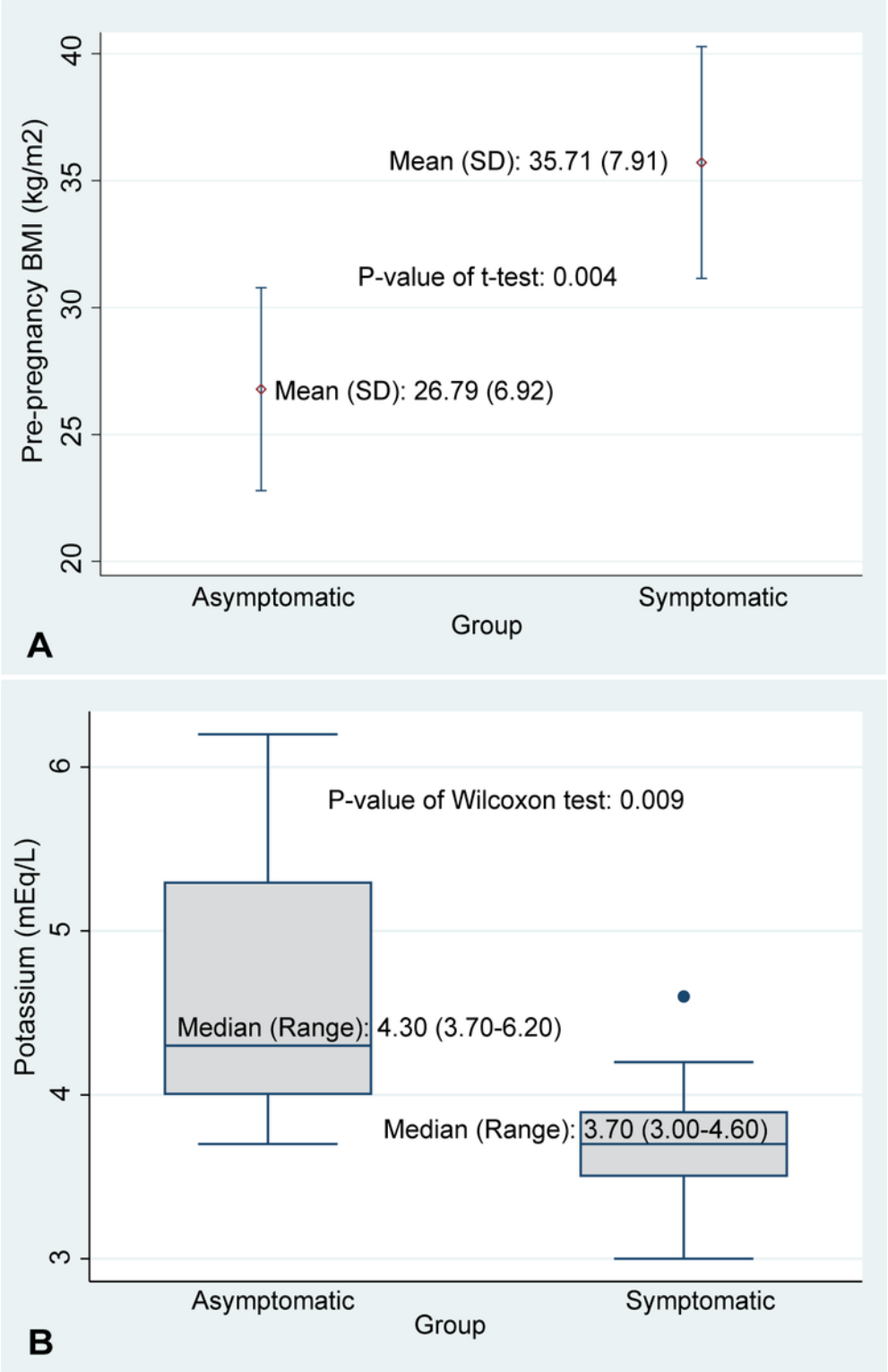

Figure 3

Distribution of pregestational BMI and potassium levels among pregnant women with COVID-19. A. Distribution of pregestational BMI by symptom status. B. Distribution of potassium levels by symptom status.

