



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## COVID-19, thrombosis and pregnancy

Jahnvi Daru<sup>a</sup>, Katie White<sup>b</sup>, Beverley J. Hunt<sup>b,\*</sup>

<sup>a</sup> Institute for Population Health Science, Queen Mary University of London, London, UK

<sup>b</sup> Thrombosis & Haemophilia Centre, Guys and St Thomas' Hospital, London, UK

### ARTICLE INFO

#### Keywords:

Thrombosis  
COVID-19  
Pregnancy  
Thromboprophylaxis  
Post partum

### ABSTRACT

Increased thromboembolic events have been seen in patients hospitalised with COVID-19 pneumonia, especially those with acute respiratory distress syndrome requiring intensive care support. The coronavirus pandemic has had varied effects on pregnant women globally. Concerns about the potential for thromboembolic events in the prothrombotic period of pregnancy and puerperium when combined with COVID-19 infection, and the impact this may have on maternal and infant morbidity and mortality has led to the development of expert-led guidance providing increased use of thromboprophylaxis in this group. We discuss the impact of SARS-CoV-2 on national and international guidance to prevent thromboembolic events in pregnant women.

### 1. Introduction

Coronavirus disease 2019 (Covid-19) is an acute viral illness, first detected in Wuhan city, Hubei Province, China in December 2019. It is a single stranded RNA virus, of the genus betacoronavirus, that enters cells via ACE-2 (ACE2) receptors.

Over 185 million cases have been reported globally, with approximately 4 million deaths according to the WHO Coronavirus dashboard, accurate as of 9<sup>th</sup> July 2021.

The spectrum of disease varies from being asymptomatic, having mild flu-like symptoms to severe acute respiratory distress syndrome and multi-organ failure. It is the development of COVID-19 pneumonia which requires hospital admission for the management of hypoxia. The term moderate is applied to those who require supplementary oxygen and severe or critical if the patient requires mechanical ventilation or high flow nasal oxygen or CPAP. Less than 5% of infected patients are admitted to hospital and with modern treatment with dexamethasone, a minority require intensive care support [1]. Common symptoms of mild COVID-19 include dyspnoea, fever, altered sense of taste or smell and a cough but the spectrum of symptoms is wide.

Pregnant women have a similar presentation, but they are more likely to be asymptomatic (greater than two-thirds) compared to non-pregnant women of the same age [2]. Often their symptoms can overlap with normal physiological symptoms of pregnancy.

Covid 19 can be diagnosed on symptoms and contact history alone and then confirmed by real time reverse transcriptase polymerase chain reaction (RT-PCR).

The main method of transmission is through person-person contact of respiratory droplets or aerosol particles (generated during coughing/speaking or medical procedures). They can be inhaled, deposited on mucous membranes or picked up through touching mucous membranes with hands that have been soiled with the virus containing respiratory droplets. The infectious dose needed to transmit an infection from person to person has not yet been established.

Vaccination is the strongest tool against Covid-19. In the UK, The Joint Committee on Vaccination and Immunisation (JCVI) have advised all pregnant women should be vaccinated, based on real world data from America where >100,000 pregnant women have been vaccinated with the mRNA vaccines; Pfizer or Moderna [3]. In these women there has been no evidence of harm to the mother or the baby, with the vaccine being similar to other vaccines such as the flu and pertussis vaccines which have been given safely in pregnancy for a number of years [4].

#### 1.1. Haemostatic changes in COVID-19

Admission for the management of Covid 19 pneumonia is characterised by a high prevalence of thrombotic complications, which are associated with more severe disease and increased mortality. The rates of hospital-associated VTE are particularly high and arterial thrombotic rates are increased too [5]. Pregnancy is a prothrombotic state so it has been thought they are at increased risk of thrombosis and many international organisations have issued guidance for thromboprophylaxis.

