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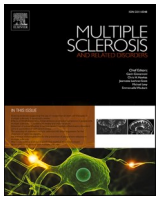

Correspondence

COVID-19 in the pregnant or postpartum MS patient: Symptoms and outcomes☆

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ABSTRACT

Women with multiple sclerosis (MS) are often of childbearing age. Thirty-six women with MS who were pregnant ($n = 27$) or within 6 weeks postpartum ($n = 9$) were reported in the North American COViMS registry and their COVID-19 outcomes were described. One pregnant and one postpartum woman were hospitalized. No deaths occurred. To compare COVID-19 clinical outcomes in pregnant and postpartum females with females who were not pregnant or postpartum, a 1:2 propensity score match was performed. While not powered to detect small differences, it was reassuring that no increased risks for those with MS who were pregnant/postpartum were revealed.

1. Introduction

Pregnancy and the postpartum period impart physiological, hormonal and immunologic changes that are associated with decreased ability to clear infections and a hypercoagulable state, Abu-Raya et al. (2020) and Overton et al. (2022) raising particular concerns for pregnant women with COVID-19. Indeed, worse COVID-19 outcomes are consistently observed in pregnant and postpartum women versus non-pregnant counterparts. Data from the United States indicate increased intensive care unit (ICU) admissions and invasive ventilation for pregnant women with COVID-19 versus nonpregnant women of similar age; in Sweden, ICU admission was over 5 times more likely among pregnant and postpartum women with COVID-19 than in non-pregnant women of similar age (Collin et al., 2020); and in the United Kingdom COVID-19 outcomes were worse in pregnant women (Knight et al., 2020).

The COViMS (COVID-19 Infections in Multiple Sclerosis and Related Diseases) Registry is a de-identified, cross-sectional dataset on patients with multiple sclerosis (MS)and other CNS demyelinating diseases and confirmed or highly suspected infection with SARS-CoV-2. The COViMS Registry opened early in the pandemic, specifically queried about pregnancy or the postpartum period at time of COVID-19, and continues to accrue data on new cases. Salter et al. (2021) Based on the aforementioned concerns, we present results assessing how pregnant and/or postpartum women with MS who developed COVID-19 fared using data from COViMS Registry.

2. Methods

COViMS Registry received non-human subject research designation from the Washington University Institutional Research Board, and collected de-identified information on COVID-19 outcomes entered beginning April 1, 2020. Registry entries were made by health care professionals in North America, and were requested to contribute reports only after a minimum of 7 days and/or sufficient time has passed to observe the disease course through resolution of acute illness or death. Demographic and clinical characteristics collected included whether the individual was pregnant or postpartum (defined as less than 6 weeks out from pregnancy). This analysis included only women with MS in the COViMS Registry up to March 10, 2022 (excluded male and non-binary patients) and identified women who were pregnant or postpartum. Descriptive statistics summarized demographic and clinical characteristics and comparisons were made using chi-squared tests, Fisher's exact tests or t-tests, as appropriate.

To compare COVID-19 clinical outcomes in pregnant and postpartum females with females who were not pregnant or postpartum, a 1:2 propensity score (PS) match was performed. The PS was estimated using a multivariable logistic regression with the pregnant/postpartum status as the outcome and the following factors which have been shown to influence COVID-19 outcomes selected a priori, age, race and ethnicity, prior or current disease modifying therapy category (anti-CD20s versus other/none), ambulation, year of COVID-19 (2020, 2021, 2022), vaccination status, COVID-19 treatment with monoclonal antibodies, cardiovascular disease, diabetes, hypertension, morbid obesity, and MS clinical course (CIS, MS) (Salter et al., 2021). The logistic model predicted probability was used in a nearest neighbor matching without replacement (caliper=0.2*logit [PS standard deviation]) to pair pregnant/postpartum women with those who were not pregnant/postpartum in the registry. Differences in clinical outcome from COVID-19 between the PS-matched cohort were evaluated using a McNemar's test or Wilcoxon signed rank test, as appropriate. Analyses were conducted in SAS v9.4; significance level was set at 0.05. To maximize capture of important safety signals, no adjustments were made for multiplicity.

