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ORIGINAL ARTICLE

COVID-19 coagulopathy in pregnancy: Critical review, preliminary recommendations, and ISTH registry—Communication from the ISTH SSC for Women's Health

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Abstract

Background: Novel coronavirus (SARS-CoV-2), which causes COVID-19, has thus far affected more than 15 million individuals, resulting in more than 600 000 deaths worldwide, and the number continues to rise. In a large systematic review and meta-analysis of the literature including 2567 pregnant women, 7% required intensive care admission, with a maternal mortality ~1% and perinatal mortality below 1%. There has been a rapid increase in publications on COVID-19–associated coagulopathy, including disseminated intravascular coagulopathy and venous thromboembolism, in the non-pregnant population, but very few reports of COVID-19 coagulopathy during pregnancy; leaving us with no guidance for care of this specific population.

Methods: This is a collaborative effort conducted by a group of experts that was reviewed, critiqued, and approved by the International Society on Thrombosis and Haemostasis Subcommittee for Women's Health Issues in Thrombosis and Hemostasis. A structured literature search was conducted, and the quality of current and emerging evidence was evaluated. Based on the published studies in the non-pregnant and pregnant population with a moderate to high risk of bias as assessed by Newcastle-Ottawa scale and acknowledging the absence of data from randomized clinical trials for management of pregnant women infected with SARS-CoV-2, a consensus in support of a guidance document for COVID-19 coagulopathy in pregnancy was identified.

Results and Conclusions: Specific hemostatic issues during pregnancy were highlighted, and preliminary recommendations to assist in the care of COVID-19–affected pregnant women with coagulopathy or thrombotic complications were developed. An international registry to gather data to support the management of COVID-19 and associated coagulopathy in pregnancy was established.

KEYWORDS

COVID-19 , COVID-19 pregnancy registry, pregnancy and coagulopathy, pregnancy and venous thromboembolism, thromboprophylaxis in pregnancy

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1 | INTRODUCTION

The novel coronavirus (SARS-CoV-2), previously known as 2019-nCoV, which causes COVID-19, has thus far affected more than 15 million individuals, resulting in more than 600 000 deaths worldwide,[1] and the number continues to rise. Most patients have mild symptoms and fully recover. However, the infection can be severe in some individuals, especially those with comorbidities, and may progress to pneumonia, respiratory compromise, and multi-organ failure, with a significant impact on hospital and intensive care (ICU) admissions and overall mortality.

Pregnancy, by virtue of its inherent physiological adaptations, would be expected to increase the risk of morbidity associated with COVID-19, particularly owing to: (a) a relatively immunocompromised state secondary to alterations within the body's cell-mediated immune response and inflammatory mechanisms,[2] (b) alteration of pulmonary function,[2] and (c) a hypercoagulable state established in preparation for prevention of postpartum hemorrhage and restoration of hemostasis following birth.[3] These changes indeed hamper interpretation of coagulation-related laboratory data in association with COVID-19. In contrast to previous coronavirus outbreaks responsible for Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) during which pregnant women were noted to experience high rates of severe morbidity and mortality, thus far the COVID-19 infection overall does not appear to affect pregnant women more severely than the general population.[2,4,5] However, severe disease does occur,[4-7] with potential for evolution of coagulopathy, multi-organ failure, and even maternal death.[8-10]

The purpose of this report is to: (a) examine the current evidence of COVID-19 outcomes in pregnancy, (b) highlight the specific pregnancy-related hemostatic issues, (c) provide recommendations to guide care of COVID-19–affected pregnant women with respect to coagulopathy, and (d) introduce an international registry to systematically analyze the occurrence and impact of coagulopathy in women with COVID-19 during pregnancy and the post partum period.

Essentials

- COVID-19 in pregnancy poses a challenge. Current data shows 7%-10% intensive care unit admissions with 1% maternal mortality.
- No guidance available for management of COVID-19 coagulopathy or venous thromboembolism during pregnancy.
- Specific hemostatic issues during pregnancy are highlighted with recommendations for care of COVID-19 affected pregnant women.
- An international registry is established to support management of COVID-19 coagulopathy in pregnancy.

2 | METHODS, SEARCH STRATEGY, AND RISK OF BIAS ASSESSMENT

This is a collaborative effort conducted by a group of experts, which was reviewed, critiqued, and approved by the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee for Women's Health Issues in Thrombosis and Hemostasis.

