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Sars-CoV2 infection in pregnant women with multiple sclerosis

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Abstract

Background: In the general population, maternal SARS-CoV-2 infection during pregnancy is associated with worse maternal outcomes; however, only one study so far has evaluated COVID-19 clinical outcomes in pregnant and postpartum women with multiple sclerosis, showing no higher risk for poor COVID-19 outcomes in these patients.

Objective: In this multicenter study, we aimed to evaluate COVID-19 clinical outcomes in pregnant patients with multiple sclerosis.

Methods: We recruited 85 pregnant patients with multiple sclerosis who contracted COVID-19 after conception and were prospectively followed-up in Italian and Turkish Centers, in the period 2020-2022. A control group of 1354 women was extracted from the database of the Multiple Sclerosis and COVID-19 (MuSC-19). Univariate and subsequent logistic regression models were fitted to search for risk factors associated with severe COVID-19 course (at least one outcome among hospitalization, intensive care unit [ICU] admission and death).

Results: In the multivariable analysis, independent predictors of severe COVID-19 were age, body mass index $\geqslant 30$, treatment with anti-CD20 and recent use of methylprednisolone. Vaccination before infection was a protective factor. Vaccination before infection was a protective factor. Pregnancy was not a risk nor a protective factor for severe COVID-19 course.

Conclusion: Our data show no significant increase of severe COVID-19 outcomes in patients with multiple sclerosis who contracted the infection during pregnancy.

Keywords: Multiple sclerosis, pregnancy, COVID-19, SARS-CoV-2 infection, COVID-19 outcomes, risk factors

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Introduction

Based on the average number of daily deaths, COVID-19 has been one of the leading causes of death in the most affected countries,[1] and concerns have been raised especially for groups identified as "vulnerable individuals" which include people with multiple sclerosis (MS) and pregnant women.

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Pregnant women are in general at higher risk of respiratory infection, especially viral ones, mainly related to two mechanisms: (1) immunological changes, resulting in a polarization of CD4 + T cells toward a Th2 phenotype and a reduced clearance of infected cells;[2] and (2) anatomical changes in the respiratory system, such as elevation of the diaphragm and splaying of the thoracic cage due to the enlarged uterus, decreasing the functional residual capacity and ability to clear secretions, despite an increased oxygen consumption.[3,4] Existing data about COVID-19 and pregnancy are limited and most of them derives from the obstetric literature and deal with pregnancy in the general population. Published case series and systematic reviews have shown that in the general population COVID-19 is associated with an increased risk of adverse maternal outcomes, such as mortality, intensive care unit (ICU) admission and infections requiring antibiotic treatment.[5–7]

MS typically affects young adults with a higher prevalence in women, and it is often diagnosed in women of childbearing age.[8] Family planning is therefore becoming increasingly relevant to patients, family members and health care professionals. Moreover, in a US study pregnancy rates in MS women appeared to be on the rise between 2006 and 2015 against the opposite trend in the general population[9] and an increasing number of pregnancies are being conceived while on treatment with DMDs.[10] While over the past decade several MS studies have addressed the safety of DMDs in pregnancy and lactation,[11] only one small study so far has evaluated COVID-19 clinical outcomes in pregnant and postpartum women with MS.[12] Importantly, management of pregnant women with MS requires further considerations because of (1) the unique immunological environment during pregnancy and postpartum, (2) immunomodulatory therapy use and (3) disease activity.[13] Moreover, in the MS population, recent data suggested that exposure to anti-CD20 agents (such as ocrelizumab or rituximab) and recent use (<1 month) of methylprednisolone may increase the risk of severe COVID-19.[14]

Given the dearth of research in the field, an international initiative was launched on April 2022 within the Musc-19 study group, aimed to assess: (1) whether pregnancy in MS is associated with an increased risk of severe COVID-19 disease in the mother, (2) maternal and fetal outcomes in pregnant MS women with COVID-19 infection/disease and (3) the impact of COVID-19 during pregnancy on MS clinical course. In this article, we report data on severity of COVID-19 disease during pregnancy in MS women, taking into account the main clinical and demographic confounders.

