ARTICLE

# Natalizumab, Fingolimod, and Dimethyl Fumarate Use and Pregnancy-Related Relapse and Disability in Women With Multiple Sclerosis

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## Abstract

### Objective

To investigate pregnancy-related disease activity in a contemporary multiple sclerosis (MS) cohort.

### Methods

Using data from the MSBase Registry, we included pregnancies conceived after December 31, 2010, in women with relapsing-remitting MS or clinically isolated syndrome. Predictors of intrapartum relapse and postpartum relapse and disability progression were determined by clustered logistic regression or Cox regression analyses.

### Results

We included 1,998 pregnancies from 1,619 women with MS. Preconception annualized relapse rate (ARR) was 0.29 (95% confidence interval 0.27–0.32), fell to 0.19 (0.14–0.24) in the third trimester, and increased to 0.59 (0.51–0.67) in early postpartum. Among women who used fingolimod or natalizumab, ARR before pregnancy was 0.37 (0.28–0.49) and 0.29 (0.22–0.37), respectively, and increased during pregnancy. Intrapartum ARR decreased with preconception dimethyl fumarate use. ARR spiked after delivery across all DMT groups. Natalizumab continuation into pregnancy reduced the odds of relapse during pregnancy (odds ratio 0.76 per month [0.60–0.95], $p$ = 0.017). DMT reinitiation with natalizumab protected against

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MSBase Study Group coinvestigators are listed at links.lww.com/WNL/B381.

## Glossary

**ARR** = annualized relapse rate; **CI** = confidence interval; **CIS** = clinically isolated syndrome; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IQR** = interquartile range; **MS** = multiple sclerosis; **OR** = odds ratio; **RRMS** = relapsing-remitting MS.

postpartum relapse (hazard ratio [HR] 0.11 [0.04–0.32], $p < 0.0001$). Breastfeeding women were less likely to relapse (HR 0.61 [0.41–0.91], $p = 0.016$). We found that 5.6% of pregnancies were followed by confirmed disability progression, predicted by higher relapse activity in pregnancy and postpartum.

### Conclusion

Intrapartum and postpartum relapse probabilities increased among women with MS after natalizumab or fingolimod cessation. In women considered to be at high relapse risk, use of natalizumab before pregnancy and continued up to 34 weeks gestation with early reinitiation after delivery is an effective option to minimize relapse risks. Strategies of disease-modifying therapy use have to be balanced against potential fetal/neonatal complications.

Multiple sclerosis (MS) is a leading cause of neurologic disability among young people and is typically diagnosed in women in their 20s and 30s.[1] Pregnancy and family planning are important life events in this group and pose special challenges for MS treatment planning.

Pregnant women are excluded from randomized controlled trials of disease-modifying therapies (DMTs), and there is limited trial evidence to inform management through pregnancy and postpartum. Historical studies of women treated with no or low-efficacy platform therapies demonstrated a fall in relapse activity during pregnancy, reaching a trough in the third trimester followed by an increase in early postpartum.[2-4] There has been a substantial increase in the number of DMTs over the past decade.[5] Several recent studies included pregnancies of women treated with newer DMTs, although these are limited by small sample size.[6-9] Disease activity in the antenatal and postpartum periods in the setting of modern DMT use remains unclear.

Further investigation is important to inform clinical management of women with MS who are planning pregnancy. We accessed data from the MSBase Registry to examine relapse activity before, during, and after pregnancy in a contemporary cohort. We contrast relapse outcomes in our modern cohort with historical cohorts. We further determine the predictors for relapse in pregnancy and postpartum, as well as the prevalence and predictors of confirmed disability progression after delivery.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase Registry has approval from the Alfred Health Human Research Ethics Committee and ethics approval or exemption from the local research ethics committee at each participating site, according to applicable local laws and regulations. Written informed consent was obtained from all enrolled patients participating in the registry in accordance with the Declaration of Helsinki.

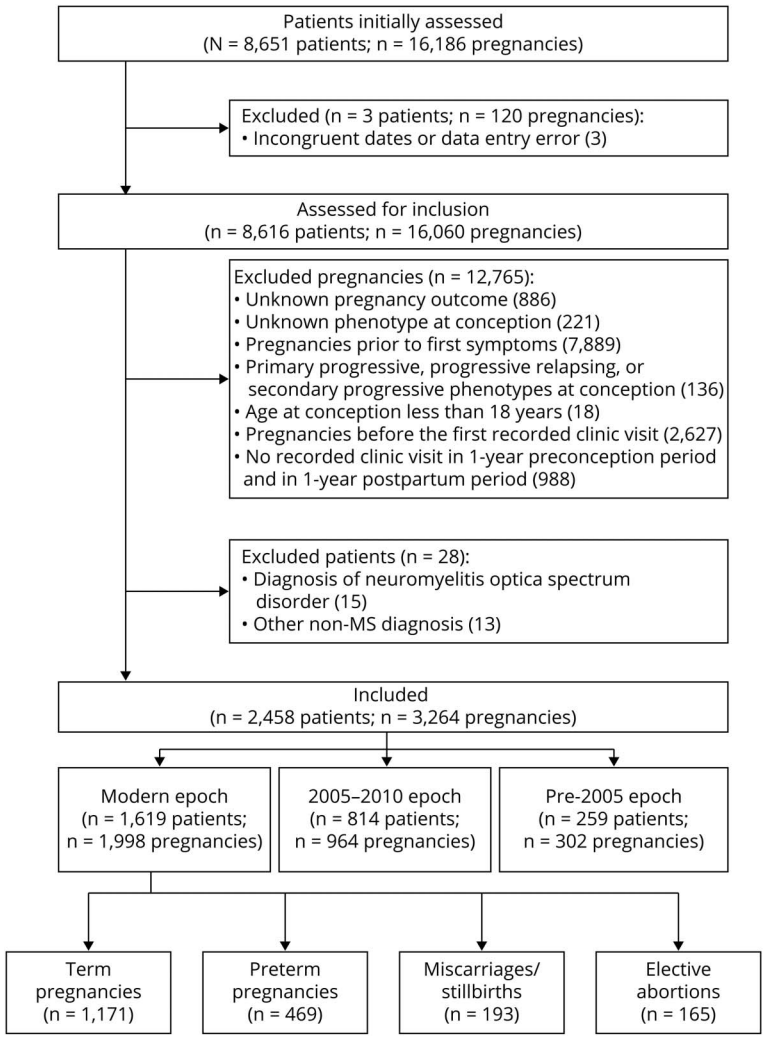
### Study Population

We conducted a multicenter retrospective cohort study using prospectively ascertained pregnancy data from the MSBase Registry.[10] MSBase is an international registry of MS and neuroimmunologic conditions. Most participating sites are tertiary MS referral centers. Participating sites agree to collect a minimum dataset that includes patient sex, birthdate, MS onset date, clinic visit dates, Expanded Disability Status Scale (EDSS; a nonlinear ordinal disability scale, range 0–10) assessments, relapse, and treatment information. Any patient with MS who attends a participating center and provides informed consent can be enrolled in the registry. Data are collected in real time at most participating centers and entered using MSBase-specific data entry systems. Longitudinal data were extracted from MSBase on May 27, 2019.