In a virtual meeting facilitated by the ISTH, the authors discussed and identified an unmet need for guidance regarding management of COVID-19 coagulopathy in pregnancy. All recognized that the ISTH published guidance did not address pregnancy-specific issues. The authors thus planned to work together to develop preliminary recommendations based on expert opinion, given the paucity of evidence in the literature, together with developing an international registry to facilitate a global concerted effort to gain more insight into the issues of coagulopathy and thrombosis in the context of COVID-19 in pregnancy. Consensus was obtained between all authors, as well as the co-chairs of ISTH Women's Health Issues in Thrombosis and Hemostasis Scientific and Standardization Committee (SSC) that the main questions to be addressed in the document would relate to guidance regarding cut-off values for various lab tests that help diagnose coagulopathies in association with COVID-19, as well as guidance regarding management of coagulopathy and venous thromboembolism (VTE) thromboprophylaxis in COVID-19–affected pregnancies.

A structured literature search was conducted using MEDLINE (1946 to 16 July 2020), EMBASE (1947 to 16 July 2020), and EPUB Ahead of Print & Other Non-Indexed Citations (inception to 16 July 2020). The search was conducted using the medical subject headings (MeSH) terms: COVID19, SARS COV, and coagulopathy, thrombosis, venous thromboembolism, coagulation disorders, and anticoagulation. For pregnancy affected by COVID-19 illness and coagulopathy, the MeSH terms included all the above terms and pregnancy. The search was limited to publications in the English language. Articles were included if they represented a randomized controlled trial, cohort study, case-control study, or case series of at least 10 non-pregnant patients with COVID-19 infection. Given limited data, for pregnancy, case series with fewer than 10 participants and case-reports were included. The Risk of Bias for individual studies was assessed using the Newcastle-Ottawa scale (NOS).[11] The maximum number of stars a study could be awarded was 8 and studies receiving more than 6, 4–6, and <4 stars were considered to be at low, intermediate, and high risk of bias, respectively. Studies with high risk of bias were excluded.

Figure S1 in supporting information summarizes our search strategy and approach.

3 | COVID-19 AND PREGNANCY OUTCOMES

Following removal of duplicates, 669 papers were identified for COVID-19 and pregnancy outcomes, 184 of which were selected

for full text review. Ten retrospective cohort studies and one prospective cohort study met the inclusion criteria and were retained (Figure S1A). Reported outcomes included: admission, pregnancy complication, death, thromboembolism, or coagulopathy. Follow-up was at least to the end of the admission. Outcome data were available for at least 90% of patients. The risk of bias assessment according to the NOS is summarized in Table 1. The support for the assessments for individual studies is available in Table S1 in supporting information.

The pregnancy data remain conflicting and will likely continue to be updated as more studies of affected pregnancies become available. Several publications have presented findings of COVID-19 in pregnancy, including a recent systematic review and meta-analysis of 17 studies including 2567 pregnancies.[5,6,12-14] Increased maternal mortality and poor obstetric outcomes, including the risk of preterm birth, intrauterine growth restriction, and perinatal death have been demonstrated in association with other coronaviruses such as SARS and MERS[12,15,16] In COVID-19 infection, case fatality rate in pregnant women appears to be comparable to non-pregnant women of reproductive age.[2,4,5] However, the propensity for severe disease in pregnancy does exist, especially with advanced gestation, having been noted in 8% of COVID-19–affected pregnant women in a series from China,[7] and in 9% to 10% in reports from New York, with 4% listed as critical.[6,17]

According to data from the Centers for Disease Control and Prevention (CDC) in the United States, among women aged 15 to 44 years with COVID-19, pregnant women were hospitalized at a higher rate compared to non-pregnant women (31.5% versus 5.8%), pregnant women were also more likely to be admitted to the ICU and to receive mechanical ventilation.[18] The United Kingdom's Obstetric Surveillance System (UKOSS)[4] data are consistent with these estimates, describing pregnant women admitted to hospital with COVID-19 infection in 4.9/1000 maternities, with 9% progressing to the need for critical care support, and with maternal mortality in 7.5% of those requiring critical care. In a series of 64 COVID-19–affected pregnant women who were hospitalized in 12 institutions in the United States, 69% and 31% had severe and critical disease, respectively, with admission at a mean of 30 weeks' gestation.[19] All those with critical disease were treated with prophylactic or therapeutic anticoagulation throughout hospital admission. Intubation, when required, was typically needed on day nine with no maternal deaths. Preterm birth occurred in 75% (15/20) of women with critical disease. No stillbirths or neonatal deaths were recorded.[19] Likewise, in a report from Wuhan, China, including 118 COVID-19–affected pregnancies, fever and cough were the most frequently observed symptoms, seen in more than 70%.[7] Lymphopenia was observed in 44%, while severe illness was noted in 8%. Of the 118 pregnancies, 68 (58%) have been delivered, 93% by cesarean delivery, with the sole indication of COVID-19 concerns noted as a reason for the procedure in 61%. Preterm birth was reported in 21%, eight of which were iatrogenic. Increased risks of iatrogenic preterm births and caesarean deliveries were also shown in the recent systematic review of 2567 women with COVID-19 in pregnancy.[5] Contrasting evidence exists with respect to the potential for vertical transmission. A rate of neonatal SARS-CoV-2 positivity is estimated between 1% and 2%.[5] Suspected perinatal SARS-CoV-2 infection, with evidence of immunoglobulin (Ig)M and IgG antibodies in neonates, has been reported.[20,21] Similarly, positive neonatal nasopharyngeal samples from infected mothers together with evidence of placental inflammation and fibrin deposition were also described.[22] Thus, vertical transmission is possible, though it appears to be rare.[5] Caution is warranted with respect to interpretation of test results as potential contamination from maternal secretions or tissues must be excluded.

