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.

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Review Article

Thromboembolic risk in pregnant women with SARS-CoV-2 infection – A systematic review

Diana Leal [a, *, 1], Joana Ferreira [b, c, d, 1], Armando Mansilha [a, e, f]

[a] Faculdade de Medicina da Universidade do Porto, Porto, Portugal
[b] Department of Vascular Surgery, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal
[c] Centro Académico Hospital da Senhora da Oliveira, Guimarães, Portugal
[d] Department of Angiology and Vascular Surgery, Hospital CUF, Porto, Portugal
[e] Head of the Department of Angiology and Vascular Surgery, Centro Hospitalar Universitário de São João, Porto, Portugal
[f] Head of the Department of Angiology and Vascular Surgery, Hospital CUF, Porto, Portugal

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ABSTRACT

The infection by SARS-CoV-2 is associated with a thromboembolic complications risk theoretically increased. Pregnancy, isolated, is considered a pro-thrombotic state.

This systematic review has the main goal to evaluate the thromboembolic risk in pregnant women with COVID-19 disease, namely for pulmonary embolism (PE) and deep vein thrombosis (DVT). The secondary goal is the evaluation of the need for thromboprophylaxis in these cases.

Three databases - PubMed, Scopus and Web of Science – were searched on October 2021, using the following Mesh terms and keywords: "(covid-19 OR SARS-CoV-2 OR Covid) AND (pregnancy) AND (coagulopathy OR blood coagulation disorders OR thrombotic complications OR thromboembolic risk OR venous thromboembolism OR venous thrombosis)". Information about thrombotic complications in pregnancy and thromboprophylaxis was collected, by two independent reviewers.

In total, 12 articles were analyzed, corresponding to 18205 pregnant women with SARS- CoV-2 infection. A total of 85 cases of thromboembolic events were diagnosed (0.46%, 95% CI 0.37–0.58%), of which only 17 reported the use of thromboprophylaxis (20.00%, 95% CI 12.10–30.08%). There were 3 deaths due to thromboembolic complications (3.53%, 95% CI 0.73–9.97%).

In conclusion, in pregnant women, the SARS-CoV-2 infection increases the risk of thromboembolic complications. However, the risk is not greater than in the general population. It is recommended thromboprophylaxis with low molecular weight heparin for hospitalized pregnant women, and in groups with moderate to high thromboembolic risk at home self-isolation.

Introduction

The infection by SARS-CoV-2 has proven since early, in December 2019, with the first case of COVID-19 in Wuhan – China, becoming a big challenge for the world as we knew it. The scientific community saw itself forced to join efforts and evidence, in such a short period of time, while trying, on the other hand, to stop the global spread of the virus.

SARS-CoV-2 belongs to the coronavirus family – an RNA-positive-stranded virus – whose connection to angiotensin-converting enzyme 2 (ACE2) allows entry into host cells, such as pulmonary, renal or intestinal, as well as in blood vessels – the most affected by SARS-CoV-2 [1,2]. In that way, the disease manifestations can go from merely respiratory symptoms to vascular alterations, such as thromboembolic complications.

Many studies came to prove this virus has a strong pro-thrombotic component, explained by endothelial dysfunction, inflammation, cytokine release, hypercoagulability, and hypoxia, as well as, physical inactivity, imposed by self-isolation [3].

On the other hand, pregnancy is a period of physiologic hemostasis alterations, with higher levels of coagulation factors (factors I, VII, VIII, X, XII and factor of Von Willebrand), an increase of up to 50% of fibrinogen and D-dimers levels and decrease of fibrinolytic capacity (by the lower levels of protein S) [4,5]. All these factors contribute to a pro-thrombotic state.

The Royal College of Obstetricians & Gynaecologists recommends that pregnant women should be stratified according to the

* Corresponding author. Faculty of Medicine, University of Porto, Rua da Boavista, n.480, Nespereira-Lousada, Porto, Portugal.
E-mail address: leal_dm@hotmail.com (D. Leal).
[1] Shared first authorship.

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individual risk for VTE (venous thromboembolism). Generally, in self-isolation at home, hydration and mobilization are enough for prevention. However, if the individual risk, for some reason, is higher, thromboprophylaxis should be considered [6].

This systematic review has the main goal to evaluate the thromboembolic risk in pregnant women with COVID-19 disease, namely for pulmonary embolism (PE) and deep vein thrombosis (DVT). The secondary goal is the evaluation of the need for thromboprophylaxis in these cases.

