Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis

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Abstract

Background: As pregnancy is a physiological prothrombotic state, pregnant women may be at increased risk of developing coagulopathic and/or thromboembolic complications associated with COVID-19. Objectives: To investigate the occurrence of haemostatic and thrombo-embolic complications in pregnant women with COVID-19. Search Strategy: Two biomedical databases were searched between September 2019 and June 2020 for case reports and series of pregnant women with COVID-19. Additional registry cases known to the authors were included. Steps were taken to minimise duplicate patients. Selection criteria: Pregnant women with COVID-19 based either on a positive swab or high clinical suspicion e.g. symptoms and radiographic evidence. Data Collection and Analysis: Information on coagulopathy based on abnormal coagulation test results or clinical evidence of disseminated intravascular coagulation (DIC), and on arterial or venous thrombosis, were extracted using a standard form. If available, detailed laboratory results and information on maternal outcomes were analysed. Main Results: 1063 women met the inclusion criteria, of which three (0.28%) had arterial and/or venous thrombosis, seven (0.66%) had DIC, and a further three (0.28%) had coagulopathy without meeting the definition of DIC. Five hundred and thirty-seven women (56%) had been reported as having given birth and 426 (40%) as having an ongoing pregnancy. There were 17 (1.6%) maternal deaths in which DIC was reported as a factor in two. Conclusions: Our data suggests that coagulopathy and thromboembolism are both increased in pregnancies affected by COVID-19. Detection of the former may be useful in the identification of women at risk of deterioration.

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Shortened running title: Haematological complications of COVID in pregnancy

Abstract

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Data Collection and Analysis: Information on coagulopathy based on abnormal coagulation test results or clinical evidence of disseminated intravascular coagulation (DIC), and on arterial or venous thrombosis, were extracted using a standard form. If available, detailed laboratory results and information on maternal outcomes were analysed.

Main Results: 1063 women met the inclusion criteria, of which three (0.28%) had arterial and/or venous thrombosis, seven (0.66%) had DIC, and a further three (0.28%) had coagulopathy without meeting the definition of DIC. Five hundred and thirty-seven women (56%) had been reported as having given birth and 426 (40%) as having an ongoing pregnancy. There were 17 (1.6%) maternal deaths in which DIC was reported as a factor in two.

Conclusions: Our data suggests that coagulopathy and thromboembolism are both increased in pregnancies affected by COVID-19. Detection of the former may be useful in the identification of women at risk of deterioration.

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Keywords: COVID-19, SARS-CoV-2, pregnancy, birth, venous thrombosis, arterial thrombosis, coagulopathy, disseminated intravascular coagulopathy, haematological complications.

Tweetable Abstract: Disseminated intravascular coagulopathy in 0.66% of 1063 pregnant women with COVID-19; arterial +/ venous thrombosis in 0.28%

Introduction

Outside pregnancy severe COVID-19 is prothrombotic and proinflammatory, and the presence of coagulopathy is associated with a poorer prognosis; 71% of patients who die have disseminated intravascular coagulopathy (DIC) as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria compared with 0.6% among survivors [1].

In the non-pregnant population, severe COVID-19 coagulopathy is characterised by a significantly elevated D-dimer concentration. Elevated D-dimers/fibrin degradation products are also seen in DIC as diagnosed according to the ISTH criteria [2,3] and the pregnancy-specific DIC scoring system which has been developed to account for the relevant physiological adaptations [4]. However, unlike coagulopathy associated with other underlying causes, COVID-19 is less commonly associated with prolongation of prothrombin time (PT) and activate partial thromboplastin time (APTT) or thrombocytopenia [5,6]. Fibrinogen appears to be at least initially well preserved although there have been reports of low fibrinogen, particularly in non-survivors [1,7,8].

Accumulating data demonstrate increased risk of thromboembolism in COVID-19, predominantly in the most severe intensive care unit (ICU) cases [9-12]. Middledorp et al found a 25% incidence at 7 days, rising to 48% at 14 days in ICU patients [9]. Similarly, Cui et al. demonstrated that 20/81 (25%) of patients admitted to ICU developed thromboembolic complications, of which 8 died [10].