4 | COVID-19 COAGULOPATHIES IN THE NON-PREGNANT PATIENTS

After duplicates were excluded, the search strategy yielded 1257 records, of which 371 underwent full-text review. In total, 24 reports met the inclusion criteria (Figure S1B). Reported outcomes included death, thromboembolism, or coagulopathy and follow-up was at least to the end of the admission. Outcome data were available for at least 90% of patients. The risk of bias assessment, according to the NOS, is summarized in Table 1 and support for the judgements for individual studies is available in the Table S1. Cases of disseminated intravascular coagulopathy (DIC) in the non-pregnant population had pro-coagulant DIC, characterized by high fibrinogen and D-dimer concentrations and a prothrombotic presentation.[23]

ISTH interim guidance and Expert Opinion[24,25] for recognition and management of coagulopathy in non-pregnant COVID-19 patients, alongside guidance for VTE management in hospitalized patients[26] have now been published. The key points are summarized in Table 2. It is to be noted that none of the three guidance documents have addressed pregnancy-specific issues, a gap the current document aims to address.

5 | COVID-19 COAGULOPATHIES IN PREGNANCY

Based on our search, only four publications relevant to COVID-19 coagulopathy in pregnancy were identified . All were case reports.[8,27-29] Coagulopathy or thrombotic complications were reported in these studies. Outcome data were available for at least 90% of patients. All studies were assigned moderate risk of bias with the risk of bias assessment for the reports, according to the NOS, summarized in Table 1. The support for our judgements is available in Table S1.

The first study is a single report of two cases of COVID-19–related coagulopathy observed in the third trimester of pregnancy.[8] This report documents rapidly progressive thrombocytopenia (nadir 78×10^9/L in case 1 and 54×10^9/L in case 2), activated partial thromboplastin time (APTT) prolongation (peak of 41.2 and 60 seconds in the two cases, respectively), low fibrinogen (nadir 2.2 g/L in case 1 and 0.8 g/L in case 2), and D-dimer elevation (17× and 12× the upper range of normal for pregnancy in the two cases,

TABLE 1 Study characteristics and quality based on the risk of bias assessment Newcastle-Ottawa scale

Author, country	Single vs multicenter	Design	Number of patients/ pregnancies	Inclusion criteria	Risk of bias assessment (NOS)[a]				
					Selection ★★★★	Comparability ★	Outcome ★★★	Total/8	Risk of bias: 1-3: high 4-6: moderate 7-8: low
COVID-19 (Pregnant)									
National cohort study using the UK Obstetric Surveillance System (UKOSS)[4] United Kingdom	Multicenter	Prospective Cohort	427	COVID-19	★★★	-	★★	5	Moderate
Ferrazzi[57] Italy	Single	Retrospective cohort	42	COVID-19	★★★	-	★★★	6	Moderate
Breslin[6] Unites States	Single	Retrospective cohort	43	COVID-19	★★★	★	★★★	7	Low
Qiancheng[58] China	Single	Retrospective cohort	24	COVID-19	★★★	★	★★★	7	Low
Pierce-Williams[19] United States	Multicenter	Retrospective cohort	64	COVID-19	★★★	★	★★★	7	Low
Yan[59] China	Multicenter	Retrospective cohort	116	COVID-19	★★★	★	★★★	7	Low
Collin[60] Sweden	Multicenter	Retrospective cohort	53	COVID-19	★★★	★	★★★	7	Low
Ellington[18] United States	Multicenter	Retrospective cohort	91 412	COVID-19	★★★	-	★★★	6	Moderate
Pereira[61] Spain	Single	Retrospective cohort	60	COVID-19	★★★	-	★★	5	Moderate
Sentilhes[62] France	Single	Retrospective cohort	54	COVID-19	★★★	-	★★	5	Moderate
Nayak[63] India	Single	Retrospective cohort	977	COVID-19	★★★	★	★★★	7	Low
COVID-19 coagulopathy (non-pregnant)									
Tang[30] China	Single	Prospective cohort	183	COVID-19	★★★	-	★★	5	Moderate
Klok[64] Netherlands	Multicenter	Prospective cohort	184	COVID-19	★★	-	★★	4	Moderate
Middeldorp[65] Netherlands	Single	Prospective cohort	198	COVID-19	★★★	★	★★	6	Moderate