Women ≥18 years of age with diagnosis of a clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS) before conception were included.[11] We included women with at least 1 visit recorded in both the 1 year before and after pregnancy with known pregnancy outcome. Exclusion criteria were applied as described in figure 1. We defined 3 epochs: (1) modern with pregnancies beginning in 2011, (2) pregnancies in which conception occurred between 2005 and 2010, and (3) pregnancies beginning before 2005. DMTs were categorized by relative efficacy into low-efficacy (interferon beta, glatiramer acetate, teriflunomide, azathioprine), medium-efficacy (fingolimod, dimethyl fumarate, daclizumab), and high-efficacy (natalizumab, alemtuzumab, rituximab, ocrelizumab, mitoxantrone, cyclophosphamide) groups.[12]

Relapse was defined as onset of focal or multifocal neurologic symptoms or signs lasting at least 24 hours in the absence of fever or infection. Annualized relapse rates (ARRs) were calculated for the 1-year preconception, pregnancy, and 1-year postpartum periods. Relapse in pregnancy and first 3

**Figure 1** Flowchart of Pregnancy and Patient Inclusion/Exclusion




MS = multiple sclerosis.

months postpartum were used as outcomes. Preterm was defined as pregnancy <37 weeks leading to live birth. Abortions were pregnancies ending through medical intervention. Miscarriages were pregnancies that ended spontaneously before 20 weeks, and stillbirths were pregnancies that ended at or after 20 weeks.

Conception EDSS score was defined as the EDSS score recorded closest to conception and within 1 year before conception. Early postpartum EDSS score was the EDSS score closest to and within 6 months of delivery, and 1-year postpartum EDSS score was the EDSS score recorded closest to 1 year after delivery and within 6 months. Disability progression was defined as an increase in EDSS score by at least 1.5 steps if the baseline EDSS score was 0, at least 1 step if the baseline EDSS was between 1 and 5.5 inclusive, and at least 0.5 step if the baseline EDSS score was >5.5. Six-month confirmed disability progression was defined as disability progression sustained over 2 subsequent visits relative to the conception EDSS score, with a minimum duration of 6 months between each EDSS assessment. EDSS scores were excluded if there was a relapse onset recorded in the preceding 30 days, except when determining the early postpartum EDSS score.

## Statistical Analysis

Unpaired *t* test, 1-way analysis of variance, Mann-Whitney *U* test, Wilcoxon matched-pairs sign-rank test, Kruskal-Wallis test, $\chi^2$ test, and Fisher exact test were used for comparisons as appropriate. Separate regression analyses were performed for term/preterm pregnancies and abortions/miscarriages/stillbirths. Regression analyses were clustered by patient identification to account for women with multiple included pregnancies, recognizing that intraindividual factors may influence outcomes. Clustered logistic regression was used to determine predictors of relapse in pregnancy. Clustered Cox regression was used to assess predictors for time to relapse postpartum and time to confirmed disability progression. DMT reinitiation and breastfeeding were encoded as time-varying covariates. The Global Schoenfeld test was used to assess Cox models for proportional

hazards. Multivariable models were adjusted for country of residence and number of visits in pregnancy or 1 year postpartum in addition to the variables presented in the respective results tables. Sensitivity analyses were used to assess outcomes exclusively in the RRMS cohort. Akaike information criterion was used to select the best-fitting model. A 2-tailed value of $p < 0.05$ was considered significant. Analyses were performed in R version 3.6.2 with tidyverse, miceadds, sandwich, and survival packages (R Foundation for Statistical Computing, Vienna, Austria).[13-19]

### Data Availability

Patient-level data sharing is possible in principle but will require permissions/consent from each contributing data controller.

## Results

We screened 16,186 pregnancies from 8,651 patients for inclusion. Of these, 1,998 pregnancies from 1,619 patients were included in our modern epoch (figure 1). One thousand six hundred forty (82.1%) pregnancies were term/preterm, and 358 (17.9%) were abortions/miscarriages/stillbirths. The median number of pregnancies from each patient was 1 (interquartile range [IQR] 1–1, range 1–6). The number of pregnancies from each contributing country can be found in e-table 1 (doi.org10.5061/dryad.0vt4b8gxt).

Table 1 shows characteristics of pregnancies in the modern epoch. Disease phenotype at conception was predominantly RRMS (91.3%). Of patients who had CIS at the time of their pregnancy, 77 of 153 patients (50.3%) converted to RRMS by the time of their last recorded visit. Patients with CIS had a median follow-up period of 7.2 years (IQR 4.9–9.7 years) between the date of first symptoms and their last recorded visit.

### Change in Preconception DMT Use and Pregnancy Relapse Rates Across Epochs

We contrasted our modern cohort with those from historical epochs (table 1). Considering the 1 year before pregnancy, use of DMTs during this period increased over time (47.7% before 2005 vs 79.7% in the modern epoch). The median DMT washout period significantly shortened over time (12 months before 2005, 2.8 months in 2005–2010, and 0 months from 2011 on). Therapy continuation up to and into pregnancy increased (efigure 1, doi.org10.5061/dryad.0vt4b8gxt).

In term/preterm pregnancies, preconception ARR fell across epochs from 0.584 (95% confidence interval [CI] 0.486–0.697) before 2005 to 0.400 (95% CI 0.356–0.448) between 2005 and 2010 to 0.291 (95% CI 0.265–0.320) from 2011 on (figure 2). In all epochs, ARR decreased during pregnancy to similar troughs in the third trimester. In the first 3 months postpartum, ARR increased. This was highest before 2005 (0.694 [95% CI 0.500–0.938] vs 0.586 [95% CI 0.513–0.666] in the modern epoch). Among modern pregnancies that ended in abortion/miscarriage/stillbirth, we observed the ARR to rise after pregnancy end (0.440 [95% CI 0.311–0.604] vs before conception 0.294 [0.239–0.358]; figure 3).

### Pregnancies in the Modern Epoch

In the modern epoch, 242 term/preterm pregnancies (14.8%) were associated with high-efficacy DMT use before conception, of which 219 (90.5%) were natalizumab (characteristics by DMT class in etable 2 doi.org10.5061/dryad.0vt4b8gxt). Medium-efficacy DMTs were used before 207 pregnancies (12.6%), with fingolimod accounting for 147 (71.0%) and dimethyl fumarate for 57 (27.5%). Conception EDSS score was ≥2 for 35.4% of pregnancies with preconception medium- or high-efficacy DMT use compared to 21.7% of pregnancies with low-efficacy or no DMT use.

In figure 4A, we plot the ARR of pregnancies associated with preconception natalizumab, fingolimod, dimethyl fumarate, or low-efficacy or no DMT use (characteristics by specific DMT in etable 3 doi.org10.5061/dryad.0vt4b8gxt). The ARR fell during pregnancy in low-efficacy and no DMT groups. The ARR rose during the second and third pregnancy trimesters among pregnancies associated with preconception natalizumab use. Of the fingolimod group, ARR increased in early pregnancy followed by a decrease in the third trimester. The ARR decreased through pregnancy for the dimethyl fumarate group. ARR spiked in early postpartum for all groups but was higher in the natalizumab (0.881 [95% CI 0.645–1.18]), fingolimod (0.947 [95% CI 0.656–1.32]), and dimethyl fumarate (0.809 [95% CI 0.404–1.45]) groups compared to the low-efficacy (0.474 [95% CI 0.385–0.578]) and no DMT (0.508 [95% CI 0.368–0.684]) groups.

