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.

Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching

OBJECTIVE: The first cases of the novel coronavirus (sever acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection were reported in Wuhan in December 2019.[1] More than 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. Early reports focused solely on the fetal risks; however, the emphasis has correctly shifted toward maternal health.[2–6] A recent study reported a hospitalization rate of 52%, including a rate of 10% in intensive care unit (ICU) admission.[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 the coronavirus disease 2019 (COVID-19). The objective of our study was to compare the clinical outcomes and laboratory findings of pregnant women at ≥20 weeks' gestation infected with SARS-CoV-2 with a cohort of nonpregnant women with a confirmed diagnosis of COVID-19 after closely matching the 2 groups using a propensity score.

STUDY DESIGN: This was a retrospective study conducted in the following 4 large university hospitals in France and Belgium between January 1, 2020, and May 13, 2020: (1) Antoine Béclère, Clamart, Paris, France; (2) Bicêtre Hospital, Le Kremlin-Bicêtre, France; (3) Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France; and (4) Brugmann University Hospital, Brussels, Belgium. The study received ethical approval from the Brugmann University Hospital ethics committee (Comité d'Ethique 2020/88) and the institutional review board of the French College of Obstetricians and Gynecologists (Comité d'Ethique de la Recherche en Obstétrique et Gynécologie OBS-2020-0402). Inclusion criterion was female patients of reproductive age with positive SARS-CoV-2 infection confirmed by real-time polymerase chain reaction tests of nasopharyngeal swab samples. Included patients were then divided into the following 2 groups: group 1, nonpregnant controls, and group 2, pregnant cases. The primary outcome was admission to the ICU. The secondary outcomes included hospitalization for clinical deterioration, need for supplemental oxygen therapy (OT), and endotracheal intubation (ETI). The following variables were analyzed: patient age, ethnicity, weight, height, body mass index (BMI), preexisting medical conditions (diabetes mellitus types 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, and D-dimers coagulation tests. All data were anonymized. Hospitalization for clinical deterioration was defined as an admission to a regular care facility, a dedicated COVID-19 ward, or an ICU owing to complications directly related to a confirmed COVID-19 diagnosis. Common reasons for admission included severe dyspnea, desaturation (oxygen saturation of <95% in 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 ultrasonography. Maternal weights used were those from the booking visit. Lymphocytopenia was defined as an absolute lymphocyte count of $<1\times10^9$ cells/L. An activated partial thromboplastin ratio level of >1.2 was considered as abnormal. Data were analyzed with the statistical software package Statistical Product and Service Solutions (version 25.0, IBM SPSS Statistics; SPSS Inc, Chicago, IL), R (version 3.6.2, R Core Team, 2019), and Excel (version 15.0; Microsoft, Redmond, WA). 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 *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 the 2 groups. The covariate balancing propensity score R package and survey R packages were used to determine the propensity score as previously described.[7] A 2-sided $P<.05$ was considered to be statistically significant.

RESULTS: A total of 201 patients met the inclusion criteria. In addition, the following 11 patients were excluded from the study: 6 nonpregnant patients (4 receiving hemodialysis, 1 patient affected by trisomy 21, and 1 patient with complex congenital heart disease) and 5 pregnant patients (all at <20

weeks' gestation). This left 190 eligible patients for the final analysis who were divided into the following 2 groups: a nonpregnant control group 1 (107 of 190 patients) and the pregnant case group 2 (83 of 190 patients). Table 1 indicates the propensity score matching for a variety of predefined variables. The first part of the table (before matching) indicates that, in almost all cases, the 2 groups had different means or proportions for the different variables before matching was applied. The mean age in the control group was significantly higher than that in the case group (36.46±6.89 vs 31.97±6.24 years; $P<.001$), but no statistically significant differences were observed for BMI or comorbidities between the 2 groups. The second part of the table presents the results after matching in which we observe that the means, standard deviations, and the proportions are now much closer between the 2 groups. The absolute standardized difference values are equal to 0, indicating that the 2 groups now had similar means or proportions for the different variables after matching was applied. Based on this matching table, we consider the nonpregnant and pregnant groups to be similar on covariates chosen for the propensity score. Table 2 presents the differences between the control and case groups in relation to the symptoms and laboratory test results at presentation. The incidences of fever and cough did not differ significantly between the 2 groups (57.8% vs 60.6% [$P=.765$] and 78.3% vs 73.1% [$P=.495$], respectively). Nevertheless, dyspnea, anosmia or ageusia, fatigue and 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, C-reactive protein (CRP), creatinine, and D-dimers between the 2 groups. Other laboratory test results were similar in both the groups. Table 3 presents the comparison of primary and secondary outcomes between the 2 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 nonpregnant women (11.08% vs 2.38%; $P=.024$). In addition, they were also at higher risk for hospital admission because of COVID-19 respiratory decompensation such as dyspnea and hypoxemia (58.21% vs 17.4%; $P<.001$), for the need for OT (36.04% vs 17.24%; $P=.006$), and for ETI (10.16% vs 1.67%; $P=.022$). However, there were no cases of mortality in either of the 2 groups.