(Continues)

TABLE 1 (Continued)

Author, country	Single vs multicenter	Design	Number of patients/ pregnancies	Inclusion criteria	Risk of bias assessment (NOS)[a]				
					Selection ★★★★	Comparability ★	Outcome ★★★	Total/8	Risk of bias: 1-3: high 4-6: moderate 7-8: low
Tang[66] China	Single	Retrospective cohort	449	COVID-19	★	★	★★	4	Moderate
Fogarty[67] Ireland	Single	Retrospective cohort	83	COVID-19	★★★	-	★★★	6	Moderate
Panigada[68] Italy	Single	Prospective cohort	24	COVID-19	★★	-	-	2	High
Llitjos[69] France	Single	Retrospective cohort	26	COVID-19	★★	-	-	2	High
Cui[70] China	Single	Retrospective cohort	81	COVID-19	★★	-	★	3	High
Helms[71] France	Multicenter	Prospective cohort	150	COVID-19	★★★	★	★★	6	Moderate
Ranucci[72] Italy	Single	Retrospective cohort	16	COVID-19	★★	-	★	3	High
Poissy[73] France	Single	Retrospective cohort	107	COVID-19	★★	-	★	3	High
Spiezia[74] Italy	Single	Prospective cohort	22	COVID-19	★★		★	3	High
Lodigiani[75] Italy	Single	Retrospective cohort	388	COVID-19	★★★	-	★★	5	Moderate
Stoneham[76] United Kingdom	Single	Retrospective cohort	274	COVID-19	★★★★	★	★★	7	Low
Longchamp[77] Switzerland	Single	Retrospective cohort	25	COVID-19	★★	-	★★	4	Moderate
Ren[78] China	Multicenter	Retrospectivecohort	48	COVID-19	★★	-	★★	4	Moderate
Al-Samkari[79] United States	Multicenter	Retrospective cohort	400	COVID-19	★★	-	★★	4	Moderate
Hippensteel[80] United States	Single	Retrospective cohort	106	COVID-19	★★	-	★★	4	Moderate
Fraissé[81] France	Single	Retrospective cohort	92	COVID-19	★★	-	★★	4	Moderate
Santoliquido[82] Italy	Single	Retrospective cohort	84	COVID-19	★★	-	★★	4	Moderate

(Continues)

TABLE 1 (Continued)

Author, country	Single vs multicenter	Design	Number of patients/ pregnancies	Inclusion criteria	Risk of bias assessment (NOS)[a]				
					Selection ★★★★	Comparability ★	Outcome ★★★	Total/8	Risk of bias: 1-3: high 4-6: moderate 7-8: low
Rieder[83] Germany	Single	Prospective cohort	190	COVID-19	★★★	★	★★★	7	Low
Pavoni[84] Italy	Single	Retrospective cohort	40	COVID-19	★★★	-	★★★	6	Moderate
Nougier[85] France	Single	Retrospective cohort	78	COVID-19	★★★	★	★★★	7	Low
COVID-19 coagulopathy (pregnant)									
Vlachodimitropoulou[8] Canada	Single	Case report	2	★	★★	★★	★	6	Moderate
Martinelli[27] Italy	Single	Case report	1	★	★	★	★	4	Moderate
Mohammadi[29] Iran	Single	Case report	1`	★	★	★	★	4	Moderate
Ahmed[28] United Kingdom	Single	Case Report	1	★	★★	★★	★	6	Moderate

Abbreviation:: NOS, Newcastle Ottawa scale.

[a]The number of stars is the standard assessment method used in this scale. The maximum number of stars a study could be awarded was 8 and studies receiving more than 6, 4–6, and <4 stars were considered to be at low, intermediate, and high risk of bias, respectively.

