Title

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Journal

Multiple Sclerosis Journal - Experimental Translational and Clinical, 8(2)

ISSN

2055-2173

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Publication Date

2022-04-01

DOI

10.1177/20552173221104918

Peer reviewed

MSJ Experimental Translational Clinical

Original Research Article

Peripartum disease activity in moderately and severely disabled women with multiple sclerosis

Multiple Sclerosis Journal—Experimental, Translational and Clinical

April–June 2022, 1–13

DOI: 10.1177/20552173221104918

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Abstract

Background: The effects of pregnancy on multiple sclerosis (MS) inflammatory activity are not well described in women with moderate to severe disabilities.

Objective: To quantify the peripartum annualized relapse rate (ARR) in women with MS with an Expanded Disability Status Scale (EDSS) ≥ 3.

Methods: We performed a retrospective cohort study of 85 pregnancies in 74 subjects with preconception EDSS ≥ 3. We quantified peripartum ARR and tested for risk factors predictive of peripartum relapses, postpartum brain magnetic resonance imaging activity (new T2 or gadolinium-enhancing lesions), and disability worsening.

Results: There were 74 live births, with a 56% operative delivery rate. In subjects with relapsing-remitting MS, ARR decreased to 0.11 during the third trimester of pregnancy compared to 0.59 in the year preconception and increased to 1.22 in the 3 months postpartum. Women with a higher preconception EDSS had higher odds of postpartum relapses and clinically significant worsening of disability as compared to subjects with a lower EDSS.

Conclusions: Moderately to severely disabled women with MS have a lower risk of relapse during pregnancy as compared to preconception, followed by a marked increase postpartum. Further studies are needed to identify ways to reduce peripartum inflammatory activity and disability progression in women with MS with moderate to severe disability.

Keywords: Multiple sclerosis, relapsing-remitting multiple sclerosis, pregnancy, postpartum period, disease progression, breastfeeding

Date received: 7 October 2021; accepted: 16 May 2022

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disorder in which autoimmune destruction of myelin in the brain, optic nerves, and spinal cord causes episodic neurologic symptoms and/or progressive neurologic disability. Given that a large proportion of patients with MS are women of childbearing age, it is essential that patients and clinicians understand how MS is affected by pregnancy, and conversely, how pregnancy and breastfeeding can modify the course of the disease. Prior studies have demonstrated that most women with MS can safely become pregnant, give birth, and breastfeed their children, and can expect a reduced relapse rate during pregnancy as compared to the year preconception, followed by an elevated risk of relapse in the 3–6 months postpartum.[1–3] While available evidence suggests that higher preconception disability as measured on the Expanded Disability Status Scale (EDSS) is predictive of postpartum relapses,[4,5] the majority of pregnancies reported to date have occurred in women with no or minimal disability.[1,2,6–12] Limited data exist to guide peripartum counseling and management of women with MS with moderate (EDSS 3.0–5.5) or severe (EDSS ≥ 6) disability.

The dearth of studies focused on pregnancy in disabled women with MS may be related to the slow

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pace of disability progression in most patients, and specifically in younger women. The small number of reported pregnancies in moderately to severely disabled women with MS may also reflect altered clinical counseling and decision-making, where women with higher disabilities are counseled against or opt not to have children.[13] We established an international, multicenter collaboration to report on this understudied population. Our objective was to quantify peripartum annualized relapse rates (ARR) in a retrospective cohort of women with MS with EDSS ≥ 3, to describe any adverse obstetrical or neonatal outcomes, and to identify risk factors associated with peripartum relapses, magnetic resonance imaging (MRI) activity (new T2 and/or gadolinium-enhancing [Gd+] lesions) and disability progression. We hypothesized that, similar to less disabled women, moderately to severely disabled women with MS would experience decreased relapses during pregnancy as compared to the year preconception, followed by an increased ARR postpartum.

Materials and methods

Study design and setting

This was an observational, retrospective cohort study using prospectively collected data at six tertiary care MS centers in the United States, Canada, and the United Kingdom. Female patients with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) with preconception EDSS ≥ 3 who became pregnant between 1 January 2000 and 1 May 2021 were included. Data were collected by investigators at each site using a standardized data entry form, and de-identified prior to secure transfer to the primary site, Brigham and Women's Hospital (BWH).