3. Results

The COViMS Registry on March 10, 2022 included 4270 patients and 4095 had MS. 3079 MS patients were female (75.2%) and 36 (1.2%)

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were pregnant ($n = 27$) or postpartum ($n = 9$). Cases were reported from 26 different medical centers representing most regions of the United States and Canada. The majority were relapsing-remitting MS patients and fully ambulatory (Table 1A). Postpartum patients were significantly older than the pregnant patients ($p<0.001$). The majority of pregnant and postpartum patients had COVID-19 in 2020 (64.7%), prior to the availability of COVID-19 vaccinations. Postpartum women more frequently had symptoms of fever ($p = 0.048$), fatigue ($p = 0.007$), pain ($p = 0.032$) and sore throat ($p = 0.029$) compared to pregnant women (Table 1B). Most women were not hospitalized (pregnant, 96.3%; postpartum, 88.9%). One pregnant woman was hospitalized, and one postpartum woman was hospitalized in the ICU. One (11.1%) postpartum woman had pneumonia. Two (7.4%) pregnant women who were each receiving ocrelizumab were treated for COVID-19 with monoclonal antibodies against SARS-CoV-2; neither was hospitalized. No deaths were reported.

Thirty-one pregnant/postpartum women (86%) were able to be propensity matched 1:2 to women with MS reported in the COViMS Registry who were not pregnant/postpartum. Five pregnant women could not be matched due to a combination of characteristics for the factors considered in the propensity matching model. The combination of factors, such as younger age, no comorbidities, later year of COVID-19 infection and race, made finding a suitable match among the non-pregnant women infeasible. No significant difference in clinical outcomes from COVID-19 were observed between the PS-matched groups ($p = 0.99$). Pregnant or postpartum MS-affected women in COViMS Registry were not differentially treated with COVID-19 monoclonal antibody treatment ($p = 0.99$).

4. Discussion

Multiple reports from around the world have indicated increased risks for worse outcomes from COVID-19 during pregnancy and the postpartum period (Collin et al., 2020; Knight et al., 2020; Zambrano et al., 2020). Women with MS are often of child-bearing age. Questions regarding the safety of becoming pregnant (Bonavita et al., 2021), including during the ongoing COVID-19 pandemic (Krysko et al., 2021; Yam et al., 2020), have been raised. We queried the North-American COViMS Registry for reports of women with MS and COVID-19 who were pregnant or within 6 weeks postpartum. This is the largest series reported to date on women with MS and COVID-19 who were pregnant or postpartum. We compared 31 pregnant and postpartum women with 62 propensity-matched non-pregnant, non-postpartum women with MS reported in the COViMS Registry and worse outcomes were not observed among pregnant/postpartum MS-affected women with COVID-19. We speculate that, unlike the general pregnant/postpartum population with COVID-19, women with MS typically receive intense care from multiple physicians, including obstetricians specialized in high risk pregnancies and that the additional medical attention led to better outcomes than for those without MS. Though we did not identify worse outcomes, the power of this study only allowed for relatively large effect sizes (Cohen's $d = 0.7$ or higher) to be observed for continuous variables and extremely large differences in proportions. Nevertheless, the point estimates observed are reassuring, but not definitive.

Data on Neuromyelitis Optica (NMO) and MOG antibody disorder (MOGAD) patients were also entered in COViMS Registry (Newsome et al., 2021). As of March 10, 2022, three women with MOGAD who were pregnant and one woman with NMO who was postpartum during COVID-19 were reported, in addition to the 36 with MS. The two MOGAD patients had mild courses not requiring hospitalization, but the NMO patient (on rituximab) required hospitalization. Increased sample sizes are needed to assess whether there is an impact of pregnancy/-postpartum period on people with these diseases.

Limitations to this study include that information in COViMS Registry was voluntarily reported, and a potential reporting bias exists. COViMS Registry data are not population-based and therefore lack denominators and the numerators overestimate the proportion of severe cases as asymptomatic cases are likely underreported. The potential for incomplete follow-up exists and it is not known whether the babies born to these mothers have any negative consequences from COVID-19. Additional potential unknown is that other confounders cannot be taken into account. However, registry data can provide a reflection of the real-world medical situations faced by patients and clinicians. In addressing the main question of how pregnant and postpartum women with MS fare upon being infected with SARS-CoV-2, we used a control population from within the same registry that was propensity-matched 2:1 to the population of interest, based on identified factors influencing COVID-19 outcomes, which mitigated some limitations.

