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

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Abstract

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 in UK, we report clinical characteristics, laboratory findings and clinical complications in 36 pregnant women in comparison to propensity matched cohort non-pregnant women with COVID-19. Pregnant women had lower haemoglobin and higher lymphocyte counts but no differences were observed in other haematological or biochemical parameters on admission compared non-pregnant women. There was no significant difference in the duration of hospital admission between the two groups; median duration of hospitalisation was 2 days (1-77) for pregnant

women vs 8 days (1-49 days) for non-pregnant women. Significantly higher proportion of non-pregnant women required mechanical ventilation [11/36 (31%) vs 3/36 (8%), p=0.03] and received thromboprophylaxis with low molecular weight heparin within 24hrs of admission [25/36 (69%) vs 15 /36(42%), p=0.03] compared to pregnant women. One pregnant woman required extracorporeal membrane oxygenation. A numerically higher proportion of non-pregnant women were given steroids [8 (22%) vs 3 (8%), p=0.08]. Rate of thrombosis was similar in both group (only 1 woman in each group). None developed major bleeding or died in either group. Three women delivered successfully during the hospital admission.
Data suggests that clinical course is not different between women with or without pregnancy. Use of thromboprophylaxis on admission however was inconsistent, demonstrating need for establishing evidence-based guidance for COVID-19 during pregnancy.

Corona virus disease 19 (COVID-19) infection is a global pandemic which has caused death in millions of people across the world. The impact of COVID-19 infection on pregnant women remains relatively unknown[1,2] but the physiological changes of pregnancy and hypercoagulabity of COVID-19 may further increase thrombotic risk[3,4]. Another consideration is COVID-19 associated coagulopathy which is well documented in the non-pregnant population, but little remains known about COVID-19 coagulopathy during pregnancy[5,6] . The aims of this study were to establish the demographic characteristics, laboratory findings and clinical complications in pregnant women with COVID-19 in comparison to a propensity matched cohort of non-pregnant women with COVID-19.

Methods

Study design and participants

The study includes both retrospective and prospective data collection. Data was collected as part of the Coagulopathy associated with COVID-19 [CA-COVID-19] study using a pre-designed

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standardised case record form (CRF) ~~by the clinicians directly involved in patient care~~ held on a central electronic secure REDCap database (REDcap v10.0.10; Vanderbit University, US), hosted by Imperial College London. CA-COVID-19 is 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. However, 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 of propensity matched cohort of non-pregnant women with COVID-19 admitted to hospital during the first wave of the COVID-19 pandemic (1st of March to 31st May 2020). All patients had SARS-CoV-2 confirmed by real time polymerase chain reaction (RT-PCR) on nasopharyngeal swabs or lower respiratory tract aspirates.

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. Results were presented as percentages for categorical data, median and range for skewed continuous data, and means (95% confidence interval). Groups were compared using the Chi-squared test for categorical data, and the T-test for continuous data (as appropriate). Propensity score matching and standardised mean differences of the covariables between pregnant and non-pregnant women were performed using R and Stata and rest of the analysis was performed using GraphPad Prism® version 8.3.1 (GraphPad Software, Inc. La Jolla, USA). Two-tailed $p<0.05$ were considered statistically significant.

Results

A total of 36 pregnant women were admitted with confirmed COVID-19 from 1st of March to 31st of 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 was no differences in the demographics and the comorbidities between pregnant and non-pregnant women (Figure 1 summarises the standardised mean differences of the baseline characteristics between two groups). Pregnant women had 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 prothrombin time, activated partial thromboplastin time, fibrinogen, or D-dimer levels between the two groups. Laboratory parameters on admission to hospital with COVID-19 between groups is summarised in Table S1 of the supplementary material.

There was no significant difference in the duration of hospital admission in those with COVID-19 between pregnant or non-pregnant women; median duration of hospitalisation 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 hospital discharge) are summarised in Table 2. A significantly higher proportion of non-pregnant women required mechanical ventilation [11/36 (31%) vs 3/36 (8%), p=0.03] and received thromboprophylaxis with low molecular weight heparin (LMWH) within 24hrs of admission [25/36 (69%) vs 15/36 (42%), p=0.03] (Table 2). One pregnant woman required extracorporeal membrane oxygenation (ECMO) in addition to mechanical ventilation but none of the non-pregnant women required VV-ECMO. A numerically higher proportion of non-pregnant women were given steroids [8 (22%) vs 3 (8%), p=0.08]. The rate of thrombosis was similar in both groups (only 1 woman in each group). 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. None developed major bleeding or died in either group. Three women delivered successfully during the hospital admission and had clinically relevant minor bleeding which was treated with tranexamic acid.