There were 207 term/preterm pregnancies treated with natalizumab preconception with no other DMT initiated during pregnancy (characteristics in etable 4 doi.org10.5061/dryad.0vt4b8gxt). Earlier natalizumab discontinuation was associated with earlier return of disease activity (figure 4B). The intrapartum ARR did not rise when natalizumab was continued beyond the first trimester. In the early postpartum period, the ARR was highest for the groups with natalizumab stopped before the end of the first trimester.

Dimethyl fumarate was used before 54 term/preterm pregnancies, with no other DMT started during pregnancy (etable 5 doi.org10.5061/dryad.0vt4b8gxt). No significant increase in the ARR was observed with dimethyl fumarate washout, although our cohort size was limited (figure 4C). Relapse occurred in 11.8% (4 of 34) of pregnancies associated with washout and 5% (1 of 20) with continuation of dimethyl fumarate into early pregnancy.

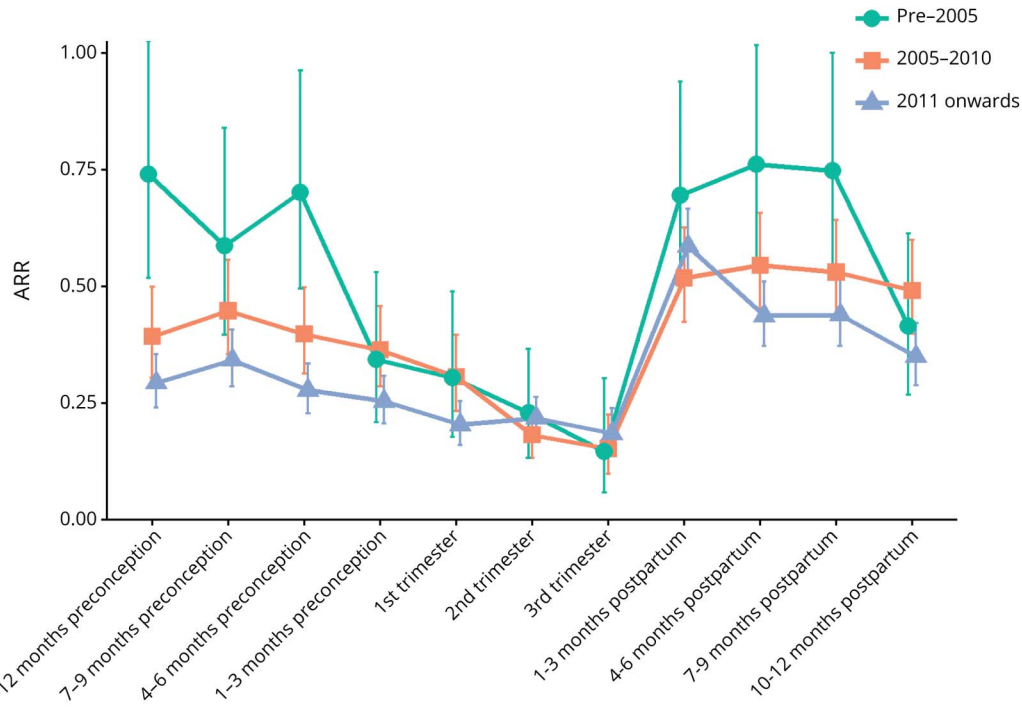
Of 143 term/preterm pregnancies associated with fingolimod use and no other DMT in pregnancy (etable 6 doi.org10.5061/dryad.0vt4b8gxt), cessation was followed by a rise in relapse activity during pregnancy (figure 4D). The ARR fell in the third trimester but was higher among pregnancies with fingolimod ceased within the first trimester than before pregnancy. After delivery, the ARR was highest with fingolimod cessation in early pregnancy (1.31 [95% CI 0.698–2.24]).

**Table 1** Demographic and Clinical Characteristics of Pregnancies in Modern and Historical Epochs

| | 2011 On (n = 1,998) | | | |
|---|---|---|---|---|
| | Term and preterm pregnancies (n = 1,640) | Miscarriages, abortions, and stillbirths (n = 358) | 2005–2010 (n = 964) | Before 2005 (n = 302) |
| **Pregnancy duration, median (IQR), mo** | 8.90 (8.38–9.17) | 1.84 (1.31–2.46) | 8.85 (8.08–9.17) | 8.76 (7.77–9.06) |
| **Age at conception, median (IQR), y** | 32.0 (28.8–35.1) | 34.1 (29.9–37.1) | 31.2 (28.6–34.1) | 30.2 (27.3–33.6) |
| **Time from first symptoms to conception, median (IQR), y** | 6.21 (3.39–10.2) | 6.72 (3.56–10.5) | 5.94 (3.24–9.50) | 5.95 (3.47–8.92) |
| **Phenotype at conception, n (%)** | | | | |
| **RRMS** | 1,499 (91.4) | 325 (90.8) | 873 (90.6) | 281 (93.0) |
| **CIS** | 141 (8.6) | 33 (9.2) | 91 (9.4) | 21 (7.0) |
| **EDSS score at conception, median (IQR)** | 1.5 (0–2)[a] | 1.5 (1–2)[b] | 1.5 (1–2)[c] | 1 (0–2)[d] |
| **ARR in 1 y before conception, mean (SD)** | 0.288 (0.600) | 0.293 (0.628) | 0.468 (1.70) | 0.555 (0.930) |
| **DMT used in 1 y before conception, n (%)** | | | | |
| **None** | 346 (21.1) | 60 (16.8) | 356 (36.9) | 158 (52.3) |
| **Interferon beta** | 597 (36.4) | 137 (38.3) | 447 (46.4) | 114 (37.7) |
| **Glatiramer** | 238 (14.5) | 40 (11.2) | 108 (11.2) | 13 (4.3) |
| **Natalizumab** | 219 (13.4) | 61 (17.0) | 16 (1.7) | 0 |
| **Fingolimod** | 147 (9.0) | 38 (10.6) | 0 | 0 |
| **Dimethyl fumarate** | 57 (3.5) | 13 (3.6) | 0 | 0 |
| **Alemtuzumab** | 15 (0.9) | 2 (0.6) | 0 | 0 |
| **Azathioprine** | 6 (0.4) | 4 (1.1) | 20 (2.1) | 4 (1.3) |
| **Rituximab** | 7 (0.4) | 1 (0.3) | 0 | 0 |
| **Teriflunomide** | 3 (0.2) | 2 (0.6) | 0 | 0 |
| **Daclizumab** | 3 (0.2) | 0 | 0 | 0 |
| **Azathioprine/interferon beta concurrently** | 1 (0.1) | 0 | 11 (1.1) | 10 (3.3) |
| **Mitoxantrone** | 1 (0.1) | 0 | 4 (0.4) | 1 (0.3) |
| **Interferon beta/glatiramer concurrently** | 0 | 0 | 1 (0.1) | 0 |
| **Cyclophosphamide** | 0 | 0 | 1 (0.1) | 1 (0.3) |
| **Cyclophosphamide/interferon beta concurrently** | 0 | 0 | 0 | 1 (0.3) |
| **DMT washout period, median (IQR), mo** | 0 (0–7.97) | 0 (0–3.38) | 2.79 (0–12) | 12 (0–12) |
| **DMT continued into pregnancy, median (IQR), mo** | 0 (0–0.953) | 0.756 (0–1.38) | 0 (0–0.887) | 0 (0–0.682) |
| **Time to DMT reinitiation after delivery, median (IQR), mo[e]** | 2.40 (0.854–4.93) | 0 (0–1.02) | 3.09 (0.493–5.85) | 2.17 (0–5.20) |
| **Breastfeeding, n (%)** | | | | |
| **No** | 1,191 (72.6) | — | — | — |
| **Yes** | 449 (27.4) | — | — | — |
| **Duration of breastfeeding, median (IQR), mo[f]** | 3.22 (1.61–5.95) | — | — | — |
| **Follow-up duration before conception, median (IQR), y** | 3.89 (1.83–6.93) | 4.48 (2.29–7.91) | 3.24 (1.45–5.78) | 3.06 (1.29–5.53) |
| **Follow-up duration after delivery, median (IQR), y** | 2.44 (1.07, 4.08) | 2.74 (1.33, 4.45) | 8.14 (6.49–9.75) | 14.2 (12.4–16.9) |