The pulmonary thromboses seen are a mix of macrovascular hospital-associated pulmonary embolism and microvascular thromboses

\* Corresponding author.

E-mail address: [Beverley.hunt@gstt.nhs.uk](mailto:Beverley.hunt@gstt.nhs.uk) (B.J. Hunt).

<https://doi.org/10.1016/j.tru.2021.100077>

Received 17 August 2021; Accepted 30 September 2021

Available online 5 October 2021

2666-5727/© 2021 The Authors. Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

(immunothrombosis) secondary to lung inflammation. There are also increased rates of arterial thrombosis such as myocardial and cerebral infarction, along with increased extracorporeal circuit thrombosis. [6] This prothrombotic state was initially thought to be mediated through disseminated intravascular coagulation (DIC) but actually the changes do not fulfil the International Society of Thrombosis and Haemostasis (ISTH) guidelines for DIC [7]. The prothrombotic changes are in keeping with the acute phase response, which produces very high levels of fibrinogen, Factor VIII and von Willebrand factor.

Immunothrombosis is the process of inflammation due to the innate immune system, hypoxia and the local expression of tissue factor (TF) resulting in pulmonary microvascular thrombosis, which contributes to the progressive respiratory dysfunction seen in patients affected by SARS-CoV-2 infection, but is also seen in any form of acute respiratory distress syndrome (ARDS).

VTEs in those with COVID-19 pneumonia are driven by a strong activation of all aspects of Virchow's triad; patients are less mobile, have a prothrombotic state and the endothelium is activated. This may be exacerbated in pregnant women because of their background prothrombotic state and reduced flow in their leg veins.

### 1.2. Haemostasis in pregnancy

Pregnancy is widely known to be a hypercoagulable state. This largely stems from increase in prothrombotic factors such as VII, VIII, X, XII, von Willebrand factor and fibrinogen, and a decrease in protein S and altered fibrinolysis [8]. This physiological response is designed to prevent excessive blood loss following delivery, however in some women, this effect is exaggerated and they go on to develop an increased thrombosis risk.

Risk stratification for pregnant women to prevent venous thromboembolic events is routine in many high income settings. In the UK for example, most healthcare professionals use the Royal College of Obstetricians and Gynaecologists Greentop guideline number 37a which has a traffic light system for antenatal and postnatal risk assessment [9]. Based on the score, women at high risk will receive thromboprophylaxis for varying lengths of time.

### 1.3. Impact of COVID-19 on pregnant women

From the early period of the pandemic pregnant women were identified as being at risk of developing severe disease if they contracted COVID-19. In particular, increased disease severity is reported in women in the third trimester, age >35 years, BMI >25, pre-existing medical comorbidities (especially diabetes mellitus) and those from a black or minority ethnic background [2].

There is also data suggesting that pregnant women, who become unwell with COVID-19 are more likely to require admission to intensive care for respiratory support, however whether this is related to more severe infection or other factors is yet to be determined [2,10].

### 1.4. Impact of COVID-19 on infants

Pregnant women with symptomatic infection in the third trimester are more likely to experience an iatrogenic preterm birth [2]. This is likely to be secondary to numerous factors, including the need for mechanical ventilation, which is more readily achieved post delivery [2,10, 11].

There are documented cases of transplacental SARS-CoV-2 transmission [12]. The vast majority of infants are not affected by maternal infection [13]. There is also minimal risk of transmission of SARS-CoV-2 in affected women who are breastfeeding, or rooming with a newborn infant [13].

### 1.5. Thrombosis in pregnant women with COVID-19

There are published reported cases of coagulopathy [14] and thromboses in pregnant women infected with SARS-CoV-2 infection and pneumonia in pregnancy. In a systematic review by Serevante et al. there were three cases of thromboembolic disease, with two of these having received thromboprophylaxis [15]. Early on in the pandemic, Pereria et al. reported a case series of sixty women developing SARS-CoV-2 infection with respiratory distress in pregnancy, of these twenty five women received thromboprophylaxis with low molecular weight heparin. There were two reported episodes of deep vein thrombosis [16].

