bjh short report

The clinical course of COVID-19 in pregnant *versus* non-pregnant women requiring hospitalisation: results from the multicentre UK CA-COVID-19 study

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Summary

The impact of COVID-19 infection on pregnant women remains relatively unknown but the physiological changes of pregnancy and hypercoagulability of COVID-19 may further increase thrombotic risk. In this retrospective multicentre observational study, we report clinical characteristics and outcomes in 36 pregnant women requiring hospitalisation for COVID-19 compared to a propensity-matched cohort of non-pregnant women. Pregnant women had a lower haemoglobin and higher lymphocyte counts but no differences in other haematological or biochemical parameters on admission compared to non-pregnant women. There was no significant difference in the duration of hospitalisation; median two days (1–77) for pregnant *versus* eight days (1–49) for non-pregnant women. A higher proportion of non-pregnant women required mechanical ventilation [11/36 (31%) vs 3/36 (8%), $P = 0{\cdot}03$] and received thromboprophylaxis with low-molecular-weight heparin (LMWH) within 24 h of admission [25/36 (69%) vs 15 /36(42%), $P = 0{\cdot}03$] compared to pregnant women. One pregnant woman required extracorporeal membrane oxygenation. The rate of thrombosis was similar in both groups (one in each group). No women developed major bleeding or died. Data suggest that although non-pregnant women had a severe clinical course, overall outcomes were not different between women with or without pregnancy. The use of thromboprophylaxis was inconsistent, demonstrating a need for establishing evidence-based guidance for COVID-19 during pregnancy.

Keywords: COVID-19, pregnancy, thrombosis, bleeding, coagulopathy.

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Introduction

Coronavirus disease 19 (COVID-19) is a global pandemic and its impact on pregnant women remains relatively unknown. COVID-19-associated coagulopathy is well documented in the non-pregnant population and in conjunction with the physiological changes of pregnancy may further increase the risk of thrombosis in this group.[1-6] The aims of this study were to establish the demographic characteristics, laboratory findings and clinical outcomes in pregnant women in comparison to a propensity-matched cohort of non-pregnant women with COVID-19.

Methods

Study design and participants

This was a retrospective multicentre observational study. The study was approved by the Human Research Authority (HRA) and Health and Care Research Wales (HCRW) and the local Caldicott Guardian in Scotland (reference number: 20/HRA/1785). Individual informed consent was waived because of the observational nature of the study. Data were collected from patient clinical records by the treating medical team with no breach of privacy or anonymity. Data were collected as part of the Coagulopathy associated with COVID-19 [CA-COVID-19] study: a multicentre study across the UK to assess the natural history of patients admitted to hospital with COVID-19 and up to 90 days from discharge from those who survived hospital admission (https://clinicaltrials.gov/ct2/show/NCT04405232). This paper includes only the pregnant women admitted with COVID-19 to 12 National Health Service (NHS) Trusts in the UK and an equal number from a propensity-matched cohort of non-pregnant women with COVID-19 admitted to hospital during the first wave of the COVID-19 pandemic (1 March to 31 May 2020). All patients had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) confirmed by real-time polymerase chain reaction (RT-PCR).

Statistical analysis

Propensity score matching was performed using the nearest-neighbours method, with a desired ratio of 1:1 between pregnant and non-pregnant women. The patient characteristics between the two groups were summarised and compared using descriptive statistics. Cofactors expected to affect overall survival [age, body mass index (BMI), ethnicity, diabetes mellitus (DM), lung disease, renal disease, smoking history, previous history of venous thromboembolism (VTE)] were used for propensity matching. Propensity score matching and standardised mean differences of the covariables between pregnant and non-pregnant women were performed using R and Stata and the rest of the analysis was performed using GraphPad Prism® version 8.3.1 (GraphPad Software Incorporated, San Diego, CA, USA). Two-tailed values of $P < 0{\cdot}05$ were considered statistically significant.