TABLE 2 Hemostatic parameters in COVID-19 coagulopathies in non-pregnant women. A summary of published studies, ISTH guidance, and expert opinion for recognition and management in hospitalized patients

	Normal values	Pathological alterations in COVID-19		ISTH Interim Guidance and Expert Opinion[24-26]
PT	9.9–13.1 seconds	Prolonged in 50% of non-survivors but only 7% of survivors ($P < .0001$)[30]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy • Admit if PT is prolonged • Monitor PT at least twice daily in all hospital admitted patients • In bleeding patients (rare in COVID-19), maintain PT ratio < 1.5
APTT	24–36 seconds	No significant changes at admission but significant prolongation of PT and not APTT at day 4[67]		
D-dimer	0–0.5 μg/mL	>0.5 μg/mL is associated with severe disease compared[86] Significantly elevated in critically ill patients compared to non[87]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy • Admit if markedly raised • Monitor at least twice daily in all hospital admitted patients
Platelet	150–450 × 10^9/L	<100 × 10^9/L is associated with severe disease or in critically ill[30,87,88] Increased platelet counts in severe cases due to cytokine storm[43,89]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy • Admit if count < 100×10^9/L • Monitor at least twice daily in all hospital admitted patients • In bleeding patients (rare in COVID-19), maintain count > 50 × 10^9/L
Fibrinogen	2–4 g/L	Increased > 4 upon admission with significant difference between survivors and non-survivors[30,67]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy and admit if >2 g/L • Monitor at least twice daily in all hospital admitted patients • In bleeding patients (rare in COVID-19), maintain >2.0 g/L
FDPs		Increased[30,90]		
Lupus Anticoagulant		Positive[71]		
VTE risk		Number of patients admitted to ICU	Number (percentage) of patient developed VTE	• Prophylactic LMWH in all patients (including non-critically ill) who require hospital admission, in the absence of contraindications (active bleeding and platelet count <25 × 10^9/L). Abnormal PT or APTT not a contraindication) • Consider VTE in the setting of rapid respiratory deterioration and/or high D-dimer • Consider CT angiography or ultrasound of the venous system of the lower extremities to evaluate presence/absence of VTE
		184[64,91]	28 (27%)	
		75[65,66]	35 (47%)	
		150[71]	64 (42%)	
		48[75]	8 (16.7%)	

respectively), which improved within 48 hours of delivery in both cases. The thrombocytopenia and elevated liver enzymes encountered in both individuals present a laboratory profile reminiscent of HELLP syndrome (hemolysis, elevated liver enzymes, low platelets syndrome), highlighting the need for awareness of this type of presentation in context of COVID-19 (and in absence of a hypertensive disorder of pregnancy) to help guide clinical management.[8] The finding of low fibrinogen encountered in both instances differs from reports within the non-pregnant COVID-19 population,[30] and warrants further scrutiny, given the association of hypofibrinogenemia with post partum hemorrhage.[8] Aside from this report, there are no publications or guidance addressing the identification, prognostic significance, or management of COVID-19–related coagulopathies during pregnancy. In contrast to the presentation of DIC in the non-pregnant population with COVID-19, which was on the thrombotic side of DIC, the two cases of coagulopathy in pregnant women with COVID-19 were of a hyperfibrinolytic DIC phenotype, characterized by low fibrinogen and bleeding tendency.[23]

Three other case reports highlight the prothrombotic risk of COVID-19, in young pregnant women admitted with COVID-19 infection, without personal or family history of thrombosis.[27-29] The first of these cases highlighted the course of a woman with elevated body mass index (BMI) who developed a segmental pulmonary embolism during the course of her COVID-19 illness,[27] the second described a woman who presented with abdominal pain and vomiting, was found to be positive for SARS-CoV-2, and was eventually diagnosed with ovarian vein thrombosis.[29] The third case report presented COVID-19 illness during pregnancy in a young woman with a BMI of 35 kg/m^2 and poorly controlled Type 2 diabetes mellitus, which was complicated by basilar artery stroke, pulmonary embolism, and maternal mortality.[28] All three patients required oxygen support and either non-invasive or invasive ventilation. Alongside obesity, a comorbidity common to both these cases, which was previously reported to increase the risk of severity of COVID-19,[27] diabetes mellitus has also been implicated as a risk factor for development of severe COVID-19 illness and increased mortality.[31,32]

TABLE 3 Coagulation parameters in normal pregnancy (third trimester) and possible alterations in COVID-19 in association with pregnancy