Participants

Electronic medical record (EMR) and database screening to identify potential subjects meeting the inclusion criteria were performed at each site by co-investigators. At BWH, a database containing prospectively collected clinical and imaging data from all visits to the Brigham MS Center was queried for patients with a diagnosis of MS in which at least one visit in the year 2000 or later was characterized by both pregnancy and EDSS ≥ 3. The subjects from the University of California, San Francisco (UCSF) were a subset of a previously described cohort of patients with MS or clinically isolated syndrome who became pregnant between 2005 and 2018.[12] The original cohort included 155 pregnancies in 119 women followed at the UCSF MS and Neuroinflammation Center with prospectively recorded clinical data. These pregnancies were manually screened to identify cases with preconception EDSS ≥ 3 and a diagnosis of MS, all of which were included in the current study. At the Queen Mary University of London, an internal database containing pregnancies occurring in women with MS dating back to the year 2007 was queried to find all subjects with EDSS ≥ 3 in the year prior to pregnancy. At Northwestern University and the University of Pennsylvania, the EMR was queried for patients who were female and had billing diagnosis codes of both pregnancy and multiple sclerosis at the same visit. Records were then manually searched to find pregnancies with preconception EDSS ≥ 3. Due to EMR limitations at both sites, the EMR query could only find records dating back through 2016. At the University of Toronto, an internal database containing clinical information from every patient visit performed at the MS center was queried for patients who had at least one visit in the year 2000 or later with EDSS ≥ 3 and a documented pregnancy at the same or a subsequent visit. To try to ensure complete case ascertainment, co-investigators at each site (co-authors on this manuscript) were also asked to query their personal patient databases for women who experienced pregnancy in the year 2000 or later with preconception EDSS ≥ 3.

We included patients with a diagnosis of RRMS or SPMS, as defined by the diagnostic criteria at the time care was provided.[14–16] One patient with a documented diagnosis of progressive relapsing MS at the time of pregnancy was re-classified into the SPMS cohort for this study after chart review by an MS expert neurologist.[17] We excluded patients with known positive anti-aquaporin-4 or anti-MOG antibodies (removes patients with neuromyelitis optica spectrum disorders [NMOSD] and MOG antibody disease [MOGAD], respectively). The initial queries returned 163 potential subjects total between all institutions. Records were then manually screened to confirm preconception EDSS ≥ 3, absence of exclusion criteria, and presence of the minimal data set (see *Data Collection*). All eligible subjects meeting these criteria were included in the current cohort.

Standard protocol approvals, registrations, and patient consents

The primary study site for collation of de-identified patient data and for statistical analysis was BWH in Boston, Massachusetts. The Mass General Brigham Institutional Review Board (IRB) approved the retrospective analysis of EMR-derived data (Protocol

#2020P003964). Each contributing site received local ethical board approval. This study was exempt for the requirement of participant consent at all sites.

Data collection

MS clinical data were extracted from the EMR and research databases by co-investigators at each site. The minimal data set required for inclusion in this study was: diagnosis, age at conception, EDSS and disease duration at conception, and pregnancy outcome (live birth, elective termination, miscarriage, or stillbirth). When EDSS was not explicitly included in the medical record, this was extrapolated by an MS expert neurologist if sufficient data were available in the treating neurologist's note regarding the neurologic examination, relevant symptoms, and ambulatory abilities. Additional data collected when available included relapse occurrence and timing with respect to conception in the interval between 12 months preconception and 12 months after pregnancy end, peripartum MRI activity (new T2-hyperintense and/or Gd + enhancing lesions), peripartum DMT use, and EDSS scores in the year preconception and year postpartum. Clinical relapses were defined as new or worsening neurologic symptoms lasting at least 24 h, at least 1 month after a prior relapse, in the absence of fever or infection, and without other explanation, as diagnosed and documented in the EMR and/or research database by the treating neurologist. Neuroradiology reports and clinicians' notes regarding brain MRIs were reviewed for the presence of new T2-hyperintense lesions and Gd + lesions (when contrast was administered). Treatments, risk factors, and outcomes were verified in both the EMR and research database where available.

Obstetrical data extracted from the EMR included medical complications during pregnancy or delivery, abnormalities identified on fetal ultrasound, gestational age at pregnancy end, and delivery method. Neonatal outcome measures were recorded when available in delivery notes and included Apgar scores, birth weight, and any information on dysmorphisms or medical complications in the baby at birth. Breastfeeding status (exclusive, nonexclusive, or none) and duration were recorded, and breastfeeding was assumed to be nonexclusive unless notes explicitly indicated exclusive breastfeeding.

Outcomes

The primary outcome was the ARR in patients with RRMS during each time interval during and after pregnancy as compared to the 12 months prior to conception. Time intervals consisted of each trimester during pregnancy, 1–3 months postpartum, 4–6 months postpartum, and 7–12 months postpartum. Secondary outcomes included a comparison of preconception and postpartum brain MRI activity, and an analysis of predictors of intra- and postpartum relapses, postpartum brain MRI activity, and worsening of disability. An "active" MRI was defined as an MRI with new T2-hyperintense and/or Gd + lesions within the time frame of interest. To measure the accumulation of disability, we assessed if patients experienced a clinically meaningful worsening in EDSS from preconception baseline to first available post-delivery EDSS and to EDSS closest to 12 months after delivery. Preconception EDSS was defined as the EDSS at the visit closest to but not after the calculated date of conception. A clinically meaningful worsening was defined as a 1.0-point increase for baseline score 3.0–5.5, and a 0.5-point increase for baseline score ≥ 6.

