Exclusive Breastfeeding and the Effect on Postpartum Multiple Sclerosis Relapses

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IMPORTANCE  Women with multiple sclerosis (MS) experience an elevated risk of relapse after giving birth. The effect of exclusive breastfeeding on postpartum risk of MS relapse is unclear.

OBJECTIVES  To determine the effect of exclusive breastfeeding on postpartum risk of MS relapse and to investigate the effect of introducing supplemental feedings on that risk.

DESIGN, SETTING, AND PARTICIPANTS  Data on 201 pregnant women with relapsing-remitting MS were collected prospectively from January 1, 2008, to June 30, 2012, with 1 year follow-up post partum in the nationwide German MS and pregnancy registry. The effect of the intention to breastfeed exclusively (no regular replacement of breastfeeding meals with supplemental feedings) for at least 2 months compared with nonexclusive breastfeeding (partial or no breastfeeding) on the first postpartum MS relapse, using Cox proportional hazards regression model adjusted for age and disease activity, before and during pregnancy was analyzed. Data analysis was performed from August 30, 2013, to May 25, 2015.

EXPOSURE  Exclusive breastfeeding defined as at least 2 months of breastfeeding without regular replacement of any meal by supplemental feeding.

MAIN OUTCOME AND MEASURE  First postpartum MS relapse.

RESULTS  Of 201 women, 120 (59.7%) intended to breastfeed exclusively for at least 2 months and 81 (40.3%) breastfed and included supplemental feeding (42 [20.9%]) or did not breastfeed (39 [19.4%]). Thirty-one women (38.3%) who did not breastfeed exclusively had a relapse within the first 6 months post partum compared with 29 women (24.2%) who intended to breastfeed exclusively for at least 2 months (unadjusted hazard ratio, 1.80; 95% CI, 1.09-2.99; P = .02; adjusted hazard ratio, 1.70; 95% CI, 1.02-2.85; P = .04). The time to first postpartum relapse after the introduction of supplemental feedings did not differ significantly between women who previously breastfed exclusively and those who did not (P = .60).

CONCLUSIONS AND RELEVANCE  The findings of this study suggest that exclusive breastfeeding is a modestly effective MS treatment with a natural end date. Our study provides further evidence that women with MS who breastfeed exclusively should be supported to do so since it does not increase the risk of postpartum relapse.
Approximately 20% to 30% of the women with multiple sclerosis (MS) in historical and contemporary cohorts experience a relapse within the first 3 to 4 months post partum.\(^{1,2}\) Even in the modern treatment era, there are no documented interventions for effective prevention of postpartum relapse. The effect of exclusive breastfeeding—a natural and overall beneficial option for mother and child\(^ {3—10} \)—on postpartum risk of MS relapse is controversial.\(^ {4,5} \) A few studies\(^ {2,6} \) found that exclusive breastfeeding for at least the first 2 months post partum might be beneficial; other studies, which defined breastfeeding crudely and/or measured breastfeeding retrospectively, did not confirm a beneficial effect on the postpartum risk of relapse.\(^ {7—9} \) Because exclusive breastfeeding is physiologically different from breastfeeding with supplemental feeding or not breastfeeding\(^ {10} \) and social pressures strongly influence breastfeeding choices the effect must be measured carefully and prospectively. It is also important to examine this issue in a large, modern cohort because the results of older cohorts may no longer be generalizable to women who receive MS medications before pregnancy.

To clarify the role of exclusive breastfeeding on the postpartum risk of MS relapse, we assembled a large, prospective cohort of pregnant women with MS, most of whom received treatment before pregnancy. We also examined whether the introduction of supplemental feedings is associated with a return of disease activity to test the hypothesis that exclusive breastfeeding acts like a treatment with a natural end date.

Methods

Study Population

This study included 201 women with relapsing-remitting MS\(^ {11} \) who voluntarily enrolled in the nationwide German MS and pregnancy registry (Deutsches Multiple Sklerose und Kinderwunschregister) between January 1, 2008, and June 30, 2012. Only women who enrolled in the registry during pregnancy were included in this study. Most women who enrolled responded to advertisements; some were recruited after referral by their treating health care professionals. The registry is approved by the local institutional review board of the Ruhr-University Bochum. Details on the registry, which was established in 2006, have been published.\(^ {12} \) All women provided written informed consent; no financial compensation was provided. Data were deidentified.

Data Collection

Women are contacted after study entry in each remaining trimester of pregnancy, the first 6 weeks post partum, and months 3, 6, and 12 post partum to complete a structured, interviewer-administered questionnaire by telephone or in person during visits to the St Josef Hospital, Bochum outpatient clinic. Briefly, during pregnancy, a detailed history of MS (diagnosis, disease activity, and treatment) and reproductive history are obtained as well as intention to breastfeed. Follow-up interviews gathered other information on the state of pregnancy and delivery, type of delivery, outcome of pregnancy, relapses, and medications.

