COVID-19 and Hypercoagulability: Potential Impact on Management with Oral Contraceptives, Estrogen Therapy and Pregnancy

Daniel I. Spratt MD

Rachel J. Buchsbaum MD

The Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Maine Medical Center, Portland ME (DS); Division of Hematology/Oncology, Tufts University School of Medicine, Boston MA (RB)

Corresponding author:

Daniel Spratt, MD

Division of Reproductive Endocrinology and Infertility

Maine Medical Center

Portland, ME 04102

Phone: 207-771-5549

Email: spratd@mmc.org

The authors have nothing to disclose.

Key Words: COVID-19, coronavirus, hypercoagulability, oral contraceptives, estrogen therapy, pregnancy

The novel coronavirus, SARS-CoV-2, has proven unusual with respect to the spectrum of its pathological effects. In addition to damage inflicted on the lungs, kidneys, heart and other organ systems, reports have emerged of hypercoagulable states in patients hospitalized with COVID-19 (1-3). Macro- and micro-vascular thrombosis in venous and arterial beds along with venous thromboembolic events (VTEs) occur with a troublesome frequency (1,2). A recent study found increased platelet activation and aggregation in patients infected with SARS-CoV-2, with increased expression of platelet adhesion protein P-selectin along with altered gene expression in multiple pathways, which may underlie platelet hyper-reactivity contributing to thromboinflammation in COVID-19 disease (4). Although all of the underlying mechanisms of COVID-associated hypercoagulability are not clear, multiple laboratory abnormalities related to coagulation occur commonly in hospitalized COVID-19 patients including increased levels of D-dimer, fibrinogen, fibrin, fibrinogen degradation products, and cytokines as well asdecreased antithrombin,variable platelet counts over the course of disease, and platelet-fibrin microthrombi in the pulmonary arterial vasculature on early autopsy studies (1-3). With this initial information regarding hypercoagulability, several groups have suggested routine coagulation prophylaxis with low molecular weight heparin or unfractionated heparin in patients upon hospitalization with COVID-19 (3), with consideration of escalation to intermediate and/or full therapeutic anticoagulation in the event of clinical disease progression according to established institutional risk algorithms. Our medical centers and others across the United States are implementing this strategy.

As more information emerges regarding the effects of SARS-CoV-2 on coagulation, questions arise as to whether infection with this virus aggravates the risk of VTEs and strokes associated with combined oral

contraceptives (COC's) and other estrogen therapies as well as pregnancy-associated risks. COC use is associated with a 2- to 6-fold increase in risk for VTEs (5). The risk for stroke is increased in young women from about 4 to about 8 in 100,000 women per year. Similar data exist for oral hormone replacement therapy (HRT) in menopausal women (6) and oral estrogen therapy in male-to-female transgender patients. In pregnancy, the risk of VTEs increases 4-5 fold (7). The mechanisms for these increases in thrombogenesis and the duration of the effect after discontinuing therapy remain unclear. A common recommendation is to discontinue estrogen-containing preparations two weeks before planned activities that may increase thrombogenesis such as surgery or long flights, although clear data are not yet available to support this recommendation.

As this Commentary is being submitted, no reports of increased incidence of VTEs in pregnant women or women taking estrogen preparations who also have COVID-19 have emerged. However, a preliminary report indicates that vascular abnormalities in the placenta can accompany SARS-CoV-2 infection (8). Many uncertainties remain regarding the effects of both SARS-CoV-2 and estrogen on coagulation. The emergence of this pandemic and the curious impact of this virus on hypercoagulability emphasize the continuing need for additional research into coagulation pathology in women. Pressing questions in the large intersecting patient populations of women who are pregnant or taking estrogen therapy and those who have COVID-19 include:

- Does the microvascular thrombosis encountered in severe COVID-19 also affect placental vasculature and if so, to what extent?
    - Does the cytokine storm seen with severe COVID-19 in parallel with microvascular thrombosis have effects on placental and fetal health?