Methods

Study population

According to the defined objectives, comprehensive research involving the thromboembolic risk, as well as its prevention, was conducted in our study population: pregnant women with SARS-CoV-2 infection.

Eligibility criteria

The inclusion criteria were: articles written in English or Portuguese; systematic reviews, case reports, cross-sectional, prospective or retrospective cohort studies; in humans; with full text available; studies whose outcome was venous thrombotic complications and/or thromboprophylaxis.

The exclusion criteria were: articles whose outcomes were measured in the fetus or general population; that did not correlate pregnancy with venous thrombotic complications; theoretical recommendations and all studies whose outcome was coagulopathy and not thromboembolic risk. It was also excluded articles without clinical data and with incomplete data.

Search strategy and selection process

To answer the proposal goals, it was made a comprehensive literature search through 3 databases: PubMed, Scopus and Web of Science, on 25th October 2021.

In order to identify all the studies that correlate thromboembolic risk with pregnancy and COVID-19, according to PRISMA guidelines, the search was conducted by two independent reviewers, using the following Mesh terms and keywords: *"(covid-19 OR SARS-CoV-2 OR Covid) AND (pregnancy) AND (coagulopathy OR blood coagulation disorders OR thrombotic complications OR thromboembolic risk OR venous thromboembolism OR venous thrombosis)*".

The articles were selected according to the eligibility criteria above-mentioned, independently, by two reviewers. Initially, a selection by title and abstract analysis was conducted, followed by a full reading selection. The review protocol can be accessed in Appendix 1.

Data collection

Information relative to the number of participants, median age, median gestational age, thromboprophylaxis (dosing and regimen), type of thromboembolic event, hematological changes, follow-up time and ultimate outcomes (for pregnant woman – ex. death, and fetus) were collected and synthesized by the two reviewers, independently. All the controversial situations were decided between the reviewers consensually.

Study quality assessment

The quality evaluation was made through the National Heart, Lung and Blood Institute Scales, and it is presented in Figs. 1 and 2, according to study type.

Any conflicts between the two reviewers were resolved by consensus.

Outcome measures

The measured outcomes were the frequency of occurrence of venous thromboembolic events (VTE) – defined as DVT (deep vein thrombosis) and PE (pulmonary embolism) - and thromboprophylaxis in the targeted population. Other rare and non-specified venous thromboembolic events were reported and analyzed in the results. The results are presented in percentage, using 95% confidence intervals, estimated through the Clopper-Pearson method. Furthermore, it still stratified the occurrence of these events according to thromboprophylaxis status.

Results

Study Selection

With the above-mentioned research, it was obtained 35 articles from PubMed, 5 from Scopus, 21 from Web of Science and 4 by bibliographic reference checking.

After 23 duplicated removal, 42 studies were integrally read, for the inclusion phase, and discussed between the 2 reviewers about their inclusion/exclusion in this paper. One case report was excluded for finding itself analyzed in another included study. In total, 12 articles were selected to be part of this systematic review (Fig. 3).

In Table 1, it can be found detailed information about any individual study, and, in Table 2 of the supplement file, the reasons that led to the refusal of each one of the articles read integrally not included.

Study analyses

Of the 12 articles, 1 is a systematic review, 6 are observational studies (3 retrospectives and 3 prospectives), 1 is cross-sectional and 4 are case reports. The publication dates are comprised between October 2020 and August 2021.

In what concerns to the origin country, 3 are from the United States of America, 2 from the United Kingdom, 2 from India, 1 from Canada, 1 from Spain, 1 from Oman, 1 from Iran and 1 from Turkey.

The number of participants included, in each study, varies between 1 and 6550 pregnancies with SARS-CoV-2 infection, either in outpatient management, ward hospitalization or Intensive Care Units (ICU).

The median age of the pregnant women is between 22 and 33 years old, and the gestational age 29–42 weeks of pregnancy (the majority 3rd trimester pregnancies).

It was included pregnant women with swab confirmation diagnosis by RT-PCR or antigen test, and clinically suspected to have COVID-19 disease.

Studies were of fair and good quality as assessed by the National Heart, Lung and Blood Institute quality assessment scales for observational studies and systematic reviews. All the observational studies had a score of greater than 10 and the systematic review of 6.