Laboratory parameter	Normal values			Non- pregnant women	Possible alterations in pregnancy with COVID-19	Potential prognostic markers	Levels reported in severe COVID-19 outside pregnancy[a]
	Third trimester of pregnancy						
PT	8.5–11.0 seconds			16.0 seconds	• ↑COVID coagulopathy Or DIC • PPH	Yes	3 s extension >6 in 47.6% of non-survivors with DIC compared to 3 in survivors
APTT	25.5–42.5 seconds			27.0–37.0 seconds	• ↑COVID coagulopathy Or DIC • PPH • Consumption events • ↓FVIII release	Yes	5 s extension
D-dimer	0.16–1.7 μg/mL				• ↑COVID coagulopathy Or DIC • ↑Acute phase reactant • VTE • Trauma • Liver/ renal disease	Yes (severe disease and in hospital mortality Cut off: 2.0 μg/mL)	2.12 in non survivors Vs 0.61 in survivors >3 in 86% non-survivors with DIC
Platelet count Mean (range)	Third trimester 225 (57–505) × 10^9/L	Delivery 217 (63–552) × 10^9/L	PP 264 (91–575) × 10^9/L	273 (111–999) × 10^9/L	• ↓COVID coagulopathy Or DIC • ↑PPH • Cytokines induced	Yes Thrombocytopenia (severe disease + mortality)	<100 in 33% of non-survivors <50 in 24% non-survivors with DIC
Fib	2.48–5.06 g/L			2.5–4.0 g/L	• ↓COVID coagulopathy Or DIC • ↑Acute phase reactant • Inflammation • ↓PPH	Yes	5.16 in non survivors vs 4.5 in survivors (non signifcant difference) <1 in 29% non-survivors with DIC
FDPs	<15 μg/mL			3.09 ± 1.96 μg/mL	• ↑COVID coagulopathy Or DIC • Acute phase reactant		7.6 in non survivors vs 4.0 in survivors

Note: Please note this table is a guide. Age and ethnic variations exist and need to be considered. References:[30,34,39,40,43,89].

Abbreviations: APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulopathy; FDPs, fibrin degradation products; Fib, fibrinogen; PP, post partum; PT, prothrombin time; VTE, venous thromboembolism.

[a]Reference:30; 71% of non-survivors developed DIC (ISTH DIC score of ≥5) vs 0.6% of survivors.

5.1 | Pregnancy-specific guidance

Based on our understanding of the specific key physiological alterations associated with pregnancy (Table 3) and the current available evidence on COVID-19 in pregnancy as well as COVID-19 coagulopathies, we highlight specific issues that require careful considerations in pregnancy when interpreting the hemostatic parameters and cut-off values suggested for monitoring and management of COVID-19 coagulopathy in the non-pregnant population. We also provide preliminary recommendations to guide laboratory assessments and clinical management of COVID-19 coagulopathy in pregnant patients. Due to a low level of certainty of the evidence, and recognizing that future research may alter these recommendations, we have used the word "suggest" rather than "recommend."

5.1.1 | Prothrombin time (PT) and APTT

We suggest the use of PT ratio and APTT ratio[33] during pregnancy with a ratio ≥1.5 as cut-off for coagulopathy, rather than reliance on prolonged PT and APTT measured in seconds.

Evidence and rationale

Due to the increase in coagulation factors toward term, PT and APTT are shortened in pregnancy, especially during the third trimester. Alongside gestational age-specific ranges for PT and APTT based on samples from 1130 pregnant women, Liu et al reported median PT and APTT levels at 36 weeks of 9.60 and 31.00 seconds, respectively.[34]

5.1.2 | Fibrinogen

We suggest an individualized assessment of fibrinogen activity levels, with specific attention to hypofibrinogenemia in the obstetric setting. Further studies are required to confirm fibrinogen thresholds and their prognostic utility in the setting of COVID-19 in pregnancy.

Evidence and rationale

Fibrinogen increases in pregnancy, with levels reported to be as high as 3.7 to 6.2 g/L during the third trimester.[35] In one study the median level at 36 weeks of pregnancy was noted to be 3.86 g/L.[34] Fibrinogen < 3 g/L had an assigned weight of 25 in the pregnancy-specific DIC score.[36] Furthermore, during the course of a post partum hemorrhage (PPH), a study of 128 women demonstrated that fibrinogen ≤ 2 g/L had a positive predictive value of 100% for severe PPH.[37] Tang et al reported no significant change in the fibrinogen level between COVID-19 survivors and non-survivors on admission.[30] By late hospitalization, however, the fibrinogen level was significantly lower in non-survivors. Thus, elevated fibrinogen level is likely to be a reflection of the inflammatory state, but if the patient is deteriorating and developing coagulopathy, low levels can be seen. Hypofibrinogenemia (compared to normal pregnancy levels) was seen in the two case reports of acute coagulopathy with COVID-19 in pregnancy,[8] one patient had a severe PPH requiring blood products, the other had fibrinogen concentrate pre-operatively and did not experience excessive bleeding.