Risk factors for outcomes

Several potential risk factors for each of the outcomes were investigated, including preconception EDSS, moderate (EDSS 3–5.5) versus severe (EDSS ≥ 6) disability preconception, relapses and MRI activity in the year prior to pregnancy, relapses during pregnancy, and breastfeeding status (the presence of either nonexclusive or exclusive breastfeeding for at least 3 months). We also evaluated treatment factors including DMT initiation within 3 months postpartum and use of B cell depleting therapies (ocrelizumab or rituximab). Cessation of natalizumab or fingolimod can lead to rebound relapses within several months, and recent studies have suggested that pregnancy does not protect against this risk.[18–20] We, therefore, evaluated intra- and postpartum relapse activity in pregnancies where natalizumab or fingolimod was stopped between 3 months preconception and the end of the first trimester of pregnancy, termed "periconception natalizumab cessation" (PNC) and "periconception fingolimod cessation" (PFC).

Statistical analyses

Descriptive statistics were reported with mean and standard deviation (SD), median, and range, or frequency, as appropriate. We evaluated clinical relapses and MRI activity in patients with RRMS only, given that these indicators of inflammatory disease activity are not as common or clinically relevant in patients with progressive MS.[21,22] Disability progression was analyzed in the entire cohort.

We assessed the primary outcome by comparing ARR in each time interval using a mixed-effects Poisson regression model with a time offset, random person-

specific relapse rate, and robust standard errors. We also compared MRI activity before conception to postpartum. For this analysis, we calculated the proportion of active MRIs in the 12 months preconception and compared this to the 12 months postpartum. Comparisons of paired data based on McNemar's test used only pregnancies with MRIs available in both time periods. To estimate the association between the predictors and each of the outcomes, we used a logistic regression model with each dichotomous outcome and each predictor separately. To fully investigate the impact of severe disability on postpartum outcomes, EDSS score and dichotomized EDSS (< 6 vs. ≥ 6) were each considered as potential predictors.

Alpha was set at 0.05, and all tests were two sided. Where subjects did not have data available regarding a particular exposure or outcome of interest, we excluded those subjects from the relevant analysis. We reported the total number of subjects (N) with relevant data available for each analysis. The mixed-effects Poisson regression was performed in Stata version 17 (College Station, TX). All other analyses were performed with RStudio. Given the exploratory nature of the secondary analyses, we did not adjust for multiple comparisons.

Results

Participants

An initial screen of each EMR or database revealed a total of 163 potential subjects, out of which 89 were excluded after a detailed chart review due to not meeting inclusion criteria or lack of availability of the minimal data set (Figure S1). Seventy-four subjects with 85 pregnancies were confirmed eligible based on the criteria above and all were included in the study. Median EDSS at conception was four and most subjects (90%) had a diagnosis of RRMS (Table 1). Peripartum DMT use patterns were available in 79 pregnancies (Table 2).

Birth outcomes

Pregnancy and neonatal outcomes, including miscarriage rate and gestational age at delivery, were similar to those of the general population (Table 3). Assisted reproductive technology (ART), defined as intrauterine insemination or in vitro fertilization, was used in 10% of pregnancies with available information. We observed that 56% of live births resulted from operative deliveries (assisted vaginal or cesarean section). Limited data were available on fetal complications and birth defects. One baby was born small for gestational age (2130 g, 0.3 percentile) with a cardiac defect (atrioventricular canal) to a woman with SPMS who had been receiving cyclophosphamide and IV steroids every 2 months through the end of the first trimester. The pregnancy had been unplanned and was not reported to providers until the second trimester. There were no other reported birth defects in babies who were exposed to DMTs during pregnancy or in the 6 months prior to pregnancy. There was a high rate of breastfeeding (78% of cases with available data), with an average breastfeeding length of 5.5 months (Table 3). As limited data regarding exclusivity of breastfeeding were available, exclusive and nonexclusive breastfeeding were grouped together into "any breastfeeding." Preconception EDSS was not predictive of breastfeeding occurrence ($p = 0.7$, median difference in EDSS for subjects who did and did not breastfeed = 0, 95% CI −0.5–1.0, Wilcoxon rank-sum test).

Peripartum inflammatory activity

We evaluated relapse activity in subjects with RRMS, which included 77 pregnancies in 67 subjects. Preconception ARR was 0.59; relapses decreased during pregnancy and were lowest during the first (ARR = 0.15) and third (ARR = 0.11) trimesters (Figure 1 and Table S1). We assessed for predictors of relapses during pregnancy and found that preconception EDSS, relapses in the year preconception, and MRI activity in the year preconception were not significantly associated with intrapartum relapses. Postpartum, relapses increased markedly with ARR = 1.22 during the 3 months after delivery. In months 4–6 postpartum, the ARR declined to 0.33, which was not significantly different than pre-pregnancy.

We assessed MRI activity in the year preconception and the year postpartum in patients with RRMS. In the year before pregnancy, 32% (12/37) of subjects had new T2 lesions, 26% (10/38) had Gd + lesions, and 35% (14/40) had either new T2 or Gd + lesions. In the year postpartum, 51% (28/55) had new T2 lesions, 40% (17/43) had Gd + lesions, and 56% (31/55) had either new T2 or Gd + lesions. There were only 31 subjects with RRMS with available information on MRI scans in both intervals, of whom 12 (39%) had pre-pregnancy MRI activity and 15 (48%) had postpartum MRI activity (OR = 2.5, 95% CI 0.4–26.3, p = 0.43, McNemar's test). These 31 subjects did not differ significantly in baseline characteristics from the entire cohort of subjects with RRMS, although they received more frequent MRI scans (Table S2). Thus, while limited data were available, we did not observe a statistically

Table 1. Characteristics of the study cohort.

