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BRIEF REPORT

Hematologic characteristics and coagulopathy in pregnancy with COVID-19 succeeding the first wave: a multicenter retrospective cross-sectional study

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Abstract

Background: Early reports have demonstrated an association of COVID-19 infection during pregnancy and postpartum period with coagulopathy and bleeding complications and indicated that pregnant people with COVID-19 are more likely to experience coagulopathy and venous thromboembolism. A recent report concerning such complications during the first wave of the pandemic was reassuring; however, no publications have evaluated these issues in the context of increased illness severity with the emergence of SARS-CoV-2 variants of concern.

Objectives: We performed a retrospective, multinational cohort study in Canada, Romania, and the United Kingdom, aiming to provide a comprehensive analysis of the hematologic test characteristics of pregnancies affected by COVID-19 after the first wave of the pandemic.

Results: Three-hundred-seventy patients were evaluated. Markers of inflammation and endothelial dysfunction were significantly elevated, in keeping with observations in the nonpregnant population. Reassuringly, despite more severe disease noted in succeeding waves of the pandemic, there was no significant evidence of COVID-19-associated coagulopathy, and overall, no association was demonstrated between isolated coagulation abnormalities and bleeding risk. Notably, fibrinogen below 2g/L was again linked with the risk of postpartum hemorrhage. Finally, venous thromboembolism risk was low but noted more frequently in those with severe illness despite thromboprophylaxis.

Conclusion: Our findings add valuable insights into the nature of hematologic test characteristics, bleeding, and thrombotic complications for those affected with COVID-19 in pregnancy, reassuring readers of the low incidence of bleeding and thrombotic complications but inviting further debate as to the degree of thromboprophylaxis that may benefit the subgroup with severe disease.

KEYWORDS
coagulation, COVID-19, hematologic tests, pregnancy, venous thromboembolism

Essentials

- Data from academic tertiary hospitals in Canada, the United Kingdom, and Romania were collected.
- Bleeding, clotting, and inflammation parameters in pregnant people with COVID-19 were analyzed.
- No laboratory or clinical evidence of increased bleeding risk was reported.
- A low risk of clotting was reported, though higher with severe illness, despite low-dose blood thinners.

1 | INTRODUCTION

Having incited vascular and endothelial damage in the pulmonary system, the SARS-CoV-2 virus prompts an immune-mediated inflammatory response, resulting in the development of COVID-19-associated coagulopathy (CAC) [1]. Hematological abnormalities in COVID-19 have been identified as biomarkers of disease progression and unfavorable outcomes [2]. Early pregnancy reports have also demonstrated an association of COVID-19 infection during the peripartum period with coagulopathy and bleeding complications [3] and indicated that pregnant people with COVID-19 are more likely to experience coagulopathy and thromboembolism [4,5]. In some instances, disseminated intravascular coagulation (DIC) has added to the complexity [6].

Research studies addressing these issues in pregnancy are scarce but mandatory, given the unique coagulation profile adjustments in this category of patients. In our recent report from the International Society for Thrombosis and Haemostasis registry on pregnancy and COVID-19 associated coagulopathy (ISTH COV-PREG-COAG) registry, with data from the first wave of the pandemic [7], we described isolated abnormal coagulation parameters in 20% of the cohort, more frequently noted with moderate/severe disease and overall low rates of bleeding and thrombosis. However, in contrast to the first wave [8], the emergence of SARS-CoV-2 variants of concern in subsequent waves was associated with a high likelihood of severe illness following COVID-19 diagnosis in pregnancy [9]. Yet, information regarding the evolution of hematologic characteristics in pregnant people after the first pandemic wave (hereafter referred to as subsequent waves) remains unknown. Thus, the aim of this study was to provide a comprehensive analysis of the hematologic features of pregnancies affected by COVID-19, with a focus on coagulation, bleeding, and thrombosis, and to characterize these according to the severity of illness.