Results

A total of 36 pregnant women were admitted with confirmed COVID-19 from 1 March to 31 May 2020 in participating centres across the UK. The median age of the women was 31 (range 19–50) with 86·2% in third trimester. As the control group was propensity-matched, there were no differences in the demographics and the comorbidities between pregnant and non-pregnant women (Fig 1; Figure S1 and Table SI summarise the matching of the groups and their baseline demographics and clinical characteristics). Pregnant women had a lower haemoglobin and higher lymphocyte counts with a trend towards higher white-cell counts on admission compared to non-pregnant women. However, there was no difference in other haematological parameters, including coagulation tests and D-dimer levels, between the two groups. Laboratory parameters on admission to hospital with COVID-19 are summarised in Table SII.

There was no significant difference in the duration of hospitalisation between pregnant and non-pregnant women; median duration was 2 days (1–77) for pregnant women vs 8 days (1–49 days) for non-pregnant women. Medical interventions and clinical outcomes during admission or after discharge (thrombotic events up to 90 days from discharge) are summarised in Table I. A significantly higher proportion of non-pregnant women required invasive and non-invasive mechanical ventilation [11/36 (31%) vs 3/36 (8%), $P = 0{\cdot}03$] and received standard dose thromboprophylaxis with LMWH within 24 h of admission [25/36 (69%) vs 15/36 (42%), $P = 0{\cdot}03$; Table I]. One pregnant woman (but none of the

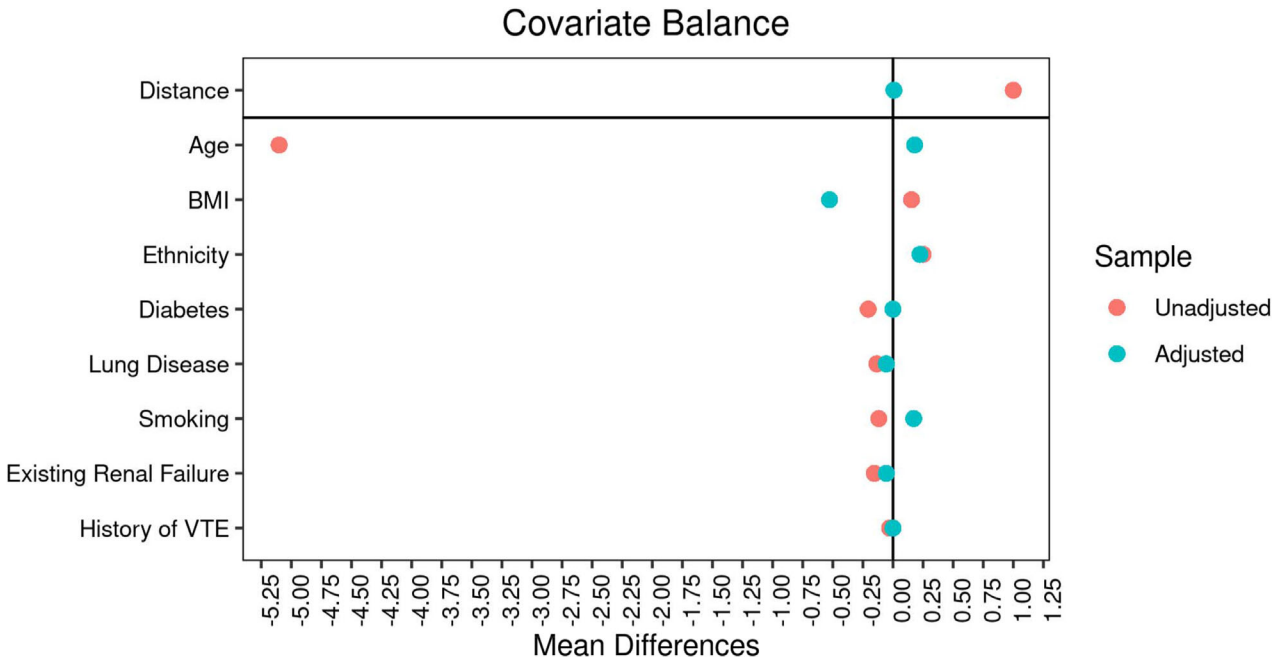

Fig 1. Love plot demonstrating standardised mean differences of the baseline characteristics between pregnant and non-pregnant women pre and post propensity matching (unadjusted and adjusted for baseline variables). VTE, venous thromboembolism.