Characteristics of the study cohort	
Before conception	
No. of subjects	74
No. of pregnancies	85
Diagnosis, no. of pregnancies (no. of subjects)	
Relapsing remitting (RRMS)	77 (67)
Secondary progressive MS (SPMS)	8 (7)
Disease duration at conception, mean years (SD)	9.2 (5.9)
Race, no. of pregnancies (no. of subjects)	
Asian	6 (5)
Black	12 (12)
Hispanic	6 (3)
White	39 (32)
Other	2 (2)
Unknown	20 (20)
No. of pregnancies contributed by each subject	
1	66
2	6
3	1
4	1
Age at conception, mean years (SD)	33 (5)
EDSS at conception, by pregnancy	
Median (range)	4 (3–7)
No. of moderate disability (3–5.5)	57
No. of severe disability (≥ 6)	28
EDSS change over the year prior to conception, by pregnancy	
EDSS improved or unchanged, no.	42
EDSS significantly worsened, no.	12
Unavailable EDSS one year preconception, no.	31
Use of assisted reproductive technology, no. pregnancies	
Yes	7
No	60
Unknown	18

significant difference in MRI activity postpartum as compared to preconception when comparing within subjects in our cohort. Of note, for subjects categorized as having SPMS, zero of seven with available information experienced clinical relapses during or after pregnancy, and one of the three with available scans had evidence of postpartum MRI activity.

Predictors of postpartum inflammatory activity

We tested for predictors of postpartum relapses in subjects with RRMS (Table 4). Relapses within the 3 months and 12 months postpartum were significantly more likely in subjects with a higher prepregnancy EDSS and in women who experienced intrapartum relapses. Conversely, the odds of having a relapse within 3 months postpartum were decreased in women who breastfed for at least 3 months as compared to women who did not breastfeed or who breastfed for less than 3 months. Use of ART, preconception relapses, and DMT resumption within 3 months of delivery were not significantly associated with postpartum relapses. We also more closely examined postpartum relapse activity in relation to timing of postpartum DMT initiation (Table S3). Out of 32 pregnancies followed by at least one relapse in the year postpartum, the first postpartum relapse preceded DMT initiation in 24 (75%) and followed DMT initiation in 8 (25%).

We assessed for predictors of postpartum MRI activity in subjects with RRMS (Table 4). The odds of having new postpartum MRI activity were elevated in patients who also had an active MRI in the year preconception. We found no association between

Table 2. Peripartum DMT uses in patients with moderate to severe disability.

Preconception DMT use, during pregnancy	
No DMT in the year prior to conception, *N* (%)	20 (24)
Stopped 6–12 months prior to conception, *N* (%)	4 (5)
Interferon-β's, *N*	1
Rituximab, *N*	2
Alemtuzumab, *N*	1
Stopped < 6 months prior to conception, *N* (%)	19 (22)
Interferon-β's, *N*	3
Glatiramer acetate, *N*	1
Dimethyl fumarate, *N*	1
Fingolimod, *N*	2
Daclizumab, *N*	1
Ocrelizumab, *N*	5
Rituximab, *N*	3
Natalizumab, *N*	3
Stopped at conception or during the first trimester, *N* (%)	31 (36)
Interferon-β's, *N*	6
Glatiramer acetate, *N*	7
Dimethyl fumarate, *N*	5
Fingolimod, *N*	4
Cyclophosphamide, *N*	1
Natalizumab, *N*	8
Stopped in the second trimester, *N* (%)	1 (1)
Glatiramer acetate, *N*	1
Continued throughout pregnancy, *N* (%)	4 (5)
Glatiramer acetate, *N*	4
Unknown timing of DMT relative to conception, *N* (%)	6 (7)
Peripartum DMT use in pregnancies with intrapartum relapses	
DMT used within 6 months preconception, *N*	11
Periconception natalizumab cessation (PNC), *N*	5
Dimethyl fumarate stopped at conception, *N*	1
Dimethyl fumarate stopped in the first trimester, *N*	1
Glatiramer acetate stopped at conception, *N*	1
Daclizumab stopped 2 months before conception, *N*	1
Interferon-β stopped at conception, *N*	2
No DMT was used within the 6 months preconception, *N*	4

postpartum MRI activity and relapses prior to or during pregnancy, breastfeeding status or early resumption of DMT after delivery.

Rebound relapse activity

We examined relapse activity in subjects with RRMS who had peripartum cessation of natalizumab (PNC) or fingolimod (PFC). Out of 10 PNC pregnancies with peripartum relapse data available, five (50%) had a relapse during pregnancy. PNC as compared to all other patterns of DMT use was predictive of intrapartum relapse in our cohort (OR = 5.3, 95% CI 1.3–21.8, $p = 0.01$, chi-squared test). There were 5 PNC pregnancies followed by at least one relapse within the 12 months postpartum; in two cases, the first postpartum relapse occurred after DMT initiation (one while on dimethyl fumarate, one while receiving natalizumab), while in three cases, the relapse occurred prior to DMT initiation. Out of the five PNC pregnancies followed by postpartum relapse, three were also preceded by at least one relapse in the year preconception.