2 | METHODS

2.1 | Data collection and analysis

This was a multinational, retrospective cross-sectional study involving 3 tertiary academic hospitals (County Emergency Hospital Cluj-Napoca, Romania; Mount Sinai Hospital, Canada; and The Royal Free National Heath Service Foundation Hospital, United Kingdom). In each institution, all consecutive patients with COVID-19 and laboratory investigations near the time of diagnosis were included. One coauthor in each institution abstracted the study, and another audited the data. A case report form, consisting of 569 elements, was used to collect data. All consecutive patients with COVID-19 in each respective institution who had laboratory investigations around the time of diagnosis were included in the study.

Pregnancy- and trimester-specific laboratory ranges were used to determine abnormalities [10,11]. Laboratory data included general and special hematology and coagulation indices and biochemical parameters based on their previously reported prognostic value in COVID-19. Coagulopathy was considered present when any coagulation parameter abnormality, bleeding, or thrombotic event was encountered. Questions regarding anticoagulation focused on low-molecular-weight heparin, the agent of choice for thromboprophylaxis in pregnancy [12]. Clinical variables were similarly defined as reported by the ISTH COV-PREG-COAG registry [7]. Specifically, COVID-19 severity was deemed asymptomatic (SARS-CoV-2 positive, absent clinical symptoms), mild (outpatient management), moderate (hospitalization, without critical care), or severe (intensive care unit admission). [7]

Determination of DIC in the nonpregnant population is based on criteria proposed by ISTH, including platelet count, fibrin-related markers (D-dimer or fibrin degradation products), prothrombin time, and fibrinogen [13]. However, the hormonally altered hemostatic milieu in pregnancy is characterized by procoagulant activity, recognized by the pregnancy DIC score, which incorporates the platelet count, fibrinogen, and difference in prothrombin time (patient's result compared with average control for a given laboratory), while excluding D-dimer [14]. A comparison between the ISTH and pregnancy DIC scores was performed.

Local ethics approval was provided at the level of each participating site. Data was entered under a study number following the de-identification of individual records. Charts and electronic records were reviewed to abstract relevant data, which was then downloaded into an SPSS (IMB, SPSS Inc) spreadsheet. Descriptive statistics included frequencies and percentages for categorical variables and means (SDs) or medians (IQR) for continuous variables, depending on the normality of distribution. Group comparisons for categorical variables were made using chi-squared or Fisher's exact tests, as applicable.

3 | RESULTS AND DISCUSSION

We describe the hematologic and laboratory characteristics of a multinational cohort of 370 pregnant women diagnosed with

COVID-19 who underwent laboratory assessment and received care in a participating center (Canada [*n* = 49], Romania [*n* = 276], and UK [*n* = 45]). Patients were identified via databases maintained in each center, which included all pregnant patients with a positive polymerase chain reaction for COVID-19. Data were collected from June 2020 to March 2022. Where relevant, current data representing subsequent waves of the pandemic were compared with data from the first wave previously reported from the ISTH COV-PREG-COAG registry [7].

3.1 | Demographic and clinical data

Detailed demographic and clinical findings are shown in Table 1. Throughout the pandemic, most patients had asymptomatic/mild disease; however, the proportion with moderate/severe illness was higher in the subsequent waves compared with the first wave [73 [20%] vs 53 [12%]; *P* = .004]. This is in keeping with the reported literature and the emergence of the Delta variant in the second wave of the pandemic [15].

3.2 | Hematologic and biochemical data

Table 2 details hematologic and biochemical parameters in the context of disease severity. Anemia was more frequent in moderate/severe cases than asymptomatic/mild cases. The same was true for leukopenia, neutropenia, and lymphopenia. The findings are in keeping with reports within the nonpregnant population correlating their presence with the severity of illness and are thought to be secondary to the expression of the ACE-2 receptor on the lymphocyte surface enhancing susceptibility to infection with the SARS-CoV-2 virus leading to cell lysis, as well as cytokine activation contributing to lymphocyte apoptosis [18].

Correspondingly, we found significant elevations of C-reactive protein (CRP), procalcitonin, and ferritin in patients with moderate/severe compared with mild/asymptomatic disease, reflecting the prominence of inflammatory state and endothelial dysfunction in case of more severe illness, mechanisms now established to play a central role in the underlying pathology of the disease [19]. A higher incidence of elevated CRP and hyperferritinemia was noted in the subsequent waves compared with the first wave [7], consistent with the higher proportion of severe illness encountered in the current data and further supporting the rising acuity of disease observed during pregnancy with the emergence of the Delta variant [15]. Further supporting this phenomenon was the increased frequency of high transaminase levels in those with moderate/severe illness, previously reported in the nonpregnant population to be directly related to disease severity and seen more frequently in those with high CRP levels [20].