Abbreviations: ARR = annualized relapse rate; CIS = clinically isolated syndrome; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range; RRMMS = relapsing-remitting multiple sclerosis.
[a] 1,482 pregnancies with recorded EDSS score within 1 year before conception.
[b] 333 pregnancies with recorded EDSS score within 1 year before conception.
[c] 826 pregnancies with recorded EDSS score within 1 year before conception.
[d] 222 pregnancies with recorded EDSS score within 1 year before conception.
[e] Of pregnancies after which the patient restarted a DMT within 12 months postpartum.
[f] Calculated from pregnancies after which patients breastfed.

**Figure 2** ARRs Before Conception, During Pregnancy, and Postpartum Across Epochs for Term/Preterm Pregnancies

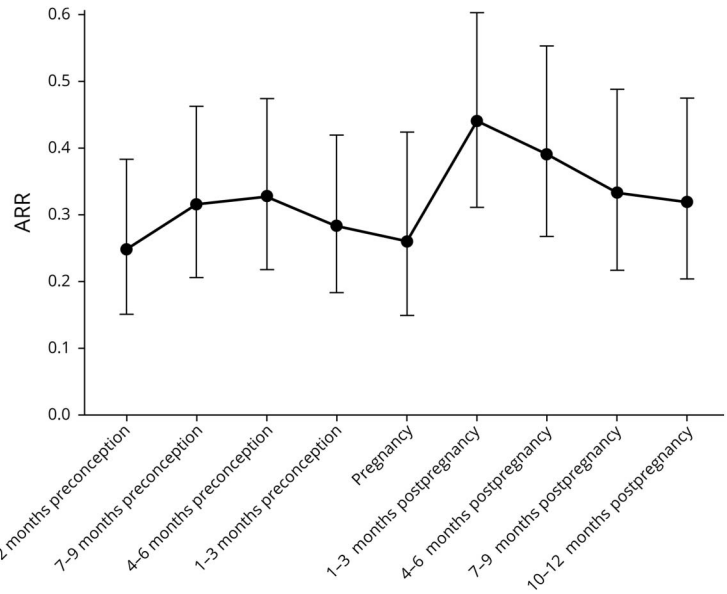



Bars represent 95% confidence intervals. ARR = annualized relapse rate.

## Predictors of Intrapartum Relapse

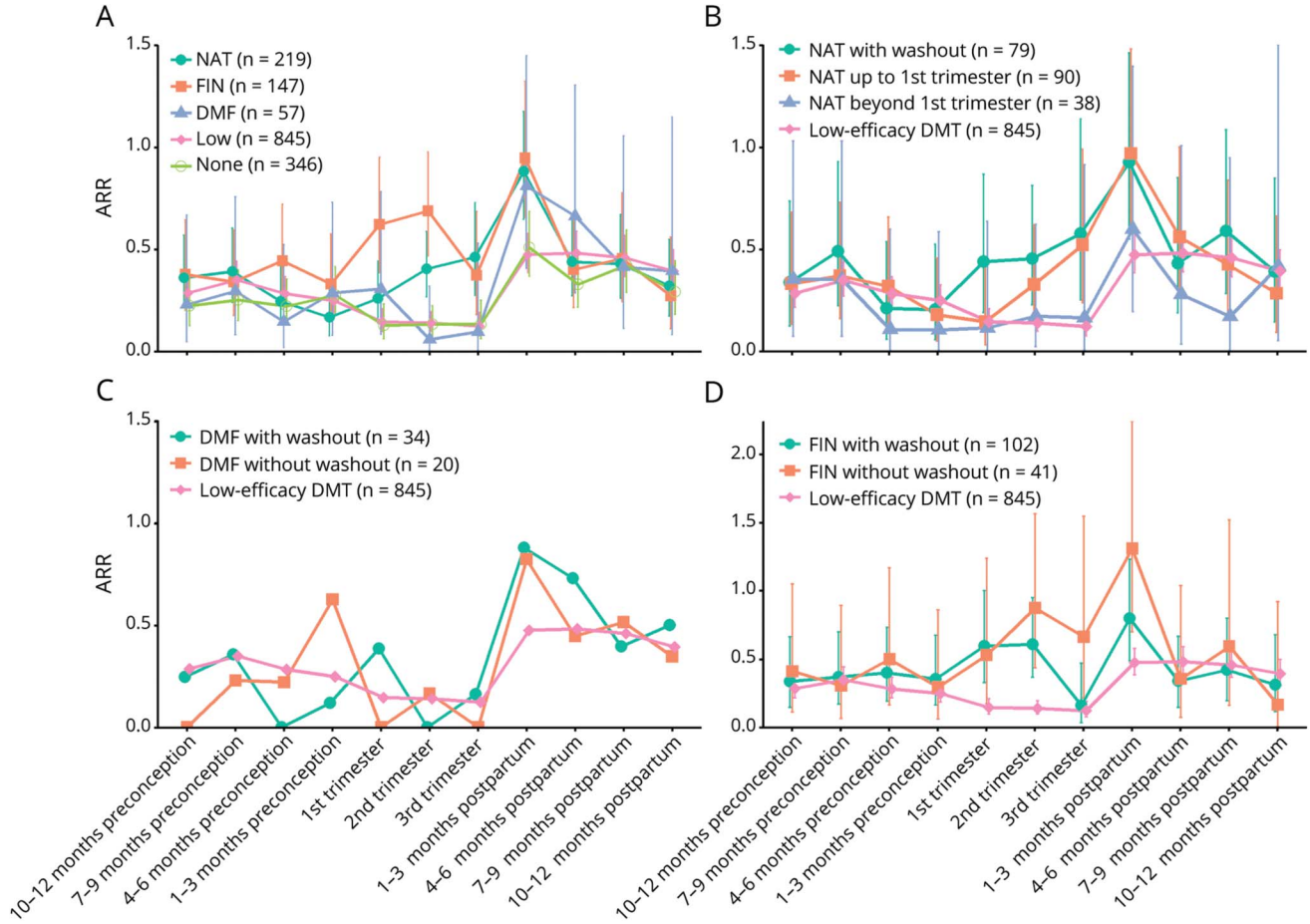
Intrapartum relapse occurred in 194 (11.8%) term/preterm pregnancies (etable 7 doi.org10.5061/dryad.0vt4b8gxt). Pregnancies associated with preconception natalizumab, fingolimod, dimethyl fumarate, or low-efficacy or no DMT use were included for regression analyses of relapse occurrence. Natalizumab and fingolimod use before pregnancy, higher preconception ARR, and younger age were independent risk factors for relapse in pregnancy in multivariable analysis (table 2). Use of dimethyl fumarate before pregnancy was not associated with