	Ko et al.	Santhosh et al.	Jevtic et al.	Jering et al.	Metz et al.	Melguizo et al.	Thambiah et al.
1. WAS THE RESEARCH QUESTION OR OBJECTIVE IN THIS PAPER CLEARLY STATED?	Y	Y	Y	Y	Y	Y	Y
2. WAS THE STUDY POPULATION CLEARLY SPECIFIED AND DEFINED?	Y	Y	Y	Y	Y	Y	Y
3. WAS THE PARTICIPATION RATE OF ELIGIBLE PERSONS AT LEAST 50%?	Y	Y	Y	Y	Y	Y	Y
4. WERE ALL THE SUBJECTS SELECTED OR RECRUITED FROM THE SAME OR SIMILAR POPULATIONS (INCLUDING THE SAME TIME PERIOD)? WERE INCLUSION AND EXCLUSION CRITERIA FOR BEING IN THE STUDY PRESPECIFIED AND APPLIED UNIFORMLY TO ALL PARTICIPANTS?	Y	Y	Y	Y	Y	Y	Y
5. WAS A SAMPLE SIZE JUSTIFICATION, POWER DESCRIPTION, OR VARIANCE AND EFFECT ESTIMATES PROVIDED?	NR	NR	NR	Y	NR	NR	NR
6. FOR THE ANALYSES IN THIS PAPER, WERE THE EXPOSURE(S) OF INTEREST MEASURED PRIOR TO THE OUTCOME(S) BEING MEASURED?	Y	Y	Y	Y	Y	Y	Y
7. WAS THE TIMEFRAME SUFFICIENT SO THAT ONE COULD REASONABLY EXPECT TO SEE AN ASSOCIATION BETWEEN EXPOSURE AND OUTCOME IF IT EXISTED?	Y	Y	Y	Y	Y	Y	Y
8. FOR EXPOSURES THAT CAN VARY IN AMOUNT OR LEVEL, DID THE STUDY EXAMINE DIFFERENT LEVELS OF THE EXPOSURE AS RELATED TO THE OUTCOME (E.G., CATEGORIES OF EXPOSURE, OR EXPOSURE MEASURED AS CONTINUOUS VARIABLE)?	NA	NA	NA	NA	NA	NA	NA
9. WERE THE EXPOSURE MEASURES (INDEPENDENT VARIABLES) CLEARLY DEFINED, VALID, RELIABLE, AND IMPLEMENTED CONSISTENTLY ACROSS ALL STUDY PARTICIPANTS?	Y	Y	Y	Y	Y	Y	Y
10. WAS THE EXPOSURE(S) ASSESSED MORE THAN ONCE OVER TIME?	NA	NA	NA	NA	NA	NA	NA
11. WERE THE OUTCOME MEASURES (DEPENDENT VARIABLES) CLEARLY DEFINED, VALID, RELIABLE, AND IMPLEMENTED CONSISTENTLY ACROSS ALL STUDY PARTICIPANTS?	Y	Y	Y	Y	Y	Y	Y
12. WERE THE OUTCOME ASSESSORS BLINDED TO THE EXPOSURE STATUS OF PARTICIPANTS?	NR	NR	NR	NR	NR	NR	NR
13. WAS LOSS TO FOLLOW-UP AFTER BASELINE 20% OR LESS?	Y	Y	Y	Y	Y	Y	Y
14. WERE KEY POTENTIAL CONFOUNDING VARIABLES MEASURED AND ADJUSTED STATISTICALLY FOR THEIR IMPACT ON THE RELATIONSHIP BETWEEN EXPOSURE(S) AND OUTCOME(S)?	Y	Y	Y	Y	Y	Y	Y

Fig. 1. Quality assessment tool for observational cohort and cross-sectional studies. (Y – Yes; NR – Not Reported; NA – Not Applicable.)

Main results

The total number of pregnant women evaluated for this systematic review was 18205. Of these, 84 venous thromboembolic events (VTE) were registered: 29 DVT, 11 PE, 1 venous cava inferior thrombosis, 1 extrahepatic portal vein thrombosis, 1 sinus venous thrombosis and 41 venous thromboembolisms not specified. In that way, 0.46% (95% CI 0.37–0.57%) of the pregnant COVID-19 women evaluated had a thromboembolic event.