A detailed breastfeeding history with the exact date of introduction of supplemental feedings and return of menses was obtained. We attempted to avoid the Hawthorne effect by informing women about the broad context of the MS and pregnancy registry but not the detailed research question of the effect of exclusive breastfeeding. Raw data (number of relapses during the first 6 months post partum) of 72 patients involved in this study were included in a recently published meta-analysis\(^ {13} \) and were presented at the 2011 American Academy of Neurology meeting.\(^ {14} \) Data analysis for the present study was performed from August 30, 2013, to May 25, 2015.

Definition of Exposures

Exclusive breastfeeding was defined as breastfeeding for at least 2 months without regular replacement of any meal by supplemental feeding. Nonexclusive breastfeeding was defined as no breastfeeding or combining breastfeeding with the introduction of regular supplemental feeding in the first 2 months post partum for reasons other than relapse symptoms. The date of the first supplemental feeding was documented as the date when the first breastfeeding meal was fully replaced by any kind of supplemental feeding: formula, other liquid, or solids. We also recorded the first date of postpartum return of menses as a surrogate marker for the exclusivity of breastfeeding.

Definition of Primary Outcome

An MS relapse was defined as the appearance, reappearance, or worsening of symptoms of MS neurologic dysfunction lasting for at least 24 hours that could not be explained by a current infection, fever, or other causes.\(^ {15} \) Relapses were confirmed with the patients’ treating neurologists.

Statistical Analysis

Descriptive statistics using mean (SD) were compared using 2-sided \(t \) tests if the variables were normally distributed. In cases of nonnormally distributed variables, we used the Wilcoxon rank sum test. A \(\chi^2 \) test and Fisher exact test were performed to assess differences between categorical variables.

All results presented are based on the intention to breastfeed. The time of onset of the first postpartum relapse was determined by using the Kaplan-Meier method. Adjusted and unadjusted hazard ratios (HRs) were calculated using Cox proportional hazards regression methods. Estimates of exclusive breastfeeding were adjusted for relapse frequency in the 2 years before pregnancy (≤1 or >1 year), pregnancy relapse (yes or no), and age (categorized around the median). If a covariate changed the \(\beta \) coefficient of the main effect by more than 15% or demonstrated an association with both the exposure and outcome \((P < .20)\), it was considered a confounder. Disease duration, treatment with disease-modifying therapy (DMT) before pregnancy, and becoming pregnant while receiving DMT (yes or no) were tested but did not meet these criteria for confounding.

The time to first postpartum relapse after the introduction of supplemental feeding and return of menses (as a surrogate of breastfeeding duration) was determined with the
same methods described above. The return of menses was categorized around the median in 2 groups.

To examine whether resuming DMT shortly after delivery could reduce the risk of postpartum relapse we first examined the distribution of women who breastfed and/or resumed DMT within 30 days postpartum. Consistent with the lack of safety information of using DMT medications during lactation, these behaviors were virtually mutually exclusive: only 2 women breastfed at least some of the time (only 1 exclusively) and resumed DMT within 30 days. This small number precluded our ability to examine the effects independently. Thus, we divided our cohort into 3 groups based on their breastfeeding and DMT use behavior. These groups were as follows: (1) exclusive breastfeeding without early resumption of DMT (within 30 days of delivery [reference category]), (2) breastfeeding with some supplemental feeding or no breastfeeding and did not resume DMT within 30 days, and (3) breastfeeding with some supplemental feeding or no breastfeeding and resumed DMT within 30 days. We chose 30 days as the cut-off time because DMT agents have a delay in onset of action ranging from 3 to 6 months and the risk of postpartum relapse is highest in the first 3 to 4 months post partum.1

We also assessed propensity score-adjusted Cox proportional hazards regression models as a method of observational studies to account for bias in a choice of treatment or behavior (in our study, breastfeeding) in a nonrandomized setting.16 The multivariable logistic regression model used to develop the propensity score for nonexclusive breastfeeding included all the following variables: relapse frequency before pregnancy, relapse frequency during pregnancy, use of DMT before pregnancy, use of DMT at the time of conception (yes or no), disease duration, and age, using the same variable definitions as for the multivariable Cox regression models. We controlled for sufficient overlap in the propensity scores between exclusive and nonexclusive breastfeeding women. Propensity score quintiles were then used in the Cox regression models.

A 2-tailed value of \( P < .05 \) was considered significant. Statistical analyses were conducted using SAS, version 9.2 (SAS Institute).