non-pregnant women) required extracorporeal membrane oxygenation (ECMO) in addition to mechanical ventilation. A numerically higher proportion of non-pregnant women was given steroids [8 (22%) vs 3 (8%), $P = 0{\cdot}08$]. The rate of thrombosis was similar in both groups (one in each). Pulmonary embolism (PE) was diagnosed on day 5 of admission (day 4 of mechanical ventilation) in a woman with pregnancy and day 27 of admission (day 19 of mechanical ventilation) in a non-pregnant woman. No women developed major bleeding or died in either group. Three women delivered successfully during hospital admission and one had clinically relevant minor bleeding treated with tranexamic acid.

In contrast to the higher proportion of non-pregnant women receiving thromboprophylaxis with LMWH within 24 h of admission, there was a trend toward pregnant women being discharged with LMWH thromboprophylaxis for up to six weeks [14/36 (39%) vs 6/36 (17%), $P = 0{\cdot}06$]. However, nobody developed thrombosis within 90 days of hospital discharge in either group.

Discussion

Pregnant women had similar outcomes to propensity-matched non-pregnant women, although a higher proportion of non-pregnant women required mechanical ventilation. The lower haemoglobin and higher lymphocyte count in pregnant women are in keeping with the expected pregnancy-induced physiological change rather than being COVID-induced.[7] Severe COVID-19 is both pro-thrombotic and pro-inflammatory in nature and it has been suggested that rates of coagulopathy and thromboembolism may therefore be higher than in the non-pregnant population which is of concern given that coagulopathy is associated with a poorer prognosis.[8] In this study, admission laboratory parameters showed similar patterns in pregnant and non-pregnant women with COVID-19.

Importantly, the non-pregnant patients appeared to be more aggressively managed; notably with mechanical ventilation (31% vs 8%), steroids (22% vs 8%), haemostatic support (17% vs 8%) and antiplatelet agents (3% vs 0%). This may suggest that they had more severe disease than pregnant women or that management in pregnancy is driven by varied obstetric indications and contraindications. This is in contrast to some studies that suggest that the risk of being admitted to the intensive care unit (ICU) is higher in COVID-positive pregnant women compared with COVID-positive non-pregnant women. However, these studies did not use propensity-matched analysis[9] to identify a truly matched control population, leaving room for confounding factors such as pre-existing comorbidities and gestational age.

This study demonstrates that although uncommon, severe disease requiring intensive intervention such as support with ECMO may occur in pregnant women and should be treated actively, as for those who are not pregnant.

Interventions in the management of thrombotic risk on admission and on discharge were varied. This may reflect the

Table I. Summary of medical interventions and clinical outcomes during admission or after discharge (thrombotic events up to 90 days from discharge).

Interventions	Pregnant	Non-pregnant	*P* value
Mechanical ventilation	3 (8%)	11 (31%)	**0·03**
ECMO	1 (3%)	0 (0%)	–
Antiplatelet agent	0 (0%)	2 (6%)	0·49
Thromboprophylaxis on admission	15 (42%)	25 (69%)	**0·03**
Thromboprophylaxis on discharge	14 (39%)	6 (17%)	0·06
Thrombolysis	0 (0%)	0 (0%)	–
IVIg	0 (0%)	0 (0%)	–
Tocilizumab	0 (0%)	0 (0%)	–
Steroids	3 (8%)	8 (22%)	0·08
Haemostatic support	3 (8%)	6 (17%)	0·47
Outcomes			
Renal failure	1 (3%)	3 (8%)	0·61
HIT	0 (0%)	0 (0%)	–
Minor bleeding	1 (3%)	1 (3%)	1·00
Major bleeding	0 (0%)	0 (0%)	–
Venous thrombosis	1 (3%)	1 (3%)	1·00
Arterial thrombosis	0 (0%)	0 (0%)	–
Multiorgan failure	2 (6%)	3 (8%)	1·00
Secondary infection	6 (17%)	5 (14%)	1·00
Death	0 (0%)	0 (0%)	–
Hospital-associated thrombosis following 90-days post discharge	0 (0%)	0 (0%)	–

ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; IVIg, intravenous immunoglobulin.

concerns on admission for bleeding or impending delivery in the pregnant cohort whilst increased thromboprophylaxis on discharge in the pregnant population likely reflects national VTE prevention guidance for those who delivered during the admission.

Severe disease was demonstrated in three pregnant patients (8%). All three required ICU admission, mechanical ventilation and steroids with one requiring ECMO who went on to develop multiorgan failure. The numbers from our study match that of those of studies in China and New York where severe disease was noted in 8% and 9–10% of the affected pregnant women respectively.[10,11] Of note two of our three severe patients were in their third trimester and one in their second demonstrating that severe disease is not limited to later gestational age.

To date, most of the literature indicates favourable clinical outcomes of pregnant women with COVID-19 and comparable to that of non-pregnant counterparts but there is a lack of appropriately matched controls to say this with confidence;[12,13] this is the main strength of our study. We were not able to compare the outcomes with pregnant women without COVID-19 as the study was not designed to include non-COVID-19 patients. A systematic review of 1 063 pregnant women with COVID-19 found a higher rate of haematological complications (1·26%) than in pregnant women without COVID-19 (0·45%), but these cases were not propensity-matched.[14]

The main limitation of the study is the small number and retrospective data collection. However this was mitigated by collecting data using a pre-designed standardised case record form (CRF) and a well-controlled group was included with 1:1 propensity score matching using the nearest-neighbours method.

Our findings suggest haematological complications such as thrombosis and bleeding in pregnant women with COVID-19 are no more common in pregnant than non-pregnant women. However, as we included only the women from first wave of the COVID-19 pandemic, it is possible that that subsequent cohorts of pregnant women later in the pandemic might be sicker especially with the emergence of new variants of SARS-CoV-2. Further studies will be required to assess this. Larger studies will be required to determine the safety and benefit of LMWH prophylaxis in this group but there was no signal for harm or loss of efficacy in these data. The use of thromboprophylaxis on admission was inconsistent, demonstrating a need to establish evidence-based guidance for COVID-19 infection during pregnancy.

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Author contributions

DAJ conceived the study, acquired the funding, and was involved in data collection, data verification, data analysis, data interpretation, writing the original draft reviewing and editing the manuscript. CCT contributed to data analysis, writing the original manuscript and editing it. ML interpreted the data and revised the manuscript. PN was involved in study design, data collection and editing the manuscript. All the other authors contributed to data collection, interpretation of the data and editing the manuscript. All the authors critically reviewed and approved the final manuscript.

Conflicts of interest

PN received research grants from Novartis, Principia and Rigel, unrestricted grants from Sanofi, Chugai and Octapharma, and honoraria from Bayer. SS has also received

meeting sponsorship, speaker fees and/or consultancy from Bayer, Pfizer, NovoNordisk, Sobi, Chugai/Roche and Shire/Takeda. ML received speaker fees/consulting/advisory from Leo Pharma, Pfizer, Takeda, Sobi, Takeda, Pfizer and AstraZeneca. DJA received funding from Bayer plc to set up the multicentre database of the study as an investigator-initiated funding and research funding from Leo Pharma. The remaining authors declare no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Baseline demographics and clinical background.

Table SII. Laboratory parameters on admission to hospital with COVID-19.

Fig S1. Propensity score matching analysis.

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