Material and methods

Study design and participants

This international, retrospective cohort study included 85 women with MS extracted from the database of the Multiple Sclerosis and COVID-19 (MuSC-19), followed up in 24 Italian and 11 Turkish centers that agreed to participate in the project. MuSC-19 is an international platform linked to the Italian MS Register, set up to collect clinical and patient-reported data of persons with MS who have been diagnosed with COVID19. Inclusion criteria for the pregnancy group were: age between 18 and 50 years, diagnosis of MS according to McDonald criteria,[15–18] pregnancy and a laboratory-confirmed SARS-COV-2 infection diagnosed after conception in the period 2020–2022. A confirmed case was defined as a patient with a positive test (reverse transcriptase polymerase chain reaction on nasal and pharyngeal swabs) for SARS-COV-2 or, for unvaccinated patients, a positive serological test obtained at any point during the observation period. A control group of 1354 non-pregnant MS women with COVID-19, matched for demographic characteristics, was extracted from the same database (MuSC-19). Data on MS phenotype, disease duration, Expanded Disability Status Scale (EDSS) score, DMDs, smoking habits, alcohol and substances consumption were collected. Recorded COVID-19 outcomes were hospitalization, ICU admission, or death. In case of missing data, requests for clarification were sent to the coordinator of each participating center.

Outcomes

The primary outcome was a composite measure of maternal COVID-19 mortality and morbidity including at least one of the following: hospitalization, admission to ICU or death.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v 24.0. Continuous variables were reported as mean ± standard deviation (SD), while categorical as number with percentage. Differences in baseline and clinical characteristics between pregnant and non-pregnant women were assessed by Chi-square test or Mann Whitney exact test, as appropriate. Univariate and subsequent logistic regression models were fitted to search for risk factors associated with severe COVID-19 course (at least one outcome among hospitalization, ICU admission and death). Variables included were as follows: age (grouped into intervals of 10 years), body mass index (BMI) categorized into

Table 1. Baseline demographic and clinical characteristics of patients, by pregnancy.

		Total ($N=1439$)	No pregnancy ($N=1354$)	Pregnancy ($N=85$)	p
Age, years, mean (SD)		35.9 (7.95)	35.90 (8.04)	35.2 (6.43)	0.21
BMI (kg/m^2), mean (SD)		24.1 (5.78)	24.10 (5.78)	24.5 (5.80)	0.70
Presence of at least one comorbidity	No	1343 (93.3%)	1265 (93.4%)	78 (91.8%)	0.50
	Yes	96 (6.7%)	89 (6.6%)	7 (8.2%)	
MS phenotype	Relapsing remitting MS (RRMS)	1372 (95.3%)	1289 (95.2%)	83 (97.6%)	0.30
	Progressive MS (PMS)	67 (4.6%)	65 (4.8%)	2 (2.4%)	
Last EDSS, median [IQR]		1.5 [1.0–2.5]	1.5 [1.0–2.5]	1.0 [1.0–2.5]	0.90
Disease duration (years), mean (SD)		6.8 (5.80)	6.7 (5.71)	8.3 (6.86)	0.016*
Previous methylprednisolone, *n* (%)	No	1332 (92.6%)	1255 (92.7%)	77 (90.6%)	0.47
	Yes	107 (7.4%)	99 (7.3%)	8 (9.4%)	
Disease modifying treatment	Untreated	139 (9.7%)	123 (9.1%)	16 (18.8%)	0.016*
	Interferon	175 (12.2%)	162 (12.0%)	13 (15.3%)	
	Anti-CD20	173 (12.0%)	165 (12.2%)	8 (9.4%)	
	Other	952 (66.2%)	904 (66.8%)	48 (56.5%)	
Vaccine before infection, *n* (%)	Not vaccinated before	1328 (92.3%)	1246 (92.0%)	82 (96.5%)	0.14
	Vaccination before Covid-19	111 (7.7%)	108 (8.0%)	3 (3.5%)	
Hospitalization		136 (9.4%)	125 (9.2%)	11 (12.9%)	0.48
ICU admission		10 (0.6%)	10 (0.7%)	0	
Death		5 (0.3%)	5 (0.4%)	0	

