Multiple sclerosis

Original research

Early postpartum treatment strategies and early postpartum relapses in women with active multiple sclerosis

Sabrina Haben,1 Andrea I Ciplea,1 Marianne Tokic,2 Nina Timmesfeld,2 Sandra Thiel,1 Ralf Gold,1 Annette Magdalene Langer-Gould,3 Kerstin Hellwig

ABSTRACT

Background  Relapse risk after delivery is increased in women with active multiple sclerosis (MS), the best strategy to reduce it is unknown. We aimed to assess the association of four different postpartum strategies with relapses during the first 6 months post partum.

Methods  This cohort study includes data prospectively collected through structured telephone interviews from the German Multiple Sclerosis and Pregnancy Registry. Pregnancies with active MS (fingolimod or natalizumab treatment OR relapse within 1 year before pregnancy) and postpartum follow-up of ≥6 months were included. We compared four strategies: (1) intention to breastfeed exclusively without disease-modifying therapy (DMT) (exclusive breastfeeding ≥2 months or switching to non-exclusive/ weaning within 2 weeks after a relapse during the first 2 months), (2) early treatment with natalizumab/ fingolimod and (3) other DMT initiated within 6 weeks post partum before a relapse. If women did not or only partially breastfed, or started DMT ≤6 weeks after delivery after a relapse or later, we assumed (4) no-DMT-no-exclusive-breastfeeding-strategy. Main outcome was time to postpartum MS relapses.

Results  In 867 women with 911 pregnancies, most (n=416) intended to breastfeed exclusively or had no-DMT-no-exclusive-breastfeeding-strategy (n=290); fewer started fingolimod (n=38), natalizumab (n=74) or another DMT (n=93) early. Recurrent time-to-event analysis showed a statistically significant reduction in relapse hazard only with the natalizumab/fingolimod-strategy as of months 3–4 post partum compared with intention-to-breastfeed-exclusively-strategy. The very early relapse risk was highest in no-DMT-no-exclusive-breastfeeding-strategy.

Conclusion  In active MS, an early postpartum treatment strategy should be determined well before delivery. Natalizumab/fingolimod-strategy reduced postpartum relapse hazard from month 3, but none diminished the early postpartum relapse hazard.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Exclusive breast feeding has been shown in several studies to reduce the multiple sclerosis relapse risk post partum, however, as cohorts mainly composed of patients with low or moderate disease activity it is unknown whether protective effects are to be expected in women with highly active disease as well.

WHAT THIS STUDY ADDS

- We found that in women with active disease only restarting natalizumab or fingolimod within the first 6 weeks post partum significantly reduced relapse hazard as of month 3 after delivery, however, none of the different examined postpartum treatment strategies seemed to be able counteract the very early postpartum relapse risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Women with active multiple sclerosis need to be advised to restart highly and rapid effective disease-modifying treatment soon after delivery. Choosing breastfeeding compatible options might be preferred.

INTRODUCTION

During the first months after delivery, the relapse risk in women with multiple sclerosis (MS) is increased and dependent on disease activity before or during pregnancy and the withdrawal of higher efficient disease-modifying therapies (DMTs) such as natalizumab (NTZ) and fingolimod (FTY).1,2 Various publications suggest that exclusive breastfeeding (exBF) might protect against postpartum (pp) relapses3-4 but most studies did not stratify by disease activity. In our own previous publication, the majority of women had been on first-line treatments, only about 11% had received a second-line therapy (NTZ) before pregnancy.3 Meanwhile, second-line therapies are administered more often and earlier in the treatment of MS.9 Studies on DMT-resumption show conflicting results and there is up to now no proof that early resumption of DMT after delivery reduces the early relapse risk pp.5,9,10,11 Whether women with active disease benefit from exBF or early resumption of DMTs is yet unknown. Therefore, the objective of this study was to assess associations of different early pp treatment strategies (exBF, early restart of: NTZ/FTY, other DMTs or no apparent strategy) with the pp relapse risk in a cohort of women with active MS.