In what concerns prophylaxis, from 84 VTE, 26 report this topic. 17 (20.24%, 95% CI 12.25–30.41%) received thromboprophylaxis, of which 1 received low-molecular-weight heparin (LMWH) –

	Servante et al.
IS THE REVIEW BASED ON A FOCUSED QUESTION THAT IS ADEQUATELY FORMULATED AND DESCRIBED?	Y
2. WERE ELIGIBILITY CRITERIA FOR INCLUDED AND EXCLUDED STUDIES PREDEFINED AND SPECIFIED?	Y
3. DID THE LITERATURE SEARCH STRATEGY USE A COMPREHENSIVE, SYSTEMATIC APPROACH?	Y
4. WERE TITLES, ABSTRACTS, AND FULL-TEXT ARTICLES DUALLY AND INDEPENDENTLY REVIEWED FOR INCLUSION AND EXCLUSION TO MINIMIZE BIAS?	Y
5. WAS THE QUALITY OF EACH INCLUDED STUDY RATED INDEPENDENTLY BY TWO OR MORE REVIEWERS USING A STANDARD METHOD TO APPRAISE ITS INTERNAL VALIDITY?	Y
6. WERE THE INCLUDED STUDIES LISTED ALONG WITH IMPORTANT CHARACTERISTICS AND RESULTS OF EACH STUDY?	Y
7. WAS PUBLICATION BIAS ASSESSED?	NR
8. WAS HETEROGENEITY ASSESSED? (THIS QUESTION APPLIES ONLY TO META-ANALYSES.)	NA

Fig. 2. Quality assessment tool for systematic reviews. (Y – Yes; NR – Not Reported; NA – Not Applicable.)

therapeutic dose – and 16 received LMWH – prophylactic dose (of 7 that specified, 3 were weight-based dosing and 4 standard prophylactic dosings). 9 (10.71%, 95% CI 5.02–19.37%) did not receive, of which 2 received LMWH on admission.

The majority of hematological changes reported were thrombocytopenia, raising in d-dimers value, hyperfibrinogenemia (however, 0,27% had hypofibrinogenemia), as well as prolonged coagulation times: activated partial thromboplastin time (aPTT) and prothrombin time (PT).

Santosh et al. [7] makes a labor evaluation in pregnant women with COVID-19, according to gestational age and type of delivery. It stands out a preponderance of 49% of term birth, face to 24% of post-term and 6,8% pre-term. Highlight still to 3,4% 1st trimester miscarriages and 3,4% 2nd trimester miscarriages. About the type of delivery, 50% were vaginal, 8,3% instrumentalized delivery, 13% elective Low Segment Cesarian Section (LSCS) and 29% emergency LSCS.

It's important to note that 3 deaths were associated with thrombotic complications in pregnant women with SARS-CoV-2 infection, making a total percentage of 3.53% (95% CI 0.73–9.97%).

Table 1 highlights the major conclusions of each study.

Discussion

COVID-19 as a risk factor for thromboembolic complications in the general population

Several studies show that COVID-19 patients present a hypercoagulability state, with a higher risk of VTE. The analysis of 184 patients in ICU demonstrated a higher risk of thrombotic complications (venous thrombosis and/or arterial complications), even with thromboprophylaxis – cumulative incidence = 31% (27% of venous events, with pulmonary embolism (PE) highlighted (81%) and 3,1% arterial events) [8]. Cases of extracorporeal circuits thrombosis were also reported [9].

These alterations, more evident in severe illness in ICU, can be explained by two major mechanisms: angiopathy with thrombus formation in microcirculation, and hypercoagulability with hyperfibrinogenemia, in the systemic circulation. The second cause is what clarifies the major events mentioned previously, such as venous thrombosis [8].

COVID-19 as a risk factor for thromboembolic complications in the pregnant population

For some time, the scientific evidence existent pointed to no differences in severity of the infection between pregnant women and the remaining population. However, more recent studies concluded that the serious comorbidity risk, with multiple organ dysfunction and death, it's bigger in this group. The higher the value of d-dimer (>1 mg/mL), the higher the death risk [10]. In a study that analyses COVID-19 in pregnant women and then in fetal and newborns, Dashraath et al. [11] synthesize that 2% of pregnant women will require mechanical ventilation and 39% will deliver pre-term. For the fetus, about 2% developed a miscarriage and 10% were born with intrauterine growth restriction.

The ISTH recommends that all patients with COVID-19 have monitoring of their levels of d-dimers, platelets counts and PT. In that way, all patients presented with raised d-dimers, prolonged PT, platelets count $<100 \times 10^9$/L or low fibrinogen, should be admitted to hospitalization [12]. Koumoutsea et al. [13] add in pregnant patients the evaluation of aPTT and fibrinogen too.