Conversely, hypoferritinemia was more often noted in those with asymptomatic/mild disease, an observation consistent with the high prevalence of iron deficiency during pregnancy [11] and the relative absence of acute phase reaction in those less severely ill [21].

3.3 | Coagulation parameters

Details of coagulation parameters thrombotic and bleeding complications are presented in Table 2. With prior reports of hematologic derangements and CAC in those with moderate/severe illness, given the higher incidence of moderate/severe illness in this data from the subsequent waves, we expected to encounter a higher prevalence of CAC. However, reassuringly, our findings were overall benign.

There was no significant difference in the presence of isolated coagulation abnormalities between those with asymptomatic/mild vs moderate/severe disease and no difference in the frequency of isolated coagulation abnormalities in those with moderate/severe illness in the first wave compared with subsequent waves [23 [49%] vs 49 [67%]; *P* = .06]. However, prolonged activated partial thromboplastin time (aPTT) was seen significantly more frequently in moderate/severe compared with asymptomatic/mild disease, with the observation remaining consistent between the first and subsequent waves [9 [32%] vs 12 [18%]; *P* = .175]. While prolonged aPTT can be linked to a higher risk of bleeding, we did not observe this in our sample, where 2 (14%) individuals with prolonged aPTT had postpartum haemorrhage (PPH) while 15 did not (5%, *P* = .175), and the presence of both aPTT and PPH were encountered in only 0.6% of the overall cohort.

As with data from the first wave, the severity of illness did not influence the presence of thrombocytopenia, the incidence of which (12% in the current dataset) is in line with the incidence of gestational thrombocytopenia, which is typically encountered in the third trimester of pregnancy when the majority of COVID-19 diagnosis was made [22]. Similarly, there was no difference according to severity of illness in the frequency of hypofibrinogenemia, a finding which remained consistent between the first and subsequent waves. While hypofibrinogenemia according to pregnancy-specific values was present in 46 (17%) of our overall cohort, hypofibrinogenemia <2 g/L was noted in only 8/250 (3%) for whom these data were available. However, PPH was more frequent in those with fibrinogen <2 g/L than in those with fibrinogen over this threshold (3/8 [38%] vs 10/242 [4%], *P* = .005). This finding is consistent with the reported association of fibrinogen <2 g/L with PPH [23].

Despite reports in the nonpregnant population of a correlation of DIC with CAC [24], using ISTH criteria, no cases of DIC were recorded in our data [25]. Conversely, using the pregnancy-specific DIC score [17], 9% of patients met the criteria for DIC without a significant difference according to the severity of illness.

Perplexingly, elevated D-dimer levels were observed more frequently in the asymptomatic/mild group than in the moderate/severe group. This may, in part, be the result of assay variability among centers [26]; it may also potentially be accounted for by the fact that the site with a higher proportion of elevated D-dimers also had a higher proportion of individuals who had asymptomatic/mild disease, which was diagnosed in the late third trimester when physiologically D-dimers tend to be highest.

TABLE 1 Maternal demographics and clinical characteristics of COVID-19 infection course.