5.1.3 | Platelet count

We suggest using the clinically relevant platelet count threshold of ≤100 × 10^9/L to define thrombocytopenia during pregnancy, as would be the case for pregnancies not affected by COVID-19. A platelet count that is critical for bleeding risk in pregnancy varies according the clinical situation; while a threshold of 30 × 10^9/L is used during pregnancy, a minimum platelet count of 50 × 10^9/L is required for delivery.

Evidence and rationale

There is a drop in platelet count in pregnancy and gestational thrombocytopenia affects 5% to 11% of pregnant women in the second and third trimesters.[38] Medians and ranges of platelet counts in various trimesters compared to the non-pregnant state have been reported.[35,39] While there is no evidence in the literature regarding platelet count thresholds specific to COVID-19–affected pregnancies, pragmatic guidance regarding this parameter is included in the interest of inclusivity.

5.1.4 | D-dimer

We suggest markedly elevated D-dimers several-fold above the upper range of normal for pregnancy (noting that a level of 2 μg/mL can still be seen in normal pregnancy) should be considered as indicative of coagulopathy.

Evidence and rationale

D-dimer levels increase progressively in pregnancy and peak in the third trimester. One study reported levels of: 0.11 to 0.40 μg/mL, 0.14 to 0.75 μg/mL, and 0.16 to 1.3 μg/mL in first, second, and third trimester, respectively,[40] while in another study 1.7 μg/mL was reported as the upper limit in the third trimester.[35] Yet another report found a D-dimer > 0.5 μg/mL in 99% of women during the third trimester.[41] In the recent study by Tang et al, an elevated D-dimer was one of the predictors of mortality in the non-pregnant population with COVID-19, with levels of 2.12 μg/mL (range 0.77–5.27 μg/mL) in COVID-19 non-survivors compared to 0.61 μg/mL (range 0.35–1.29 μg/mL) in survivors.[30] A level of 2 μg/mL can still be within the normal range for pregnant women and the significance of mild to moderate D-dimer elevation in pregnancy remains unknown. While further data are required before a threshold for pregnant women can be suggested, in the interim given clear evidence of association between D-dimer elevation and COVID-19 coagulopathy/mortality in the non-pregnant state, significant D-dimer elevations should raise suspicion of potential deterioration and should be evaluated carefully.

5.1.5 | Fibrin-degradation products (FDPs)

We suggest that any elevated levels of FDP should be taken as an early pathological sign, especially when associated with abnormalities of other parameters of coagulopathy.

Evidence and rationale

FDP levels were elevated in non-pregnant non-survivors of COVID-19.[30] FDP levels do not seem to undergo significant change during normal pregnancy, but increase markedly during labor and the first week after normal delivery.[42] Significantly elevated levels are observed in association with complicated pregnancies, such as abruptio placentae, eclampsia, intrauterine fetal death, and PPH.[42] The reported range of FDPs in association with COVID-19 outside pregnancy is 4.0 ~ 15.0 μg/mL, with an average of 7 μg/mL.[30]

5.1.6 | DIC

We suggest the use of pregnancy-modified ISTH DIC score, to differentiate overt and non-overt DIC during pregnancy.[36]

Evidence and rationale

Scoring systems for diagnosis of DIC have been developed by the Japanese Association for Acute Medicine (JAAM)[43] and ISTH.[44] The pregnancy-modified ISTH score was calculated based on a population of 24 646 pregnancies without and 87 with DIC (n = 24 693), had a 96% specificity,[36] and in an independent study attained a sensitivity of 78% and a specificity of 97%.[45] This modified score has proven useful for the identification of patients at risk for obstetrical hemorrhage requiring blood product transfusion[36,46,47] and can be applied in COVID-19–affected pregnancies.