Gunduz et al. [14] highlighted the need for a high suspicion index, in earlier phases of evaluation of sinus venous thrombosis, since the hematological parameters may not have disturbances – PT, aPTT and platelets can be within the normal ranges, covering up a thrombosis clinical condition. In COVID-19 pregnant women, with thromboembolic risk factors (ex. hereditary thrombophilia, malignancies, etc.), the monitoring should be even more careful. The authors underline some red flags, like non-response to analgesia, visual changes, neurological deficits, or even convulsive states.

In this review, 0,46% of the pregnant women developed a venous thromboembolic event. In another systematic review, Wu et al. [15] estimate an incidence of PE of 17% (95% CI, 13–21%) and

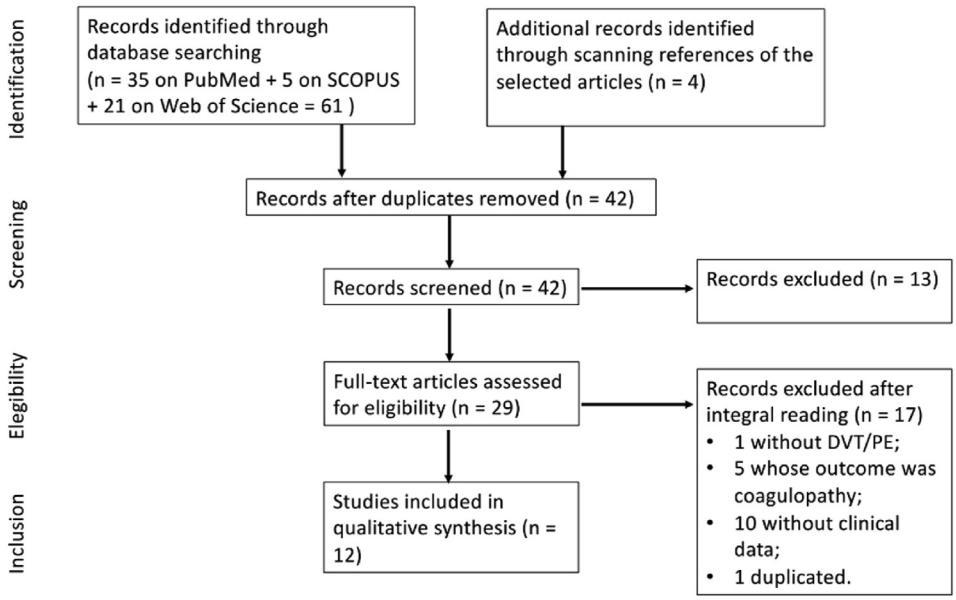

Fig. 3. Article selection flowchart.

DVT of 42% (95% CI, 25–60%), in severe COVID-19 cases in the general population. However, compared with pregnant women without SARS-CoV-2 infection, in which the absolute risk of thromboembolic complications is 0.1% [16], COVID-19 is responsible for the increase seen in our results.

On the other hand, if we analyze the number of deaths, considering the median age of the cases, and the fact that mostly all women were previously healthy, we have a prevalence of 3.53%. A thorough evaluation shows that one of the deaths matches one of the nine cases where thromboprophylaxis was discarded, corresponding to a massive pulmonary embolism. Here can arise the link between thromboprophylaxis and the prevention of fatal outcomes, even if the thrombotic event can't be prevented at all. However, more studies are needed to make strong conclusions about this possible association.

Combining these two variables, guaranteeing that all pregnant women with SARS-CoV-2 infection should have correct and timely prophylaxis for these events must be a concern.

Racial differences in thromboembolic risk for pregnant women with SARS-CoV-2 infection

James et al. [17], in a risk factors analysis for VTE in the pregnant population, concluded that black pregnant women appear to be at an increased risk.

On the other hand, Ko et al. [18] made an evaluation of maternal complications of SARS-CoV-2 infection - including VTE - stratified to race/ethnicity. They concluded that non-Hispanic other/unknown represents a higher adjusted risk ratio of global maternal complications (aRR = 8.1), followed by Hispanics (aRR = 7.5), non-Hispanics Black (aRR = 5.1) and non-Hispanics White (aRR = 5.1). However, after statistical analysis, the differences between groups are not significant. If we go further in this topic, as the authors explain, these non-significant differences can be due to social and economic status, the environment in which the women live, as well as access to health care and occupational exposure, which makes race/ethnicity minorities the most affected by COVID-19 disease.

However, this study does not stratify specifically the VTE risk, but all complications due to COVID-19 according to race/ethnicity. In the future, a deeper assessment of this topic may bring a different approach to the different races/ethnicities.