Out of five PFC pregnancies, there were no intrapartum relapses; however, all five subjects had at least one relapse in the year postpartum, while five had

Table 3. Pregnancy outcomes and breastfeeding information.

Obstetrical outcomes		Pregnancies with available data
Pregnancy outcome		85
Live births, *N* (%)	74 (87)	
Spontaneous miscarriages, *N* (%)	6 (7)	
Elective termination, *N* (%)	5 (6)	
Stillbirths, *N* (%)	0 (0)	
Delivery methods		54
Spontaneous vaginal, *N* (%)	24 (44)	
Assisted vaginal, *N* (%)	6 (11)	
Cesarean section, *N* (%)	24 (44)	
Neonatal outcomes		
Gestational age at birth, mean weeks (SD)	39.0 (1.7)	65
Preterm (< 37 weeks gestation), *N* (%)	8 (11)	74
Birth weight, grams (mean ± SD)	3310 ± 628	35
Apgar scores		26
1 min, mean (SD)	8 (1.3)	
5 min, mean (SD)	9 (0.3)	
Breastfeeding information		
Pregnancies followed by any breastfeeding, *N* (%)	54 (78)	69
Length of breastfeeding, mean months (SD)	5.5 (4.4)	48

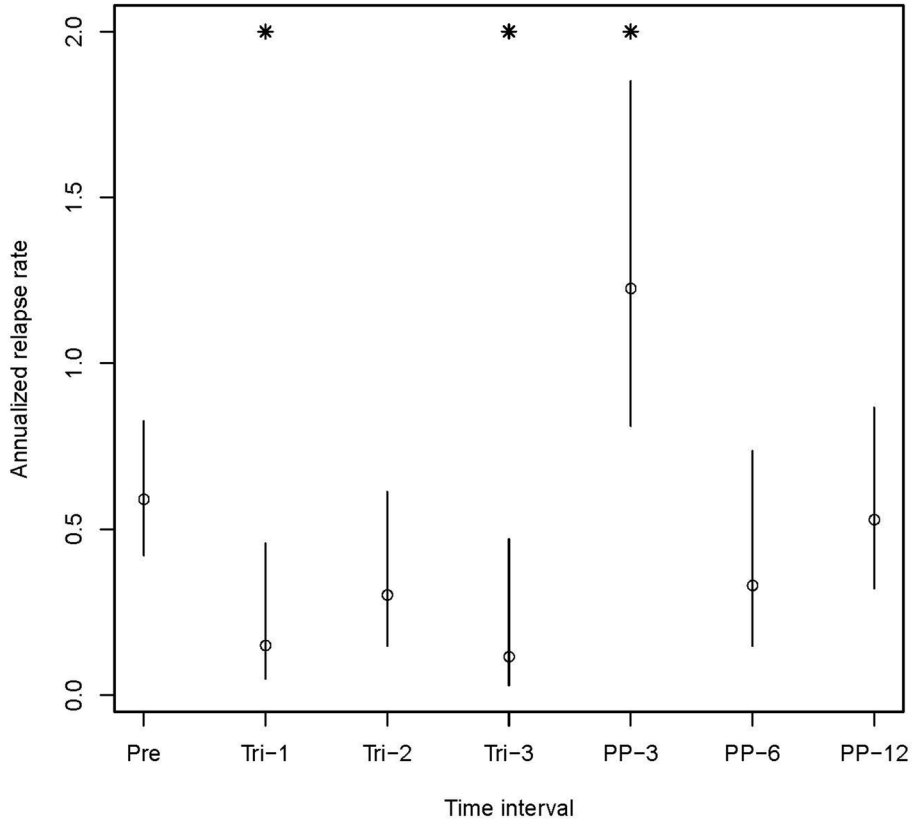

Figure 1. Peripartum annualized relapse rates. Compared to the year prior to pregnancy, a significant decrease in ARR was observed in trimesters 1 and 3 and a significant increase was observed in the first 3 months postpartum. Time intervals compared were: Pre (12 months preconception), Tri-1 (first trimester), Tri-2 (second trimester), Tri-3 (third trimester), PP-3 (months 1–3 postpartum), PP-6 (months 4–6 postpartum), and PP-12 (months 7–12 postpartum). *$p < 0.05$.

Table 4. Predictors of postpartum clinical and MRI activity.