* Statistically significant.

four groups (normal weight, underweight, overweight and obesity) according to the current cut-off points determined by the World Health Organization (WHO),[19] presence of pregnancy, presence of at least one comorbidity (yes/no), EDSS [20] score at last visit, disease duration in years, disease modifying treatment (categorized into: untreatment, treatment with interferon, treatment with anti-CD20 and other treatment), recent use of methylprednisolone (<1 month) and vaccination for COVID-19 before Sars-Cov-2 infection (yes/no). p values < 0.05 were considered significant.

Results

Characteristics of the study sample

The whole database of MuSC-19 platform included 3770 women of which 85 (2.3%) patients from Italian and Turkish centers fulfilled the inclusion criteria for the pregnancy group. A control group of 1354 women with confirmed Covid-19 and matched for age (between 18 and 50 years) was selected from the whole database of MuSC-19. Table 1 shows baseline and clinical characteristics in the whole sample ($N=1439$) and differences between pregnant and non-pregnant women. The two groups were matched for the main clinical and demographic characteristics except for the disease duration, that was longer in the pregnancy group (8.3 years vs 6.7 years, $p=0.016$) and the proportion of not treated women that was higher in the pregnancy group (18.8% vs 9.1%, $p=0.016$). Table 2 illustrates demographic and clinical characteristics of pregnant patients ($N=85$) and differences between Italian ($N=31$) and Turkish ($N=54$) cases. The two groups significantly differ for three variables, as Turkish patients were older (36.2 years old vs 33.4 years old, $p=0.019$), more frequently not vaccinated against SARS-COV2 (100% vs 90.3%, $p=0.046$), and presented only Delta infections against 16.1% Omicron Italian cases ($p=0.005$).

Maternal outcomes

A severe COVID-19 course, experiencing at least one outcome among hospitalization, ICU admission and death, was observed in 11 women (12.9%) in the pregnancy group and in 140 women (10.3%) in the control

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Table 2. Baseline demographic and clinical characteristics of pregnant patients, by Country.

		Total ($N=85$)	Italy ($N=31$)	Turkey ($N=54$)	p
Age, years, mean (SD)		35.2 (6.43)	33.4 (6.42)	36.2 (6.28)	0.019*
BMI (kg/m^2), mean (SD)		24.5 (5.80)	24.5 (6.34)	24.4 (5.52)	0.48
Presence of at least one comorbidity—*n* (%)	No	78 (91.8%)	30 (96.8%)	48 (88.9%)	0.20
	Yes	7 (8.2%)	1 (3.2%)	6 (11.1%)	
MS phenotype—*n* (%)	PMS	2 (2.4%)	1 (3.2%)	1 (1.9%)	0.99
	RRMS	83 (97.6%)	30 (96.8%)	53 (98.1%)	
Last EDSS, median [IQR]		1.0 [1.0 - 2.5]	1.5 [1.0 - 2.5]	1.0 [1.0 - 2.5]	0.08
Disease duration (years), mean (SD)		8.3 (6.86)	8.3 (8.82)	8.40 (5.53)	0.35
Disease modifying treatment—*n* (%)	Untreated	16 (18.8%)	8 (25.8%)	8 (14.8%)	0.22
	Interferon	13 (15.3%)	3 (9.7%)	10 (18.5%)	
	Anti-CD20	8 (9.4%)	1 (3.2%)	7 (13.0%)	
	Other	48 (56.5%)	19 (61.3%)	29 (53.7%)	
Previous methylprednisolone—*n* (%)	No	77 (90.6%)	26 (83.9%)	51 (94.4%)	0.13
	Yes	8 (9.4%)	5 (16.1%)	3 (5.6%)	
Vaccine before infection—*n* (%)	No	82 (96.5%)	28 (90.3%)	54 (100.0%)	0.046*
	Yes	3 (3.5%)	3 (9.7%)	0 (0.0%)	
Hospitalization—*n* (%)	No	77 (90.6%)	30 (96.8%)	47 (87.0%)	0.14
	Yes	8 (9.4%)	1 (3.2%)	7 (13.0%)	
ICU admission—*n* (%)	No	85 (100.0%)	31 (100.0%)	54 (100.0%)	
Death—*n* (%)	No	85 (100.0%)	31 (100.0%)	54 (100.0%)	

