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Are clinical outcomes worse for pregnant women ≥ 20 weeks' gestation infected with COVID-19? A multicenter case-control study with propensity score matching

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INTRODUCTION

The first cases of a novel coronavirus (SARS-CoV-2/COVID-19) were reported in Wuhan in December 2019 (1). Over 12.1 million people have been infected with over 550,000 deaths. These cases include an increasing number of pregnant women, however we are still relatively early in our understanding of the severity of the disease on pregnancy and vice versa. Early reports focused solely on the fetal risks, however, the emphasis has correctly shifted towards maternal health (2-6). A recent study reported a hospitalization rate of 52% including 10% in intensive care unit (ICU) (5). Nevertheless, the available literature is somewhat conflicting with some studies suggesting that pregnancy is not associated with markers of disease severity and others reporting worse outcomes. This contradiction implies the need for larger and more methodologically robust matched case-control studies to clarify the association between pregnancy and COVID-19.

The objective of our study was to compare clinical outcomes and laboratory findings in infected pregnant women ≥ 20 weeks with a cohort of non-pregnant COVID-19 positive women after closely matching the two groups using a propensity score.

METHODS

Study design, population and outcomes

This was a retrospective study conducted in 4 large university hospitals in France and Belgium between 1st January 2020 and 13th May 2020: 1) Antoine Béclère, Clamart, Paris, France, 2) Bicêtre Hospital, Le Kremlin-Bicêtre, France, 3) Centre Hospitalier Sud Francilien, Corbeil-Essones, France, and 4) University Hospital Brugmann, Brussels, Belgium. The study received ethical approval from the University Hospital Brugmann Ethical committee (CE

2020/88) and the institutional review board of the French College of Obstetricians and Gynecologists (CEROG OBS-2020-0402). Inclusion criteria were: female patients of reproductive age with positive SARS-CoV2 RT-PCR tests in nasopharyngeal swabs samples. Included patients were then divided into two groups: Group 1, non-pregnant controls and Group 2, pregnant cases. The primary outcome was admission to ICU. The secondary outcomes included: hospitalization for clinical deterioration, need for supplemental oxygen therapy (OT) and endotracheal intubation (ETI).

Data collection

The following variables were analyzed: patient age, ethnicity, weight, height, body mass index (BMI), pre-existing medical conditions (diabetes mellitus type I and II, hypertension and asthma), symptoms, physical examination, pregnancy status and gestational age at the initial presentation. Laboratory tests analyzed included: hemoglobin, white blood cell count (WBC), platelet count, absolute neutrophil and lymphocyte counts, liver function tests (alanine transaminase (ALT), aspartate transaminase (AST)), lactate dehydrogenase, fibrinogen, D-dimers coagulation tests. All data were anonymized.

Outcomes and variables definitions

Hospitalization for clinical deterioration was defined as an admission to a regular care facility, a dedicated COVID-19 ward or an ICU due to complications directly related to a confirmed COVID-19 infection. Common reasons for admission included severe dyspnea, desaturation (oxygen saturation (SaO_2) < 95% on room air) and sepsis. Hospital admissions for problems other than those reflecting a deteriorating condition were excluded. In all cases, pregnancy was confirmed using high resolution abdominal or vaginal ultrasound. Maternal weights used were those from the booking visit. Lymphocytopenia was defined as

an absolute lymphocyte count of < $1x10^9$ cells/liter. An activated partial thromboplastin (aPTT) ratio level greater than 1,2 was considered as abnormal.

Statistical analysis

Data were analyzed with the statistical software packages SPSS 25 statistical software (IBM SPSS statistics), R version 3.6.2 (R Core Team, 2019), and Excel version 15.0 (Microsoft, Redmond, WA, USA). We used the Fisher's exact test to compare the proportions of binomial categorical variables. After checking the normal distribution of continuous variables, we used the Student's T-test or the Mann-Whitney U test to compare their means in the 2 groups of the study. We undertook a propensity score analysis to match women between both groups. The CBPS R package and survey R packages were used to determine the propensity score as previously described (7). A two-sided $p<0.05$ was considered to be statistically significant.

RESULTS

Patients characteristics and propensity score matching

A total of 201 patients met the inclusion criteria. Eleven patients were excluded from the study: six non-pregnant patients (four receiving hemodialysis, one patient affected by trisomy 21, one patient with complex congenital heart disease) and five pregnant patients (all < 20 weeks gestation). This left 190 eligible patients for the final analysis who were divided into two groups: a *non-pregnant* control group 1 (N=107) and the *pregnant* case group 2 (N=83).