Relation between thromboembolic risk and thromboprophylaxis

Of the 84 venous thromboembolic events, only 26 reported information about thromboprophylaxis, and 58 have missing information. It's difficult to make any conclusion on that point, however, in a careful reading of the studies, one by one, Servante et al. [19], Jectvic et al. [20], Kripalani et al. [21], Metz et al. [22] and Gunduz et al. [14] underline the greatest thromboembolic risk in this subpopulation and support the need for thromboprophylaxis.

Metz et al. [22] show that if a risk stratification is done, the group of pregnant women with severe to critical COVID-19 disease had a higher risk of complications, like VTE, (not statistically significant compared with the same severity subgroup of the general population), and benefit from prophylaxis with LMWH. Other studies are needed to evaluate the risk-benefit of therapeutic vs prophylactic dose of LMWH. In the subgroup of mild-moderate disease, since only one thrombotic event was reported, also more studies are needed to prove the benefit of thromboprophylaxis in these patients.

Patell et al. [23], in a stratified analysis of VTE incidence by type of thromboprophylaxis, in the general population, determined that without prophylaxis, the incidence was 41.9% (95% CI, 28.1–57.2), versus an incidence of 19.8% (95% CI, 13.2–28.6%), 11.9% (95% CI, 4.3–28.6%) and 10.5% (95% CI, 4.2–23.8%) with standard-dose prophylaxis, intermediate-dose prophylaxis and therapeutic-dose anticoagulants respectively. In our study, since only 26 cases reported data regarding prophylactic pharmacotherapy, it is difficult to correctly interpret bias-free. In the future, more specific studies about dosing and therapeutic/prophylactic regimen can bring benefits to this subgroup of the population.

However, the ISTH [12] recommends thromboprophylaxis to all hospitalized pregnant women, with weight-adjusted LMWH, as well as post-partum women. At discharge, an individual risk stratification must be done, according to disease severity and patient comorbidities. For less severe infections and a short period of hospitalization, which did not result in delivery, it's recommended 10–14 days of LMWH. For severe disease, particularly for 3rd

Table 1
Resume of articles analyses and their main conclusions (aRR: absolute risk reduction; CI: contra-indication; DVT: deep vein thrombosis; ICU: intensive care unit; LBW: low birth weight; LMWH: low molecular weight heparin; LSCS: low segment cesarian section; NM: not mentioned; PE: pulmonary embolism; RT-PCR: real time polymerase chain reaction; UK: United Kingdom; USA: United States of America; VTE: venous thromboembolism).

Study Title	Clinical characteristics of COVID-19 in pregnant women: A retrospective descriptive single-center study from a tertiary hospital in Muscat, Oman [7]	Pulmonary embolism in pregnancy with COVID-19 infection: A case report [24]	Venous sinus thrombosis during COVID-19 infection in pregnancy: a case report [14]	Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19 [25]	Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis [19]	Disease Severity and Perinatal Outcomes of Pregnant Patients with Coronavirus Disease 2019 (COVID-19) [22]
Author	Jayasree Santhosh et al.	Sogand Goudarzi et al.	Zahide Betül Gunduz et al.	Karola S. Jering et al.	Juliette Servante et al.	Torri D. Metz et al.
Publication date	16th October 2020	8th December 2020	8th December 2020	15th January 2021	5th February 2021	4th April 2021
Origin Country	Oman	Iran	Turkey	US	UK	USA
Study type	Retrospective study	Case report	Case report	Observational study	Systematic review	Observational study
Number of participants	60 (52% outpatient, 37% hospitalized and 12% at ICU)	1	1	6380	1063	1219
COVID-19 diagnosis	RT-PCR of nasopharyngeal and oropharyngeal swabs.	RT-PCR.	RT-PCR.	Documented cases identified through ICD-10-CM code U07.1.	Positive swab or high clinical suspicion of COVID-19.	Molecular or antigen test for SARS-CoV-2.
Median age(years)	32 +- 6	22	22	28,3	NM	NM
Gestational age (weeks)	35 (30–37)	30 (+5 days)	35	97,8%: 3rd trimester 1,4%: 2nd trimester (0,8%: NM)	NM	37.7
Number of thrombotic events	2	1	1	15	4	9
Type of venous thrombotic events	PE	PE	Venous sinus thrombosis	VTE	1 inferior vena cava; 2 PE; 1 thrombosis dialysis associated	DVT/PE
Number receiving thromboprophylaxis prior to event (Type and dose)	NM	0	LMWH on admission.	NM	4 • 1 therapeutic LMWH • 3 enoxaparin 40 mg subcutaneously daily (prophylactic dose)	5 with prophylactic LMWH 4 without thromboprophylaxis
Number of deaths	0	1	0	0	2	0
Haematological changes	NM	Elevated aPTT, d-dimers and hyperfibrinogenemia.	Hyperfibrinogenemia (899 g/l) and elevated d-dimers (6,38 mg/l). Thrombocytopenia.	NM	Risk of haematological changes is 1,26% in COVID-19 pregnant women, face to 0,45% in pregnant women without the disease.	NM
Following time	March 24th to July 31st 2020	NM	10 days	April 1st to November 23rd 2020	NM	1st March to 31st July 2020
Main conclusions	49% of term birth, 24% post-term, 6,8% pre-term.	In this case is highlighted the mortality associated to thrombotic complications at 3rd trimester pregnancy, as well as noted the need to act prophylactic in those cases (ex. LMWH).	In earlier phases of Venous sinus thrombosis, PT and aPTT can be within normal ranges. If other risk factors present besides COVID-19 (ex. Pregnancy, malignancies, etc) the thromboembolic risk is even higher. The medical team should be alert to atypical situations such as non-responders to analgesia, visual changes, neurological deficits or convulsive states.	Pregnant women with COVID-19 have a higher risk of developing VTE, than women without the infection (0,2% vs 0,1%).	Thromboembolic risk is greater in non survivors than in survivors. This supports that, pregnant women with SARS-CoV-2 infection should do thromboprophylaxis with LMWH, except when delivery is expected in 12 h (or another CI). The scheme must be sustained 10 days after discharge.	Severity of COVID-19 disease is associated with a higher risk of thromboembolic events in targeted population (similar to general population), even with thromboprophylaxis.