There are also reported case series from Wuhan and France where pregnant women with severe COVID-19 infection did not develop any thromboembolic complications [17]. [[18] It is unclear whether these women received thromboprophylaxis. Similarly, in the UK the Obstetric Surveillance System and the MBRRACE-UK report on maternal death have documented cases of pregnant women admitted with COVID-19 pneumonia. In a rapid report published in mid 2020, there were two reported thromboembolic events contributing to maternal death [19], in both instances women received thromboprophylaxis. In a related publication from the same team, there were 427 cases of pregnant women affected by SARS-CoV-2, no cases of thromboembolic events were described [20]. Placental thrombotic complications related to coronavirus have been reported. These include pre-eclampsia, preterm delivery and HELLP syndrome, as a consequence clinicians should be vigilant for these in pregnant women admitted with coronavirus pneumonia.

The Royal College of Obstetricians and Gynaecologists (RCOG) issued guidance documents early on in the pandemic, recommending the widespread use of thromboprophylaxis for pregnant women admitted with SARS-CoV-2 infection [11]. This is likely to have contributed to the low rates of thromboembolism seen in the UK pregnant population affected by SARS-CoV-2 infection. The prevalence of thromboembolic events in pregnant women with SARS-CoV-2 infection who are untreated with thromboprophylaxis remains unknown. For pregnant women who do develop a VTE, the treatment remains unchanged, women are offered treatment dose low molecular weight heparin [11].

### 1.6. Prevention of thrombosis in pregnancy

Most organisations overseeing the care of women in pregnancy including the RCOG and the American College of Obstetrics and Gynaecologists have made recommendations on thromboprophylaxis for women admitted with SARS-CoV-2 infection, which is in line with the management of those who are non-pregnant with admission with COVID-19 pneumonia. Guidance documents in this area are highly variable and based largely on expert consensus, as outlined in a review by D'Souza et al. [21] The recommended dosing regimens in UK are the same as outlined in Greentop guideline number 37a [9].

The RCOG advocates the use of thromboprophylaxis for all women admitted to hospital with SARS-CoV-2 infection, whether minor, moderate or severe, for the duration of their admission. Women with known thrombophilia or those already on LMWH prophylaxis should continue, and may require extended or higher dose prophylaxis depending on their VTE score. We advise discussing complex cases with an expert in VTE. For women affected, who do not require admission, a risk assessment should be performed in accordance with the existing risk stratification tool, which consider COVID-19 infection as a transient risk factor [9]. For women with ongoing morbidity, longer duration of thromboprophylaxis should be considered [11].

As the pandemic has progressed, senior clinicians and policy makers have adapted protocols to account for emerging evidence on treatment and prevention strategies. The same also applies to thromboprophylaxis, except with the caveat that the natural history of thromboembolic

events in pregnant women with SARS-CoV-2 infection is difficult to interpret with the widescale use of thromboprophylaxis, especially in the UK pregnant cohort.

### 1.7. Dosing of thromboprophylaxis

Early in the pandemic due to the concerns about the high rates of image proven venous thromboembolism seen on imaging despite standard thromboprophylaxis, many critical care units used higher doses of LMWH up to therapeutic doses. However in retrospect much of the changes seen on CT pulmonary angiogram were due to immunothrombosis (microvascular thromboses secondary to inflammation within the pneumonia), a feature of any patient with ARDS. Indeed, subsequent RCTs have failed to show benefit of higher doses compared to standard weight adjusted thromboprophylaxis in those who have severe COVID-19. There is however evidence of benefit of therapeutic doses of anticoagulation with LMWH in those with moderate disease with minimal increase in bleeding risk in the aTTACC/Activ4a/REMAP-CAP multiplatform randomised controlled trial [22]. Data from 2219 participants were analysed and the probability that therapeutic anticoagulation increased organ support-free days compared to thromboprophylaxis was 99% (adjusted odds ratio 1.29, 95% credible interval 1.04 to 1.61) [22]. The adjusted absolute increase in survival to hospital discharge without organ support with therapeutic anticoagulation was 4.6% (95% credible interval 0.7 to 8.1). Major bleeding occurred in 1.9% and 0.9% of participants in the therapeutic anticoagulation and thromboprophylaxis arms respectively [22]. Pregnant women were excluded in one of the trials and probably were in the others, but we believe the data can be applied to pregnant women. However, a careful risk assessment must take place, for example a woman peri-partum or with placenta praevia would not benefit from therapeutic anticoagulation as their bleeding risk would be too great.

