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Relapse activity during pregnancy and the postpartum year is associated with accelerated disability progression in multiple sclerosis

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ABSTRACT

Management of multiple sclerosis (MS) presents unique challenges during pregnancy, particularly regarding disease-modifying therapies (DMT) and the risk of postpartum relapses. We investigated DMT exposure and further clinical and radiological parameters to identify predictors of relapse and disability progression during pregnancy and the postpartum year. We identified 112 pregnancies in 70 women with MS followed between 2010 and 2023. After excluding pregnancies lasting <22 weeks, 96 pregnancies in 66 women, primarily with relapsing-remitting MS (RRMS), were included in the analysis. 77 pregnancies (80.2 %) developed during DMT exposure, with natalizumab, injectables, and fumarates being the most common. Relapse during pregnancy or the postpartum year occurred in 33 pregnancies, with 39.5 % happening during pregnancy and 60.5 % in the postpartum year, peaking in the first postpartum trimester. Women with pregnancies complicated by relapses during pregnancy or the postpartum year had lower rates of DMT exposure (66.7 % vs. 87.3 %, $p = 0.016$) and a non-significant trend toward higher baseline disability at conception. Disability progression within the first postpartum year was more frequent in the relapse group (25.8 % vs. 5.5 %, $p = 0.010$), with sustained differences in EDSS at two years postpartum. Postpartum MRI showed higher lesion load and more contrast-enhancing lesions in the relapse group. Spinal lesions at diagnosis and prior to conception were associated with significant higher risk of relapse during pregnancy and the postpartum year. Subgroup analysis of pregnant women treated with natalizumab indicated a lower relapse risk when natalizumab was continued into the third trimester. Pregnancy outcomes were mostly favorable, with 95.4 % term births and no significant differences in delivery mode or neonatal outcomes between women with versus without relapses during pregnancy.

Our findings emphasize the importance of DMT management, particularly the potential benefits of sustained natalizumab therapy for high-risk pregnancies. These results highlight the need for tailored treatment strategies to minimize postpartum relapses and long-term disability progression for women with MS.

Abbreviations

ARR	Annualized relapse rate
CIS	Clinically isolated syndrome
CSF	Cerebrospinal fluid
DMT	Disease-modifying therapy
EDSS	Expanded disability status scale
LMP	Last menstrual period
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
PIRA	Progression independent of relapse activity
PPMS	Primary-progressive multiple sclerosis
RAW	Relapse associated worsening
RRMS	Relapsing-remitting multiple sclerosis
SD	Standard deviation
SPMS	Secondary-progressive multiple sclerosis

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1. Introduction

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system (Walton et al., 2020). Women are more commonly affected than men, with diagnosis typically occurring during childbearing years. While fertility appears unaffected, live birth rates in women with MS are reduced (Houtchens, M.K. et al., 2020; Kopp et al., 2022). Reduced inflammatory activity during pregnancy may provide a protective effect (Confavreux et al., 1998; Langer-Gould et al., 2020). Pregnancy-induced immunological changes, including a shift toward an anti-inflammatory profile, have been proposed but remain incompletely understood (Sondergaard et al., 2020; Wisgalla et al., 2022). Postpartum rebound disease activity is common and poses a significant clinical challenge (Confavreux et al., 1998; Hellwig et al., 2009). Relapse rates during pregnancy and the postpartum year vary widely (14–66 %), peaking in the first three months postpartum (Confavreux et al., 1998; Hellwig et al., 2009, 2022, 2023). High disease activity before conception, younger age and withdrawal of treatment with natalizumab or fingolimod before or when conceiving pregnancy have been defined as independent risk factors for relapse during pregnancy (Bsteh et al., 2020; Yeh et al., 2024, 2021). Additionally, a higher preconception and intrapartum annualized relapse rate (ARR) and an Expanded Disability Status Scale (EDSS) score ≥ 2 are strong predictors of postpartum relapses (Yeh et al., 2021). Even in women without clinical relapses, postpartum MRI studies detected new lesions in up to 37 % of cases within the first postpartum year compared to the last MRI in the pre-pregnancy year (Anderson et al., 2021; Houtchens, M. et al., 2020). Relapses with incomplete recovery contribute to disease-associated disability, with relapse-associated worsening (RAW) reported in 6–10 % of pregnancies (Hellwig et al., 2022, 2023; Yeh et al., 2021). Given the significant impact of pregnancy and the postpartum period on disease activity, strategies to mitigate early postpartum relapses are crucial. For women with MS, general breastfeeding recommendations align with those for the general population. Importantly, exclusive breastfeeding has been associated with a reduced risk of early postpartum relapses, potentially serving as an additional protective factor during this high-risk period (Krysko et al., 2020; Langer-Gould et al., 2020; Yeh et al., 2021).

Over the past two decades, advances in disease-modifying therapies (DMT) have significantly improved the management of relapses in MS. However, most DMT, apart from interferons and glatiramer acetate, remain contraindicated during pregnancy and lactation due to insufficient data on fetal and neonatal safety from controlled, randomized studies. The limited efficacy of approved treatments and the lack of robust clinical guidelines make management particularly challenging for women with highly active MS, especially in light of the risk of rebound disease activity after the withdrawal of potent DMTs like fingolimod and natalizumab (Hellwig et al., 2022, 2023). This often results in treatment inertia during pregnancy, leaving both maternal and fetal health at risk (Saposnik et al., 2022).