* Statistically significant.

Table 3. Risk factors for severe Covid-19 course (hospitalization, or ICU admission or death) in the whole sample.

		Univariate analysis	Multivariate analysis
Age, 10 years		1.41 (1.13–1.77); 0.002	1.33 (1.04–1.72); 0.026
BMI classification	Normal weight	Ref.	Ref.
	Underweight	0.63 (0.25–1.61); 0.34	0.66 (0.26–1.69); 0.39
	Overweight	1.29 (0.84–1.97); 0.24	1.19 (0.77–1.85); 0.44
	Obesity	2.57 (1.61–4.09); < 0.001	2.20 (1.35–3.58): 0.002
Pregnancy		1.29 (0.67–2.49); 0.45	1.27 (0.64–2.51); 0.49
Presence of at least one comorbidity		2.10 (1.22–3.61); 0.007	1.48 (0.83–2.65); 0.18
Last EDSS		1.16 (1.05–1.29); 0.003	1.01 (0.90–1.14); 0.86
Disease duration, years		1.02 (0.99–1.05); 0.27	0.99 (0.96–1.03); 0.80
Disease modifying treatment	Untreated	Ref.	Ref.
	Interferon	0.48 (0.20–1.15); 0.10	0.49 (0.20–1.17); 0.11
	Anti-CD20	2.35 (1.21–4.55); 0.012	2.19 (1.06–4.54); 0.034
	Other	0.96 (0.53–1.73); 0.88	0.89 (0.48–1.63); 0.70
Recent use of methylprednisolone		2.74 (1.68–4.48); < 0.001	2.65 (1.59–4.41); < 0.001
Vaccination before infection		0.38 (0.15–0.95); 0.039	0.35 (0.14–0.89); 0.028

group ($p = 0.48$). In particular, in the pregnancy group, 11 women (12.9%) were hospitalized, whereas no woman was admitted to ICU and no death was reported. In the control group, 125 (9.2%) women were hospitalized, 10 (0.7%) were admitted to ICU and 5 (0.4%) died.

Predictors of severe COVID-19 course

In the multivariable analysis (Table 3), pregnancy was not associated with higher risk of severe COVID-19 course (OR: 1.27, 95% CI: 0.64–2.51; $p=0.49$). Independent predictors of severe COVID-19 course in the whole sample were older age (OR: 1.33, 95%

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CI: 1.04–1.72; $p = 0.026$), body mass index (BMI) ⩾ 30 (OR: 2.20, 95% CI: 1.35–3.58; $p = 0.002$), treatment with anti-CD20 (OR: 2.19, 95% CI: 1.06–4.54; $p = 0.034$) and recent use of methylprednisolone (OR: 2.65, 95% CI: 1.59–4.41; $p < 0.001$). Anti-Covid-19 vaccination before infection was a protective factor (OR: 0.35, 95% CI: 0.14–0.89; $p = 0.028$).