Maternal demographics and clinical characteristics (*N* = 370[a], unless otherwise specified)	*n* (%)[b,c]
Maternal age (years) *(mean [SD], 29.8 [5.5])*	
≤30	94 (52.4)
31-35	120 (32.4)
36-40	44 (11.9)
>40	12 (3.2)
Ethnicity	
White/Caucasian	302 (81.6)
African/Caribbean/Black	12 (3.2)
East Asian	2 (0.5)
South Asian	7 (1.9)
Southeast Asian	2 (0.5)
West Central Asia/Middle East	2 (0.5)
Indigenous/First Nations	1 (0.3)
Unknown	42 (11.4)
Body mass index (*N* = 345[a]) *(median, 28.7; Q1/Q3, 26.3/31.0)*	
Underweight (<18.5)	1 (0.3)
Healthy weight (18.5-24.9)	52 (15.1)
Overweight (25.0-29.9)	163 (47.2)
Obese (≥30)	129 (37.4)
Overweight/obese (≥25)	292 (84.6)
Multipara	328 (88.6)
Underlying condition	324 (87.6)
Chronic hypertension	14 (3.8)
Diabetes mellitus	6 (1.6)
Cardiovascular disease	5 (1.4)
Antiphospholipid syndrome	2 (0.5)
Respiratory disease	18 (4.9)
Asthma (*N* = 18[a])	15 (83.3)
Gastrointestinal disease	9 (2.4)
Immunological disorder	15 (4.1)
Timing of COVID-19 diagnosis *(Antepartum weeks: N = 351[a]; median, 37.9; Q1/Q3, 31/39; range, 6-42)* *(Postpartum days: N = 19[a]; median, 1; Q1/Q3, 1/6; range, 0-27)*	
First trimester (wk)	15 (4.1)
Second trimester (wk)	43 (11.6)
Third trimester (wk)	293 (79.2)
Postpartum (d)	19 (5.1)
Positive COVID testing	
Naso-pharyngeal swab (PCR)	367 (99.2)
Serology – IgM/IgG	5 (1.4)
Cerebrospinal fluid	1 (0.3)
Placenta swab	7 (1.9)
Breastmilk	1 (0.3)
Any symptoms	208 (56.2)
Cough (*N* = 369[a])	128 (34.7)
Fever (*N* = 369[a])	87 (23.6)
Shortness of breath (*N* = 367[a])	54 (14.7)
Anosmia (*N* = 365[a])	41 (11.2)
Pneumonia	67 (18.8)
Fatigue/malaise (*N* = 366[a])	43 (11.7)
Headache (*N* = 366[a])	29 (7.9)
Flu-like illness/myalgia (*N* = 366[a])	29 (7.9)
Chest pain/tightness (*N* = 366[a])	26 (7.1)
Sore throat (*N* = 366[a])	53 (14.5)
Nasal congestion/coryza (*N* = 366[a])	53 (14.5)
Tachycardia (*N* = 366[a])	25 (6.8)
Diarrhea (*N* = 369[a])	10 (2.7)
Arthralgia (*N* = 366[a])	7 (1.9)
Tachypnea (*N* = 366[a])	17 (4.6)
Severity of disease	
Asymptomatic	162 (43.8)
Mild (common COVID symptoms)	135 (36.5)
Moderate (hypoxia, hospitalization)	50 (13.5)
Severe (ICU admission)	23 (6.2)
Hospitalization if symptomatic (*N* = 208[a])	84 (40.4)
Hospitalization LOS (d) *(median, 6; Q1/Q3, 3-13.8)*	
ICU admission if hospitalized (*N* = 84[a])	26 (31.0)
ICU LOS (d) *(median, 10; Q1/Q3, 5-14.5)*	
Maternal death (*N* = 207[a])	1
High-flow nasal cannula	26 (7)
Noninvasive mechanical ventilation	9 (2.4)
Invasive mechanical ventilation	14 (3.8)
Extra-corporeal membrane oxygenation	1 (0.3)

ICU, intensive care unit; IgM/IgG, immunoglobulin M/G; LOS, length of stay; PCR, polymerase chain reaction.

[a]"*N*" refers to the total number of responses received for a particular field (denominator).

[b]"*n*" refers to the indication of the presence of a particular finding (nominator).

[c]"%" refers to the proportion of each finding as a function of the total responses.

TABLE 2 Pregnancy- and trimester-specific hematological, biochemical, and coagulation parameters, as well as bleeding and thrombotic complications according to the severity of COVID-19 infection.