METHODS

Study population and data collection

We included pregnancies, enrolled into the German Multiple Sclerosis and Pregnancy Registry...
Multiple sclerosis

(DMSKW)\textsuperscript{12}—a nationwide prospective cohort study of pregnant women with MS, meeting the following criteria: live birth between November 2007 and March 2020, active MS, enrolment during pregnancy, completed pp follow-up of ≥6 months and known breastfeeding status. ‘Active MS’ was defined as treatment with NTZ or FTY in the year preceding pregnancy or until the first trimester of pregnancy (because of the higher relapse risk after withdrawal of these drugs during pregnancy and pp).\textsuperscript{2,11,14} OR having had a relapse in the year before pregnancy regardless of DMT treatment (known to be associated with a higher pp relapse risk).\textsuperscript{1,15} Women treated with DMTs with long-lasting effect (alemtuzumab, cladribine, ocrelizumab or rituximab) before or during pregnancy, or who continued NTZ beyond the first trimester of pregnancy were excluded due to the small sample size at data cut-off. Data were collected during regular, standardised telephone interviews with the patients during pregnancy and the pp period as previously described.\textsuperscript{12}

This study contains data on 380 cases included and published also in preceding manuscripts/under review.\textsuperscript{3,10}

Exposure and outcome

We defined four early pp strategies: (1) intention to breastfeed exclusively without DMT: breast feeding for ≥2 months without regular replacement of any meal by supplemental feeding.\textsuperscript{3} exBF stopped the day when at least one meal was fully replaced by any supplemental feeding. Women who initially breastfeed exclusively but replaced a meal or weaned within 2 weeks after a relapse in the first 2 months pp were also included into the exBF strategy, as we assumed the intention to breastfeed exclusively. Three other early treatment strategies included early (during the first 6 weeks pp and before a relapse) restart of DMTs with (2) NTZ or FTY (NTZ/FTY-strategy) or (3) any other DMTs (other DMT-strategy). Those who did not or only partially breastfeed and did not restart DMTs early or only after a relapse in the first 6 weeks were grouped, in the last strategy and (4) no DMT-no-exclusive-breastfeeding-strategy (no-DMT-no-exBF-strategy). Those who breastfed exclusively under a DMT were included into the respective DMT-strategy if treatment was started before the first relapse (even if started >6 weeks pp); if treatment started after a relapse, they were included into the exBF-strategy. MS relapse was defined using current criteria\textsuperscript{16}; those occurring within the first 6 months pp were included into analyses.

Statistical analysis

Descriptive analyses were performed with analysis of variance, the Kruskal-Wallis or \( \chi^2 \) test where applicable. Mean cumulative functions were used to describe the accumulated number of relapses over time per strategy.

To analyse the association of relapse hazard rates with the different strategies, adjusted HRs calculated by the Andersen-Gill extension of the Cox proportional hazard model for recurrent events were used. Age, disease duration, relapses under second-line DMT before pregnancy as well as relapses during pregnancy were used as covariates to adjust for differing disease activities. Baseline hazards were stratified by inclusion criteria groups (NTZ/FTY vs relapse under other/no DMT in the year before pregnancy) to account for possible differing disease activities. To evaluate whether the strategies where stable in effect over time, three time intervals (each lasting 2 months) were included in the model as time-varying covariates. For each time interval, the difference between exBF and the other strategies was tested using Wald test and p values and CIs were adjusted for multiple testing via Bonferroni correction.

To analyse a possible association between measures of disease characteristics and activity prior to delivery (age, disease duration, relapses before, relapse during pregnancy as well as a second-line DMT (NTZ or FTY) before the pregnancy) with pp strategy choice, a multinomial logistic regression model was applied. Statistical analyses were conducted using R V4.1.2 with a two-sided significance level of .5% and 95% CI are reported.\textsuperscript{17}

RESULTS

Of 2507 pregnancies in the DMSKW database with live birth until March 2020, 911 fulfilled the inclusion criteria (figure 1). Forty-two women contributed two pregnancies and one contributed three pregnancies. Mean age at last menstrual period was 32.45 (SD 4.20) years and pregnancies had been diagnosed with MS for a median of 4.79 (IQR 1.91–8.66) years before pregnancy. Approximately half of the pregnancies met the criteria of active MS by having been treated with NTZ or FTY in the year before pregnancy (46.70%), the remaining cases were distributed almost evenly between those who relapsed under first line (28.7%) or no treatment (24.7%) in the year prior to pregnancy. Baseline characteristics of the four strategies are shown in table 1.

