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

妊娠中のCOVID-19凝固障害:批評的レビュー、予備的勧告、ISTH登録事業

ISTH SSC for Women's Healthからの報告

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SARS-CoV2 を原因とする新型コロナウイルス感染症(COVID-19)は、2020 年 10 月 30 日現在、感染者数が全世界で 4510 万人、死者数は 118 万人に上り増加し続けている。しかし、中等度呼吸器症候群(MERS)や重症急性呼吸器症候群(SARS)のコロナウイルス感染症では,妊婦の重篤な罹患率や死亡率が高かったが、COVID-19 感染症全体では一般の妊婦に比べて重症化していない。妊婦 2567 名を含む大規模なシステマティックレビューとメタアナリシスでは、7%が集中治療入院を必要とし、母体死亡率は 1%以下、周産期死亡率は 1%以下であった。また、妊娠中の COVID-19 感染と凝固障害に関する報告は非常に少なく、その管理については指針がないのが現状である。そこで、本論文では以下を目的としている。1. 妊娠中の COVID-19 の治療成績に関する現在のエビデンスを検討する 2. 妊娠に関連した止血の問題点を明らかにする 3. COVID-19 に罹患した妊婦の凝固障害に関する管理の指針となる推奨事項を提供する 4. 妊娠中および分娩後の COVID-19 感染女性における凝固障害の発生と影響を体系的に分析するための国際的な登録を導入することの 4 つである。

これは、国際血栓症学会(International Society on Thrombosis and Haemostasis; ISTH)の血栓症と止血における女性の健康問題に関する小委員会(Subcommittee for Women's Health Issues in Thrombosis and Hemostasis; WHITH)の査読、批評、承認を受けた専門家グループによる共同研究である。文献検索は、MEDLINE(1946 年～2020 年 7 月 16 日)、EMBASE(1947 年～2020 年 7 月 16 日)、EPUB Ahead of Print & Other Non-Indexed Citations(開始～2020 年 7 月 16 日)を用いて行われた。MeSH term の用語を COVID19, SARS COV, and coagulopathy, thrombosis, venous thromboembolism, coagulation disorders, and anticoagulation として検索された。COVID-19 感染症の非妊娠患者 10 名以上を対象としたランダム化対照試験、コホート研究、症例対照研究、またはケースシリーズが対象とされた。妊娠患者はデータが限られているため、10 名未満のケースシリーズ、症例報告が含まれた。個々の研究のバイアスのリスクは、Newcastle-Ottawa スケール(NOS)を用いて評価された。(表 1)

以下に結果を述べる。

COVID-19 と妊娠転帰

669 編の論文が同定され、そのうち 184 編がフルテキストレビューとして選択された。10 件のレトロスペクティブコホート研究と 1 件のレプロスペクティブコホート研究が基準を満たしていた。最近のシステマティックレビューやメタアナリシスを含む 17 の研究(妊娠 2567 例を含む)など、妊娠中の COVID-19 の知見がいくつかの論文で報告されており、母体死亡、早産、胎児発育不全、周産期死亡の増加が示されている。妊娠中の死亡率は、生産年齢の非妊娠女性と同等とされている。しかし、妊娠中に重症

化する症例は特に妊娠後期で顕著であり、中国のケースシリーズでは、COVID-19 感染妊婦の 8%に認められており、ニューヨークの報告では 9～10%に認められ、4%が重篤されている。米国の疾病対策予防センター（CDC）のデータによると、15 歳から 44 歳までの COVID-19 感染者のうち、妊娠中の女性は非妊娠中の女性に比べて入院率が高く（31.5% vs. 5.8%）、ICU 入院や、人工呼吸器を要する率も高いとされている。英国の産科サーベイランスシステム（UKOSS）のデータでは、これらの推計と一致しており、COVID-19 感染症で入院した妊婦数は 1000 名当たり 4.9 名であり、9%が集中治療を必要とし、そのうち 7.5%が死亡したとされている。米国の 12 施設に入院した COVID-19 感染妊婦 64 名を対象とした研究では、平均妊娠 30 週で入院し、それぞれ 69%が重症、31%が重篤あった。すべての重症患者では、入院中に抗凝固療法が予防的もしくは治療的に行われ、人工呼吸は入院 9 日目に必要であり、死亡例はなかった。早産は、重症女性の 75%（15/20）に認めた。死産、新生児死亡はなかった。中国・武漢からの COVID-19 感染妊婦 118 例の報告では、発熱と咳症状の頻度が最も高く、70%以上に認めた。また、リンパ球減少が 44%にみられ、重症は 8%であった。118 例中 68 例（58%）が分娩に至り、93%が帝王切開分娩であったが、そのうち 61%が COVID-19 を主要因とするものであった。早産は 21%に認めたが、8 例は医原性であった。COVID-19 感染妊婦 2567 名の最近のシステマティックレビューでも、医原性の早産や帝王切開分娩のリスクが増加したとされている。また、垂直感染の可能性も指摘されており、新生児の SARS-CoV-2 陽性率は 1%から 2%と推定されている。新生児が IgM 抗体および IgG 抗体を有した症例や、感染妊婦から産まれた新生児の鼻咽頭サンプルが陽性であり、さらに胎盤の炎症とフィブリン沈着を伴った症例が報告されている。