Discussion

In this multicenter, international study, pregnancy was not associated with higher risk of severe COVID-19 in women with MS.[14,21–23] Taken together with results of a smaller study on 31 COVID-19 MS pregnancy,[12] our findings seem to be in contrast with data from the obstetric literature regarding the general population, where pregnant subjects have increased risk of severe COVID-19 compared with non-pregnant women of similar age.[21–24] In particular, despite a similar rate of SARS-CoV-2 infection,[25,26] pregnant women with COVID-19 in the general population appear to be at higher risk of acute respiratory distress syndrome (aRR, 34.4), death (aRR, 17.0), sepsis (aRR, 13.6), mechanical ventilation (aRR, 12.7), shock (aRR, 5.1), ICU admission (aRR, 3.6), acute renal failure (aRR, 3.5), thromboembolic disease (aRR, 2.7) and adverse cardiac event/outcome (aRR, 2.2).[27]

A number of explanations could account for these different findings. We can speculate that at least part of the better outcomes in women with MS derives from the strict medical attention applied to those patients. Pregnancy in patients with MS is often considered by gynecologists as a "high risk pregnancy" and can receive more intensive specialized care. Moreover, the awareness of an underlying immunological disease during the pandemic may have promoted in MS women more than in the general population the adoption of a healthier lifestyle (e.g. strictly avoiding smoking and alcohol, excessive weight gain, controlling and treating comorbidities). In addition, the majority of the studies conducted on the general population had a collection period in early 2020,[6,7,27] while we kept on collecting data since 2022, when the growing knowledge of COVID-19 had given clearer insights into how the virus works and helped improving the strategies of prevention and treatment. Such improvement, together with virus mutations and less aggressive variants in 2021–2022, could account for milder outcomes. Moreover, even if we have no data on treatment with monoclonal antibodies or anti-viral drugs in our sample, it is possible that the access to therapies for Sars-Cov2 infection could have contributed to the observed less severity of COVID19. However, we cannot rule out the hypothesis that our sample was not powered enough to detect rare outcomes. In our sample, the majority of pregnant patients were recruited during Delta wave (94.1%) and only 5.9% during Omicron wave. Since the proportion of patients in the Omicron wave was very low, this variable i not included in the multivariable analysis.

In our study, risk factors for Covid-19 severity in the pregnant group were the same as previously observed in the general population of MS patients. In fact, severe COVID-19 was associated with older age, BMI of 30 or more, exposure to anti-CD20 agents and recent use of methylprednisolone.[14,28–30] As for anti-CD20, it would be of interest to assess the impact of the wash-out period duration on the risk of both COVID-19 infection and course severity. However, these data are not available for the present analysis.

Furthermore, even if in our sample only a minority of patients were vaccinated against Sars-Cov2 (3.5%), our study confirms that vaccination represents a significant protective factor from severe infection course[31] also in pregnancy. Even though pregnant women were not included in the initial clinical trials of COVID-19 vaccines, evidence about their safety and effectiveness during pregnancy has been growing, suggesting that the benefits of receiving COVID-19 vaccination outweigh any known or potential risks of vaccination during pregnancy.[32–37]

Some limitations in our study are worth noting. Besides the relatively small sample size, we did not collect data about COVID-19 symptoms. In addition, pregnancy and control groups were not fully matched, in particular for disease duration and the proportion of DMD treatment; however, the multivariable model was adjusted for these variables together with other possible confounders. Despite these limitations, our data are reassuring and suggest that pregnancy in MS women generally does not confer a higher risk of poor COVID-19 outcomes, which can assist physicians and patients in the family planning during the ongoing pandemic era.

Still, data from the general population rise some concerns about worse COVID-19 course during pregnancy and many questions regarding maternal and fetal outcomes during Sars-CoV-2 infection remain unanswered. Therefore, waiting for further evidence in the field, careful prevention of COVID-19 should be pro-actively implemented in MS women with pregnancy plan, following the continuously updated recommendations from the national and international health organizations.

Finally, collection of data in the Musc-19 dataset is continuing and we are going to further address the issues of pregnancy and fetal outcomes as well as the impact of COVID19 in pregnancy on MS course.

Declaration of Conflicting Interests

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