Current treatment strategies for managing MS during pregnancy are largely shaped by clinical experience, resulting in considerable variability across centers and countries (Graber et al., 2024; Hemmer, et al. 2023; Krysko et al., 2023; Vukusic et al., 2023). This highlights the need for robust, systematic research to optimize approaches that balance effective disease control with the safety of both mother and child. The present study aims to fill critical gaps by investigating pregnancy outcomes and disease activity in women with MS treated at a tertiary care center. Specifically, it focuses on identifying predictors of relapse during pregnancy and the postpartum period, with particular emphasis on DMT exposure, and provides valuable insights into treatment strategies and contribute to a better understanding of the efficacy and safety profile of DMTs during pregnancy and lactation. By identifying relapse predictors and characterizing disease activity, the results have the potential to guide clinical decision making, reduce relapse-associated disability, and ultimately improve care for women with MS during and after pregnancy.

2. Methods

2.1. Study population

Pregnant women with MS according to the 2017 revised McDonald criteria or clinically isolated syndrome (CIS) were identified by screening longitudinal data collected during routine clinical visits in the Neuroimmunology outpatient clinic of the Department of Neurology, University Hospital Zurich, between 2010 and 2023. This study was approved by the Ethics Board of the Canton of Zurich (KEK-ZH—Nr. 2024-00239). Inclusion criteria were available follow-up data starting at least during the first trimester of pregnancy, with a minimum postpartum follow-up of 2 months. Further analysis of clinical and radiological disease activity during pregnancy and the postpartum period was performed on pregnancies with a minimum duration of 22 gestational weeks (Fig. 1).

2.2. Variables

Data collected during routine follow-up visits included clinical assessments, imaging data (MRI), laboratory parameters (blood and cerebrospinal fluid [CSF]), smoking history, and treatment-related data. Exposure to DMT was defined as follows: administration of interferons, glatiramer acetate or fumarates during pregnancy; fingolimod intake within 2 months prior to conception; natalizumab infusion within 3 months prior to conception; and alemtuzumab or CD20-depleting agent infusion within 4 months prior to conception. Exclusive breastfeeding was defined as breastfeeding for at least 2 months without the addition of regular formula.

2.3. Outcomes

Relapses were defined as the occurrence of a new neurological symptom or sign or the worsening of a preexisting symptom or sign, lasting at least 24 h, and occurring at least one month after the previous relapse (Thompson et al., 2018). Annualized relapse rates (ARR) were calculated for each trimester by dividing the number of relapses by the time period (in years) and the total number of pregnancies during that period for the pre-pregnancy year, the duration of pregnancy and the postpartum year. The first pregnancy trimester was defined as the time from the last menstrual period (LMP) up to 97 days, the second pregnancy trimester from day 98 to 194, and the third pregnancy trimester from day 195 to delivery (Pettker et al., 2017).

EDSS scores were recorded at several time points: at conception (up to 3 months before), at delivery (± 3 months), in the early postpartum period (3 - 6 months postpartum), and at 1 and 2 years postpartum (each

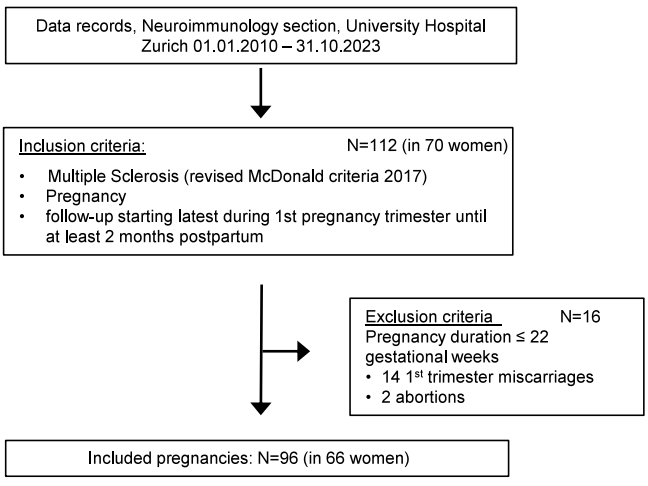

Fig. 1. Flowchart of patient selection with inclusion and exclusion criteria.

Table 1
Demographic and clinical characteristics.