5.1.7 | Hypercoagulability and VTE risk

1. Given the possible increase in coagulopathy and VTE risk with COVID-19, as for the non-pregnant population, weight-adjusted VTE prophylaxis with low molecular weight heparin (LMWH) should be considered in all pregnant and post partum women admitted to hospital with COVID-19 infection in the absence of active bleeding and with a platelet count above 30×10^9/L,[48,49] provided urgent delivery is not anticipated or timing is beyond 24 hours post partum. If potential need for emergent delivery in a critically ill woman is likely, and during the immediate post partum period, thromboprophylaxis should be considered individually, with input from a multidisciplinary team including specialists of maternal medicine and thrombosis and hemostasis.
2. Prolonged PT and APTT should not be considered as a contraindication for thrombo-prophylaxis.
3. If anticoagulation is contraindicated in admitted patients, mechanical prophylaxis (intermittent pneumatic compression) should be instituted.
4. In preparation for discharge, a careful and individualized VTE risk assessment should be performed taking into consideration other VTE risk factors to plan duration of LMWH after discharge:
   - For those with a less severe condition and a short period of hospitalization, which did not result in delivery, 10 to 14 days of LMWH may be appropriate.
   - For those with a severe disease, with very high D-dimer levels, particularly in the third trimester, this may mean continuation of LMWH throughout the rest of pregnancy and post partum.
   - For post partum women, the duration of thromboprophylaxis may vary from 2 to 6 weeks, depending on other risk factors, mode of delivery, severity of COVID-19 infection, and duration of admission.
   - Dose, duration, and type of anticoagulation should be determined individually for critically ill patients and those with complex medical conditions during hospitalization and after discharge, in collaboration with experts in critical care, thrombosis, and hemostasis, and maternal-fetal medicine.
5. For the majority of women with mild-moderate disease who are managed at home, VTE risk assessment should be performed carefully. For those who are low risk, hydration, appropriate nutrition, mobilization, and control of pyrexia should be encouraged. Use of anti-embolic stockings at home may be encouraged. LMWH thromboprophylaxis should be considered in the presence of immobility, high fever, dehydration, or additional maternal risk factors for VTE, which are highlighted in the Royal College of Obstetricians and Gynaecologists (RCOG) guideline.[50]

Evidence and rationale

Pregnancy is a hypercoagulable state, with a 4- to 6-fold increased risk of VTE and a further increase in this risk in the post partum period.[51-53] Admission of pregnant women to hospital is associated with 18-fold increased VTE risk that is sustained after discharge, especially for women older than 35 years, in the third trimester of pregnancy, and admitted for 3 days or longer.[54] The RCOG guideline recommends that thromboprophylaxis with LMWH is offered to pregnant women when admitted to hospital,[34] unless there is a specific contraindication.

The risk of bleeding from the use of LMWH for thromboprophylaxis is small. In a systematic review, the risk of bleeding in obstetrics from therapeutic and prophylactic LMWH was <2%.[55] Currently, there does not appear to be an increase in bleeding risk with COVID-19 coagulopathy, though caution may be warranted in presence of hypofibrinogenemia, where fibrinogen replacement may be prudent.[8] If bleeding occurs, treatment should follow the principles of sepsis-related coagulopathy and coagulopathy associated with PPH.[56]

6 | KNOWLEDGE/RESEARCH GAPS AND THE ISTH INTERNATIONAL REGISTRY

COVID-19 is a new and evolving disease. The literature addressing the issues of coagulopathy and thrombosis in pregnancy in

association with COVID-19 is sparse and so far, there is no available high-quality evidence to support patients' care. It is our hope that the recommendations provided here, based on expert opinion, will be of value to those providing care to pregnant women. However, the rapidly evolving nature and the magnitude of the pandemic have led to an acceleration in global research and new publications are emerging on a daily basis. As better evidence accumulates on these aspects of care in pregnancy, an update will be provided.

In order to facilitate the accumulation of knowledge in this area, the ISTH Subcommittee for Women's Health Issues in Thrombosis and Hemostasis has established an international registry to address issues specifically relevant to pregnancy in the setting of COVID-19 and associated coagulopathy and thrombosis with the potential to close some of the current gaps. The goals of this registry are to gather data on the occurrence of coagulopathies in COVID-19–affected pregnancies in order to examine the link between hemostatic derangements and disease severity; to evaluate the risk and nature of thrombosis; to assess the use, effects, and complications of anticoagulant therapies; and to explore the effects of COVID-19–related coagulopathy and its treatment on maternal and fetal/neonatal outcomes. The registry (https://redcap.isth.org/surveys/?s=4JPX9W98RH) is now available on the ISTH academy website (https://academy.isth.org/isth). Additionally, the project details are available on the ISTH SSC website (https://www.isth.org/members/group.aspx?id=100375). We invite the international scientific community to participate to help advance knowledge and support patient care.

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CONFLICTS OF INTEREST

All authors have no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

RAK, TK, TI, OE, JT, SK, AKM, and MO developed the concept, contributed to the interpretation of data, and provided intellectual input and recommendations. RAK and MO drafted the manuscript. SK conducted the structured literature search, gathered relevant studies, and conducted the quality assessment. MO and AKM designed the registry and data collection tool, which was reviewed and approved by all authors. The ISTH Subcommittee for Women's Health Issues in Thrombosis and Hemostasis critically reviewed the manuscript and the recommendations and approved the recommendations and the registry.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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