The most common early pp strategy was exBF in n=416 (45.7%) of pregnancies, followed by no-DMT-no-exBF-strategy (n=290, 31.8%), 205/911 (22.5%) restarted DMTs early: n=93/205 (45.4%) with other-DMT-strategy, mainly injectables (n=77/93, 82.8%) and n=112/205 (54.6%) with NTZ/FTY-strategy. Only few, n=23/416 (5.5%) stopped exBF within the first 2 months pp due to a relapse. Only 38 of n=677 who breastfed did so while on DMT (n=25 exclusively and n=13 partially) mainly (76.3%) on interferon-beta and 14 on glatiramer acetate and 9 on monoclonal antibodies (NTZ n=7 and OCR n=2). For further details on those 25 pregnancies breast feeding exclusively while on DMT see online supplemental table 1.

Disease activity before and during pregnancy and immunomodulatory treatment before pregnancy differed between the pp strategies (table 1). Preganancies breast feeding exclusively were less likely to have been on second-line before conception (only 37.5%), whereas NTZ/FTY-strategy and no-DMT-no-exBF-strategy pregnancies had more often been treated with second-line treatments before conception (95.5% and 51.0%, respectively).

Pregnancies with second-line treatment before conception and relapse during pregnancy were more likely to choose the NTZ/FTY-strategy (OR 32.6, 95%CI 12.1 to 87.9, p<0.001) and OR 2.35, 95%CI 1.45 to 3.83, p<0.001) instead of exBF strategy (see online supplemental table 2).

pp disease activity

Overall, 337/911 (37.0%) pregnancies relapsed at least once during the first 6 months pp (table 2). In the NTZ/FTY-strategy and other DMT-strategy 76% of the cases remained relapse free during this time frame; in contrast for exBF-strategy and no-DMT-no-exBF-strategy this was the case in only 62% and 56% (table 2). When inspecting the mean cumulative function of the different strategies (figure 2), no-DMT-no-exBF-strategy had the highest overall number of cumulated relapses with a stable relapse risk. The exBF-strategy appears to remain stable in relapse risk throughout the 6-month pp period observed, whereas the NTZ/FTY-strategy shows a decline in relapse risk, most noticeable past the 4-month mark.
In the recurrent time-to-event analysis, pregnancies with no-DMT-no-exBF-strategy had the highest early pp relapse hazard (figure 3), although this finding was not statistically significant. Compared with exBF the NTZ/FTY-strategy showed a statistically significant reduction in relapse hazard rate from month 3 onwards (months 3–4: HR 0.31, 95% CI 0.12 to 0.82, p=0.008; months 5–6: HR 0.27, 95% CI 0.07 to 0.98, p=0.043; figure 3) but not during the first 2 months pp. For all other strategies, no significant differences were found compared with exBF-strategy for none of the three different time frames (figure 3).