	All, $N = 96$ (100.0)	Relapse, $N = 33$ (34.4)	No relapse, $N = 63$ (65.6)	p value
MS subtype				**0.049**
RRMS, n (%)	87 (90.6)	28 (84.8)	59 (93.7)	
SPMS, n (%)	7 (7.3)	5 (15.2)	2 (3.2)	
CIS, n (%)	2 (2.1)	0 (0.0)	2 (3.2)	
Age at conception (y), mean (SD)	32.39 (3.8)	32.06 (3.9)	32.52 (3.8)	0.572
Disease duration at conception (y), median (IQR)	5.25 (0;18)	6.00 (0;18)	5.00 (0.2;13.8)	0.434
Any relapse in year before pregnancy (%)	28 (29.2)	10 (30.3)	18 (28.6)	0.859
No° of relapse in 1 year pre-pregnancy, mean (SD)	0.36 (0.6)	0.39 (0.7)	0.35 (0.6)	0.782
No° of relapse in 2 years pre-pregnancy, mean (SD)	0.66 (0.9)	0.70 (0.9)	0.63 (0.9)	0.756
0, n (%)	53 (55.2)	18 (54.5)	35 (55.6)	0.589
1, n (%)	30 (31.3)	9 (27.3)	21 (33.3)	
≥2, n (%)	13 (13.5)	6 (18.2)	7 (11.1)	
Symptoms at conception				0.107
Visual, n (%)	6 (6.3)	0 (0.0)	6 (9.5)	
Sensory, n (%)	20 (20.8)	4 (12.1)	16 (25.4)	
Motor, n (%)	2 (2.1)	1 (3.0)	1 (1.6)	
Brain stem, n (%)	2 (2.1)	0 (0.0)	2 (3.2)	
Urinary, n (%)	1 (1.0)	0 (0.0)	1 (1.6)	
Multiple, n (%)	26 (27.1)	13 (39.4)	13 (20.6)	
None, n (%)	39 (40.6)	15 (45.5)	24 (38.1)	
Fatigue at conception				0.814
Yes, n (%)	32 (36.8)	11 (39.3)	21 (35.6)	
No, n (%)	55 (63.2)	17 (60.7)	38 (64.4)	
Information missing, n (%)	9 (9.4)	5 (15.2)	4 (6.3)	
EDSS at conception, median (IQR)	1 (0;4)	1.5 (0;4)	1 (0;3.5)	0.165
No disability (0–2)	80 (83.3)	25 (75.8)	55 (87.3)	0.219
Mild disability (2.5 - 3.5)	15 (15.6)	7 (21.2)	8 (12.7)	
Ambulatory impairment, no assist device (4.0 - 5.5)	1 (1.0)	1 (3.0)	0 (0.0)	
Cane required (6.0–6.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Wheelchair required (> 7.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Last DMT before conception:				0.426
None, n (%)	11 (11.5)	5 (15.2)	6 (9.5)	
Injectables, n (%)	26 (27.1)	8 (24.2)	18 (28.6)	
Fumarates, n (%)	23 (24.0)	7 (21.2)	16 (25.4)	
Alemtuzumab, n (%)	1 (1.0)	1 (3.0)	0 (0.0)	
Fingolimod, n (%)	1 (1.0)	1 (3.0)	0 (0.0)	
Natalizumab, n (%)	27 (28.1)	10 (30.3)	17 (27.0)	
B cell depleting therapy, n (%)	7 (7.3)	1 (3.0)	6 (9.5)	
Periconceptional DMT exposure				**0.016**
Exposed, n (%)	77 (80.2)	22 (66.7)	55 (87.3)	
Unexposed, n (%)	19 (19.8)	11 (33.3)	8 (12.7)	
Breastfeeding				0.532
Exclusively, n (%)	75 (85.2)	26 (89.7)	49 (83.1)	
No breastfeeding, n (%)	13 (14.8)	3 (10.3)	10 (17.0)	
Information missing, n (%)	8 (8.3)	4 (12.1)	4 (6.3)	
Duration of breastfeeding (m), median (IQR)	4 (2;18)	4 (2;15)	4 (2;18)	0.249

Abbreviations: MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; CIS = clinically isolated syndrome; SD = standard deviation; IQR = interquartile range;.
EDSS = expanded disability status scale; symptoms incl. fatigue and EDSS score were assessed at conception (≤ 3 months before); DMT = disease modifying therapy.

± 3 months).

Disability progression within the first postpartum year was assessed using the standard definition of a worsening of at least 1.5 EDSS points for baseline EDSS = 0, at least 1 point for baseline EDSS between 1.0 and 5.5, and at least 0.5 points for baseline EDSS ≥ 6.0.

MRI data were collected at diagnosis, in the time period of conception (up to 3 months before) and postpartum (within 6 months after delivery). An experienced neuroradiologist (N.N.) performed a retrospective MRI analysis, including lesion load evaluation. Additional outcome parameters were infections during pregnancy, delivery mode and gestational age. Preterm birth was defined as birth that occurred before completion of 37 weeks of gestation.

2.4. Statistical analyses

Statistical analyses were conducted with IBM SPSS Statistics version 29.0.0.0, with a two-sided significance level of alpha = 0.05. Descriptive statistics are presented as mean (standard deviation, SD) or median (range) for continuous variables, and as number (percent) for categorical variables. Complete case analysis was utilized to handle missing data. For comparisons of normally distributed continuous variables, a two-sample *t*-test was used. For variables with a non-normal distribution, the Mann-Whitney U test (Wilcoxon rank-sum test) was employed. The Pearson chi-square (or exact chi-square) test was applied to binary or categorical variables to compare clinical, radiological, and serological parameters between pregnancies complicated by relapses and those which were not.