	Asymptomatic/mild		Moderate/severe		
	N[a]	*n* (%)[c,d]	*N*[a]	*n* (%)[c,d]	*P* value[e]
General Hematological Parameters[b]					
WBC (x 10(9)/L) *9.6 (7.4, 11.9; 1.9-22.0)*					
Leukopenia (<5.7 in T1; <5.6 in T2; <5.9 in T3/PP)	297	27(9.1)	73	14 (19.2)	.014
Leukocytosis (>13.6 in T1; >14.8 in T2; >16.9 in T3/PP)	297	19 (6.4)	73	2 (2.5)	*.129*
Neutrophils (x 10(9)/L) *7.3 (5.4-9.5, 1.2-19.9)*					
Neutropenia (<3.6 in T1; <3.8 in T2; <3.9 in T3/PP)	295	18 (6.1)	73	12 (16.4)	.004
Neutrophilia (>10.1 in T1; >12.3 in T2; >13.1 in T3/PP)	295	26 (8.8)	73	2 (2.7)	.08
Lymphocytes (x 10(9)/L) *1.5 (1.0-1.9, 0.17-3.8)*					
Lymphopenia (<1.1 in T1; <0.9 in T2; <1.0 in T3/PP)	295	52 (17.6)	73	35 (47.9)	<.001
Hematocrit (%) *0.36 (0.3-0.4, 0.3-0.5)*					
General Biochemical Parameters [b]					
C-reactive protein (mg/L) *9.3 (4.1-25.7, 0.3-268.9)*					
Elevated C-reactive protein (>20.3 in T1/T2; >8.1 in T3/PP)	276	132 (47.8)	59	49 (83.1)	<.001
Ferritin (ug/L) *31 (16-68, 4-1116)*					
Hypoferritinemia (<50[i])	198	151 (76.3)	53	19 (35.8)	<.001
Hyperferritinemia (>130 in T1; >230 in T2; >116 in T3/PP)	198	19 (9.6)	53	17 (32.1)	<.001
Albumin (g/L) *31 (27.7-34.3, 22-56)*					
Hypoalbuminemia (<31 in T1; <26 in T2; <23 in T3/PP)	49	2 (4.1)	55	3 (5.5)	*1.000*
AST (IU/L) *24 (18-32, 3-488)*					
Elevated AST (>23 in T1; >33 in T2; >32 in T3)	277	44 (15.9)	67	36 (53.7)	<.001
ALT (IU/L) *16 (12-26, 3-454)*					
Elevated ALT (>30 in T1; >33 in T2; >25 in T3)	271	53 (19.6)	71	32 (45.1)	<.001
Lactate dehydrogenase (IU/L) *212 (179-256, 99-1330)*					
Creatinine (µmol/L) *46.9 (40.1-53.9, 23-146)*					
Elevated creatinine (>62 in T1; >71 in T2; >80 in T3/PP)	279	5 (1.8)	70	4 (5.7)	*.084*
Procalcitonin[h] *0.07 (0.04-0.14, 0.01-5.1)*					
Elevated procalcitonin[f] (≥0.08 until 28 w; ≥0.11 at 36 w-DD; ≥5 PP)	135	35 (25.9)	10	7 (70.0)	*.007*
Coagulation Parameters					
Isolated abnormal coagulation parameters	297	215 (72.4)	73	49 (67.1)	*.507*
Hemoglobin (g/L) *119 (109-127, 79-152)*					
Anemia (<110 g/L)	297	65 (21.9)	73	28 (38.4)	.004
Platelet count (x 10(9)/L) *224 (175-270, 10-509)*					
Thrombocytopenia (<150)	297	38 (12.8)	73	9 (12.3)	.915
Thrombocytosis (>391 in T1; >409 in T2; >429 in T3/PP)	297	3 (1.0)	73	0	*.617*
aPTT (s) *26.8 (25-29.4, 17.8-42.8)*					
Prolonged aPTT (>38.9 in T1; >38.1 in T2; >35.0 in T3/PP)	284	6 (2.1)	67	12 (17.9)	*<.001*
Fibrinogen (g/L) *4.7 (3.9-5.7, 0.54-9.8)*					
Hypofibrinogenemia (<2.4 in T1; 2.9 in T2; 3.7 in T3/PP)	228	36 (15.8)	48	10 (20.8)	.394

(Continues)

TABLE 2 (Continued)