	Relapses within 3 mo postpartum		Relapses within 12 mo postpartum		MRI activity in the 12 mo postpartum	
Predictor	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at conception	0.97 (0.88, 1.06)	$p = 0.480$ ($N = 68$)	0.94 (0.85, 1.03)	$p = 0.183$ ($N = 62$)	0.92 (0.82, 1.03)	$p = 0.143$ ($N = 55$)
Disease duration at conception	0.93 (0.84, 1.03)	$p = 0.184$ ($N = 66$)	0.91 (0.82, 1.01)	$p = 0.073$ ($N = 60$)	0.95 (0.86, 1.05)	$p = 0.321$ ($N = 55$)
Use of ART	1.11 (0.17, 7.3)	$p = 0.913$ ($N = 53$)	0.44 (0.07, 2.89)	$p = 0.389$ ($N = 48$)	0.45 (0.07, 2.76)	$p = 0.386$ ($N = 42$)
Relapses in the 1 year prior to conception	0.69 (0.24, 1.95)	0.480 ($N = 67$)	1.85 (0.67, 5.15)	$p = 0.236$ ($N = 61$)	1.25 (0.42, 3.7)	$p = 0.691$ ($N = 53$)
MRI activity on pre-conception MRI	1.08 (0.25, 4.70)	0.919 ($N = 37$)	1.91 (0.44, 8.35)	$p = 0.391$ ($N = 34$)	14 (2.25, 87.24)	$\mathbf{p = 0.005}$ ($N = 31$)
Relapses during pregnancy	3.34 (1.01, 11.02)	**0.048** ($N = 66$)	7.8 (1.56, 38.88)	$\mathbf{p = 0.012}$ ($N = 60$)	1.21 (0.33, 4.44)	$p = 0.775$ ($N = 53$)
Breastfed for at least 3 months postpartum	0.28 (0.08, 0.98)	**0.046** ($N = 55$)	0.67 (0.22, 2.03)	$p = 0.483$ ($N = 51$)	1.27 (0.38, 4.29)	$p = 0.697$ ($N = 43$)
Early resumption (within 3 m) of DMT after delivery	1.44 (0.48, 4.32)	0.518 ($N = 58$)	1.18 (0.40, 3.46)	$p = 0.761$ ($N = 54$)	1.3 (0.41, 4.16)	$p = 0.658$ ($N = 48$)
Higher disability (EDSS)	1.78 (1.16, 2.72)	**0.008** ($N = 68$)	1.84 (1.16, 2.92)	$\mathbf{p = 0.010}$ ($N = 62$)	0.74 (0.47, 1.17)	$p = 0.199$ ($N = 55$)

at least one relapse in the year preconception. In four of the PFC pregnancies, the first postpartum relapse occurred prior to DMT resumption. In the remaining pregnancy, a relapse occurred at 8 months postpartum despite restarting fingolimod at 6 weeks postpartum. Preconception EDSS scores were not significantly higher in the PFC ($p = 1$, median difference in EDSS for subjects in the PFC group compared to those with all other patterns of DMT use $= -0.0$, 95% CI -2.0–1.0, Wilcoxon rank-sum test) and PNC ($p = 0.23$, median difference in EDSS for subjects in PNC group compared to those with all other patterns of DMT use $= -0.50$, 95% CI -1.0–0.0, Wilcoxon rank-sum test) groups as compared to the cohort as a whole. Thus, the above effects were not related to confounding from differences in preconception disability.

Use of B cell depleting therapies

There were 10 subjects treated with B cell-depleting therapies (ocrelizumab or rituximab) in the year before pregnancy, with preconception EDSS scores ranging from 3 to 7 (Table 2). Subjects had been treated for an average of 10.6 months (range: 3–39) and had received an average of 1.9 (range: 1–5) total treatments prior to conception. Loading doses separated by 2 weeks or doses that were split due to a history of infusion reactions were counted as one treatment. Out of seven subjects who received their last infusion within 6 months of conception and had available relapse information, none had a relapse within the 6 months prior to conception or during pregnancy. One of the seven had a relapse during the year postpartum, which occurred 7 months after delivery, before restarting DMT; the subject had previously received only one treatment with rituximab 3 months prior to conception. There were two subjects who received their last infusion between 6 and 12 months prior to conception and had relapse data available. Neither had relapses during the 6 months prior to conception, while one experienced one relapse during her second trimester of pregnancy and four relapses within the year postpartum, prior to restarting DMT. That subject had received only one treatment with rituximab given 9 months prior to conception. No patients who were started on B cell-depleting therapies after pregnancy experienced a relapse within the year postpartum after DMT initiation (Table S3).

Disability progression

We assessed disability progression in subjects with relapsing or progressive MS (Table S4). Median EDSS for the entire cohort at the first postpartum visit was 4, range: 0–8. Out of 76 pregnancies with available

Table 5. Predictors of postpartum disability worsening.