**Figure 3** ARRs Before Conception, During Pregnancy, and Postpregnancy for Abortions/Miscarriages/Stillbirths in the Modern Epoch




Bars represent 95% confidence intervals. ARR = annualized relapse rate.

**Figure 4** Annualized Relapse Rates (ARRs) Before Conception, During Pregnancy, and Postpartum for Term/Preterm Pregnancies in the Modern Epoch




By disease-modifying therapy (DMT) used before conception (A), of pregnancies associated with preconception natalizumab (NAT) use (B), of pregnancies associated with preconception dimethyl fumarate (DMF) use (C), and of pregnancies associated with preconception fingolimod (FIN) use (D). In panel A, pregnancies associated with preconception NAT, FIN, or DMF use are compared to those with low-efficacy or no DMT use. In panels B, C, and D, pregnancies associated with NAT, DMF, or FIN use are grouped according to whether the drug was continued into pregnancy or stopped (i.e., washout) before conception. Bars represent 95% confidence intervals.

elevated odds of relapse. Continuing natalizumab into pregnancy was protective, with 24.5% reduction in odds of relapse per month continued (odds ratio [OR] 0.755 [95% CI 0.600–0.951], $p = 0.017$). Sensitivity analyses excluding the CIS cohort did not reveal any significant differences compared to the primary analysis (etable 8 doi.org10.5061/dryad.0vt4b8gxt).

Sixteen (4.5%) abortions/miscarriages/stillbirths had pregnancy relapse (etable 9 doi.org10.5061/dryad.0vt4b8gxt). Due to small numbers, only univariable analyses were conducted. Preconception ARR was the only significant risk factor (OR 2.49 [95% CI 1.29–4.82], $p = 0.0068$).

## Predictors of Postpartum Relapse

Among term/preterm pregnancies, 223 (13.6%) were followed by relapse in the 3 months after delivery at a median time of 34 days (IQR 16.5–61 days) postpartum (etable 10 doi.org10.5061/dryad.0vt4b8gxt). Those who relapsed had a higher ARR before (0.481 vs 0.258, $p < 0.0001$) and during (0.540 vs 0.157, $p < 0.0001$) pregnancy and were more likely to be managed on high- or medium-efficacy DMT before pregnancy (39.5% vs 25.5%).

Factors independently predictive of early postpartum relapse were conception EDSS score ≥2 and higher preconception ARR and intrapartum ARR (table 3). Preconception use of natalizumab, dimethyl fumarate, or no DMT were associated with increased hazards of relapse relative to the use of low-efficacy treatments after adjustment for covariates. Reinitiation with high-efficacy therapies was independently protective against postpartum relapse and reduced the hazard of relapse by 88.9% (hazard ratio [HR] 0.111 [95% CI 0.0382–0.322], $p < 0.0001$ compared to none reinitiated). Women who breastfed were less likely to relapse (HR 0.611 [95% CI 0.409–0.914], $p = 0.016$). Sensitivity analyses excluding the CIS cohort did not reveal any significant differences to the primary analysis (etable 11 doi.org10.5061/dryad.0vt4b8gxt).

Thirty-five patients (9.8%) with abortions/miscarriages/stillbirths relapsed in the first 3 months after their pregnancy

**Table 2** Predictors of Relapse During Pregnancy for Term/Preterm Pregnancies

| | Unadjusted OR (95% CI) | *p* Value | Adjusted OR (95% CI) | *p* Value |
|---|---|---|---|---|
| **Age at conception, y** | | | | |
| **<35** | 1.00 | | 1.00 | |
| **≥35** | 0.426 (0.277–0.656) | 0.00011 | 0.383 (0.236–0.623) | 0.00011 |
| **EDSS score at conception** | | | | |
| **<2** | 1.00 | | 1.00 | |
| **≥2** | 1.28 (0.909–1.80) | 0.16 | 1.14 (0.771–1.70) | 0.50 |
| **Missing** | 1.12 (0.655–1.91) | 0.68 | 1.16 (0.637–2.11) | 0.63 |
| **ARR in 1 y before conception** | 1.66 (1.33–2.07) | <0.0001 | 1.51 (1.18–1.91) | 0.00084 |
| **DMT used before conception** | | | | |
| **Natalizumab** | 2.54 (1.69–3.82) | <0.0001 | 3.25 (1.95–5.43) | <0.0001 |
| **Fingolimod** | 2.96 (1.88–4.67) | <0.0001 | 2.38 (1.35–4.20) | 0.0026 |
| **Dimethyl fumarate** | 1.16 (0.480–2.79) | 0.75 | 1.46 (0.537–3.95) | 0.46 |
| **Low-efficacy** | 1.00 | | 1.00 | |
| **None** | 0.900 (0.569–1.42) | 0.65 | 0.543 (0.240–1.22) | 0.14 |
| **DMT washout period** | 0.985 (0.956–1.02) | 0.34 | 1.06 (0.997–1.13) | 0.060 |
| **Natalizumab continued into pregnancy** | 0.917 (0.791–1.06) | 0.25 | 0.755 (0.600–0.951) | 0.017 |
| **Fingolimod continued into pregnancy** | 1.09 (0.884–1.33) | 0.43 | 0.953 (0.753–1.21) | 0.69 |
| **Dimethyl fumarate continued into pregnancy** | 0.375 (0.0434–3.24) | 0.37 | 0.298 (0.0223–3.97) | 0.36 |
| **Low-efficacy DMT continued into pregnancy** | 0.908 (0.786–1.05) | 0.19 | 0.986 (0.864–1.13) | 0.84 |

Abbreviations: ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; OR = odds ratio.
Predictors of relapse in pregnancy were assessed with clustered logistic regression. Multivariable model included reported variables and were adjusted for country of residence and number of clinic visits during pregnancy (not shown). Akaike information criterion of multivariable model was 1,057.

ended (etable 12 doi.org10.5061/dryad.0vt4b8gxt). Preconception ARR was the only significant predictor for relapse in both univariable and multivariable analyses (etable 13 doi.org10.5061/dryad.0vt4b8gxt).