CONCLUSION: Our propensity score–matched case-control study has indicated that pregnant women diagnosed with COVID-19 at ≥20 weeks' gestation have more severe outcomes than their nonpregnant counterparts. 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 demographic features. Liu et al[2] observed that pregnant women had low fever at presentation, higher WBC counts, and more consolidation on chest computed tomography scans. Blitz et al[3] described that among hospitalized women who received a diagnosis of COVID-19, pregnant women are not at increased risk for ICU admission. Qiancheng et al[4] reported 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 been documented in a cohort of patients from Iran.[6] These studies indicate 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 reported that pregnant women had higher rates of ICU admission and need for supplemental OT and ETI than nonpregnant women. 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

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

	Before matching				After matching		
Variable	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, y	36.46±6.89	31.97±6.24	68.26	.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	.556	5.60	5.60	0.00
Asthma	10.28	8.43	6.34	.804	8.34	8.34	0.00
BMI, kg/m^2	28.25±6.30	27.97±6.41	4.40	.752	28.02±6.25	28.02±6.63	0.00

Data are presented as percentages and mean±standard deviation.

ASD, absolute standardized difference; *BMI*, body mass index; *DM*, diabetes mellitus.

Badr. Coronavirus disease 2019 in pregnancy. Am J Obstet Gynecol 2020.

TABLE 2
Comparison of symptoms and laboratory test results at presentation between the 2 groups

Symptom	Control group 1 (n = 107)	Case group 2 (n = 83)	*P* value
Symptoms at presentation			
Fever	63 (60.6)	48 (57.8)	.765
Cough	76 (73.1)	65 (78.3)	.495
Dyspnea	46 (44.7)	25 (30.1)	.049
Anosmia or ageusia	36 (34.6)	15 (18.1)	.013
Fatigue and myalgia	70 (67.3)	26 (31.3)	<.001
URT symptoms (runny nose, blocked nose, sore throat)	41 (39.4)	9 (10.8)	<.001
Gastrointestinal symptoms (diarrhea, abdominal pain, nausea, vomiting)	22 (21.2)	8 (9.6)	.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	<.001
Platelet count, $\times 10^9$/L	236.91±123.39	228.97±92.55	.896
WBC count, $\times 10^9$/L	6.93±4.55	7.49±3.38	.066
Lymphocyte count, $\times 10^9$/L	1.45±0.81	1.17±0.51	.116
Lymphocytopenia	13 (29.5)	31 (45.6)	.114
Neutrophil count, $\times 10^9$/L	4.74±3.97	3.84±3.26	.876
Prothrombin time activity, %	97.46±13.55	102.40±11.28	.160
aPTT ratio	1.05±0.18	1.08±0.22	.131
Abnormal aPTT	5 (13.5)	19 (31.1)	.056
Fibrinogen, mg/dL	513.25±135.07	488.56±133.43	.339
AST, IU/L	47.97±36.60	35.49±23.85	.004
ALT, IU/L	45.50±40.44	27.84±30.51	<.001
CRP, mg/dL	73.50±78.23	34.17±37.10	.014
Creatinine, mg/L	0.69±0.16	0.61±0.41	<.001
LDH, IU/L	320.08±119.48	246.00±4.58	.396
D-dimers, ng/mL	781.50±508.58	1112.00±388.69	.046

Data are presented as number (percentage) and mean±standard deviation.

ALT, alanine transaminase; *aPTT*, activated partial thromboplastin time; *AST*, aspartate transaminase; *CRP*, C-reactive protein; *LDH*, lactate dehydrogenase; *URT*, upper respiratory tract; *WBC*, white blood cell.

Badr. Coronavirus disease 2019 in pregnancy. Am J Obstet Gynecol 2020.

more validity to the strength of our findings. However, as with all retrospective designs, there are certain limitations. These include missing data of laboratory examinations, making it difficult to evaluate more deeply the differences between the pregnant and nonpregnant 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 have biased our finding of increased disease severity in this group. However, the participating centers involved did not drastically alter their management of patients with COVID-19 on the basis of pregnancy, except in cases of deterioration during the third trimester, when emergency delivery was sometimes needed to alleviate the additional physiological demands of pregnancy (data not indicated in this study). Based on this study and those of some other groups,[1–6] we advise clinicians to exercise prudence when planning the management of pregnant women diagnosed with COVID-19, particularly in the latter half of the pregnancy, when maternal risk of clinical decompensation and complications may be higher.