非妊婦における COVID-19 関連凝固障害

1257 件が検索され、そのうち 371 件がフルテキストレビューされ、24 件の報告が基準を満たしていた。妊娠していない集団における播種性血管内凝固症候群（DIC）では、フィブリノゲン値ならびに D-dimer の高値および血栓形成促進傾向を特徴としていた。

非妊娠 COVID-19 患者における凝固障害の診断と管理についての ISTH 暫定指針と専門家の意見および入院患者における VTE 管理のガイダンスが発表された。重要なポイントは表 2 にまとめられている。ただし、妊娠特有の問題を取り上げられていないことに留意する。

妊婦における COVID-19 関連凝固障害

妊娠中の COVID-19 関連凝固障害に関連する文献は、4 件のみで、すべてが症例報告であった。最初の研究は、妊娠後期に観察された COVID-19 関連凝固障害の 2 症例の報告であり、急速に進行する血小板減少症（nadir は各々、症例 1：78×10^9/L、症例 2：54×10^9/L）、活性化部分トロンボプラスチン時間（APTT）延長（各々、症例 1 では 41.2 秒と症例 2 では 60 秒）、低フィブリノゲン（nadir は症例 1：2.2 g/L と症例 2：0.8g/L）、および D-dimer 値の上昇（症例 1：妊婦正常範囲上限の 17 倍、症例 2：12 倍）を認めた。しかし、これらは分娩後 48 時間以内に改善した。血小板減少症と肝酵素の上昇は、HELLP 症候群を想起させるが、COVID-19 において（妊娠高血圧腎症の欠如）同様の特徴があることを認識し、適切に対応する必要がある。低フィブリノゲン血症は、非妊娠 COVID-19 感染の報告とは異なっており、また分娩後出血による低フィブリノゲン血症を考慮すると、より注意が必要である。つまり、非妊娠 COVID-19 感染における DIC では血栓症を特徴とするが、対照的に 2 例の妊娠 COVID-19

感染の DIC における凝固障害では、低フィブリノゲンおよび出血傾向を特徴とする線溶亢進型 DIC であった。

また、他の 3 つの症例報告では、既往歴や家族歴がないにも関わらず、COVID-19 感染で入院した若年妊婦における COVID-19 の血栓形成促進リスクを強調している。1 例目は、COVID-19 罹患中に BMI 上昇とともに肺塞栓症を発症した。2 例目は、腹痛と嘔吐を呈し、最終的には卵巣静脈血栓症を発症した。3 例目は、BMI が 35 kg/m^2 のコントロール不良の 2 型糖尿病で、脳底動脈梗塞、肺塞栓症の合併から妊産婦死亡に至った。3 症例すべてで酸素投与か人工呼吸器を必要とした。肥満は、COVID-19 の重症化リスクを高めることが以前に報告されていたが、糖尿病もまた、重症化した COVID-19 の発症と死亡率の増加の危険因子として示唆されている。

妊婦特有のガイダンス

非妊婦における COVID-19 関連凝固障害のモニタリングおよび管理のために提案されている止血パラメータおよびカットオフ値を解釈する際に、妊娠に伴う生理的変化と妊娠中の COVID-19 感染および COVID-19 関連凝固障害に関する現在までのエビデンスに基づいて、妊娠中に慎重な考慮を必要とする問題点を、表 3 に示した。また、妊娠中の COVID-19 関連凝固障害の検査値評価および臨床管理指針において暫定的な推奨事項が作成された。エビデンスレベルが低いため、今後の研究により、これらの推奨事項が変更される可能性があることから、「推奨」ではなく「提案」という言葉が使用された。

・プロトロンビン時間（PT）と活性化トロンボプラスチン時間（APTT）

秒単位で測定された PT と APTT の実数値によるのではなく、妊娠中は PT 比と APTT 比 1.5 以上を凝固障害のカットオフ値として使用することを提案している。