Table 1 demonstrates the propensity score matching for a variety of pre-defined variables. The first part of the table (before matching) indicates that in almost all cases, the two

groups had different means/proportions for the different variables before matching was applied. The mean age in control group was significantly higher than that in case group (36.46 ± 6.89 years versus 31.97 ± 6.24 years; p<0.001) but no statistically significant differences were observed for BMI or comorbidities between the two groups. The second part of the table presents the results after matching where we observe that the means, standard deviations and the proportions are now much closer between the two groups. The absolute standardized difference values (ASD), are equal to 0, indicating that the two groups now had similar means/proportions for the different variables after matching was applied. Based on this matching table, we consider the non-pregnant and pregnant groups similar on covariates chosen for the propensity score.

Symptoms and laboratory tests at presentation

Table 2 displays the differences between the control and case groups in relation to symptoms and laboratory tests at presentation. The incidences of fever and cough did not differ significantly between the groups (57.8% versus 60.6%; p=0.765, and 78.3% versus 73.1%; p=0.495, respectively). Nevertheless, dyspnea, anosmia/ageusia, fatigue/myalgia, upper respiratory tract symptoms, gastrointestinal symptoms, and other symptoms, such as headache, chest discomfort, and cutaneous rash were all significantly lower in pregnant women. Moreover, there was significant difference of hemoglobin level, AST, ALT, CRP, creatinine and D-Dimers between the 2 groups. Other laboratory tests were similar in both groups.

COVID-19 severity among pregnant and non-pregnant women

Table 3 demonstrates the comparison of primary and secondary outcomes between both groups of the study after applying the propensity score matching and performing a series of logistic regressions. Pregnant women were at higher risk for ICU admission than non-pregnant women (11.08% versus 2.38%; p= 0.024). In addition, they were also at higher risk for hospital admission because of COVID-19 respiratory decompensation such as dyspnea and hypoxemia (58.21% versus 17.4%; p<0.001), for the need for OT (36.04% versus 17.24%; p=0.006), and for ETI (10.16% versus 1.67%; p=0.022). However, there were no cases of mortality in either of the 2 groups.

DISCUSSION

Main finding

Our propensity score-matched case control study has demonstrated that pregnant women infected with COVID-19 ≥ 20 week's gestation, have more severe outcomes than their non-pregnant counterparts.

Comparison with the literature

A small number of case-control studies have been published but few of those have attempted to match cases against the controls for a variety of parameters and/or demographic features. Liu et al (2) observed that the pregnant women had less fever at presentation, higher WBC counts and more consolidation on CT-chest scans. Blitz et al (3) described that among hospitalized women who are infected with COVID-19, pregnant women are not at increased risk for ICU admission. Qiancheng et al (4) showed that pregnancy was not associated with increased severity of the disease, shorter virus clearance time, or longer hospital stay after comparing 28 cases to 54 controls. On the contrary,

significant maternal mortality has also been documented in a cohort of patients from Iran (6). These studies demonstrate not only the difficulties in determining the absolute risk of clinical deterioration specifically related to pregnancy but also the importance of correct case and control group matching. In our study, we showed that pregnant women had higher rates of ICU admission, need for supplemental OT and ETI compared to non-pregnant women.

Strengths and limitations

This is the first multicenter case-control study of COVID-19 in pregnancy using a propensity score. We have included a relatively high number of pregnant women in the study almost matching the number of available controls, lending more validity to the strength of our findings. However, as with all retrospective designs there are certain limitations. These include missing data for laboratory examinations, making it difficult to evaluate more deeply the differences between the pregnant and non-pregnant populations. One relevant criticism could be that the threshold for diagnostic evaluation, hospitalization and certain treatments, may in fact be lower for pregnant women than for others, which may bias our finding of increased disease severity in this group. However, the participating centers involved did not drastically alter their management of COVID-19 patients on the basis of pregnancy, except in cases of deterioration during the third trimester, where emergency delivery was sometimes needed to alleviate the additional physiological demands of pregnancy (data not shown in this study).

Conclusion

On the basis of this study and that of some other groups (1-6), we advise clinicians to exercise prudence when planning the management of pregnant women with COVID-19 infections, particularly in the latter half of the pregnancy, when maternal risk of clinical decompensation and complications may be higher.