### Specific Induction-Like and Depletion Therapies and Pregnancy-Related Relapse

Of specific induction-like and depletion therapies, alemtuzumab was used before 22 term/preterm pregnancies (median time from first dose 1.59 years, IQR 0.48–2.08 years). Relapse occurred during 2 pregnancies (9.1%), and no pregnancies were followed by early postpartum relapse. Rituximab was used before 7 pregnancies (median time from initiation 0.83 years, IQR 0.74–1.47 years). There were no intrapartum relapses, and 2 (28.6%) pregnancies were followed by postpartum relapse with subsequent DMT reinitiation with rituximab and ocrelizumab. Cladribine was used before 3 pregnancies at a median time of 5.75 years prior (range 4.25–6.78 years). Of these, 1 pregnancy was associated with intrapartum relapse in a woman whose last DMT before conception was fingolimod. No pregnancy was followed by early postpartum relapse.

### Postpartum Disability Progression

Of term/preterm pregnancies, 850 (51.8%) had conception, early postpartum, and 1-year postpartum EDSS scores available. Confirmed disability progression events occurred after 48 (5.6%) pregnancies (etable 14 doi.org10.5061/dryad.0vt4b8gxt). In multivariable analysis, a higher ARR during pregnancy (HR 1.67 [95% CI 1.25–2.22], $p = 0.00052$) and relapse occurrence postpartum (HR 2.54 [95% CI 1.21–5.33], $p = 0.014$) were independently predictive of disability progression (etable 15 doi.org10.5061/dryad.0vt4b8gxt).

## Discussion

In this observational modern-era study of pregnancies in women with RRMS or CIS, predictors for relapse in pregnancy were higher preconception ARR and natalizumab or fingolimod use before pregnancy. Natalizumab continuation into pregnancy was protective. Predictors of early postpartum relapse included higher conception EDSS score and higher ARR before and during pregnancy. Natalizumab, dimethyl

**Table 3** Predictors of Time to Relapse in Early Postpartum for Term/Preterm Pregnancies

| | Unadjusted HR (95% CI) | *p* Value | Adjusted HR (95% CI) | *p* Value |
|---|---|---|---|---|
| **Age at conception, y** | | | | |
| **<35** | 1.00 | | 1.00 | |
| **≥35** | 0.613 (0.435–0.864) | 0.0052 | 0.717 (0.506–1.02) | 0.061 |
| **EDSS score at conception** | | | | |
| **<2** | 1.00 | | 1.00 | |
| **≥2** | 2.22 (1.67–2.95) | <0.0001 | 1.77 (1.29–2.44) | 0.00044 |
| **Missing** | 1.33 (0.831–2.14) | 0.23 | 1.37 (0.793–2.37) | 0.26 |
| **ARR in 1 y before conception** | 1.54 (1.32–1.80) | <0.0001 | 1.28 (1.06–1.55) | 0.012 |
| **ARR in pregnancy** | 1.45 (1.28–1.63) | <0.0001 | 1.20 (1.03–1.41) | 0.023 |
| **DMT used preconception** | | | | |
| **Natalizumab** | 2.01 (1.41–2.87) | 0.00011 | 2.14 (1.44–3.20) | 0.00018 |
| **Fingolimod** | 1.82 (1.19–2.79) | 0.0054 | 1.41 (0.837–2.39) | 0.20 |
| **Dimethyl fumarate** | 1.84 (0.987–3.44) | 0.055 | 2.25 (1.17–4.34) | 0.016 |
| **Low-efficacy** | 1.00 | | 1.00 | |
| **None** | 0.989 (0.668–1.46) | 0.95 | 2.39 (1.08–5.28) | 0.031 |
| **DMT washout period** | 0.966 (0.937–0.995) | 0.024 | 0.925 (0.867–0.985) | 0.016 |
| **DMT continued into pregnancy** | 0.996 (0.935–1.06) | 0.91 | 1.04 (0.944–1.15) | 0.41 |
| **DMT class reinitiated postpartum** | | | | |
| **Natalizumab** | 0.320 (0.118–0.862) | 0.024 | 0.111 (0.0382–0.322) | <0.0001 |
| **Alemtuzumab** | 5.12 (1.20–21.9) | 0.028 | 0.320 (0.0675–1.52) | 0.15 |
| **Anti-CD20** | 4.30 (0.567–32.7) | 0.16 | 2.43 (0.262–22.6) | 0.43 |
| **Fingolimod** | 1.19 (0.565–2.50) | 0.65 | 0.461 (0.196–1.09) | 0.076 |
| **Dimethyl fumarate** | 1.36 (0.460–4.02) | 0.58 | 0.980 (0.383–2.51) | 0.97 |
| **Low-efficacy** | 0.418 (0.232–0.753) | 0.0037 | 0.389 (0.207–0.730) | 0.0033 |
| **None** | 1.00 | | 1.00 | |
| **Breastfeeding** | | | | |
| **No** | 1.00 | | 1.00 | |
| **Yes** | 0.884 (0.635–1.23) | 0.47 | 0.611 (0.409–0.914) | 0.016 |

Abbreviations: ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HR = hazard ratio.
Predictors of time to relapse in early postpartum were assessed with clustered Cox regression analyses. DMT reinitiation postpartum and breastfeeding were encoded as time-varying covariates. Multivariable model included reported variables and were adjusted for country of residence and number of clinic visits during 1 year postpartum (not shown). Akaike information criterion of multivariable model was 3083, and Global Schoenfeld test $p = 0.52$.

fumarate, or no DMT use before pregnancy was associated with increased hazards of postpartum relapse relative to low-efficacy DMT use. Postdelivery DMT initiation, particularly with natalizumab, was protective. Women who breastfed were less likely to relapse. Reassuringly, pregnancy-related disability progression events were uncommon and driven by pregnancy and postpartum relapse activity.

We observed decrements in prepregnancy and postpartum relapse rates over time. Over the past 2 decades, there have been significant advances in the MS treatment landscape that enable more effective disease control. DMT use increased over time, and the therapeutic strategy of DMT continuation to or beyond conception markedly increased in our modern cohort compared to historical cohorts. These observations

likely explain in part the improved disease control seen in our modern cohort. Another contributory explanation is the evolution of MS diagnostic criteria leading to earlier diagnosis, as well as diagnosis of patients with milder courses.[20]

In our modern cohort, the historically established pattern of ARR decline during pregnancy and postpartum spike was recapitulated in those on no or low-efficacy DMT before pregnancy. Relapse activity increased during pregnancy in the natalizumab and fingolimod treatment groups. After natalizumab cessation, relapse activity increased through pregnancy, in keeping with disease re-emergence reported in nonpregnant natalizumab-treated cohorts.[21] Later cessation during pregnancy delayed the peak of relapse probability, and continuation beyond the first trimester prevented the return of relapse activity altogether. Natalizumab exposure in pregnancy has not been associated with specific fetal malformations or increased miscarriage risk.[22] However, use into the third pregnancy trimester has been associated with reversible hematologic abnormalities in the infant.[23] Continuation of natalizumab at 6- to 8-week intervals up to the 32nd to 34th week of pregnancy is an option to prevent relapse in those deemed at elevated relapse risk while minimizing fetal exposure.[24]

After fingolimod cessation, we observed a sharp rise in relapse activity consistent with rebound.[25] Given its teratogenic potential, fingolimod is contraindicated in pregnancy.[26] Patients with more active MS are more likely to be treated with higher-efficacy DMTs such as natalizumab and fingolimod, and this likely explains in part the greater intrapartum relapse probabilities observed. This is in addition to the well-recognized return or rebound of relapse activity in the months following drug withdrawal. In this subset of women with MS, the immunomodulatory changes of pregnancy are insufficient to protect against relapse return or rebound.