As pregnancy is already a physiologically hypercoagulable state, it seems likely that affected pregnant women would be at especially high risk of these complications. Current advice from the RCOG recommends that all pregnant women admitted with confirmed or suspected COVID-19 receive prophylactic low molecular weight heparin (LMWH), unless birth is expected within 12 hours, and continue this for 10 days following discharge [13].

Although the number of pregnant women with COVID-19 included in scientific reports as of 6$^{\text{th}}$ July 2020 stands at 6,742 [14], many of these reports include the same or overlapping cases [15]. Potential duplicate publication is particularly challenging for reports from Wuhan, China; a city of 12 million people with 50 hospitals, 19 of which have reported cases of COVID-19 in pregnancy, and many of which have multiple names in translation [16]. In the West, hospitals and registries similarly often cite the same cases. Here, we have removed potentially duplicate reports in a conservative manner: when in doubt data were excluded.

In this systematic review, we aimed to determine two estimates:

1. The rate of arterial or venous thrombosis in pregnant women with confirmed or suspected COVID-19 2. The rate of acquired coagulopathy in pregnant women with confirmed or suspected COVID-19

Methods

Case reports and series of confirmed or suspected maternal COVID-19 in pregnancy were identified according to the methodology used by Walker*et al.* [17]. Cases were included where the mother either had confirmed COVID-19 based on a positive swab or where there was high clinical suspicion in cases where a swab had not been taken (e.g. symptoms and radiographic evidence), and where the outcome of the pregnancy (either ongoing or delivered) was reported. One-hundred-sixty-five papers were identified according to this methodology and 69 papers met inclusion criteria (see **Figure 1).** Additional cases known to the authors were added from registries including the UK Obstetric Surveillance System (UKOSS) database, the East Midlands Research group (a group recently formed for the investigation of non-malignant haematological changes in pregnancy) and from the International Society on Thrombosis and Haemostasis' Pregnancy and COVID-19-Associated Coagulopathy (COV-PREG-COAG) Registry.

Coagulopathy events were recorded as stated by the authors. If haematological results were given, the DIC in pregnancy score was calculated, based on the prothrombin time, platelet count and fibrinogen levels. This

scoring system has shown a sensitivity of 88% and a specificity of 96% for the diagnosis of DIC in pregnancy [4].

Few papers specifically stated negative findings for coagulopathy or thrombosis. Cases were therefore considered negative for these events if it was specified that there were no complications during the observed clinical course, or if patients were stated to have recovered/be recovering, or discharged without mention of coagulopathy or thrombosis.

Results

Details for 1063 women with COVID-19 in pregnancy have been reported, where maternal outcomes were provided. Of these, three (0.28%) have had thromboembolic disease, seven (0.66%) have been diagnosed with DIC, with another three (0.28%) noted to have a coagulopathy. Five hundred and thirty-seven (56%) have been reported as recovered/recovering and having given birth and 426 (40%) have been reported as recovered/recovering with ongoing pregnancy (**Table 1**). In addition, Pereira *et al* described 2/60 patients with deep vein thrombosis (DVT); however, this report was discounted from the above totals (and **Table 1**) due to lack of reported pregnancy outcomes [7].

Tables 2 and **3** provide summaries of reported cases of thrombosis and coagulopathy respectively, in pregnant women confirmed or highly-suspected to have COVID-19 as taken from **Table 1** .

Of 1063 pregnant women included in our current study, there were 17 deaths (1.6%). DIC was reported in seven of these cases (41%). We also noted a higher incidence of thrombotic events in non-survivors, with pulmonary embolism occurring in two cases (distinct to the cases of DIC) and concurrent basilar artery thrombosis in one case. One hundred and thirty two/1033 (13.0%) women with COVID-19 in this study required admission to ICU.