＜エビデンスと根拠＞

妊娠中は凝固因子の増加により PT、APTT は短縮する（特に第 3 妊娠期）。妊婦 1130 名のサンプルをもとに、Liu らは妊娠 36 週時点での PT と APTT の中央値がそれぞれ 9.6 秒と 31.0 秒であることを報告している。

・フィブリノゲン値

分娩における低フィブリノゲン血症に特に注意を払いながら、フィブリノゲン値レベルを個別に評価することを提案している。妊娠中の COVID-19 感染において、フィブリノゲンの閾値とその予後予測における有用性を確認するためには、さらなる研究が必要である。

＜エビデンスと根拠＞

フィブリノゲンは妊娠中に増加し、第 3 妊娠期の間に 3.7～6.2g/L と高値であることが報告されている。さらに、分娩後出血の経過中に 128 名の女性を対象とした研究では、フィブリノゲン値 2g/L 以下は、重症分娩後出血を 100%予知できたことが示されている。Tang らは、入院時には COVID-19 生存者と非生存者の間でフィブリノゲン値に有意差はなかったが、入院の終わり頃には、非生存者のフィブリノゲン値は有意に低下していたと報告している。フィブリノゲン値の上昇は炎症状態を反映している可能性が高いが、患者が悪化して凝固障害を発症している場合には、低値が見られることがある。低フィブリノゲン血症は COVID-19 感染妊婦 2 名にみられたが、1 例は重症分娩後出血で輸血が行われ、1 例は術前のフィブリノゲン濃縮製剤投与で過剰出血は抑えられた。

・血小板数

正常妊娠の場合と同様に、妊娠中の血小板減少症の診断における血小板数の閾値は、100×10^9/L 以下で使用することを提案している。妊娠中の出血リスクに重要な血小板数は臨床状況に応じて変化し、妊娠中は 30×10^9/L の閾値が使用されているが、分娩時には 50×10^9/L とされている。

＜エビデンスと根拠＞

妊娠中は、血小板数は低下する。妊娠性血小板減少症は第 2～3 妊娠期の妊婦の 5～11%に影響を及ぼす。週数別の血小板数の中央値と正常範囲はすでに報告されているが、COVID-19 感染妊婦の血小板数の閾値に関する文献はない。しかし、実践的なガイダンスには血小板数のパラメータを含めてある。

・D-dimer 値

D-dimer 値が妊娠中の正常範囲の数倍以上に著しく上昇していることを示唆している（2μg/mL のレベルは、正常な妊娠中にも見られることに注意する）。D-dimer 値は、凝固障害の指標として考慮すべきである。

＜エビデンスと根拠＞

D-dimer 値のレベルは妊娠中に徐々に上昇し、第 3 妊娠期にピークを迎える。ある研究では第 1 妊娠期、第 2 妊娠期、第 3 妊娠期でそれぞれ 0.11～0.40μg/mL、0.14～0.75μg/mL、0.16～1.3μg/mL であったが、第 3 妊娠期では 1.7μg/mL が上限であると報告されている。Tang らの最近の研究では、非妊娠 COVID-19 感染では、D-dimer 値の上昇が死亡の予測因子の一つであり、COVID-19 非生存者では 2.12μg/mL（範囲 0.77～5.27μg/mL）であったのに対し、COVID-19 生存者では 0.61μg/mL（範囲 0.35～1.29μg/mL）となっていた。2μg/mL は妊娠中の女性にとっては正常範囲内であり、妊娠中の軽度から中等度の D-dimer 値上昇の有意性は不明である。妊婦の閾値が示唆されるまでにはさらなるデータが必要であるが、D-dimer 値の上昇と非妊婦における COVID-19 凝固症/死亡率との関連性を示す明確なエビデンスを考慮すると、有意な D-dimer 値の上昇では潜在的悪化の可能性を疑い慎重に評価するべきである。

・FDP 値

FDP 値の上昇は、特に凝固障害における他のパラメータの異常と関連している場合には、初期の病理学的徴候としてとらえるべきである。

＜エビデンスと根拠＞

COVID-19 の非妊婦非生存者では FDP 値レベルが上昇していた。FDP 値レベルは通常の妊娠中は有意な変化はないが、分娩中および正常分娩後 1 週間は著しく上昇する。子癇、子宮内胎児死亡および産後出血などでは有意に上昇する場合がある。非妊娠時の COVID-19 感染における FDP 値の範囲は 4.0～15.0μg/mL であり、平均は 7μg/mL であった。