**DISCUSSION**

The findings of our large prospective cohort study of women with active MS in the year prior to pregnancy or at high risk of disease activity due to recent cessation of NTZ or FTY suggest that the pp relapse risk is high. No-DMT-no-exBF-strategy...
During pregnancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exclusive breastfeeding strategy*</th>
<th>NTZ/FTY strategy*</th>
<th>Other DMT-strategy*</th>
<th>No DMT-no-exBF-strategy*</th>
<th>P value overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at pregnancy onset, mean (SD), year</td>
<td>31.64 (3.98)</td>
<td>32.40 (4.22)</td>
<td>31.48 (4.58)</td>
<td>31.52 (4.35)</td>
<td>0.221</td>
</tr>
<tr>
<td>MS duration at pregnancy onset, median (IQR), year</td>
<td>4.25 (1.82–7.63)</td>
<td>7.89 (4.10–11.28)</td>
<td>3.70 (0.85–7.03)</td>
<td>5.01 (1.99–8.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second-line therapy 1 year prior to pregnancy†, No. (%)</td>
<td>156 (37.5)</td>
<td>107 (95.5)</td>
<td>14 (15.1)</td>
<td>148 (51.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse 1 year prior to pregnancy with second line therapy, No. (%)</td>
<td>51 (12.3)</td>
<td>41 (36.6)</td>
<td>3 (3.2)</td>
<td>51 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse 1 year prior to pregnancy† under first line therapy, No. (%)</td>
<td>143 (34.4)</td>
<td>4 (3.6)</td>
<td>36 (38.7)</td>
<td>78 (26.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse 1 year prior to pregnancy† under no therapy, No. (%)</td>
<td>117 (28.1)</td>
<td>1 (0.9)</td>
<td>43 (46.2)</td>
<td>64 (22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Last treatment in the year prior to pregnancy†, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTZ§</td>
<td>92 (22.1)</td>
<td>72 (64.3)</td>
<td>5 (5.4)</td>
<td>84 (29.0)</td>
<td></td>
</tr>
<tr>
<td>FTY¶</td>
<td>53 (12.7)</td>
<td>31 (27.7)</td>
<td>6 (6.5)</td>
<td>52 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Interferon-beta</td>
<td>106 (25.5)</td>
<td>4 (3.6)</td>
<td>42 (45.2)</td>
<td>64 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>77 (18.5)</td>
<td>4 (3.6)</td>
<td>27 (29.0)</td>
<td>41 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>35 (8.4)</td>
<td>0 (0.0)</td>
<td>8 (8.6)</td>
<td>18 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
<td>5 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>1 (0.2)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>52 (12.5)</td>
<td>0 (0.00)</td>
<td>3 (3.2)</td>
<td>25 (8.6)</td>
<td></td>
</tr>
<tr>
<td>During pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy exposed to any DMT, No (%)</td>
<td>293 (70.4)</td>
<td>107 (95.5)</td>
<td>81 (87.1)</td>
<td>227 (78.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pregnancy exposed to second-line DMT, No (%)</td>
<td>111 (26.7)</td>
<td>98 (87.5%)</td>
<td>8 (8.6)</td>
<td>120 (41.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies with ≥1 relapse during pregnancy, No. (%)</td>
<td>107 (25.7)</td>
<td>54 (48.2)</td>
<td>23 (24.7)</td>
<td>87 (30.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First trimester</td>
<td>40 (9.6)</td>
<td>21 (18.8)</td>
<td>8 (8.6)</td>
<td>26 (9.0)</td>
<td>0.022</td>
</tr>
<tr>
<td>Second trimester</td>
<td>54 (13.0)</td>
<td>32 (28.6)</td>
<td>10 (10.8)</td>
<td>34 (11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Third trimester</td>
<td>35 (8.4)</td>
<td>30 (26.8)</td>
<td>11 (11.8)</td>
<td>49 (16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No of relapses during pregnancy, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–0)</td>
<td>0 (0–1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First trimester</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.023</td>
</tr>
<tr>
<td>Second trimester</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Third trimester</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Definition of strategies: exclusive breastfeeding strategy, women breast feeding for at least 2 months without regular replacement of any meal by supplemental feeding including those initially breast feeding exclusively but replacing a meal or weaning within 2 weeks after a relapse in the first 2 months pp; NTZ/FTY-strategy, women (re)starting NTZ or FTY treatment within 6 weeks pp before a relapse; other DMT-strategy, women (re)starting another DMT within 6 weeks pp before a relapse; no DMT-no-exBF-strategy, women neither breast feeding exclusively nor (re)starting a DMT within first 6 weeks pp or restarting DMT within this time frame but after a relapse; women exclusively breast feeding under a DMT were included in respective DMT-strategy if treatment was started (not necessarily within 6 weeks pp) before a relapse; if afterwards they were included into the exclusive breastfeeding strategy.
†Pregnancy onset defined as first day of the last menstrual period.
§Of 264 cases with NTZ exposure in the year preceding pregnancy the majority n=191 (72.4%) received their last infusion after the LMP (median 19 days, IQR 8–28) whereas only 73 (27.6%) stopped NTZ with a median 69 days before LMP (IQR 16–148); of those n=11 received a bridging therapy until pregnancy.
¶Of 161 cases with FTY exposure in the year preceding pregnancy the majority n=87 (54.0%) received their last dose after the LMP (median 34 days, IQR 28–41) whereas only 74 (46.0%) stopped FTY with a median 91 days before LMP (IQR 58–187); of those n=19 received a bridging therapy until pregnancy.