3. Results

3.1. Demographic and clinical characteristics

We identified 112 pregnancies in 70 women with MS. After excluding pregnancies with a duration of <22 weeks, 96 pregnancies in 66 women were included in the analysis, with a mean age of 32.4 (±3.8) years at conception. Demographic and clinical characteristics for these 96 pregnancies, categorized by the occurrence of a relapse during

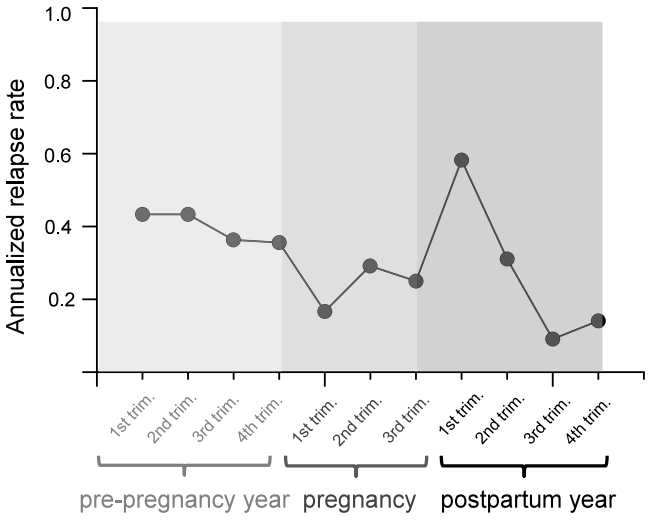

Fig. 2. Annualized relapse rate throughout the pre-pregnancy year (light grey), pregnancy (medium grey), and the postpartum year (dark grey). trim. = trimester.

pregnancy or the postpartum year, are presented in Table 1. Most pregnancies (87/96, 90.6 %) occurred in women with relapsing-remitting multiple sclerosis (RRMS), while seven pregnancies occurred in women with a secondary-progressive subtype (SPMS), and two pregnancies in women with clinically isolated syndrome (CIS).

The median disease duration until conception was 5.25 years (range 0; 18), and the median EDSS score at conception was 1.0 (range 0; 4). In 39 pregnancies (40.6 %), women were considered free of neurological symptoms around the period of conception. Approximately one-quarter (26/96, 27.1 %) of women had multiple symptoms, 20.8 % ($n = 20$) exclusively had sensory deficits, and 6.3 % ($n = 6$) had visual symptoms. Two women (2.1 %) had either only motor or brainstem symptoms, and one woman only urinary symptoms. Additional fatigue was reported in 36.8 % ($n = 32$) of cases. Most pregnancies occurred in non-smokers (62.5 %), while 26 pregnancies were in women who had quit smoking at least one year before conception, and 10 pregnancies were in active smokers at conception.

Seventy-seven pregnancies (80.2 %) were considered exposed to DMT. Eleven pregnancies (11.5 %) occurred in women who had been without DMT for at least 1 year prior to conception.

27 pregnant women (28.1 %) were on natalizumab therapy at conception or within the year before; in 26 pregnancies each (27.1 %), interferon beta or glatiramer acetate was used; and in 23 pregnancies (24.0 %), fumarates were taken. Seven pregnancies (7.3 %) were exposed to a B cell-depleting drug, one to alemtuzumab, and one to fingolimod prior to conception.

Six women continued DMT into the third trimester, with five women receiving natalizumab in extended infusion intervals of 8 weeks until the 30th to 34th gestational week due to high disease activity, and one woman continued glatiramer acetate until the beginning of the third trimester.

3.2. Clinical and radiological disease activity during pregnancy and the postpartum period

In 33 of 96 pregnancies (34.4 %), at least one relapse occurred during pregnancy or the postpartum year. Relapses were observed in 16 pregnancies (16.7 %) during pregnancy and in 24 pregnancies (25.0 %) within the first postpartum year, with 7 pregnancies (7.3 %) affected in both periods. Of the 43 total relapses, 17 (39.5 %) occurred during pregnancy and 26 (60.5 %) during the postpartum year. In cases of relapse, women primarily presented with sensory deficits (21/43, 48.8 %), multiple clinical symptoms (9/43, 20.9 %) and visual symptoms (7/43, 16.3 %). A relapse with motor deficits occurred in 4 (9.3 %) cases, a relapse with ocular motor disorder in 2 cases (4.7 %).

Annualized relapse rates (ARR) per trimester of the pre-pregnancy year, the duration of pregnancy, and the postpartum year revealed a decrease during pregnancy and an increase during the postpartum year, with a peak in the first trimester postpartum (14/43 relapses) (Fig. 2).

When comparing clinical characteristics of pregnancies with a relapse during pregnancy or the first postpartum year to those without any relapse, the relapse group was less frequently exposed to DMT than the non-relapse group (66.7 % vs. 87.3 %, $p = 0.016$). There was a non-significant trend toward a higher median EDSS at conception in the relapse group. No significant difference in the frequency of relapse during the year or 2 years prior to pregnancy was found between the groups (Table 1).

Disability progression within the first year postpartum was observed in 8/33 (25.8 %) women who had a relapse during pregnancy or the postpartum year, compared to 3/63 (5.5 %) in the non-relapse group (Table 2). The median EDSS at 1 year postpartum was 2.0 in the relapse group and 1.0 in the non-relapse group ($p < 0.001$). At 2 years postpartum, the median EDSS in the relapse group was 1.75, while it remained 1.0 in the non-relapse group ($p = 0.007$, Fig. 3). DMT was resumed in most women within the first 6 months postpartum (69.3 %), 17.6 % resumed DMT within the first month postpartum.