	3,4 2nd trimester miscarriage; 3,4% 1st trimester miscarriage. 50% vaginal delivery, 8,3% instrumentalized delivery, 13% elective LSCS and 29% emergency LSCS. Maternal complications: pre-eclampsia/PE − 2%; PE/pelvic hematoma 2%. FETAL: Macerated stillbirth − 2,1%; LBW <2500 g−32%. In conclusion: Thromboembolic complications are more frequent in COVID-19 pregnant women than in Pregnant women without COVID-19.					Other studies are necessary to evaluate: - the benefits of thromboprophylaxis in subgroup of mild-moderate disease. If therapeutic dose is more efficient than prophylactic dose.
Study Title	Pregnancy Outcomes and SARS-CoV-2 Infection: The Spanish Obstetric Emergency Group Study [26]	The clinical course of COVID-19 in pregnant versus non-pregnant women requiring hospitalization: results from the multicentre UK CA-COVID-19 study [27]	Physician experiences in management of COVID-19-associated coagulopathy in pregnancy: Communication from the ISTH SSC Subcommittee on Women's Health Issues in Thrombosis and Haemostasis [20]	Pulmonary Embolism in a COVID-19-Positive Primigravida After Caesarean Section Despite Prophylaxis [21]	Adverse pregnancy outcomes, maternal complications, and severe illness among U.S. delivery hospitalizations with and without a COVID-19 diagnosis [18]	Extrahepatic portal vein thrombosis in a pregnant patient with COVID-19: a rare thrombotic event survivor [28]
Author	Sara Cruz Melguizo et al.	Christina Crossette-Thambiah et al.	Stefan D. Jevtic et al.	Yash Kripalani et al.	Jean Y. Ko et al.	Mukta Agarwal et al.
Publication date	7th May 2021	7th May 2021	12th July 2021	16th July 2021	5th August 2021	5th August 2021
Origin Country	Spain	UK	Canada	India	USA	India
Study type	Prospective study	Retrospective study	Cross-sectional study	Case report	Retrospective study	Case report
Number of participants	1347	36	1546	1	6550	1
COVID-19 diagnosis	RT-PCR from nasopharyngeal swabs.	RT-PCR.	NM	RT-PCR swab.	Documented cases identified through ICD-10-CM code U07.1.	Previously diagnosed.
Median age (years)	33	31	NM	29	29	28
Gestational age (weeks)	NM	86,2% at 3rd trimester	NM	36,6	NM	Term pregnancy
Number of thrombotic events	21	1	9	1	19	1
Type of venous thrombotic events	10 VTE 4 PE 7 other thrombotic events not specified	PE	NM	PE	DVT and other thromboembolic disease not mentioned.	Extrahepatic portal vein thrombosis
Number receiving thromboprophylaxis prior to event (Type and dose)	NM	NM	7 LMWH • 4 - standard prophylactic dose; • 3 − weight-based prophylactic dose.	Enoxaparin 60 mg	NM	LMWH on admission.