In contrast to the higher proportion of non-pregnant women receiving thromboprophylaxis with LMWH within 24hrs of admission, there was trend toward pregnant women admitted with COVID-19 being discharged with LMWH thromboprophylaxis [14/36 (39%) vs 6/36 (17%), p=0.06]. However, nobody developed thrombosis within 90 days of hospital discharge in either group.

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Discussion

In this retrospective observational study assessing the coagulation markers and clinical outcomes in COVID-19 infection, women with pregnancy had similar outcomes to propensity matched non-pregnant women. The lower haemoglobin and higher lymphocyte count in pregnant women with COVID-19 in comparison to the matched controls was all in keeping with expected pregnancy-induced physiological change rather than being COVID induced[7]. Severe COVID-19 is both pro-thrombotic and proinflammatory in nature and it has been suggested that rates of coagulopathy and thromboembolism may be higher than in the non-pregnant population with a consensus that the presence of 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 and furthermore abnormal coagulation indices did not correlate with disease severity indices, suggesting that haemostatic changes have limited value in identifying women at risk of deterioration. In those with abnormal coagulation markers there was no major or minor bleeding indicating that correction of abnormal parameters without active bleeding is not required.

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Importantly, with regard to intervention events, the non-pregnant patients appeared to be more aggressively managed with notably more 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 did in fact have more severe disease than pregnant women or 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 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.

Interventions in the management of thrombotic risk on admission and on discharge were varied, however. This may reflect the concerns on admission for bleeding or impending delivery in the pregnant cohort whilst increased thromboprophylaxis on discharge in the

pregnant population probably reflects national VTE prevention guidance for those who delivered during the admission.

Severe disease was demonstrated in 3 patients (8%). All three required ITU 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 affected pregnant women respectively[10,11]. Of note 2 of our 3 patients were in their third trimester of pregnancy and 1 in their second demonstrating that severe disease is not limited to later gestational age as has previously been considered.

To date most of the literature reflects clinical outcomes of pregnant women with COVID-19 as being favourable and comparable to that of their non-pregnant counterparts but there is a lack of appropriately matched controls to say this with confidence[12,13] which is the main strength of our study.
The main limitation of the study is small number and retrospstive data collection however, data was collected using a pre-designed standardised case record form (CRF).

Our findings suggest haematological complications such as thrombosis and bleeding are no more commonly observed in pregnant women with COVID19 than non-pregnant women. Although larger studies will be required to determine the safety and benefit of LWMH prophylaxis in this group. Assuming standard guidance was followed there is no signal for harm or loss of efficacy on these data. Use of thromboprophylaxis on admission however was inconsistent, demonstrating need for establishing evidence-based guidance for COVID-19 during pregnancy.

Acknowledgements
Please do add something about the HaemSTAR network here. Eg: this work received support in design and delivery from HaemSTAR (www.HaemSTAR.org).

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Figure 1. Love plot demonstrating standardised mean differences of the baseline characteristics between pregnant and non-pregnant women.