Platelet levels and D-dimers were reported in several cases where haematological results did not meet the criteria for DIC and patients had not been stated to have a coagulopathy. In addition to cases noted to have a coagulopathy, D-dimer was noted to be raised (as reported by authors or above 0.5mg/l) in 31 of 38 cases [18-33, and from the COV-PREG-COAG Registry] where a value was reported or commented on. Platelets were low (as reported by authors or <100) in 15 of 102 cases where a value was reported or commented on [18, 19, 21, 23, 24, 27-30, 33-40, also cases from the COV-PREG-COAG Registry] (see Appendix 2).

Additionally, a paper from Weil Cornell Medicine in New York examining placental pathology from 20 pregnancies affected by COVID-19 (16 asymptomatic and none requiring admission to intensive care), noted evidence of fetal vascular malperfusion, also referred to as fetal thrombotic vasculopathy, in nine (45%) placentas [41]. The authors questioned the possibility of a relationship between this and the COVID-19-associated hypercoagulable state. Similar features of fetal vascular malperfusion were noted in a report from Chicago, in 12/15 placentas from women infected with COVID-19, though the incidence was the same as in two control groups: placentas from women with melanoma, and placentas from historical control pregnancies [42].

Discussion

Statement of Principle Findings

Haemostatic and thromboembolic complications have been reported in 0.98% and 0.28% of pregnant women with COVID-19 infection respectively**.**

Strengths and Limitations

Our review is the largest reported to date, even following removal of potential duplicates. The precision of our estimates is therefore greater.

Many primary studies were case reports or hospital-based series, which are at risk of bias towards cases or findings of interest, resulting in potential overestimation of complications. On the other hand, few papers specifically stated that there were no haemostatic complications in each case. Our assumption that this means an absence of complications may result in an underestimate, as theoretically complications may have been present, but not reported.

The DIC score used to identify cases from laboratory findings is a composite of prothrombin time, platelet counts and fibrinogen levels [4]. However, coagulopathy in COVID-19 is associated with a modest change in these parameters [5], meaning that the DIC score alone may be less accurate as a measure of COVID-19 coagulopathy in pregnancy. In addition, many authors did not report fibrinogen levels or prothrombin time, which will have falsely lowered our rate estimate of coagulopathy. D-dimer, like C-reactive protein (CRP), is an acute phase reactant, which can be elevated in trauma or any inflammatory condition. Elevated d-dimer levels are difficult to interpret, as the etiology of their rise can be multifactorial. D-dimer elevations can occur during an uncomplicated pregnancy, though typically they are not as pronounced as in some of the cases in this study, where the values were reported. Pneumonia as well has been associated with high D-dimer levels, as have thromboembolic events. As reported in Pereira *et al,* pregnant women who were classified as having severe clinical features of pneumonia in COVID-19 had higher D-dimer and CRP [7]. On the other hand, significant elevations of D-dimer were also noted in two reported cases of COVID-19 associated coagulopathy in pregnancy, neither of which were complicated by pneumonia or significant respiratory compromise [43]. While lack of standardisation of D-dimer thresholds in pregnancy renders interpretation challenging, in these two cases D-dimer levels were grossly elevated, at 17- and 12- fold the upper limit of normal [43].

The efficacy of D-dimer in the diagnosis of pulmonary embolism (PE) in pregnancy has been investigated, with conflicting results. The DiPEP (diagnosis of PE in pregnancy) group concluded, using D-dimer measurement by ELISA (counted as negative if <400ng/ml) and using Innovance technology (reference range 1-1.3mg/L), that D-Dimer was not useful for the diagnosis of PE in the context of pregnancy [44]. However, Van der Pol et al. reported that D-dimer measurement could be used in order to rule out PE in this group [45], using a cut of value of >1000ng/ml if nil clinical criteria were met, or <500ng/ml where wither there were clinical signs of either deep vein thrombosis; haemoptysis or where PE was the most likely diagnosis. Thus, the potential prognostic value of D-dimer in pregnancy in the setting of COVID-19 cannot be dismissed outright and deserves further investigation. Additionally, other tools for assessing hypercoagulability or other forms of coagulopathy such as Thromboelastography /Thromboelastometry are worth evaluating. An ISTH review and recommendation for the use of these technologies in obstetrics has recently been published [46].