### 1.8. Extended thromboprophylaxis post discharge

Hospital associated VTE is known to occur in hospital and for up to 90 days post discharge, indeed in the average medical patient most events occur post discharge [23]. However the length of stay of a patient ventilated for COVID-19 pneumonia is much longer than that of an average medical patient. As a result prolonging thromboprophylaxis post discharge may be sensible, however data supporting this is sparse [24]. Many clinical guidelines across Europe and in the United States recommend considering ongoing thromboprophylaxis on a case by case basis [25–27]. For pregnant women who have required ventilation, there are even fewer data recommending the length and dosing of ongoing thromboprophylaxis, the RCOG advise considering extended prophylaxis if there is ongoing morbidity [11].

## 2. Summary

The response of the medical community to the effects of the SARS-CoV-2 pandemic on pregnant women has been shaped by the experience of the H1N1 pandemic, where many pregnant women were affected by severe disease. While this hasn't been the case with COVID-19, those with risk factors for severe disease should be identified early and offered vaccination. Thromboprophylaxis should be considered in line with existing risk stratification approaches. As more data emerge, thromboprophylaxis and treatment regimens may alter, but until then following existing protocols is a cautiously pragmatic approach to adopt.

## Disclosure

JD and BJH were contributors to the RCOG Coronavirus in Pregnancy Guideline.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JD and BJH were contributors to the RCOG Coronavirus in Pregnancy Guideline