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TABLE 3
Comparison of primary and secondary outcomes between the 2 groups after applying the 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	.024
Secondary outcomes			
Hospital admission for COVID-19	17.4	58.21	<.001
Need for oxygen therapy	17.24	36.04	.006
Endotracheal intubation	1.67	10.16	.022

Data are presented as percentage.

COVID-19, coronavirus disease 2019; *ICU*, intensive care unit.

Badr. Coronavirus disease 2019 in pregnancy. Am J Obstet Gynecol 2020.

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REFERENCES

1. Abbas AR, Abbas A, Ali Y, Memon SF. Important considerations regarding the future management of coronavirus (COVID-19). Int J Surg 2020;79:6–7.
2. Liu F, Liu H, Li J, Hou L, Lan W, Wang D. Clinico-radiological features and outcomes in pregnant women with COVID-19: compared with age-matched non-pregnant women. [Electronic copy]. Available at: https://ssrn.com/abstract=3556647 2020. Accessed May 20, 2020.
3. Blitz MJ, Grünebaum A, Tekbali A, et al. Intensive care unit admissions for pregnant and nonpregnant women with coronavirus disease 2019. Am J Obstet Gynecol 2020;223:290–1.
4. Qiancheng X, Jian S, Lingling P, et al. Coronavirus disease 2019 in pregnancy. Int J Infect Dis 2020;95:376–83.
5. Vivanti AJ, Mattern J, Vauloup-Fellous C, et al. Retrospective description of pregnant women infected with severe acute respiratory syndrome coronavirus 2, France. Emerg Infect Dis 2020. [Epub ahead of print].
6. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am J Obstet Gynecol 2020;223:109.e1–16.
7. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.

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Use of remdesivir for pregnant patients with severe novel coronavirus disease 2019

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INTRODUCTION: Coronavirus disease 2019 (COVID-19) has resulted in hundreds of thousands of deaths worldwide.[1] The nucleoside analog remdesivir has shown preliminary efficacy in shortening the duration of moderate and severe COVID-19.[2,3] Data from a randomized controlled trial during the Ebola epidemic suggest safety of remdesivir in pregnancy[4]; however, pregnant women have largely been excluded from clinical trials for COVID-19 treatment options.[5] Here, we briefly describe the treatment of 3 pregnant patients hospitalized at our institution with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and imaging supportive of lower respiratory disease, who met the criteria for compassionate use protocol of remdesivir.

CASES:

Case A

A 25-year-old pregnant woman at 34 weeks of gestation presented with fever, tachycardia, and tachypnea. Chest x-ray (CXR) revealed patchy consolidations, and nasopharyngeal (NP) swab was positive for SARS-CoV-2 by real-time polymerase chain reaction (Table). On hospital day (HD) 2, the patient was transferred to the intensive care unit (ICU) for increasing oxygen requirement on nasal cannula. The patient received a total of 3 doses of remdesivir (Figure), after which additional doses were withheld because of the development of transaminitis. She was ultimately diagnosed with intrahepatic cholestasis of pregnancy (IHCP) in the setting of markedly elevated bile acids. The patient was discharged on HD 8 and underwent an uncomplicated vaginal delivery after scheduled induction at 37 weeks and 2 days of gestation for IHCP.

Case B

A 28-year-old pregnant woman at 25 weeks of gestation was transferred to our ICU for COVID-19 pneumonia and acute hypoxic respiratory failure requiring bilevel-positive airway pressure ventilation. Remdesivir was initiated on HD 2, and she received 8 doses of remdesivir. By HD 9, the patient's supplemental oxygen requirement resolved, and she was discharged home.

Case C

A 29-year-old pregnant woman at 25 weeks of gestation presented with 8 days of fever, headache, cough, and shortness of breath. She was tachypneic and tachycardic on admission. CXR revealed hazy opacities, and NP swab was positive for SARS-CoV-2. She developed hypoxia with oxygen saturation of 88% on ambient air and was placed on supplemental oxygen. A total of 2 doses of remdesivir were administered until clinical improvement, and she was discharged on HD 6.

COMMENT: As the COVID-19 pandemic continues and pregnant women remain at risk for adverse medical and obstetrical outcomes, having safe and effective therapies, such as remdesivir, is crucial for this population.[6] In our experience, all patients who were receiving supplemental oxygen had resolution of this requirement after initiation of remdesivir. However, a causal relationship cannot be concluded.