In summary, the data from this study provide some reassurance that MS patients are not at higher risk for poor COVID-19 outcomes when pregnant or postpartum. Longitudinal studies are needed to fully assess the lasting impact of COVID-19 in special populations and the possible downstream effect on children born to mothers who had COVID-19 during pregnancy.

Declaration of Competing Interest

Dr Salter reports honoraria for consulting for Gryphon Bio, LLC and research funding from Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, CMSC and the US Department of Defense. She is a member of the Editorial Board for Neurology. Dr. Salter is a member of the Data and Safety Monitoring Board for Premature Infants Receiving Milking or Delayed Cord Clamping (PREMOD2), Central Vein Sign: A Diagnostic Biomarker in Multiple Sclerosis (CAVS-MS), and Ocrelizumab for Preventing Clinical Multiple Sclerosis in Individuals With Radiologically Isolated Disease (CELLO).

Dr Cross reports consultant fees for scientific advisory boards from Biogen, Celgene, EMD Serono, Genentech, Greenwich Biosciences, Horizon, Janssen, Novartis, and TG Therapeutics outside the submitted work; grants from EMD Serono and Genentech outside the submitted work; and is secretary of the Consortium of Multiple Sclerosis Centers Board of Governors (an elected position), which is a supporter of the COVID-19 Infections in MS Registry, along with National Multiple Sclerosis Society (US) and MS Society of Canada.

Dr Cutter reports personal fees for Consulting or Advisory Boards for: Alexion, Antisense Therapeutics, Biogen, Clinical Trial Solutions LLC, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein-Buendel Incorporated, Merck/Serono, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Protalix Biotherapeutics, Recursion/Cerexis Pharmaceuticals, Regeneron, Roche, SAB Biotherapeutics, and for serving on the Data and Safety Monitoring Boards: AMO Pharma, AstraZeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green Valley Pharma, Horizon Pharmaceuticals, Immunic, Mapi Pharmaceuticals LTD, Merck, Mitsubishi Tanabe Pharma Holdings, Opko Biologics,Prothena Biosciences, Novartis, Regeneron, Sanofi-Aventis, Reata Pharmaceuticals, NHLBI (Protocol Review Committee), University of Texas Southwestern, University of Pennsylvania, Visioneering Technologies, Inc. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

Dr Fox reports personal fees from AB Science, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Greenwich Biosciences, Immunic, Janssen, Novartis, Sanofi, and TG Therapeutics. Dr. Fox has served on advisory committees for AB Science, Biogen, Genzyme, Immunic, Janssen, Novartis, Sanofi, and TG Therapeutics, and received clinical trial contract and research grant funding from Biogen, Novartis, and Sanofi.

Dr Li reports personal fees from Biogen and personal fees from Sanofi Genzyme; grants from Sanofi Genzyme, Roche, Novartis, and MS Society of Canada; is emeritus director of the University of British Columbia Multiple Sclerosis/ Magnetic Resonance Imaging Research Group, which

Table 1
A. Patient characteristics.