appeared as the worst approach. This underscores the importance of counselling patients prior to delivery and again in the very early pp period to resume a DMT (preferably NTZ or FTY), to breastfeed exclusively or both. In the first 2 months following delivery, none of the two drug treatment strategies reduced the relapse hazard significantly compared with exBF, however, recurrent time-to-event analysis did show a statistically significant beneficial effect of early NTZ/FTY (re)start after delivery in mid and late first half of the pp year, demonstrating that over time DMT-effects become apparent.

Overall, 37% in our cohort experienced one or more relapse in the first 6 months pp, which is in the higher range of other published modern cohorts where about 30%–39% relapsed only during the entire first pp year.4, 11, 18 This variation in relapse occurrence could be explained by lower disease severity in these cohorts as only 3%,11 6%18 and 11%18 were treated with highly effective DMTs or only 39% were reported to have been exposed to any DMT at all in the year before pregnancy.11,18 Cohorts from our registry comprising of the most active MS cases treated with FTY or NTZ before pregnancy report that almost half experience at least one relapse during this time frame (NTZ: 49%,11 FTY: 45% (NEURIMMINFL accepted); data overlap with present analysis). These women are especially vulnerable, as relapse activity can be associated with relevant persistent disability.10 Although severe rebound relapses seem to be more common during pregnancy, relapse risk is highest in the first few months after delivery, why effective and modifiable strategies are of interest.
If exBF is regarded as a treatment, it seems to be an attractive early strategy with multiple health benefits for mother and child. Some modern cohorts, including ours, found a reduction in the pp relapse risk compared with no-exBF or not exBF, with relapses ranging between 9% and 25% consistent with the results of a recent meta-analysis. In our present cohort, relapse risk was higher (38%) compared with other studies in those pregnancies. The ability to prevent very early pp relapses by rapid restart of fast-acting DMT after delivery seems restricted considering their immunological background. As a decline of circulating gamma producing cells—which starts already in the third trimester of pregnancy—might sensitise for these relapses, it might be too late to try to counter this process starting a treatment only after delivery. Pregnancy has been shown to not be a continuous immunosuppressed phase, but dynamic and consisting of different stages. Of note, the third trimester is characterised by an inflammatory immune state necessary to induce delivery and labour.

Whereas rapid DMT-reintroduction after delivery did not show superiority in very early relapse reduction in our cohort we observed a plausible temporal dynamic in relapse reduction over the course of first 6 months pp with the NTZ/FTY-strategy. In contrast to our cut-off of 6 weeks pp, the definition of ‘early’ DMT resumption differs between studies, ranging from a few days after delivery, 2 weeks to 1 (1, 10, 22), 2 (4) and 3 (23) months and includes highly effective therapies or injectables. Our findings are in line with several studies showing that ‘early’ DMT-resumption reduces relapses at least during the entire pp year but contrasts with those not detecting any 4 months to reduce relapse rate. The ability to prevent very early pp relapses by rapid restart of fast-acting DMT after delivery seems restricted considering their immunological background. As a decline of circulating CD4+ interferon-gamma producing cells—which starts already in the third trimester of pregnancy—might sensitise for these relapses, it might be too late to try to counter this process starting a treatment only after delivery. Pregnancy has been shown to not be a continuous immunosuppressed phase, but dynamic and consisting of different stages. Of note, the third trimester is characterised by an inflammatory immune state necessary to induce delivery and labour.