- What are the mechanisms of hypercoagulability accompanying estrogen therapies and pregnancy and COVID-19?
    - Do effects of estrogen on the renin-angiotensin axis and SARS-CoV-2 interactions with ACE2 modulate hypercoagulability?
- With respect to the SARS-CoV-2, how do markers associated with increased coagulability vary in outpatients testing positive for SARS-CoV-2 who are symptomatic (or asymptomatic)?
- Do markers of coagulation differ in pregnant women and women receiving estrogen therapies testing positive for SARS-CoV-2 compared with other women testing positive for SARS-CoV-2?
- What measures can/should be taken to reduce risks of hypercoagulability in these patient populations?

The existence of a COVID-19 registry to assess outcomes for pregnant women (priority.UCSF.edu) will facilitate the approaches to these questions.

We do not know how long the current pandemic will endure and can be reasonably certain that, like the H1N1 virus causing the 1918-1919 influenza pandemic, SARS-CoV-2 will return cyclically for years if not decades. Thus, the importance of undertaking research to answer these questions will continue with findings likely to be applicable in a wide range of clinical situations.

When clinical complications of a disease are encountered that cannot be explained by known physiology or pathophysiology, designing effective diagnostic or treatment strategies can be extraordinarily difficult. Partnerships between clinicians and basic/translational researchers are crucial to create the

scientific data upon which to base clinical management. Clinicians have reported a plethora of hematologic manifestations of SARS-CoV-2 that present puzzles calling for solutions. The as yet undefined mechanisms of COVID-19 effects on the coagulation system provide an opportunity for fresh approaches to old mysteries as well as an urgent call to action to provide basic knowledge as a foundation for effective clinical approaches to the often devastating hematological consequences of the pandemic. What new aspects of coagulation and coagulopathy does COVID-19 teach us? Can that be applied to the as yet unsolved pathophysiology of coagulopathy with estrogen therapy and pregnancy? How do these two situations of coagulopathy intersect?

Establishing models for basic research into mechanisms of hypercoagulability in COVID-19, let alone intersecting effects of COVID-19 and estrogen therapy or pregnancy, has several hurdles and will require innovative novel animal and tissue models. Already, the inability of coronaviruses to bind to rodent ACE2 is being addressed by engineering mouse strains incorporating human ACE2. Several issues complicate matters. COVID-19 has a variety of coagulation effects that appear to differ between individuals. Coagulation physiology in nonhuman animals differs from humans (7). Hypercoagulability with pregnancy (and probably estrogen therapy) does not naturally occur in other animals (7).; Although we are still primarily at an observational stage with clinicians and clinical researchers learning more about hypercoagulability manifestations of COVID-19, conversations between clinicians and basic researchers and between endocrinologists and hematologists should be nurtured to explore potential interactions between SARS-CoV-2 and pregnancy or estrogen therapy that could guide clinical management.

References:

1. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020. doi: 10.1016/j.thromres.2020.04.013.

2. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G, Dimopoulos MA. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020. doi: 10.1002/ajh.25829.

3. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18(5):1023—1026.

4. Manne BK, Denorme F, Middleton E, Portier I, Rolwey JW, Stubben C, Petrey AC, Tolley ND, Guo L, Cody M, Weyrich AS, Yost CC, Rondina MT, Campbell RA, Platelet gene expression and function in COVID-19 patients. Blood 2020. doi: 10.1182/blood.2020007214/461106.

5. Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ*. 2013;347:f5298. doi: 10.1136/bmj.f5298.

6. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297(13):1465—1477.

7. Struble E, Harrouk W, DeFelice A, Tesfamariam B. Nonclinical aspects of venous thrombosis in pregnancy. *Birth Defects Res C Embryo Today.* 2015; 105(3):190–200.

8. Shanes ED, Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental Pathology in COVID-19. *Am J Clin Pathol*. 2020 154(1):23-32.