DIC

妊娠中の DIC の診断には、pregnancy-modified ISTH DIC スコアを用いることを提案している。

＜エビデンスと根拠＞

pregnancy-modified ISTH DIC スコアは、DIC ではない妊娠 24,646 例、DIC の妊娠 87 例（n=24,693）の母集団に基づいて算出され、特異度は 96%であり、独立した研究では、感度 78%、特異度 97%であった。このスコアは、血液製剤の輸血を必要とする産科出血のリスクがある患者の同定に有用であることが証明されており、COVID-19 の影響を受けた妊娠に適用することができるとされている。

凝固亢進と VTE リスク

① COVID-19 による凝固障害と VTE リスクの増加を考慮すると、非妊婦者と同様、COVID-19 感染症で入院したすべての妊娠中および分娩後の女性において、活動性出血や血小板減少（＜30 × 10^9/L）がない限り、すぐに産まれそうにないか、または産後 24 時間を超えている場合には、体重調整低分子量ヘパリン（LMWH）による VTE 予防を考慮すべきである。重症女性の急速遂娩が必要な場合は、母体医学の専門家や血栓止血学の専門家を含むチームからの助言を得て、分娩後速やかに血栓予防を個別に検討すべきである。

② PT や APTT の延長は抗凝固療法の禁忌と考えるべきではない。

③ 入院患者で抗凝固療法が禁忌の場合は、器械的予防（間欠的空気圧迫法）を行うべきである。

④ 退院にあたっては、他の VTE リスク因子を考慮した慎重かつ個別化された VTE リスク評価を行い、退院後の LMWH の持続期間を計画すべきである。

・重症度が低く、短期間の入院であっても分娩とならない場合には、10～14 日の LMWH が適切であると考えられる。

・D-dimer 値が非常に高い重症患者では、特に第 3 妊娠期には、妊娠中および分娩後の残りの期間を通じて LMWH の継続を考慮する。

・分娩後の血栓予防の期間は、他の危険因子、分娩様式、COVID-19 感染の重症度、入院期間に応じて、2～6 週間とする 。

・重症患者や入院中および退院後に合併症がある患者に対して、抗凝固薬の投与量・期間・種類は、集中治療、血栓止血、母体胎児医学の専門家と協力して、個別に決定すべきである。

⑤ 在宅管理されている多くの軽症から中等症患者のVTEリスク評価は慎重に行う必要がある。低リスク患者には、水分補給、適切な栄養補給、適度な運動、発熱の制御を奨励するべきである。在宅での弾性ストッキングの使用を奨励してもよい。LMWHによる血栓予防は、不動、高熱、脱水症、または妊婦特有のVTEリスクが存在する場合に検討する必要がある。これらは、Royal College of Obstetricians and Gynaecologists（RCOG）ガイドラインで示されている。

＜エビデンスと根拠＞

妊娠は凝固亢進状態であり、VTE のリスクが 4～6 倍増加し、産褥ではこのリスクがさらに増加する。妊娠中に入院した妊婦は、特に 35 歳以上、妊娠後期、3 日以上の入院では、退院後も VTE リスクが 18 倍持続するとされる。RCOG ガイドラインでは、特定の禁忌がない限り、入院時に LMWH による血栓予防を妊婦に行うことを推奨している。系統的レビューでは、治療的および予防的に LMWH を投与しても産科出血のリスクは 2%未満であった。現在、COVID-19 凝固障害による出血リスクの増加は見られないが、低フィブリノゲン血症の存在下では注意が必要な場合がある。

ISTH 国際レジストリ

この分野での知識の蓄積を促進するために、ISTH の WHITH 小委員会は、妊婦における COVID-19 関連凝固障害に関する国際的なレジストリを設立した。目的は、凝固異常と重症度との関係、血栓症リスクと疾患の本質の評価、抗凝固療法の使用・効果・合併症を評価することで、COVID-19 凝固症とその治療が母児の転帰に及ぼす影響を探ることである。レジストリ（https://redcap.isth.org/surveys/?s=4JPX9 W98RH）は、ISTH academy のウェブサイト（https://acade my.isth.org/isth）に掲載されている。また、プロジェクトの詳細は、ISTH Scientific and Standardization Committee（SSC）のウェブサイト（https://www.isth.org/membe rs/group.aspx?id=10037 5）に掲載されている。

COVID-19 に関連した妊娠中の凝固障害と血栓症の問題を扱った文献はいまだ少なく、COVID-19 感染妊婦における凝固障害を適切に管理するための高いエビデンスはない。その中で提供された本ガイダンスは、限られたエビデンスと専門家の意見に基づいており、COVID-19 感染妊婦のケアにおける一つの指標として参考にされたい。