	Worse EDSS immediately postpartum		Worse EDSS 12mo postpartum	
Predictor	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age	1.08 (0.96, 1.21)	0.191 (N=77)	1.03 (0.92, 1.16)	0.600 (N=61)
Disease duration	0.98 (0.89, 1.09)	0.777 (N=75)	1.03 (0.92, 1.16)	0.635 (N=59)
Use of ART	2.93 (0.57, 15.07)	0.198 (N=61)	3.4 (0.42, 27.29)	0.250 (N=48)
Higher pre-pregnancy disability (EDSS)	2.16 (1.32-3.55)	**0.002** (N=77)	2.00 (1.20-3.34)	**0.008** (N=61)
Significant disability progression in year pre-conception	1.52 (0.33-7.12)	0.592 (N=51)	1.00 (0.17-5.98)	1 (N=40)
Relapses during pregnancy	10.10 (2.70-37.78)	**0.001** (N=74)	4.08 (1.01-16.56)	**0.049** (N=59)
MRI activity in the year postpartum	0.54 (0.14-2.07)	0.373 (N=54)	0.87 (0.20-3.85)	0.860 (N=43)
Early resumption (within 3m) of DMT after delivery	*NA*		1.75 (0.38-7.97)	0.469 (N=52)
Worse EDSS immediately postpartum	*NA*		22.5 (4.65-108.9)	**<0.001** (N=61)

information, 14 (18%) were characterized by a clinically significant worsening of EDSS at the first postpartum visit as compared to preconception. Median EDSS at the 12-month postpartum visit was 3.5, range of 1–8.5. Out of 61 pregnancies with available information, 12 (16%) showed a clinically significant worsening of EDSS at the 12-month visit as compared to preconception. We tested for predictors of postpartum disability progression (Table 5). A higher preconception EDSS and relapses during pregnancy were predictive of disability progression at both timepoints.

Comparison of subjects with moderate and severe disability

EDSS emerged as a predictor of postpartum relapses and persistent worsening of disability in the above analyses. We, therefore, assessed the expected course of peripartum disease activity in women with moderate (EDSS 3.0–5.5) as compared to severe (EDSS $\geq$ 6) preconception disability levels. We found that severely disabled women were more likely than the moderately disabled women to experience relapses in the 3 months (OR = 3.5, 95% CI = 1.2–10.7, $p = 0.023$, $N = 69$) and 12 months (OR = 3.3, 95% CI = 1.0–10.7, $p = 0.046$, $N = 63$) postpartum. We also found that women in the severely disabled group were more likely than moderately disabled women to have a clinically significant increase in disability at the first postpartum visit (OR = 8.6, 95% CI = 2.3–31.6, $p < 0.001$, $N = 76$) and at the 12-month postpartum visit (OR = 5.5, 95% CI = 1.4–21.5, $p = 0.009$, $N = 61$). Thus, subjects with preconception EDSS $\geq$ 6 had a higher risk of both postpartum relapses and disability progression than subjects with preconception EDSS 3.0–5.5.

Discussion

In our current retrospective multicenter cohort of women with MS with EDSS $\geq$ 3, we observed a significant reduction in relapses during pregnancy as compared to the year preconception, a large increase in relapses in the 3 months postpartum, and a subsequent return to baseline relapse activity. This pattern mirrors what has been described in less disabled women and establishes a framework for counseling this understudied patient population regarding expected peripartum disease course. The 95% confidence intervals of the preconception, intrapartum, and postpartum relapse rates in our cohort overlap

with previously reported peripartum relapse rates in less disabled cohorts.[1,2,5,9,12] Future studies that include patients across the disability spectrum are needed to directly assess whether the peripartum disease course differs in patients with moderate to severe disability as compared to patients with no or mild disability.

Here, we found that breastfeeding for at least 3 months was associated with reduced odds of postpartum relapses as compared to breastfeeding for less than 3 months or not at all. Acknowledging that our study excluded patients with minimal or no disability, we observed that preconception EDSS did not predict breastfeeding status, an encouraging finding when considering that women with disabilities are thought to breastfeed at lower rates than women without disabilities.[23] Our results are in line with multiple prior studies including a recent meta-analysis that found a significant reduction in postpartum relapses in the setting of breastfeeding,[12,24–28] although other studies have not reported this association.[1,3,29–31] Methodological issues with our study and prior studies include confounding effects of preconception disease activity and postpartum DMT recommendations on breastfeeding choices, as well as lack of granularity about whether breastfeeding is exclusive or partial. In the future, prospectively documenting breastfeeding status, recommendations provided by clinicians, and maternal decision-making factors would help generate higher quality data that could support the informed counseling of patients regarding a potential protective effect of breastfeeding. Furthermore, in the past, postpartum women with MS were typically advised to choose between breastfeeding their child and treating their MS with DMTs of optimal efficacy.[32] Additional studies are needed to address the risk to the infant of breastfeeding in the setting of concurrent DMT administration.

We observed that relapses during pregnancy did not significantly increase the odds of postpartum MRI activity. However, due to the small number of subjects, 15, with intrapartum relapses in our cohort, the power of this analysis was limited. MRI activity was not significantly increased postpartum as compared to preconception, a finding that must be interpreted with caution given the relatively high baseline level of MRI and clinical relapse activity in the year preconception in this cohort, and the limited number of pregnancies, 31, with available MRI scans in both time intervals.