In our small cohort of women using dimethyl fumarate before pregnancy, the intrapartum ARR remained low. The majority of our cohort stopped dimethyl fumarate use at conception or within 3 months before conception. Limited available data do not indicate increased risks of fetal abnormality or miscarriage with first-trimester drug exposure,[27] although the use of effective contraception is recommended while receiving this treatment. Dimethyl fumarate is known to cause immunomodulatory effects that persist for several months after cessation, which may help to reduce relapse risk, for instance, during pregnancy.[28] However, further study with larger cohorts is required before any conclusions can be made.

After delivery, relapse rates spiked among all DMT groups and was highest among women who used natalizumab, fingolimod, or dimethyl fumarate before pregnancy. A recent population-based cohort study did not observe a sharp rise in relapse rate postpartum.[29] Differences in cohorts likely explain these contrasting observations. Our cohort is contributed by MS subspecialist centers, and a significant proportion of patients are likely to have more active disease and require higher-efficacy infusional or oral treatments than patients managed through community clinics. In contrast, the population-based cohort was mostly treated with no or low-efficacy DMT before pregnancy and likely overall represented a group with milder disease compared to our cohort.

DMT initiation after delivery, particularly with natalizumab, protected against early postpartum relapse. This finding is compatible with the known rapid onset of efficacy of natalizumab, with benefits on disease activity noted as soon as 1 month after the first infusion.[30,31] Although we did not identify a protective effect of postdelivery anti-CD20 or alemtuzumab use, we had insufficient power to detect these given our limited numbers of patients who used these therapies. One study of women treated with alemtuzumab described sustained control of disease, including during and after pregnancy.[32] Rituximab and ocrelizumab suppress CD19 B-cell counts beyond their dosing interval of 6 months, suggesting potential long-lasting efficacy.[33] Stopping anti-CD20 therapy is not associated with rebound disease activity.[34] Several studies have shown well-controlled disease during and after pregnancy when the last dose was administered within 6 to 12 months before pregnancy.[34-38] Therefore, planned use of anti-CD20 treatment or alemtuzumab before conception is an option that can provide long-lasting disease control while minimizing DMT exposure during pregnancy and while breastfeeding.

Breastfeeding women were less likely to relapse in our modern cohort. A recent meta-analysis suggested benefit of breastfeeding in preventing postpartum relapse.[39] Exclusive breastfeeding was protective against postpartum relapse in a study of a population-based cohort.[29] An issue with a number of previous studies was their high risk of confounding. In our study, we adjusted for potential confounders, including DMT reinitiation and prior disease activity. Given that breastfeeding has maternal and newborn benefits, it should be encouraged. When considering concurrent DMT use and breastfeeding, counseling and joint clinician-patient decision-making are important because uncertainty about infant safety remains. The bioavailability of natalizumab in breastmilk is negligible, and recent guidelines support its use while breastfeeding.[24] There is minimal transfer of rituximab into mature breastmilk, and oral bioavailability is low.[40] In a small cohort of women who breastfed while on natalizumab, ocrelizumab, or rituximab, no adverse impacts on neonatal development were observed up to a median follow-up of 1 year.[41] Although these finding are supportive of neonatal safety, further work is required to determine breastfeeding compatibility, particularly for highly efficacious DMT.

Relapse occurrence during pregnancy and postpartum was a significant driver of disability progression after pregnancy. We defined disability progression events as requiring confirmation at least 6 months later to reduce misclassification with relapse-associated reversible disability.[42] Only 1 other study using data collected between 2002 and 2008 assessed disability progression after pregnancy with delayed confirmation.[43] The

authors reported a 12.6% disability progression rate among their cohort of women who were untreated or treated with low-efficacy DMTs. We observed a lower rate of 5.6% in our modern cohort. A possible explanation for this difference could be increased DMT use and availability of highly effective treatments in the modern era. Indeed, only 20% of our cohort were untreated before pregnancy compared to 41% of the previously reported cohort.[43] A consideration when interpreting our results is that just over half of our term/preterm pregnancy cohort met our criteria to be included in this analysis. Because we required 2 EDSS scores to be recorded 6 months apart after delivery, women whose pregnancies were included were likely considered at higher risk for postpartum relapse and therefore had closer clinical monitoring. Despite this limitation, it is reassuring that postpartum disability progression is uncommon in this cohort. Relapses are a well-recognized driver of long-term disability.[44] Prevention of relapses, as well as subclinical disease activity, remains an important goal to prevent subsequent disability accrual.

Our study has several limitations. Data were contributed predominantly from subspecialist MS referral centers, so caution must be applied when considering our results in the context of other MS populations. Although our inclusion criteria require patients with active follow-up around pregnancy, which ensures accuracy and completeness of recorded data, this may select for patients with more active disease who need more regular review. We were unable to evaluate MRI measures of disease activity. Whether breastfeeding was mixed or exclusive was not recorded, so we were unable to differentiate between their effects on disease activity. We had a small cohort of women treated with dimethyl fumarate before pregnancy; thus, further study is important to confirm our observations. We had limited or no pregnancies associated with prior alemtuzumab, rituximab, ocrelizumab, or cladribine use and were therefore unable to make any meaningful conclusions regarding these.

For women of child-bearing age, our data inform DMT use that best controls disease activity during and after pregnancy as part of prepregnancy counseling. In women considered at high relapse risk or those with poor prognostic factors, high-efficacy therapy continuation in pregnancy attenuates the risk of relapse and disability accrual peripregnancy. Natalizumab use (particularly in those at low risk of progressive multifocal leukoencephalopathy) before and during pregnancy up to the 32nd to 34th weeks of gestation and reinitiation within several weeks of delivery are strongly protective against relapse. Alternatively, planned use of dimethyl fumarate, an anti-CD20 therapy, or alemtuzumab can provide long-lasting, effective disease control during and after pregnancy, which also allows avoidance of drug exposure during these times. Breastfeeding should be encouraged given its multiple benefits and potential protective effect against relapse. Because the safety of DMT is not yet well established in pregnancy and breastfeeding, clinicians should carefully discuss the benefits and risks with their patients. Well-designed prospective studies will help to confirm the effect of breastfeeding and the safety of DMT use in pregnancy and lactation.