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表 2　COVID-19 感染者（非妊婦）における血液凝固マーカーの変動と入院患者の管理法に関する ISTH ガイダンスおよび専門家意見の要約

パラメータ	正常範囲	COVID-19 感染者の病的変化	ISTH 暫定ガイダンスと専門家意見
PT	9.9－13.1 秒	非生存者の 50%では延長したが、生存者では 7%にとどまった（P＜0.0001）	・ すべての COVID-19 感染者で測定し、凝固障害をモニタリングする ・ PT が延長している場合は入院 ・ すべての入院患者で PT を 1 日 2 回以上測定する ・ 出血患者（COVID-19 感染者ではまれ）では、PT ratio＜1.5 を維持する
APTT	24－36 秒	入院時には有意な変化はなかったが、入院 4 日目には APTT ではなく PT が有意に延長した	
D ダイマー	0-0.5 μg/mL	・ >0.5μg/mL は重症と関連した ・ 重症患者では､非重症患者と比較し有意に上昇した	・ すべての COVID-19 感染者で測定し、凝固障害をモニタリングする ・ 著しく上昇した場合は入院させる ・ すべての入院患者では、少なくとも 1 日 2 回測定する
血小板数	150-450 $\times10^9$/L	・ <100$\times10^9$/L は重症化した場合と関連性がある ・ 重症患者における血小板数増加はサイトカインストームによる	・ すべての COVID-19 感染者で測定し、凝固障害をモニタリングする ・ <100$\times10^9$/L の場合は入院 ・ すべての入院患者では、少なくとも 1 日 2 回測定する ・ 出血患者（COVID-19 感染者ではまれ）では、50$\times10^9$/L 以上を維持する
フィブリノゲン	2－4g/L	入院時>4g/L の増加は生存者と非生存者の間に有意差が認められた。	・ すべての COVID-19 感染者では必ず測定し、2g/L 以上の場合は入院させる ・ すべての入院患者では、少なくとも 1 日 2 回測定する ・ 出血患者（COVID-19 感染者ではまれ）では、>2.0 g/L を維持する
FDPs		増加する	
ループスアンチコアグラント		陽性となる	

VTE リスク		**ICU 入院患者の VTE 発症率に関して下記の報告がある。** **VTE 発症者数/ICU 入院患者数（%）** **28/184 (27%)** **35/75 (47%)** **64/150 (42%)** **8/48 (16.7%)**	

文献は省略してあるので論文を参照のこと

表 3　正常妊婦（第 3 期）および COVID-19 感染妊婦における血液凝固パラメータの変動

パラメータ	第 3 期正常値	分娩時	分娩後	非妊婦正常値	COVID-19 感染妊婦に起こりうる変化	予後マーカーの可能性	非妊婦重症 COVID-19 感染者の報告された値
PT	8.5-11.0 秒			16.0 秒	・↑COVID 凝固障害または DIC ・分娩後出血	有用	・3 秒の延長 ・生存者の 3 秒に対し、DIC による非生存者の 47.6%は＞6 延長
APTT	25.5-42.5 秒			27.0-37.0 秒	・↑COVID 凝固障害または DIC ・分娩後出血 ・消費性凝固障害 ・↓第 8 因子放出	有用	5 秒の延長
D ダイマー	0.16-1.7μg/mL				・↑COVID 凝固障害または DIC ・↑急性相反応物質 ・VTE ・外傷 ・肝臓疾患、腎臓疾患	有用（重症者と院内死亡：カットオフ値 2.0 μg/mL）	・非生存者の 2.12 に対し、生存者は 0.61・DIC による非生存者の 86%は>3
血小板数平均(範囲)	225 (57-505) $\times10^9$/L	217 (63-552) $\times10^9$/L	264 (91-575) $\times10^9$/L	273 (111-999) $\times10^9$/L	・↓COVID 凝固障害または DIC ・↑分娩後出血 ・サイトカイン誘導性	有用 血小板減少（重症者および死亡者）	・非生存者の 33%は<100×10^9/L ・DIC による非生存者の 24%は<50×10^9/L
フィブリノゲン	2.48-5.06g/L			2.5-4.0g/L	・↓COVID 凝固障害または DIC ・↑急性相反応物質 ・炎症 ・↓分娩後出血	有用	・非生存者の 5.16 に対し、生存者は 4.5（有意差なし）・DIC による非生存者の 29%は<1
FDPs	<15μg/mL			3.09±1.96 μg/mL	・↑COVID 凝固障害または DIC ・急性相反応物質		非生存者の 7.6 に対し、生存者は 4.0

文献は省略してあるので論文を参照のこと

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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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Final decision: Jean Connor, 18 August 2020

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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