In the CSF examined at MS diagnosis, no significant differences between the relapse and the non-relapse group were observed regarding cell count, barrier dysfunction, or specific oligoclonal bands (Table 3). When analyzing MRI activity, the prevalence of spinal lesions at diagnosis of MS and prior to conception was significantly higher in the relapse group ($p = 0.032$, $p = 0.046$). In the first postpartum MRI (within 6 months after delivery), women in the relapse group showed a significantly higher total lesion load ($p = 0.034$) and a higher number of new contrast-enhancing lesions ($p < 0.001$). In 27/33 (84.4 %) pregnancies in the relapse group, at least 10 demyelinating lesions were detected on cerebral MRI postpartum compared to 65.6 % before pregnancy. In 52.8 % of women ($n = 48$), new lesions were detected on the first cerebral MRI within 6 months postpartum. While new lesions were found in 77.4 % ($n = 24$) of the relapse group, 40 % of patients in the non-relapse group also had new lesions ($n = 24$). The number of infratentorial and spinal lesions remained largely stable in both groups throughout pregnancy (Table 3). In 30 out of 96 (31.3 %) pregnancies the criteria of no evidence of disease activity (NEDA-3) (Lu et al., 2018) were met.

3.3. Natalizumab subgroup analysis

27 women were on natalizumab therapy before or at conception. In 3 of 27 women (11.1 %), natalizumab therapy had been administered last within 3 months prior to conception, in 19 of 27 women (70.4 %) during the first trimester, and in 5 of 27 women (18.5 %), treatment was continued until the third trimester (until the 30th up to 34th gestational week) for high disease activity. A relapse during pregnancy or the postpartum year occurred in 10 of 27 women (37.0 %). Of the 22 pregnancies where natalizumab was discontinued shortly before conception or within the first trimester, 9 (40.9 %) experienced a relapse. In the 5 women who continued natalizumab until the third trimester, only a single patient (20.0 %) was affected by 3 relapses: one in the second pregnancy trimester, one in the first postpartum trimester, and one in the second postpartum trimester.

3.4. Pregnancy outcome

A total of 112 pregnancies in 70 women resulted in 96 pregnancies in 66 women with a minimum duration of 22 gestational weeks ending in 95 live births. Eleven women had 14 first-trimester miscarriages, and three women had 2 first-trimester miscarriages. Two women had an abortion, one due to an undesired pregnancy in the first trimester, and one after the diagnosis of trisomy 18 at 21 weeks gestation. One

Table 2
Clinical disease activity during pregnancy and the postpartum period.

	All, $N = 96$ (100.0)	Relapse, $N = 33$ (34.4)	No relapse, $N = 63$ (65.6)	p value
DMT restart postpartum				0.206
< 4 weeks, n (%)	16 (17.6)	6 (19.4)	10 (16.7)	
4 weeks - 3 months, n (%)	19 (20.9)	10 (32.3)	9 (15.0)	
3–6 months, n (%)	28 (30.8)	9 (29.0)	19 (31.7)	
6–12 months, n (%)	15 (16.5)	2 (6.5)	13 (21.7)	
>12 months, n (%)	13 (14.3)	4 (12.9)	9 (15.0)	
Information missing, n (%)	5 (5.2)	2 (6.1)	3 (4.8)	
Disability progression (within 1 year postpartum)				**0.010**
Yes, n (%)	11 (12.8)	8 (25.8)	3 (5.5)	
No, n (%)	75 (87.2)	23 (74.2)	52 (94.5)	
Information missing, n (%)	10 (10.4)	2 (6.1)	8 (12.7)	
EDSS at delivery, median (IQR)	1.00 (0;4)	1.50 (0;4)	1.00 (0;3)	**0.042**
No disability (0–2)	76 (81.7)	23 (69.7)	53 (88.3)	**0.042**
Mild disability (2.5 - 3.5)	16 (17.2)	9 (27.3)	7 (11.7)	
Ambulatory impairment, no assist device (4.0 - 5.5)	1 (1.1)	1 (3.0)	0 (0.0)	
Cane required (6.0–6.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Wheelchair required (> 7.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Information missing, n (%)	3 (3.1)	0 (0.0)	3 (4.8)	
EDSS early postpartum, median (IQR)	1.00 (0;4)	2.00 (0;4)	1.00 (0;4)	**0.002**
No disability (0–2)	76 (80.9)	21 (63.6)	55 (90.2)	**0.002**
Mild disability (2.5 - 3.5)	16 (17.0)	10 (30.3)	6 (9.8)	
Ambulatory impairment, no assist device (4.0 - 5.5)	2 (2.1)	2 (6.1)	0 (0.0)	
Cane required (6.0–6.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Wheelchair required (> 7.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Information missing, n (%)	2 (2.1)	0 (0.0)	2 (3.2)	
EDSS 1 year postpartum, median (IQR)	1.00 (0;4)	2 (0;4)	1.00 (0;3)	**< 0.001**
No disability (0–2)	65 (77.4)	18 (58.1)	47 (88.7)	**0.002**
Mild disability (2.5 - 3.5)	17 (20.2)	11 (35.5)	6 (11.3)	
Ambulatory impairment, no assist device (4.0 - 5.5)	2 (2.4)	2 (6.5)	0 (0.0)	
Cane required (6.0–6.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Wheelchair required (> 7.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Information missing, n (%)	12 (12.5)	2 (6.1)	10 (15.9)	
EDSS 2 year postpartum, median (IQR)	1.50 (0;6)	1.75 (0;4)	1.00 (0;6)	**0.007**
No disability (0–2)	54 (78.3)	17 (60.7)	37 (90.2)	**0.003**
Mild disability (2.5 - 3.5)	12 (17.4)	9 (32.1)	3 (7.3)	
Ambulatory impairment, no assist device (4.0 - 5.5)	2 (2.9)	2 (7.1)	0 (00.0)	
Cane required (6.0–6.5)	1 (1.4)	0 (0.0)	1 (2.4)	
Wheelchair required (> 7.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Information missing, n (%)	27 (28.1)	5 (15.2)	22 (34.9)	