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## Publication History

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Continued

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## Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B381

## References


1. Wallin MT, Culpepper WJ, Nichols E, et al. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18:269-285.
2. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis: Pregnancy in Multiple Sclerosis Group. *N Engl J Med.* 1998;339:285-291.
3. Nguyen AL, Eastaugh A, van der Walt A, Jokubaitis VG. Pregnancy and multiple sclerosis: clinical effects across the lifespan. *Autoimmun Rev.* 2019;18:102360.
4. Karp I, Manganas A, Sylvestre M-P, Ho A, Roger E, Duquette P. Does pregnancy alter the long-term course of multiple sclerosis? *Ann Epidemiol.* 2014;24:504-508.e2.
5. De Angelis F, John NA, Brownlee WJ. Disease-modifying therapies for multiple sclerosis. *BMJ.* 2018;363:k4674.
6. Alroughani R, Akhtar S, Zeineddine M, et al. Risk of relapses during pregnancy among multiple sclerosis patients. *Mult Scler Relat Disord.* 2019;34:9-13.
7. Bsteh G, Algrang L, Hegen H, et al. Pregnancy and multiple sclerosis in the DMT era: a cohort study in Western Austria. *Mult Scler.* 2020;26:69-78.
8. Alroughani R, Alowayesh MS, Ahmed SF, Behbehani R, Al-Hashel J. Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. *Neurology.* 2018;90:e840-e846.
9. Berenguer-Ruiz L, Gimenez-Martinez J, Palazón-Bru A, Sempere AP. Relapses and obstetric outcomes in women with multiple sclerosis planning pregnancy. *J Neurol.* 2019;266(10):2512-2517.
10. Kalincik T, Butzkueven H. The MSBase registry: informing clinical practice. *Mult Scler J.* 2019;25(14):1828-1834.
11. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17:162-173.
12. Tur C, Kalincik T, Oh J, et al. Head-to-head drug comparisons in multiple sclerosis: urgent action needed. *Neurology.* 2019;93:793-809.
13. R Core Team. *R: A Language and Environment for Statistical Computing [online]*. R Foundation for Statistical Computing; 2019. Available at: R-project.org/.
14. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw.* 2019;4:1686.
15. Robitzsch A, Grund S. *Miceadds: Some Additional Multiple Imputation Functions, Especially for "Mice"*; 2019. Available at: CRAN.R-project.org/package=miceadds.
16. Zeileis A. Econometric computing with HC and HAC covariance matrix estimators. *J Stat Softw.* 2004;11:1-17.
17. Zeileis A. Object-oriented computation of sandwich estimators. *J Stat Softw.* 2006;16:1-16.
18. Berger S, Graham N, Zeileis A. *Various Versatile Variances: An Object-Oriented Implementation of Clustered Covariances in R*. Faculty of Economics and Statistics, University of Innsbruck; 2017. Available at: econpapers.repec.org/paper/innwpaper/2017-12.htm. Accessed September 9, 2020.
19. Therneau TM. *A Package for Survival Analysis in R*; 2015. Available at: CRAN.R-project.org/package=survival.
20. Sorensen PS, Sellebjerg F, Hartung HP, Montalban X, Comi G, Tintoré M. The apparently milder course of multiple sclerosis: changes in the diagnostic criteria, therapy and natural history. *Brain.* 2020;143:2637-2652.
21. O'Connor PW, Goodman A, Kappos L, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. *Neurology.* 2011;76:1858-1865.
22. Friend S, Richman S, Bloomgren G, Cristiano LM, Wenten M. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. *BMC Neurol.* 2016;16:150.
23. Haghikia A, Langer-Gould A, Rellensmann G, et al. Natalizumab use during the third trimester of pregnancy. *JAMA Neurol Am Med Assoc.* 2014;71:891-895.
24. Dobson R, Dassan P, Roberts M, Giovannoni G, Nelson-Piercy C, Brex PA. UK consensus on pregnancy in multiple sclerosis: "Association of British Neurologists" guidelines. *Pract Neurol.* 2019;19:106-114.
25. Meinl I, Havla J, Hohlfeld R, Kümpfel T. Recurrence of disease activity during pregnancy after cessation of fingolimod in multiple sclerosis. *Mult Scler J.* 2018;24:991-994.
26. Karlsson G, Francis G, Koren G, et al. Pregnancy outcomes in the clinical development program of fingolimod in multiple sclerosis. *Neurology.* 2014;82:674-680.
27. Gold R, Phillips JT, Havrdova E, et al. Delayed-release dimethyl fumarate and pregnancy: preclinical studies and pregnancy outcomes from clinical trials and postmarketing experience. *Neurol Ther.* 2015;4:93-104.
28. Mehta D, Miller C, Arnold DL, et al. Effect of dimethyl fumarate on lymphocytes in RRMS: implications for clinical practice. *Neurology.* 2019;92:e1724-e1738.
29. Langer-Gould A, Smith JB, Albers KB, et al. Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort. *Neurology.* 2020;94:e1939-e1949.
30. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med.* 2003;348:15-23.
31. Butzkueven H, Licata S, Jeffery D, et al. Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study. *BMJ Open.* 2020;10:e038861.
32. Oh J, Achiron A, Celius EG, et al. Pregnancy outcomes and postpartum relapse rates in women with RRMS treated with alemtuzumab in the phase 2 and 3 clinical development program over 16 years. *Mult Scler Relat Disord.* 2020;43:102146.
33. Baker D, Pryce G, Amor S, Giovannoni G, Schmierer K. Learning from other autoimmunities to understand targeting of B cells to control multiple sclerosis. *Brain.* 2018;141:2834-2847.
34. Juto A, Fink K, Al Nimer F, Piehl F. Interrupting rituximab treatment in relapsing-remitting multiple sclerosis; no evidence of rebound disease activity. *Mult Scler Relat Disord.* 2020;37:101468.
35. Kümpfel T, Thiel S, Meinl I, et al. Anti-CD20 therapies and pregnancy in neuroimmunologic disorders. *Neurol Neuroimmunol Neuroinflamm.* 2020;8:e913.
36. Smith JB, Hellwig K, Fink K, Lyell DJ, Piehl F, Langer-Gould A. Rituximab, MS, and pregnancy. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e734.
37. Das G, Damotte V, Gelfand JM, et al. Rituximab before and during pregnancy. *Neurol Neuroimmunol Neuroinflamm.* 2018;5:e453.
38. Razaz N, Piehl F, Frisell T, Langer-Gould AM, McKay KA, Fink K. Disease activity in pregnancy and postpartum in women with MS who suspended rituximab and natalizumab. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e903.
39. Krysko KM, Rutatangwa A, Graves J, Lazar A, Waubant E. Association between breastfeeding and postpartum multiple sclerosis relapses: a systematic review and meta-analysis. *JAMA Neurol.* 2020;77:327.
40. Krysko KM, LaHue SC, Anderson A, et al. Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurological conditions. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e637.
41. Ciplea AI, Langer-Gould A, de Vries A, et al. Monoclonal antibody treatment during pregnancy and/or lactation in women with MS or neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e723.
42. Kalincik T, Cutter G, Spelman T, et al. Defining reliable disability outcomes in multiple sclerosis. *Brain.* 2015;138:3287-3298.
43. Portaccio E, Ghezzi A, Hakiki B, et al. Postpartum relapses increase the risk of disability progression in multiple sclerosis: the role of disease modifying drugs. *J Neurol Neurosurg Psychiatry.* 2014;85:845-850.
44. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol.* 2016;80:89-100.