We evaluated the impact of treatment factors on peripartum disease activity. We confirmed an association between natalizumab and fingolimod cessation and peripartum relapses, which was expected based on prior observations of rebound disease activity after cessation of these DMTs.[18–20] The lack of observed reduction in relapses or MRI activity after early DMT re-initiation postpartum should be interpreted with caution given the paucity of MRI data available and the heterogeneity in treatment strategies across multiple centers over a relatively long time period (2000–2021). We also did not have access to information regarding DMT adherence. Further, the structure of our dataset did not allow for assessment of the impact of bridging therapies with monthly steroid infusions or IVIG during breastfeeding, strategies used by many clinicians with some prior evidence of efficacy.[33–35] Acknowledging these limitations, there were very few cases, eight, of postpartum relapse after DMT initiation.

Additional limitations of this study include its retrospective nature and small sample size, which may reflect reduced pregnancy rates in moderately to severely disabled women with MS as compared to less disabled women. While we did not observe elevated rates of spontaneous abortions or adverse neonatal outcomes as compared to the general population, we may have missed events that were not reported to clinicians or documented in the medical record, such as early pregnancy losses or terminations. Relapses may also be underreported in a retrospective study. We attempted to avoid selection bias by including all eligible patients who met the inclusion criteria and minimal data set; however, the methods for subject identification varied at each institution, which may have impacted subject selection in unanticipated ways. Further, we were not able to confirm in all cases that patients had been tested for both NMOSD and MOGAD; these mimics may differ from MS in peripartum relapse risk and DMT response.

Regarding quantification of disease progression, EDSS was used to assess neurologic function over time, but this measure tends to place disproportionate weight on ambulation status. Subjects were included in the cohort based on preconception EDSS; however, it is possible that some subjects had experienced only temporary worsening of disability prior to inclusion in our study. It is also important to note that pregnancy even in the absence of MS is associated with significant stress on the body, and can affect measures that comprise

the EDSS, such as ambulation and bladder and bowel function. Our analysis of predictors of disability progression included patients with both relapsing and progressive MS, which is informed by an updated understanding of the prevalence of silent progression in MS, but complicates the application of the findings to either patient population alone.[36] Finally, the patients in our cohort were followed at tertiary care MS centers during pregnancy, and may not be representative of all MS patients, whether in terms of disability or DMT selection. It is unclear how generalizable our findings are to patients who do not receive the same level of subspecialty care.

Overall, our analyses demonstrate that in moderately to severely disabled women with MS, higher preconception disability is unfortunately associated with increased postpartum inflammatory activity and a higher risk of disability progression. Risk mitigation strategies should begin prior to pregnancy, and it is essential that clinicians ask all females with MS of childbearing age about future pregnancy plans at each visit. It would be reasonable to consider induction therapy for patients who are in the early stages of pregnancy planning.[37] In the setting of DMTs with a high risk of rebound relapses, clinicians could consider continuing natalizumab on an extended administration interval schedule throughout pregnancy,[38] or switching to a B cell-depleting therapy prior to conception.[39] Additional studies are needed to identify peripartum treatment strategies that are most likely to limit disease activity and progression in women with MS with moderate to severe disability.

Acknowledgements

We would like to thank Mariann and Adam Polgar, who manage the research database at the Brigham MS center, and Ashley Jones, the database manager for the MS Center at St Michael's Hospital.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: B. Healy has received research support from Analysis Group, Celgene (Bristol-Myers Squibb), Verily Life Sciences, Merck-Serono, Novartis and Genzyme; J. Oh has received consulting or speaking fees from Alexion, Biogen Idec, BMS, EMD Serono, Genzyme, Novartis, and Roche, and research support from Biogen Idec, EMD Serono, and Roche; D. Jacobs has received consulting honoraria from Biogen, Genentech, Novartis, EMD Serono, Banner Life Sciences, Bristol Myers Squibb, and Sanofi Genzyme, and research support from Biogen, Genentech, and UCLA; R. Dobson works within the PNU, which is funded by Barts Charity, receives grant support from the UK MS Society, BMA foundation, NIHR, MRC, Horne Family Charitable Trust, Biogen, Celgene, and Merck, and has received honoraria for advisory boards and/or educational activities from Biogen, Teva, Sanofi, Merck, Janssen, Novartis, and Roche; AD Sadovnick has research funding from Biogen MA Inc, travel funds from Biogen, and honoraria from Biogen and Momenta Pharma; "R. Bove is funded by a Harry Weaver Scholarship through the National Multiple Sclerosis Society, has received research supportfrom the National Multiple Sclerosis Society, the NIH, NSF, the Weill Innovation Fund, and the UCSF CTSI RAP program; as well as Biogen, Novartis and Roche Genentech, and consulting fees from Alexion, Biogen, EMD Serono, Genzyme Sanofi, Novartis, Roche Genentech and TG Therapeutics"; M. Houtchens served as a consultant for Roche, Novartis, Biogen, Sanofi Genzyme, and Greenwich Bioscience and has received research support from Sanofi Genzyme, Biogen, and Roche; E. Graham has served as a consultant for Roche and Novartis. B.E.L. Ostrem, A. Anderson, S. Conway, V. Zimmerman, and Y. Liu report no disclosures relevant to the manuscript.

Funding

B.E.L. Ostrem was supported by an NIH-NINDS R25 award (NS065743).

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Supplemental material

Supplemental material for this article is available online.

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