Abbreviations: DMT = disease modifying therapy; EDSS = expanded disability status scale; IQR = interquartile range.
EDSS scores were obtained at delivery (± 3 months), in the early postpartum period (3 - 6 months postpartum), and at 1 and 2 years postpartum (each ± 3 months).

newborn died due to birth at a non-viable gestational age, with a palliative care approach.

Pregnancy outcomes for those with a minimum gestational duration of 22 weeks are shown in Table 4. The delivery time point was recorded for 87 pregnancies: 83 (95.4 %) pregnancies ended at term, while four (4.6 %) were preterm. The delivery mode was known for 55 pregnancies: 35 (63.6 %) pregnancies resulted in spontaneous delivery, 16 (29.1 %) in elective Cesarean section and 4 (7.3 %) in emergency C-section. There was no significant difference in delivery timepoint, mode, or the occurrence of infections during pregnancy when comparing pregnancies with relapse activity ($N = 16$, 16.7 %) to pregnancies without relapse activity ($N = 80$, 83.3 %). Most newborns were exclusively breastfed (85.2 %, $n = 75$) for a median duration of 4 months (range 2; 18), while 14.8 % were either partially or not breastfed (Table 1). Comparing the

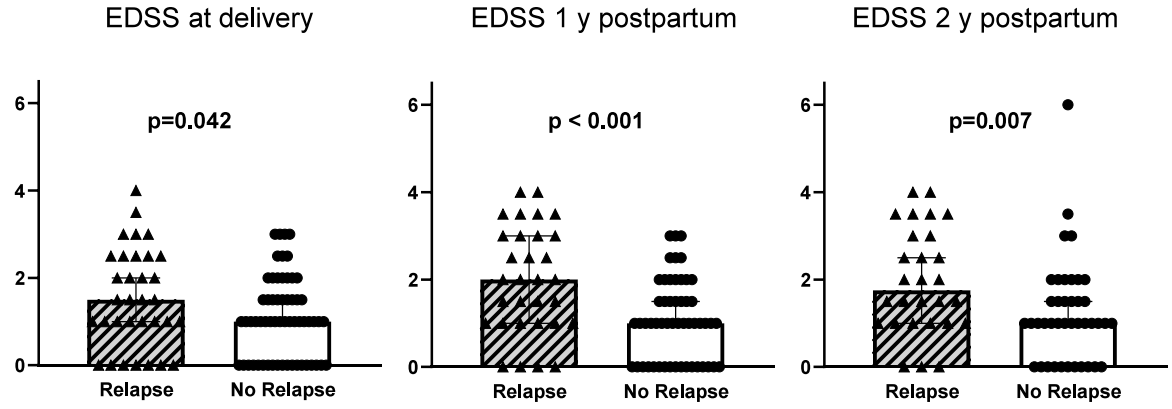

Fig. 3. EDSS throughout the postpartum period. Each dot represents one pregnant woman. Bars represent the median; error bars indicate 95 % confidence intervals. Mann-Whitney U test was performed to compare EDSS values between the group with and without relapse activity during pregnancy and the postpartum year. y = years; EDSS = expanded disability status scale.

Table 3
Serological and radiological parameters.