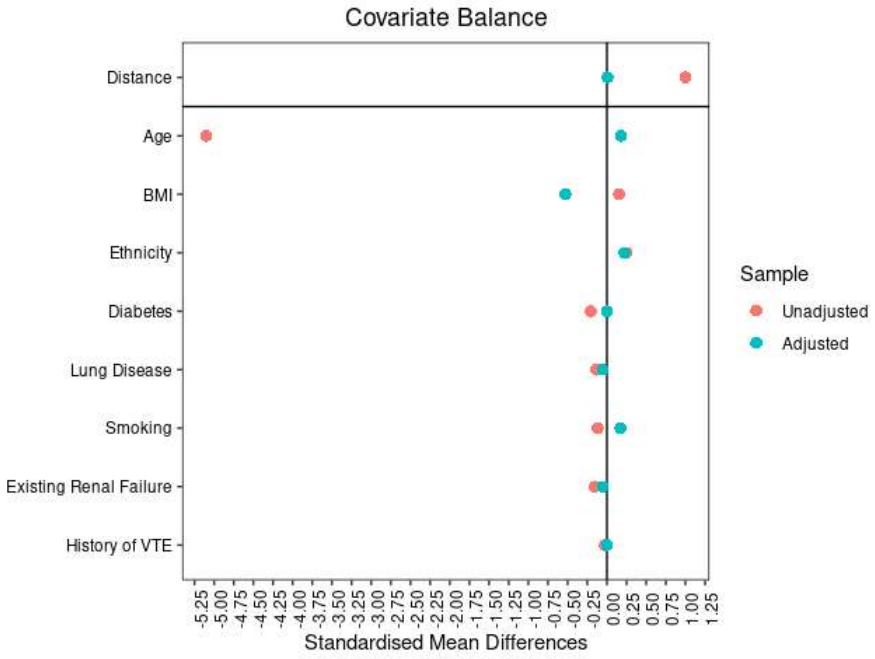

Table 2

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%)	-
Multi-organ Failure	2 (6%)	3 (8%)	1.00
Secondary Infection	6 (17%)	5 (14%)	1.00
Death	0 (0%)	0 (0%)	-
Hospital Associated thrombosis	0 (0%)	0 (0%)	-

Supplementary data

Propensity matching

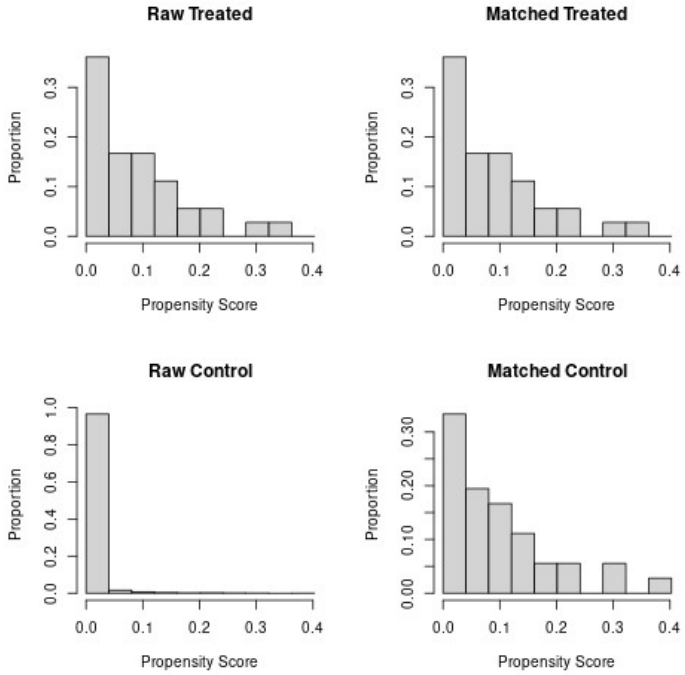

Table S1. Laboratory parameters on admission to hospital with COVID-19

Laboratory parameter	**Pregnant** Median (Interquartile Range)	**Non-Pregnant** Median (Interquartile Range)	**P Value**
Haemoglobin (g/L) (115-165)	121 (106-135)	134 (107-148)	**0.04**
White Cell Count - x109/L (3.6–11.0)	9.4 (7.5-13.3)	7.1 (5.1-9.2)	**0.05**
Platelets - 109 /L (146-360)	221 (170-258)	216 (174-272)	0.56
Neutrophils - x109/L (1.8–7.5)	4.2 (2.7-30.2)	7.0 (6.2-7.8)	0.95
Lymphocytes - x109/L (1.0–4.0)	1.28 (1.0-1.7)	0.9 (0.6-1.2)	**0.02**
PT – seconds (10-12.5)	13.3 (12.9 -14.1)	13.3 (11.6-13.6)	0.53
APTT – seconds (26-36)	33.8 (30.4-34.4)	32.9 (27.4-34.7)	0.22
Fibrinogen - g/L (1.5-4.5)	5.65 (5.2-5.8)	5.8 (5.6-6.1)	0.21
Creatinine - µmol/L (45-110)	56 (45-69)	72 (55-82)	0.07
Bilirubin (µmol/L) (1-17)	10 (6-10)	10 (6-16)	0.12
ALT (unit/L) (10-40)	41 (17-67)	45 (26-65)	0.29
CRP - mg/L (<3)	68.9 (3-182)	86 (15-150)	0.08
Ferritin - ng/mL (18-270)	2231 (2042-2383)	2219 (1652-2454)	0.62
D-dimer - ng/mL (208-318)	1330 (780-3267)	1159 (546-3304)	0.65
Troponin - ng/L (<14)	18 (5-53)	45 (8.5-852)	0.16
Lactate Dehydrogenase - U/L (<250)	608 (614-660)	654 (618-687)	0.12
Lactate	1.55 (1.5-1.6)	1.54 (1.3-1.6|)	0.8