SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Genetic fusion GREB1-NCOA2 detected by next generation sequencing.

Appendix S2. Patient consent form (Chinese version).

Appendix S3. Patient consent form (English version).

Appendix S4. Some of the positive immunohistochemical staining of UTROSCT tissues.

Appendix S5. Certificate of English editing.

Received: 16 November 2020 | Revised: 18 November 2020 | Accepted: 24 November 2020 | First published online: 16 December 2020

DOI: 10.1002/ijgo.13499

Obstetrics

Hemostasis in pregnant women with COVID-19

Alessandro Ciavarella[1] | Roberta Erra[2] | Maria Abbattista[1] | Enrico Iurlaro[2] | Massimo Boscolo-Anzoletti[1] | Manuela Wally Ossola[2] | Fabio Mosca[3] | Enrico Ferrazzi[2] | Flora Peyvandi[1,4] | Ida Martinelli[1]

[1]A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

[2]Unit of Obstetrics, Department of Mother Neonate and Child, Mangiagalli Centre, Fondazione IRCCS Ca, Granda Ospedale Maggiore Policlinico, Milan, Italy

[3]Neonatal Intensive Care Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca, Granda - Ospedale Maggiore Policlinico, Milan, Italy

[4]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Correspondence
Ida Martinelli, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, via Pace 9, Milan, 20122, Italy.
Email: ida.martinelli@policlinico.mi.it

Funding information
This study was supported by The Italian Ministry of Health – Bando Ricerca Corrente, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico.

KEYWORDS: Blood coagulation, Coronavirus, COVID-19, Pregnancy, SARS-CoV-2, Thrombosis

Pregnancy is a prothrombotic condition characterized by a procoagulant imbalance that serves to protect women from bleeding but increases their risk for venous thromboembolism (VTE).[1] Coronavirus disease 2019 (COVID-19) has not spared pregnant women with regards to VTE.[2] A coagulopathy that increases the risk of thrombosis has been reported in patients with severe COVID-19 infection.[3] At present, no data are available on the hemostatic status of pregnant women with COVID-19, and whether coagulation parameters are additionally influenced by COVID-19 remains unclear.

Pregnant women admitted to our Maternity Hub in Milan, Italy from April 10 to April 30, 2020, without known coagulation abnormalities, recent VTE, obstetrical complications, and with or without COVID-19, were included in the study. COVID-19 infection was confirmed by reverse transcriptase polymerase chain reaction assay using nasal swabs. Blood samples were collected at admission with the aim of comparing prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, factor II, factor VIII (FVIII), von Willebrand factor antigen, von Willebrand ristocetin co-factor, antithrombin (AT), protein C, protein S, platelets, and C-reactive protein (CRP) between women with and without COVID-19.

Using consecutive sampling, 21 women with COVID-19 and 48 without were included in the study. Sixty-three out of 69 (91.3%) women were in the third trimester of pregnancy, whereas the remaining 6 were in the second trimester (between 26 and 28 weeks of gestation). Mean and standard deviation for age (years) and body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) were 33.2 (5.7) and 27.4 (5.0) in women with COVID-19, and 27.1 (4.8) and 32.9 (5.3) in those without. Ten women (48%) with COVID-19 were asymptomatic, whereas 11 (52%) had mild symptoms (i.e. fever, cough, mild dyspnea, and asthenia). We observed differences in distributions

TABLE 1 Coagulation parameters of hospitalized women during pregnancy with or without COVID-19 infection

Coagulation parameters, mean (SD)	COVID−19 (n = 21)	Controls (n = 48)	*P* value
PT ratio	0.94 (0.07)	0.90 (0.05)	0.086
aPTT ratio	0.89 (0.09)	0.82 (0.06)	0.002
Fibrinogen (mg/dL)	449 (90)	517 (96.0)	0.006
D-dimer (ug/L)	2165 (2870)	3115 (2850)	0.047
Factor II (%)	111 (20)	103 (12)	0.155
Factor VIII (%)	210 (56)	191 (42)	0.185
vWF-Ag (%)	296 (87)	307 (100)	1.000
vWF-RCo (%)	232 (62)	295 (289)	0.426
Antithrombin (%)	100 (15)	87 (13)	0.002
Protein C (%)	109 (18)	107 (18)	0.821
Protein S (%)	50 (20)	41 (12)	0.066
Platelets ($\times 10^3$/uL)	495 (88)	451 (67)	0.039
CRP (mg/dL)	3.34 (3.61)	2.90 (3.59)	1.000

Abbreviations: aPTT, activated partial thromboplastin time; CRP, C-reactive protein; PT, prothrombin time; SD, standard deviation; VWF-Ag, von Willebrand factor antigen; vWF-RCo, von Willebrand ristocetin co-factor.

only in platelet count, aPTT, fibrinogen, D-dimer, and AT levels between the two groups (Table 1). Although women with COVID-19 showed decreased mean plasma levels of fibrinogen and D-dimer compared to those without, no difference was observed among CRP and FVIII levels.

A positive correlation between the severity of disease and the impairment of coagulation parameters has been reported in patients with severe COVID-19.[4] The inclusion of women who were asymptomatic or had mild symptoms does not enable the generalization of our results to pregnant women with severe COVID-19 infection.

In conclusion, coagulation parameters investigated in this pilot study were similar in pregnant women with COVID-19 who were asymptomatic or had mild symptoms, and in pregnant women without infection. However, we believe that an individual patient evaluation is warranted to prevent peripartum thromboembolic complications in women with COVID-19 whose hemostatic status has not yet been fully clarified.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

AC, RE, and IM designed the study. AC, RE, MA, and IM wrote the manuscript. EI, MWO, FM, EF, FP and IM supervised the study and were administrators. RE, EI, MWO and MBA collected the data. AC, MA, MBA and IM analyzed the data and information and wrote the first draft of the manuscript. All authors revised and approved the final version of the manuscript.

REFERENCES

1. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol*. 2006;194(5):1311-1315.
2. Martinelli I, Ferrazzi E, Ciavarella A, et al. Pulmonary embolism in a young pregnant woman with COVID-19. *Thromb Res*. 2020;191:36-37.
3. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-1026.
4. Peyvandi F, Artoni A, Novembrino C, et al. Hemostatic alterations in COVID-19. *Haematologica*. 2020. https://doi.org/10.3324/haematol.2020.262634

How to cite this article: Ciavarella A, Erra R, Abbattista M, et al. Hemostasis in pregnant women with COVID-19. *Int J Gynecol Obstet*. 2021;152:262–281. https://doi.org/10.1002/ijgo.13499