	All, *N* = 96 (100.0)	Relapse, *N* = 33 (34.4)	No relapse, *N* = 63 (65.6)	p value
CSF				
Pleocytosis at diagnosis, n (%)	51 (60.7)	17 (63.0)	34 (59.6)	0.771
Cell count, median (IQR)	11.50 (1;99)	16.00 (1;99)	9.00 (2;99)	0.116
Information missing, n (%)	12 (12.5)	6 (18.2)	6 (9.5)	
Barrier dysfunction, n (%)	4 (4.6)	2 (7.1)	2 (3.3)	0.591
Information missing, n (%)	9 (9.4)	5 (15.2)	4 (6.3)	
Specific oligoclonal bands, n (%)	89 (95.7)	32 (97.0)	57 (95.0)	0.645
Information missing, n (%)	3 (3.1)	0 (0.0)	3 (4.8)	
MRI at diagnosis				
Number of lesions				0.403
≤ 3, n (%)	14 (14.6)	3 (9.1)	11 (17.5)	
4 - 9, n (%)	31 (32.3)	13 (39.4)	18 (28.6)	
≥ 10, n (%)	51 (53.1)	17 (51.5)	34 (54.0)	
Contrast enhancing lesions				0.935
Absent, n (%)	36 (41.4)	11 (40.7)	25 (41.7)	
Present, n (%)	51 (58.6)	16 (59.3)	35 (58.3)	
Information missing, n (%)	9 (9.4)	6 (18.2)	3 (4.8)	
Infratentorial lesions				0.868
Absent, n (%)	36 (37.5)	12 (36.4)	24 (38.1)	
Present, n (%)	60 (62.5)	21 (63.6)	39 (61.9)	
Spinal lesions				**0.032**
Absent, n (%)	24 (25.3)	4 (12.1)	20 (32.3)	
Present, n (%)	71 (74.7)	29 (87.9)	42 (67.7)	
Information missing, n (%)	1 (1.0)	0 (0.0)	1 (1.6)	
MRI at conception				
Number of lesions				0.621
≤ 3, n (%)	3 (3.2)	0 (0.0)	3 (4.8)	
4 - 9, n (%)	33 (34.7)	11 (34.4)	22 (34.9)	
≥ 10, n (%)	59 (62.1)	21 (65.6)	38 (60.3)	
Information missing, n (%)	1 (1.0)	1 (3.0)	0 (0.0)	
Contrast enhancing lesions				0.551
Absent, n (%)	73 (80.2)	23 (76.7)	50 (82.0)	
Present, n (%)	18 (19.8)	7 (23.3)	11 (18.0)	
Information missing, n (%)	5 (5.2)	3 (9.1)	2 (3.2)	
Infratentorial lesions				0.201
Absent, n (%)	22 (23.4)	5 (15.6)	17 (27.4)	
Present, n (%)	72 (76.6)	27 (84.4)	45 (72.6)	
Information missing, n (%)	2 (2.1)	1 (3.0)	1 (1.6)	
Spinal lesions				**0.046**
Absent, n (%)	23 (25.6)	4 (12.9)	19 (32.2)	
Present, n (%)	67 (74.4)	27 (87.1)	40 (67.8)	
Information missing, n (%)	6 (6.3)	2 (6.1)	4 (6.3)	
MRI postpartum				
Number of lesions				**0.034**
≤ 3, n (%)	5 (5.5)	0 (0.0)	5 (8.5)	
4 - 9, n (%)	24 (26.4)	5 (15.6)	19 (32.2)	
≥ 10, n (%)	62 (68.1)	27 (84.4)	35 (59.3)	
Information missing, n (%)	5 (5.2)	1 (3.0)	4 (6.3)	
Number of new lesions				**< 0.001**
1 - 3, n (%)	33 (36.3)	10 (32.3)	23 (38.3)	
4 - 9, n (%)	15 (16.5)	14 (45.2)	1 (1.7)	
Information missing, n (%)	5 (5.2)	2 (6.1)	3 (4.8)	
New contrast enhancing lesions				**< 0.001**
Absent, n (%)	55 (67.9)	12 (41.4)	43 (82.7)	
Present, n (%)	26 (32.1)	17 (58.6)	9 (17.3)	
Information missing, n (%)	15 (15.6)	4 (12.1)	11 (17.5)	
Infratentorial lesions				0.242
Absent, n (%)	24 (26.1)	6 (18.8)	18 (30.0)	
Present, n (%)	68 (73.9)	26 (81.3)	42 (70.0)	
Information missing, n (%)	4 (4.2)	1 (3.0)	3 (4.8)	
Spinal lesions				0.555
Absent, n (%)	15 (18.3)	4 (13.3)	11 (21.2)	
Present, n (%)	67 (81.7)	26 (86.7)	41 (78.8)	
Information missing, n (%)	14 (14.6)	3 (9.1)	11 (17.5)	

Abbreviations: CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

Table 4
Pregnancy outcome.

	All, *N* = 96 (100.0)	Relapse during pregnancy, *N* = 16 (16.7)	No relapse during pregnancy, *N* = 80 (83.3)	p value
Delivery mode				0.433
Spontaneous, n (%)	35 (63.6)	7 (77.8)	28 (60.9)	
Elective C-section, n (%)	16 (29.1)	1 (11.1)	15 (32.6)	
Emergency C-section, n (%)	4 (7.3)	1 (11.1)	3 (6.5)	
Information missing, n (%)	41 (42.7)	7 (43.8)	34 (42.5)	
Preterm				0.104
Yes, n (%)	4 (4.6)	2 (15.4)	2 (2.7)	
No, n (%)	83 (95.4)	11 (84.6)	72 (97.3)	
Information missing, n (%)	9 (9.4)	3 (18.8)	6 (7.5)	
Infections during pregnancy				0.583
Yes, n (%)	6 (7.4)	2 (14.3)	4 (6.0)	
No, n (%)	75 (92.6)	12 (85.7)	63 (94.0)	
Information missing, n (%)	15 (15.6)	2 (12.5)	13 (16.3)	

Abbreviations: C-section = cesarean section.

relapse and non-relapse group there was a non-significant trend toward a higher proportion of women who breastfed exclusively in the relapse group (89.7 % vs. 83.1 %).

4. Discussion

Management of women with MS during pregnancy and breastfeeding presents a unique clinical challenge, as therapeutic decisions must carefully balance the need for effective disease control with the risks associated with drug exposure for the fetus and newborn. While the emergence of several DMT, including highly effective drugs, over the last 2 decades has greatly helped to reduce inflammatory activity and clinical relapses, the administration of these drugs during pregnancy and breastfeeding has not been systematically investigated. Whereas official drug labels are very restrictive, several national and international guidelines propose different therapeutic strategies (Graber et al., 2024; Hemmer, et al. 2023; Krysko et al., 2023; Vukusic et al., 2023).