If exBF is regarded as a treatment, it seems to be an attractive early strategy with multiple health benefits for mother and child. Some modern cohorts, including ours, found a reduction in the pp relapse risk compared with no-exBF or not exBF, with relapses ranging between 9% and 25% consistent with the results of a recent meta-analysis. In our present cohort, relapse risk was higher (38%) compared with other studies in those pregnancies. The ability to prevent very early pp relapses by rapid restart of fast-acting DMT after delivery seems restricted considering their immunological background. As a decline of circulating gamma producing cells—which starts already in the third trimester of pregnancy—might sensitise for these relapses, it might be too late to try to counter this process starting a treatment only after delivery. Pregnancy has been shown to not be a continuous immunosuppressed phase, but dynamic and consisting of different stages. Of note, the third trimester is characterised by an inflammatory immune state necessary to induce delivery and labour.

Whereas rapid DMT-reintroduction after delivery did not show superiority in very early relapse reduction in our cohort we observed a plausible temporal dynamic in relapse reduction over the course of first 6 months pp with the NTZ/FTY-strategy. In contrast to our cut-off of 6 weeks pp, the definition of ‘early’ DMT resumption differs between studies, ranging from a few days after delivery, 2 weeks to 1 (1, 10, 22), 2 (4) and 3 (23) months and includes highly effective therapies or injectables. Our findings are in line with several studies showing that ‘early’ DMT-resumption reduces relapses at least during the entire pp year but contrasts with those not detecting any or a case series which at least descriptively showed immediate

### Table 2: Postpartum clinical characteristics in the four strategies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exclusive breastfeeding strategy† n=416</th>
<th>NTZ/FTY strategy† n=112</th>
<th>Other-DMT-strategy† n=93</th>
<th>No-DMT-no-exBF-strategy† n=290</th>
<th>P value overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies with ≥1 relapse during first 6 months pp, No. (%)</td>
<td>159 (38.2)</td>
<td>27 (24.1)</td>
<td>22 (23.7)</td>
<td>129 (44.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse during first month pp, No. (%)</td>
<td>29 (7.0)</td>
<td>8 (7.1)</td>
<td>3 (3.2)</td>
<td>44 (15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse during second month pp, No. (%)</td>
<td>35 (8.4)</td>
<td>9 (8.0)</td>
<td>4 (4.3)</td>
<td>28 (9.7)</td>
<td>0.448</td>
</tr>
<tr>
<td>Relapse during third month pp, No. (%)</td>
<td>32 (7.7)</td>
<td>4 (3.6)</td>
<td>6 (6.5)</td>
<td>32 (11.0)</td>
<td>0.077</td>
</tr>
<tr>
<td>Relapse during fourth month pp, No. (%)</td>
<td>37 (8.9)</td>
<td>5 (4.5)</td>
<td>4 (4.3)</td>
<td>20 (6.9)</td>
<td>0.238</td>
</tr>
<tr>
<td>Relapse during fifth month pp, No. (%)</td>
<td>34 (8.2)</td>
<td>4 (3.6)</td>
<td>8 (8.6)</td>
<td>22 (7.6)</td>
<td>0.401</td>
</tr>
<tr>
<td>Relapse during sixth month pp, No. (%)</td>
<td>29 (7.0)</td>
<td>1 (0.9)</td>
<td>4 (4.3)</td>
<td>23 (7.9)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

†Describes number of cases with reported relapse in each month, 72 cases relapsed more than once during the first 6 months pp: n=31 with exBF-strategy, n=17 with no-exBF-strategy, n=147 cases and exclusive breast feeding in n=7 with no-exBF-strategy, n=27 with exBF-strategy, n=48 cases but only for a median duration of 6 weeks (IQR 4–18).

‡Describes number of cases with reported relapse in each month, 72 cases relapsed more than once during the first 6 months pp: n=31 with exBF-strategy, n=17 with no-exBF-strategy, n=147 cases and exclusive breast feeding in n=7 with no-exBF-strategy, n=27 with exBF-strategy, n=48 cases but only for a median duration of 6 weeks (IQR 4–18).