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Table 1: Propensity score matching for age, body mass index, and comorbidities in case and control groups.

	Before Matching				After Matching		
	Control group 1 N=107	Case group 2 N=83	ASD	p-value	Control group 1 N=107	Case group 2 N=83	ASD
Age (years)	36.46 ± 6.89	31.97 ± 6.24	68.26%	0.001	34.17 ± 7.37	34.17 ± 6.49	0.00%
DM (type I or II)	4.67%	4.82%	0.69%	1.000	4.24%	4.24%	0.00%
Hypertension	7.48%	4.82%	11.08%	0.556	5.6%	5.6%	0.00%
Asthma	10.28%	8.43%	6.34%	0.804	8.34%	8.34%	0.00%
BMI (kg/m2)	28.25 ± 6.3	27.97 ± 6.41	4.4%	0.752	28.02 ± 6.25	28.02 ± 6.63	0.00%

Abbreviations: ASD: Absolute Standardized Difference; BMI: body mass index; DM: diabetes mellitus.

206 **Table 2:** Comparison of symptoms and laboratory tests at presentation between the 2 groups.

	Control group 1 N=107	Case group 2 N=83	p-value
Symptoms at presentation			
Fever	63 (60.6%)	48 (57.8%)	0.765
Cough	76 (73.1%)	65 (78.3%)	0.495
Dyspnea	46 (44.7%)	25 (30.1%)	0.049
Anosmia/ageusia	36 (34.6%)	15 (18.1%)	0.013
Fatigue/myalgia	70 (67.3%)	26 (31.3%)	<0.001
URT symptoms (runny nose, blocked nose, sore throat)	41 (39.4%)	9 (10.8%)	<0.001
Gastrointestinal symptoms (diarrhea, abdominal pain, nausea, vomiting)	22 (21.2%)	8 (9.6%)	0.044
Others (headache, chest discomfort, cutaneous rash)	44 (42.3%)	10 (12%)	<0.001
Laboratory tests			
Hemoglobin, g/dL	12.98 ± 1.69	11.23 ± 1.32	<0.001
Platelets count, x10^9/L	236.91 ± 123.39	228.97 ± 92.55	0.896
White blood count, x10^9/L	6.93 ± 4.55	7.49 ± 3.38	0.066
Lymphocytes count, x10^9/L	1.45 ± 0.81	1.17 ± 0.51	0.116
Lymphocytopenia	13 (29.5%)	31 (45.6%)	0.114
Neutrophils count, x10^9/L	4.74 ± 3.97	3.84 ± 3.26	0.876
Prothrombin time activity, %	97.46 ± 13.55	102.4 ± 11.28	0.160
aPTT ratio	1.05 ± 0.18	1.08 ± 0.22	0.131

Abnormal aPTT	5 (13.5%)	19 (31.1%)	0.056
Fibrinogen, mg/dL	513.25 ± 135.07	488.56 ± 133.43	0.339
AST, IU/L	47.97 ± 36.6	35.49 ± 23.85	0.004
ALT, IU/L	45.5 ± 40.44	27.84 ± 30.51	<0.001
CRP, mg/dL	73.5 ± 78.23	34.17 ± 37.1	0.014
Creatinine, mg/L	0.69 ± 0.16	0.61 ± 0.41	<0.001
LDH, IU/L	320.08 ± 119.48	246 ± 4.58	0.396
D-dimers, ng/mL	781.5 ± 508.58	1112 ± 388.69	0.046

Abbreviations: ALT: alanine transaminase; aPTT: activated partial thromboplastin time; AST: aspartate transaminase; CRP: C-reactive protein; dL: deciliter; g: gram; IU: international unit; L: liter; LDH: lactate dehydrogenase; mg: milligram, ng: nanogram, URT: upper respiratory tract.

211 **Table 3:** Comparison of primary and secondary outcomes between the 2 groups after applying the
212 propensity score matching.

Variable	Control group 1 N=107	Case group 2 N=83	Adjusted p-value
Primary outcome			
ICU admission	2.38%	11.08%	0.024
Secondary outcomes			
Hospital admission for COVID-19	17.4%	58.21%	<0.001
Need for oxygen therapy	17.24%	36.04%	0.006
Endotracheal intubation	1.67%	10.16%	0.022

213 Abbreviations: COVID-19: coronavirus disease 2019; ICU: intensive care unit.

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