With occurrence of a relapse during pregnancy and the postpartum year in 34.4 % of pregnancies, our data support findings from historical and contemporary cohorts after 2010 (Anderson et al., 2021; Vukusic

et al., 2004), showing that relapse during pregnancy and the postpartum year occurred in a significant proportion of cases. In this contemporary patient cohort managed according to current standards of care, we confirmed a decrease in clinical disease activity during pregnancy, followed by a rapid increase in disease activity with a peak in the first 3 months postpartum (Anderson et al., 2021; Confavreux et al., 1998; Yeh et al., 2021). The significantly higher proportion of disability progression within 1 year (25.8 %) in the relapse group, along with higher EDSS scores up to 2 years postpartum, emphasizes the long-term impact of relapses on disability progression in women with MS, despite a return to pre-pregnancy relapse rates in the first postpartum year (Langer-Gould et al., 2020). Additionally, while relapse-associated disability progression is well-documented, it is important to consider *progression independent of relapse activity* (PIRA) as a potential contributor to disability worsening (Kappos et al., 2020). Thus, disability progression in the postpartum period may be driven by both relapse-associated worsening (RAW) and PIRA, with each factor potentially exacerbating the other. This highlights the complexity of MS progression during the peripartum period and the need for comprehensive monitoring and individualized treatment strategies.

Our data also demonstrate an association between lack of preconception DMT and relapse in pregnancy and the postpartum year (Yeh et al., 2024, 2021), whereas we did not find significant differences in preconception EDSS and annual relapse rate between the two groups.

Our finding that new lesions were detected in 77.5 % of women with a clinical relapse and in 40.0 % without clinical symptoms further underscores the fact that disease activity during pregnancy and the postpartum period may be underestimated when relying solely on clinical aspects. This highlights the importance of MRI in detecting subclinical disease activity and guiding therapeutic decisions (Anderson et al., 2021; Houtchens, M. et al., 2020).

The association between pre-pregnancy spinal lesion load and the occurrence of relapses during pregnancy and the postpartum year (Table 3) has not been previously described. Spinal lesion load is an independent predictor of high disease activity (Del Negro et al., 2022), suggesting that spinal cord imaging could potentially serve as a useful tool in assessing relapse risk during pregnancy and postpartum, and should be considered when planning preconception therapy (Lehmann et al., 2021).

In contrast to earlier studies suggesting a protective effect of breastfeeding on relapse risk (Anderson et al., 2021; Hradilek et al., 2022; Lorefice et al., 2022; Saposnik et al., 2022), we observed a non-significant trend toward a higher proportion of women in the relapse group who breastfed exclusively (Table 1). This discrepancy may reflect differences in study design, population characteristics, or breastfeeding duration, underscoring the need for individualized counseling regarding breastfeeding for women with MS.

Our data support the current trend of continuing natalizumab treatment during pregnancy for women with high disease activity, in line with previous studies showing reduced relapse rates when natalizumab is continued throughout pregnancy (Thiel et al., 2023; Yeh et al., 2021). However, the risks and benefits of this approach should be carefully evaluated. Exposure to DMT in 77 out of 96 pregnancies appeared not to increase the risk of miscarriage or birth defects. Based on clinical practice and emerging data an alternative could be switching to a DMT with lower risk of rebound activity such as B cell depleting agents. Currently, the European Medical Agency recommends effective contraception for 4 months after the last administration of ocrelizumab and for 6 months after the last administration of ofatumumab. However, given the half-life (26 days for ocrelizumab, 16 days for ofatumumab) and the fact that relevant placental transfer of these drugs is to be expected starting from 14 weeks of gestation as for endogenous IgG1-antibodies, this interval is quite conservative. Due to the reassuring safety data (for mother and child) from retrospective cohorts as well as the first prospective studies (Bove et al., 2025; Vukusic et al., 2025) and alongside with expert consensus, B cell depleting drugs may present a suitable option in women planning pregnancy in the short or mid-term (Graber et al., 2024; Krysko et al., 2023). Especially with regard to the sustained effect on peripheral B cell depletion beyond the approved 6-monthly infusion, pregnancy planning under B cell depleting agents may allow effective disease control despite interruption of therapy during pregnancy itself (Baker et al., 2020; Kappos et al., 2024). A large retrospective cohort study comparing different management strategies found that use of intravenous B cell depleting agents was the most effective one regarding the impact on relapse rates during pregnancy and the postpartum period and might be even more beneficial than natalizumab when continued until the third trimester (Gavoille et al., 2025).

In conclusion, our study emphasizes the significant impact of relapse activity during pregnancy and the postpartum year on disability progression in women with MS. A careful, individualized risk assessment is critical when counseling and treating women with MS during this time, and further studies evaluating the effects of DMTs on both maternal health and fetal outcomes are needed to refine therapeutic strategies and improve long-term outcomes.

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Lea I Walter: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Veronika Kana:** Writing – review & editing, Investigation. **Sarah Hösli:** Writing – review & editing, Formal analysis. **Michael Weller:** Writing – review & editing. **Nathalie Nierobisch:** Writing – review & editing, Data curation. **Marina Herwerth:** Writing – review & editing, Investigation. **Patrick Roth:** Writing – original draft, Supervision, Resources, Investigation, Data curation, Conceptualization.

Declaration of competing interest

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