	All			Propensity Score matched cohorts	
	Pregnant	Postpartum	*p*-value	Pregnant/ Postpartum*	Comparator Cohort
	(*N* = 27)	(*N* = 9)		(*N* = 31)	(*N* = 62)
Age*	32.2(4.1)	44.6(11.3)	*<0.001*[a]	35.6(9.0)	35.8(9.9)
Race			0.66[d]		
Non-Hispanic White	13(48.1)	6(66.7)		16(51.6)	32(51.6)
Black or African American	6(22.2)	0(0.0)		5(16.1)	14(22.6)
Hispanic or Latino	2(7.4)	1(11.1)		3(9.7)	4(6.5)
Other	3(11.1)	1(11.1)		3(9.7)	4(6.5)
Unknown	3(11.1)	1(11.1)		4(12.9)	8(12.9)
Disease Duration*	5.9(4.0)	10.3(7.5)	*0.031*[a]	7.0(5.3)	7.8(6.0)
MS or Other Demyelinating Disease Type			0.99[d]		
CIS	1(3.7)	0(0.0)		1(3.2)	0(0.0)
Confirmed MS	26(96.3)	9(100.0)		30(96.8)	62(100.0)
Ambulatory Status*			–		
Fully ambulatory	26 (100.0)	9(100.0)		31(100.0)	62(100.0)
DMT at Time of COVID-19 (collapsed)			0.27[c]		
Anti CD20	8(29.6)	1(11.1)		6(19.4)	11(17.7)
Other/None	19(70.4)	8(88.9)		25(80.6)	51(82.3)
Have comorbidities?			0.54[d]		
No	20(74.1)	5(55.6)		24(77.4)	42(67.7)
Yes	6(22.2)	4(44.4)		7(22.6)	19(30.6)
Unknown	1(3.7)	0(0.0)		0(0.0)	1(1.6)
Cancer	1(3.7)	0(0.0)	0.99[d]	0(0.0)	1(1.6)
Cardiovascular disease	0(0.0)	0(0.0)	–	0(0.0)	0(0.0)
Cerebrovascular disease	0(0.0)	0(0.0)	–	0(0.0)	0(0.0)
Chronic kidney disease	0(0.0)	0(0.0)	–	0(0.0)	0(0.0)
Chronic liver disease	0(0.0)	0(0.0)	–	0(0.0)	0(0.0)
Chronic lung disease	2(7.4)	1(11.1)	0.99[d]	2(6.5)	6(9.7)
Chronic neurological disease	2(7.4)	0(0.0)	0.99[d]	1(3.2)	1(1.6)
Diabetes	1(3.7)	0(0.0)	0.99[d]	1(3.2)	1(1.6)
Hypertension	1(3.7)	2(22.2)	0.15[d]	3(9.7)	4(6.5)
Immunodeficiency disease	0(0.0)	0(0.0)	–	0(0.0)	1(1.6)
Morbid obesity	0(0.0)	1(11.1)	0.25[d]	1(3.2)	0(0.0)
Other	2(7.4)	0(0.0)	0.99[d]	0(0.0)	9(14.5)
Year of COVID-19 Diagnosis*			0.33[d]		
2020	15(60.0)	7(77.8)		19(61.3)	36(58.1)
2021	9(36.0)	1(11.1)		10(32.3)	24(38.7)
2022	1(4.0)	1(11.1)		2(6.5)	2(3.2)
Received COVID Vaccine			0.63[d]		
No	5(18.5)	0(0.0)		5(16.1)	8(12.9)
Yes	4(14.8)	2(22.2)		6(19.4)	11(17.7)
Unknown	1(3.7)	0(0.0)		0(0.0)	0(0.0)
Not Asked/Unavailable	17(63.0)	7(77.8)		20(64.5)	43(69.4)

*Five pregnant/postpartum patients could not be propensity score matched. ValuespresentedasMean(SD),Median[P25,P75]orN(column%). *p*-values:*a*=ANOVA,*b*=Kruskal-Wallistest, *c*=Pearson'schi-squaretest,*d*=Fisher'sExacttest.

Table 1. B: Clinical outcomes.