	Asymptomatic/mild		Moderate/severe		
	N[a]	*n* (%)[c,d]	*N*[a]	*n* (%)[c,d]	*P* value[e]
Hyperfibrinogenemia (>5.1 in T1; 5.4 in T2; 6.2 in T3/PP)	228	36 (15.8)	48	7 (14.6)	.834
D-dimer (ug/mL) *656 (402-998, 4-2578)*					
Elevated D-dimer (above ULN for each institution)	160	152 (95.0)	43	26 (60.5)	<.001
DIC					
ISTH criteria	—	—	—	—	
Pregnancy score[g]	228	20 (8.8)	48	4 (8.3)	*1.000*
Thrombotic and Bleeding Complications					
Antepartum hemorrhage ≥14 wk	296	9 (3)	73	4 (6)	*.478*
Postpartum hemorrhage	266	9 (3)	62	6 (10)	*.044*
Venous thromboembolism	297	2 (0.7)	73	4 (6)	*.015*
Arterial thrombosis	—	—	—	—	—
VTE prophylaxis (overall)	296	193 (65)	71	63 (89)	<.001
LMWH SC	191	191 (100)	62	59 (95)	*.14*
UFH SC	191	0	62	2 (3)	
Direct oral anticoagulant	191	0	62	1 (2)	
Pregnancy Outcomes					
Pregnancy-induced hypertension	297	22 (7)	73	6 (8)	.814
Preeclampsia	297	15 (5)	73	5 (7)	*.564*
HELLP syndrome	297	5 (1.7)	73	0	*.588*
Gestational diabetes	297	18 (6)	73	8 (11)	.142
Intrahepatic cholestasis of pregnancy	296	5 (1.7)	73	1 (1.4)	*1.000*
Preterm prelabour rupture of membranes	297	16 (5.4)	73	4 (5.50)	*1.000*
Type of Birth					
Spontaneous vaginal delivery	250	82 (33)	59	21 (36)	.682
Assisted vaginal delivery	250	3 (1.2)	59	1 (1.7)	*1.000*
Cesarean delivery	250	165 (66)	59	37 (63)	.633
Scheduled cesarean delivery	165	127 (77)	37	13 (35)	.001
Unscheduled cesarean delivery	165	38 (23)	59	24 (65)	.001
COVID-19 is the sole reason for cesarean delivery	164	42 (26)	37	19 (51)	.002
Fetal/Neonatal Outcomes					
Livebirth[j]	264	245 (93)	59	59 (100)	*.387*
Miscarriage (loss: <20 w or <500 g)	264	14 (5.3)	59	0	*.136*
Stillbirth (loss: ≥20 w or ≥500 g)[j]	264	5 (1.9)	59	0	*.387*
Preterm birth (<37 w)	249	43 (17)	59	23 (39)	.001
Early preterm birth (<34 w)	249	17 (7)	59	10 (17)	.013
Small for gestational age (birthweight <10th centile)	249	29 (12)	59	6 (10)	.748

The sum of *N* for "asymptomatic/mild" and *N* for "moderate/severe" may not be the total *N* for the overall cohort, as the severity of illness was not specified in several cases.

ALT, alanine transferase; aPTT, activated partial thromboplastin time; AST, aspartame transaminase; DD delivery day; DIC, disseminated intravascular coagulation; HELLP, Haemolysis, Elevated liver enzymes, Low platelets; ISTH, international society on thrombosis and hemostasis; LMWH, low-molecular-weight heparin; PP, postpartum; SC, subcutaneous; T1, first trimester; T2, second trimester; T3, third trimester; UFH, unfractionated heparin;

TABLE 2 (Continued)

(Continues)

ULN, upper limit normal; VTE, venous thromboembolism.
[a]"*N*" refers to the total number of responses received for a particular field (denominator).
[b]All continuous variables are reported as median (Q1, Q3; range).
[c]"*n*" refers to the indication of the presence of a particular finding (nominator).
[d]"%" refers to the proportion of each finding as a function of the total responses.
[e]Chi-squared test reported in regular font; Fisher's exact test reported in *italics*.
[f]Paccolat et al. [16].
[g]Erez et al. [17].
[h]Values available for Romanian sample only.
[i]Hypoferritinemia definition according to Tang et al. [11].
[j]Of 362 pregnancies with available data, 39 were undelivered (31 in the asymptomatic/mild group and 8 in the moderate/severe group).