Comparison with previous studies

Sentilhes [33] found no cases of thromboembolic disease or thrombocytopenia among 54 pregnant women with COVID-19 including five women who were admitted to ICU in Strasbourg. Guan [47] reported one case of DIC among 1099 cases of laboratory confirmed COVID-19 in non-pregnant patients of all ages (0.1% of cases). Tang [1] noted a higher incidence of coagulopathy in non-survivors which is in keeping with our findings. Whilst uncommon in pregnant women with COVID-19, our data suggests that the identification of haemostatic and coagulopathic changes may have value in the identification of women at risk of deterioration.

Conclusion

Implications for clinical practice :

Despite findings of elevated D-dimer in patients who have tested positive for COVID-19 outside of pregnancy, the occurrence of DIC and thrombotic events is infrequently reported [6]. We have found this to also be the case where COVID-19 is described in pregnancy; perhaps in part due the resultant coagulopathy being distinct from DIC and/or secondary to a lack of standardised cut off values for coagulation parameters for the diagnosis of coagulopathy in COVID-19 in the context of pregnancy. Nonetheless, identification of haemostatic and thrombotic complications may still be of clinical importance in recognizing pregnant patients who are at a higher risk of mortality from COVID-19.

Implications for research

Continued collection of data on specific parameters of thrombosis and haemostasis from pregnant women affected by COVID-19 is necessary to further elucidate the incidence, prognostic value, and implications of coagulopathy, and thromboembolism in pregnancy.

More detailed investigation of coagulation abnormalities may also be useful. These could include studies such as specialised factor assays (taking into account the normal haemostatic changes that occur in pregnancy).

Determination of specific cut-off values of aberrant haemostatic parameters associated with adverse outcomes in pregnancy is needed. Given the rarity of the condition, even in the face of a global pandemic, and in absence of systematic studies or until data from randomised control trials become available, international registries can be of immense value in achieving this aim. The International Society on Thrombosis and Haemostasis has developed the Pregnancy and COVID-19-Associated Coagulopathy (COV-PREG-COAG) Registry, precisely to fulfil this aim. Participation in the Registry is open to health care providers worldwide and can be accessed at: https://redcap.isth.org/surveys/?s=4JPX9W98RH.

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Disclosure of interests

None

Contribution to authorship

KW and JT were responsible for initial study design. KO, JT and KW collated reports of COVID-19 in pregnancy using methodology as per Walker et al. [15]. WL advised on overlap of cases from China. JS collected data from these sources and from cases contributed by BM, SM, KM, and MO to draft the paper alongside KW. All authors were responsible for re-drafting and editing the manuscript and approved the final version

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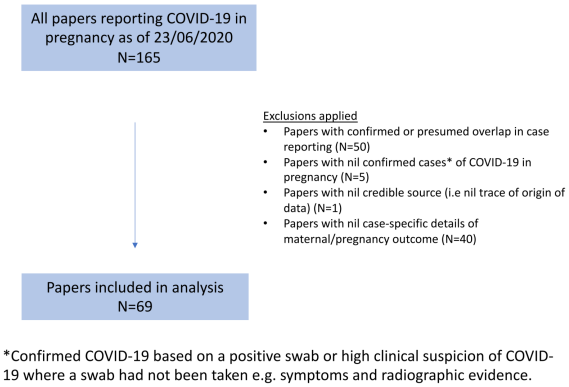
22.7 Tables.docx available at https://authorea.com/users/346411/articles/472458-haemostatic-and-thrombo-embolic-complications-in-pregnant-women-with-covid-19-a-systematic-review-and-critical-analysis

Figure 1: Flow chart of papers included in analysis



*Confirmed COVID-19 based on a positive swab or high clinical suspicion of COVID-19 where a swab had not been taken e.g. symptoms and radiographic evidence.