## References

- [1] R. Zarychanski, Therapeutic anticoagulation in critically ill patients with covid-19 – preliminary report, medRxiv (2021), 2021.03.10.21252749.
- [2] J. Allotey, E. Stallings, M. Bonet, et al., Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis, *Bmj* 370 (2020) m3320.
- [3] T.T. Shimabukuro, S.Y. Kim, T.R. Myers, et al., Preliminary findings of mRNA covid-19 vaccine safety in pregnant persons, *N. Engl. J. Med.* 384 (24) (2021) 2273–2282.
- [4] S.B. Black, H.R. Shinefield, E.K. France, B.H. Fireman, S.T. Platt, D. Shay, Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants, *Am. J. Perinatol.* 21 (6) (2004) 333–339.
- [5] A.J. Doyle, W. Thomas, A. Retter, et al., Updated hospital associated venous thromboembolism outcomes with 90-days follow-up after hospitalisation for severe COVID-19 in two UK critical care units, *Thromb. Res.* 196 (2020) 454–456.
- [6] J. Helms, C. Tacquard, F. Severac, et al., High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study, *Intensive Care Med.* 46 (6) (2020) 1089–1098.
- [7] F. Marongiu, A. Marni, E. Grandone, D. Barcellona, Pulmonary thrombosis: a clinical pathological entity distinct from pulmonary embolism? *Semin. Thromb. Hemost.* 45 (8) (2019) 778–783.
- [8] S. Robinson, K. Longmuir, S. Pavord, Haematology of pregnancy, *Medicine (United Kingdom)* 45 (4) (2017) 251–255.
- [9] Royal College of Obstetricians and Gynaecologists, Reducing the risk of venous thromboembolism during pregnancy and the puerperium, Green-top Guideline 37 (2015) 1–40.
- [10] L.D. Zambrano, S. Ellington, P. Strid, et al., Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22–October 3, 2020, *MMWR Morb. Mortal. Wkly. Rep.* 69 (44) (2020) 1641–1647.
- [11] Royal College of Obstetricians and Gynaecologists, Coronavirus in pregnancy guidance, 13th February 2021 2021, <https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-19-coronavirus-covid-19-infection-in-pregnancy-v13.pdf>, 2021, 9th July 2021.
- [12] A.J. Vivanti, C. Vauloup-Fellous, S. Prevot, et al., Transplacental transmission of SARS-CoV-2 infection, *Nat. Commun.* 11 (1) (2020) 3572.
- [13] C.M. Salvatore, J.Y. Han, K.P. Acker, et al., Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study, *The Lancet Child & Adolescent Health* 4 (10) (2020) 721–727.
- [14] E. Vlachodimitropoulou Koumoutsea, A.J. Vivanti, N. Shehata, et al., COVID-19 and acute coagulopathy in pregnancy, *J. Thromb. Haemostasis* 18 (7) (2020) 1648–1652.
- [15] J. Servante, G. Swallow, J.G. Thornton, et al., Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis, *BMC Pregnancy Childbirth* 21 (1) (2021) 108.
- [16] A. Pereira, S. Cruz-Melguizo, M. Adrien, L. Fuentes, E. Marin, T. Perez-Medina, Clinical course of coronavirus disease-2019 in pregnancy, *Acta Obstet. Gynecol. Scand.* 99 (7) (2020) 839–847.
- [17] L. Sentilhes, F. De Marcillac, C. Jouffrieau, et al., Coronavirus disease 2019 in pregnancy was associated with maternal morbidity and preterm birth, *Am. J. Obstet. Gynecol.* 223 (6) (2020), 914.e1–e15.
- [18] J. Yan, J. Guo, C. Fan, et al., Coronavirus disease 2019 in pregnant women: a report based on 116 cases, *Am. J. Obstet. Gynecol.* 223 (1) (2020), 111.e1–e14.
- [19] M. Knight, K. Bunch, A. Cairns, et al., Saving lives, improving mothers' care, March–May, 2020, in: *Rapid Report: Learning from SARS-CoV-2-Related and Associated Maternal Deaths in the UK*, University of Oxford, 2020.
- [20] M. Knight, K. Bunch, N. Vousden, et al., Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study, *bmj* (2020) 369.
- [21] R. D'Souza, I. Malhamé, L. Teshler, G. Acharya, B.J. Hunt, C. McLintock, A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19, *Acta Obstet. Gynecol. Scand.* 99 (9) (2020) 1110–1120.
- [22] P.R. Lawler, E.C. Goligher, J.S. Berger, et al., Therapeutic anticoagulation in non-critically ill patients with covid-19, medRxiv (2021), 2021.05.13.21256846.
- [23] K. MacDougall, A.C. Spyropoulos, New paradigms of extended thromboprophylaxis in medically ill patients, *J. Clin. Med.* 9 (4) (2020).
- [24] P.M. George, S.L. Barratt, R. Condliffe, et al., Respiratory follow-up of patients with COVID-19 pneumonia, *Thorax* 75 (11) (2020) 1009–1016.

- [25] J. Thachil, N. Tang, S. Gando, et al., ISTH interim guidance on recognition and management of coagulopathy in COVID-19, *J. Thromb. Haemostasis* 18 (5) (2020) 1023–1026.
- [26] G.D. Barnes, A. Burnett, A. Allen, et al., Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum, *J. Thromb. Thrombolysis* 50 (2020) 72–81.
- [27] A.C. Spyropoulos, J.H. Levy, W. Ageno, et al., Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19, *J. Thromb. Haemostasis* 18 (8) (2020) 1859–1865.