3.4 | Bleeding and thrombotic complications

Antepartum bleeding was infrequent, and its incidence did not differ from illness severity or the pandemic wave. PPH was observed in 15 (5%) patients but was significantly more frequent in those with moderate/severe disease (10%) vs asymptomatic/mild disease (3%). These findings are in keeping with observations from the ISTH COVPREG-COAG registry, where the rate of PPH in the Delta-variant wave was 6% [27]. As in the first wave, the frequency of PPH was not influenced by the pregnancy DIC score. Of those with PPH, 3 (15%) met the criteria for the DIC pregnancy score, and 10 (4%) did not (P = .075). The frequency of PPH was not influenced by an urgent cesarean section (2 [6%] vs 10 [6%]).

No arterial thrombotic events were recorded. Venous thromboembolism (VTE) was noted in 6 (2%) patients overall and was significantly higher in those with moderate/severe disease (4 [6%]) vs asymptomatic/mild disease (2 [1%]). VTEs consisted of pulmonary embolism in 4 (diagnosed by computed tomography pulmonary angiography, all with moderate/severe disease; 2 in the intensive care unit), lower extremity deep vein thrombosis in 1 (diagnosed by ultrasound based on asymptomatic disease), and lower extremity superficial thrombophlebitis in 1 based on varicose veins (clinical diagnosis, asymptomatic disease, on prophylactic anticoagulation prior to diagnosis with subsequent treatment dose for 4 weeks). These VTEs occurred despite thromboprophylaxis in 4/6 individuals and in the absence of thromboprophylaxis in 2/6 (who were subsequently diagnosed with pulmonary embolism). The rates of thromboprophylaxis remained similar between the first and subsequent pandemic waves for both asymptomatic/mild (65%) and moderate/severe disease (89%). Table 2 details the bleeding and thrombotic complications.

3.5 | Pregnancy outcomes

While examination of pregnancy outcomes was not the focus of this study, these are presented in Table 2 for completeness. There were no differences between the asymptomatic/mild and moderate/severe disease groups for common pregnancy-related complications. A higher proportion in the moderate/severe group underwent an unscheduled cesarean delivery, and more individuals in this group underwent cesarean section with COVID-19 as the sole indication. There were no differences between groups for miscarriage, stillbirth, or small for gestational age size. A higher proportion in the moderate/severe group delivered prematurely (<34 weeks).

This study is limited by its retrospective nature. Diagnosis occurred predominantly in the third trimester, reflecting the higher proportion of patients that would be tested peripartum. Not every patient in the participating institutions completed bloodwork; although given the cautious approach to the evaluation of symptomatic pregnant people, the authors feel that it is quite unlikely those who were significantly unwell and thus would have more potential to demonstrate aberrant values would have been missed. The homogenous ethnic makeup of our study does not allow us to comment on generalizability to underrepresented populations. Finally, our data preclude comment on the effect of vaccination on study findings. The strengths of the current study lie in its multinational scope and comprehensive documentation of the hematologic laboratory and clinical parameters associated with the subsequent waves of the pandemic in the pregnant population, as well as the determination of abnormal values based on pregnancy-specific laboratory ranges.

Our findings add valuable insights into the nature of hematologic characteristics, bleeding, and thrombotic complications for those affected with COVID-19 in pregnancy. The presence of markers of inflammation and endothelial dysfunction is in keeping with observations in the nonpregnant population. Reassuringly, despite more severe disease in the subsequent waves of the pandemic, there was no significant evidence of CAC, and overall, no association was demonstrated between isolated coagulation abnormalities and bleeding risk. Notably, fibrinogen below 2 g/L was again linked to the risk of PPH. Finally, VTE risk was low but noted more frequently in those with severe illness, despite thromboprophylaxis, inviting further discussion as to the degree of anticoagulation that may benefit this subgroup.

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AUTHOR CONTRIBUTIONS

M.O. conceived the project, created the case report form, coordinated multicenter data collection, analyzed and interpreted data, and wrote the first draft of the manuscript. G.N. and R.A.-K. conceived the project, provided, analyzed, and interpreted data, and critically reviewed the manuscript. M.S., M.S.C.S., G.C., and D.M. provided data and critically reviewed the manuscript. S.T. completed the literature review and wrote the first draft of the manuscript. A.K.M. conceived

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RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest related to this work.

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