(*continued on next page*)

Table 1 (*continued*)

Study Title	Clinical characteristics of COVID-19 in pregnant women: A retrospective descriptive single-center study from a tertiary hospital in Muscat, Oman [7]	Pulmonary embolism in pregnancy with COVID-19 infection: A case report [24]	Venous sinus thrombosis during COVID-19 infection in pregnancy: a case report [14]	Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19 [25]	Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis [19]	Disease Severity and Perinatal Outcomes of Pregnant Patients with Coronavirus Disease 2019 (COVID-19) [22]
			2 without thromboprophylaxis.			
Number of deaths	0	0	0	0	0	0
Haematological changes	NM	NM	65% had thrombocytopenia, 80% had d-dimers raised, 6,30% hyperfibrinogenaemia and 3,15% hypofibrinogenemia.	d-dimers raised (1,50 mg/dl)	NM	Thrombocytopenia. aPTT and d-dimers within normal ranges.
Following time	NM	1st March to 31st May 2020	NM	NM	Till discharge.	NM
Main conclusions	Higher risk of venous thrombotic events (DVT and PE) in pregnant infected women, comparing to non-infected: 1,5% vs 0,2%.	There were no differences in hematological changes and thrombotic risk between pregnant women with SARS-CoV-2 infection and non-pregnant women with SARS-CoV-2 infection. Thromboprophylaxis was inconsistent, so it can't be taken conclusions – guidelines should be more specific.	Coagulopathy in pregnant women with SARS-CoV-2 infection raises the thrombotic risk, even when thromboprophylaxis is correctly instituted.	COVID-19 is a risk factor for DVT, even with thromboprophylaxis.	The aRR for thromboembolic risk is 2,7.	Anticoagulation should be the first line therapeutic in these cases.
					The risk of thromboembolism in pregnant women with COVID-19 is twice the risk of non-COVID-19 pregnant women. 31,6% of thromboembolic events in COVID-19 pregnant group had a poor outcome (death, longer hospitalization, etc.), comparing with only 4,8% of thromboembolic events in non-COVID-19 pregnant group.	

trimester pregnancy, LMWH must be continued throughout all pregnancy time remained and post-partum (2–6 weeks depending on the duration of admission, the severity of infection, mode of delivery and other risk factors such as comorbidities).

On the other hand, The Royal College of Obstetricians and Gynaecologists [6] recommends a risk stratification in two categories for outpatients with mil-moderate disease: women at low risk of VTE are encouraged to maintain good hydration, mobilization and pyrexia control, as well as anti-embolic stockings; if a high risk of thromboembolic events is present, thromboprophylaxis must be considered individually.

Limitations

SARS-CoV-2 infection is a new subject between the scientific community, which has created a great effort for the maximum knowledge about the same being shared. However, the information shared is still very restricted. On the other hand, clinical trials in pregnant women are not allowed, and all the information disposable is given mostly by case reports, from different backgrounds.

Due to short period of data collection, strict databases selection and language limitation, there is a possibility of missing studies that could be considered relevant.

On the other hand, only a few studies analyze specifically the occurrence of thromboembolic events in the pregnant COVID-19 population and the literature tends to report the most severe ones, which can overestimate the risk of these events, as well as the specific thromboembolic prophylaxis made.

Finally, the quality of the articles published during the pandemic time is reduced and this subject has a great potential for improvement.

In the near future, the actual conclusions may present a different approach to this group of patients.

Clinical implications

This narrative review has an important role in the actual knowledge, since clinical trials are not allowed during pregnancy time, and the information remains insufficient and disaggregated. Thus, this work could help professional workers in the actuation moment, when COVID-19 and pregnancy meet.

Conclusion

The actual scientific evidence in this area is still very reduced, which is a consequence of the few reported cases of such a new disease all over the world. The risk of venous thromboembolic complications in pregnant women with SARS- CoV-2 is greater than in non-infected pregnant women, however, it is not greater than in the general population with infection admitted to hospitalization.

Although, it is recommended thromboprophylaxis with LMWH for hospitalized pregnant women, and in groups with moderate to high risk of these complications at home self-isolation.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2022.06.012.

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