	All			Propensity Score Matched cohorts		
	Pregnant	Postpartum	*p*-value	Pregnant/ Postpartum*	Comparator Cohort	*p*-value
	(*N* = 27)	(*N* = 9)		(*N* = 31)	(*N* = 62)	
Symptoms: Fever	8(29.6)	6(66.7)	*0.048*[c]	14(45.2)	20(32.3)	0.18[b]
Symptoms: Dry cough	10(37.0)	3(33.3)	0.84[c]	13(41.9)	20(32.3)	0.41[b]
Symptoms: Fatigue	5(18.5)	6(66.7)	*0.007*[c]	11(35.5)	28(45.2)	0.34[b]
Symptoms: Pain (joint, bone, muscle)	5(18.5)	5(55.6)	*0.032*[c]	10(32.3)	16(25.8)	0.58[b]
Symptoms: Sore throat	3(11.1)	4(44.4)	*0.029*[c]	7(22.6)	16(25.8)	0.85[b]
Symptoms: Shortness of breath	4(14.8)	3(33.3)	0.22[c]	7(22.6)	15(24.2)	0.99[b]
Symptoms: Ageusia (loss of taste)	4(14.8)	4(44.4)	0.064[c]	8(25.8)	20(32.3)	0.58[b]
Symptoms: Anosmia (loss of smell)	7(25.9)	5(55.6)	0.10[c]	12(38.7)	23(37.1)	0.99[b]
Symptoms: Headache	9(33.3)	6(66.7)	0.079[c]	14(45.2)	28(45.2)	0.99[b]
Symptoms: Asymptomatic	2(7.4)	0(0.0)	0.99[d]	1(3.2)	3(4.8)	0.99[b]
COVID Treatment: Monoclonal antibodies	2(7.4)	0(0.0)	0.99[d]	2(6.5)	5(8.1)	0.99[b]
Pneumonia	0(0.0)	1(11.1)	0.25[d]	1(3.2)	1(1.6)	
Clinical Severity Outcome			0.44[d]			0.99[a]
Not hospitalized	26(96.3)	8(88.9)		29(93.5)	58(93.5)	
Hospitalization only	1(3.7)	0(0.0)		1(3.2)	2(3.2)	
Hospitalization and/or ICU/Ventilation	0(0.0)	1(11.1)		1(3.2)	1(1.6)	
Death	0(0.0)	0(0.0)		0(0.0)	1(1.6)	
Clinical Severity Outcome (Dichotomized)			0.44[d]			0.99[b]
Not hospitalized	26(96.3)	8(88.9)		29(93.5)	58(93.5)	
Hospitalization, ICU/Ventilation and/or Death	1(3.7)	1(11.1)		2(6.5)	4(6.5)	

*Five pregnant/postpartum cases could not be propensity score matched.
ValuespresentedasN(column%). *p*-values:*a*=Wilcoxon sign rank test,*b*=McNemar's test.
ICU=Intensive Care Unit

has been contracted to perform central analysis of magnetic resonance imaging scans for therapeutic trials with Roche and SanofiGenzyme and has received grant support for investigator-initiated studies from Sanofi Genzyme, Novartis, and Roche; and has served on the Progressive Multifocal Leukoencephalopathy– Multiple Sclerosis Steering Committee for Biogen and given lectures, supported by nonrestricted education grants from Academy of Healthcare Learning, Biogen, Consortium of Multiple Sclerosis Centers, and Sanofi Genzyme outside the submitted work.

June Halper reports that she is a member of the steering committee of MS Link, a research interest group supported by EMD Serono.

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Dr. Scott Newsome reports consultant fees for scientific advisory boards from Biogen, Genentech, Bristol Myers Squibb,EMD Serono, Greenwich Biosciences, Novartis, Horizon Therapeutics, is an advisor for Autobahn, is the study lead PI for a Roche clinical trial, was a clinical trial adjudication committee member for a MedDay Pharmaceuticals, and has received research funding (paid directly to institution) from Biogen, Roche, Genentech, National Multiple Sclerosis Society, US Department of Defense, and Patient Centered Outcomes Institute.

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The National Multiple Sclerosis Society was involved in the design and conduct of the study; collection, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

Dr Amber Salter had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Amber Salter, Anne H. Cross, Gary R. Cutter, Robert J. Fox, David K.B. Li, Kottil Rammohan, Scott D. Newsome**: Concept and design. **Amber Salter, Robert J. Fox, Scott D. Newsome, June Halper, David K.B. Li, Pamela Kanellis, Bruce Bebo, Kottil Rammohan, Gary R. Cutter, Anne H. Cross:** Acquisition, analysis, or interpretation of data. **Amber Salter, Anne H. Cross, Scott D. Newsome:** Drafting of the manuscript. **Robert J. Fox, Gary R. Cutter, David K.B. Li, Kottil Rammohan, Bruce Bebo, June Halper, Pamela Kanellis:** Critical revision of the manuscript for important intellectual content.**Amber Salter:** Statistical analysis. **Bruce Bebo:** Obtained funding. **Amber Salter, David K.B. Li, Pamela Kanellis, Bruce Bebo, Kottil Rammohan, Gary R. Cutter, Anne H. Cross:** Administrative, technical, or material support.

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