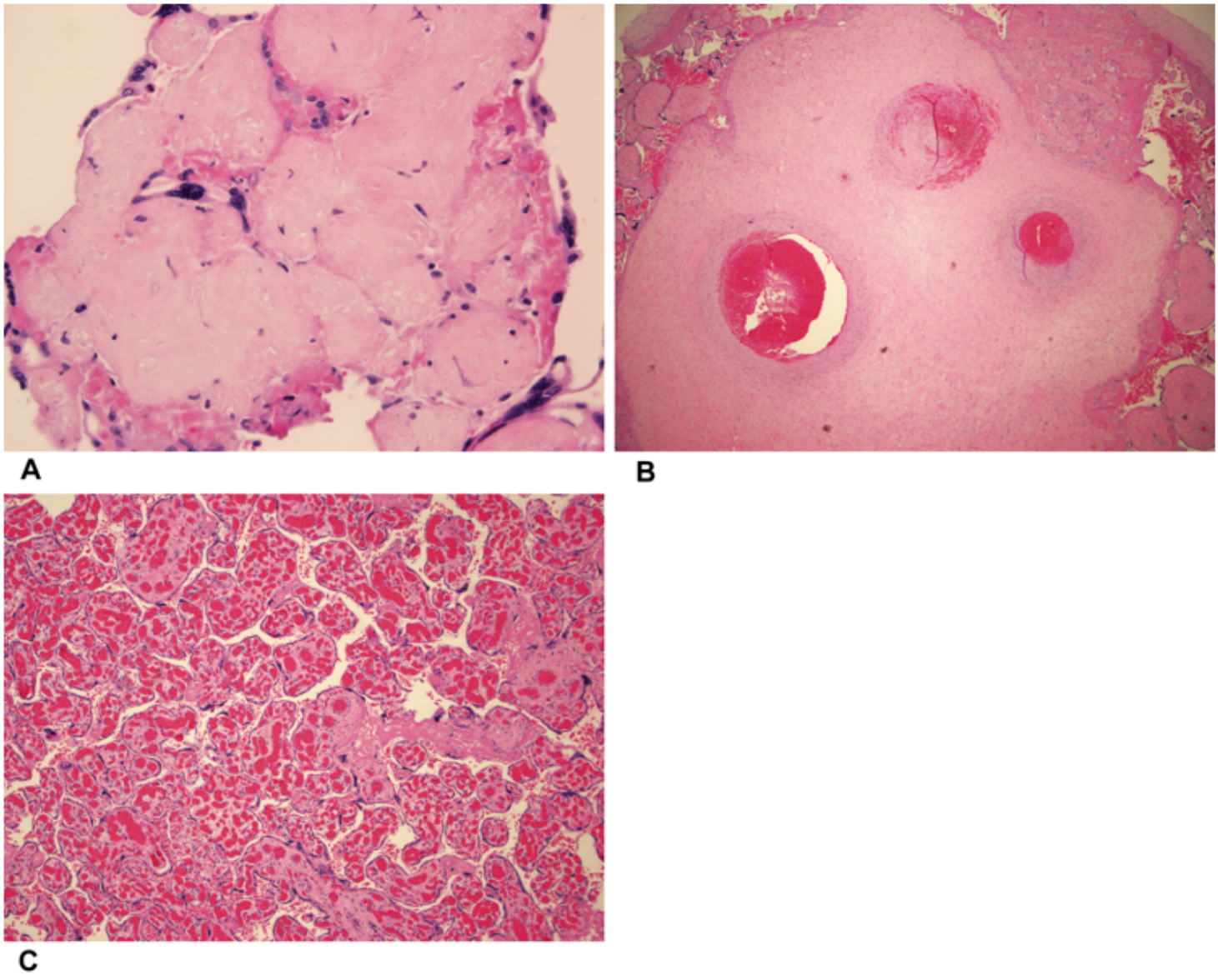

Figure 4

Placental pathology unique to symptomatic women with COVID-19 in our study population. A. Fetal vascular malperfusion (FVM), avascular villi type (n=1). B. FVM, hemorrhagic endovasculitis type (n=1). C. Chorangiosis (n=4).