*Definition of strategy: exclusive breastfeeding strategy, women breast feeding for at least 2 months without regular replacement of any meal by supplemental feeding including those initially breast feeding exclusively but replacing a meal or weaning within 2 weeks after a relapse in the first 2 months pp; NTZ/FTY-strategy, women re-starting NTZ or FTY-treatment within 6 weeks pp before a relapse; other-DMT-strategy, women re-starting another DMT within 6 weeks pp before a relapse; no-DMT-no-exBF-strategy, women neither breast feeding exclusively nor (re)starting a DMT within first 6 weeks pp or restarting DMT within this time frame but after a relapse; women exclusively breast feeding under a DMT were included in respective DMT-strategy if treatment was started (not necessarily within 6 weeks pp) before a relapse; if afterwards they were included into the exclusive breastfeeding strategy.

1No breast feeding was reported in n=9/649/95 cases in the NTZ/FTY-(other-DMT-) strategy, respectively, some but not exclusive breast feeding in n=6/147 cases and exclusive breast feeding in n=27/48 cases but only for a median duration of 6 weeks (IQR 4–18).

4Describes number of cases with reported relapse in each month, 72 cases relapsed more than once during the first 6 months pp: n=31 with exBF-strategy, n=3 with NTZ/FTY-strategy, n=6 with other-DMT-strategy and n=32 with no-DMT-no-exBF-strategy.

DMT, disease modifying therapy; FTY, fingolimod; NTZ, natalizumab; pp, post partum.
Multiple sclerosis

Given the numerous health benefits of exBF for mothers and their infants including a reduced risk of developing diabetes/ breast or ovarian cancer in the mothers, reduced risk of obesity/ diabetes, higher intelligence quotients in children and reduction of infant mortality also in high income settings, 24–26 women with chronic diseases such as MS should be able to combine both. In our study, DMT and breast feeding were basically mutually exclusive with only 4% breast feeding under DMTs. Whether a combined strategy may be effective is unclear and has to be investigated in the future. Currently, breast feeding under DMTs on label in the European Union is restricted to interferon-beta, 27 very recently glatiramer acetate 28 and ofatumumab. 29 However, there is emerging evidence that monoclonal antibodies only enter the breastmilk in small amounts 30–32 and off-label breast feeding under monoclonal antibodies in MS seems to be safe for breastfed infants 33–13 as they might not be absorbed by the child and thus not pharmacologically effective. Owing to their higher oral bioavailability and molecular properties favouring excretion into breastmilk, oral administered DMTs are currently not considered compatible with breast feeding. 34 Interestingly, two recently published case reports on cladribine 35 and dimethyl fumarate 36 show relatively low concentrations in breastmilk with a relative infant dose of below the acceptable threshold of 10%. Given that breast feeding under oral drugs is considered compatible in epilepsy with a partially reversal of prenatal valproic acid induced cognitive teratogenicity through exposed breast feeding 37–39 and breast feeding is recommended for example, under azathioprine, we need to get more and timely information of the content of oral drugs in the breastmilk.

Our study has several limitations. The sample size for the following subgroup analysis was too small to analyse and draw firm conclusions: (1) women who breastfed under DMTs, (2) women treated with DMTs with long-lasting effect (alemtuzumab, cladribine, ocrelizumab or rituximab) before or during pregnancy, (3) women who restarted DMTs with long-lasting effect pp and (4) women who restarted NTZ pp. We did not have EDSS values for the entire cohort, so we cannot postulate an effect in the severity of relapses in the strategies. Currently, it is scientifically discussed if prolactin can promote remyelination 40 and future studies should investigate its effect on severity of relapses. Also, the lacking analyses of MRI results preclude statements on effects on subclinical disease activity. We did not inquire the strategy during the interviews; therefore, it is possible that our strategy-definition differentially misclassified those in the no-DHT-no-exBF-strategy and worsened this group. exBF-strategy was not evenly distributed between the most severe cases and the rest of the cohort and although statistical analyses accounted for this imbalance residual confounding is still possible. Finally, being a registry study there may have been a selection bias, so extrapolations to community-based populations need to be made with caution.

Strengths of our study include the unique patient population and large sample size, prospective follow-up and detailed information on breastfeeding status.

CONCLUSION

In this cohort, the early NTZ/FTY restart during the first 6 weeks pp reduced pp relapse hazard significantly from month 3, compared with the exBF-strategy. Appropriate counselling should be provided to every woman before or latest during pregnancy. In the future, more data on breast feeding under DMTs are needed.
REFERENCES