### Results

Of 201 women enrolled into the study, 120 (59.7%) intended to breastfeed exclusively for at least 2 months. Of these, 4 women (3.3%) stopped breastfeeding exclusively owing to a relapse during the first 2 months. Thirty-nine women (19.4%) did not breastfeed and 42 women (20.9%) combined breastfeeding with supplemental feedings within the first 2 months post partum. Thirty-three (78.5%) women who did not breastfeed exclusively introduced supplemental feedings during the first 4 weeks post partum (median, 19 days; range, 1-59).

General characteristics at pregnancy onset, duration, and post partum are presented in Table 1. Most women (178 [88.6%]) had used DMT agents before pregnancy: 46 individuals (22.9%) had received glatiramer acetate, 107 (53.2%) had received interferon beta, 22 (10.9%) had received natalizumab, 2 (1.0%) had received intravenous immunoglobulins, and 1 (0.5%) had received rituximab. Women who breastfed exclusively were older and less likely to have received DMT before or at the time of conception. They were also less likely to have had a relapse during pregnancy and had a later return of menses compared with women who did not breastfeed exclusively. Women who breastfed exclusively were significantly less likely to restart DMT during the first 30 days post partum.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Breastfeeding</th>
<th>Nonexclusive</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>31.9 (3.8)</td>
<td>30.4 (4.7)</td>
<td>.03</td>
</tr>
<tr>
<td>MS duration, median (range), mo</td>
<td>55 (1 to 240)</td>
<td>53 (1 to 219)</td>
<td>.82</td>
</tr>
<tr>
<td>Relapse during 2 y before pregnancy, No. (%)</td>
<td></td>
<td></td>
<td>.41</td>
</tr>
<tr>
<td>0</td>
<td>28 (23.3)</td>
<td>18 (22.2)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43 (35.8)</td>
<td>35 (43.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34 (28.3)</td>
<td>20 (24.7)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>15 (12.5)</td>
<td>8 (9.9)</td>
<td></td>
</tr>
<tr>
<td>DMT prior to pregnancy, No. (%)</td>
<td></td>
<td></td>
<td>.007</td>
</tr>
<tr>
<td>101 (84.2)</td>
<td>78 (96.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During pregnancy, No. (%)</td>
<td></td>
<td></td>
<td>.07</td>
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<tr>
<td>Relapse</td>
<td>20 (16.7)</td>
<td>22 (27.2)</td>
<td></td>
</tr>
<tr>
<td>DMT</td>
<td>44 (36.7)</td>
<td>59 (72.8)</td>
<td>≤.001</td>
</tr>
<tr>
<td>Post partum</td>
<td></td>
<td></td>
<td>≤.001</td>
</tr>
<tr>
<td>First menses, median (range), d</td>
<td>185 (42 to 699)</td>
<td>64 (19 to 168)</td>
<td>≤.001</td>
</tr>
<tr>
<td>DMT during first 30 d before relapse, No. (%)</td>
<td>1 (0.8)</td>
<td>29 (35.8)</td>
<td>≤.001</td>
</tr>
<tr>
<td>Time to restart DMT after birth, median (range), d</td>
<td>241 (0 to 644)</td>
<td>39 (~152 to 379)</td>
<td>≤.001</td>
</tr>
</tbody>
</table>

Abbreviations: DMT, disease-modifying therapy; MS, multiple sclerosis.
Predictors of Nonexclusive Breastfeeding
Reported as adjusted odds ratios (95% CIs), having a relapse during pregnancy (2.79 [1.25-6.23]; P = .01) and using DMT medications at the time of conception (4.10 [2.1-8.1]; P < .001) were independent predictors of nonexclusive breastfeeding. The other factors included in the propensity score (older age, longer disease duration, more frequent relapses in the 2 years before pregnancy, and ever receiving DMT) were not independently associated with this behavior.

Predictors of Postpartum Relapse
Predictors of postpartum relapse are summarized in Table 2. Only nonexclusive breastfeeding and relapse during pregnancy were independently associated with a significantly increased risk of postpartum relapse. Older age at onset of pregnancy was associated with a decreased risk of postpartum relapse; however, this finding was not statistically significant. No associations between postpartum relapse and disease duration, DMT use before pregnancy, and ever receiving DMT) were not independently associated with this behavior.

Exclusive Breastfeeding and Postpartum Relapse
Thirty-one women (38.3%) who did not breastfeed exclusively for at least 2 months had a relapse in the first 6 months postpartum compared with 29 women (24.2%) who breastfed exclusively. Women who did not breastfeed exclusively for at least 2 months had a significantly increased risk of relapse in the first 6 months post partum (unadjusted HR, 1.80; 95% CI, 1.09-2.99; P = .02). After adjusting for age, prepregnancy relapse frequency, and relapse during pregnancy or using the propensity score method to account for additional factors associated with breastfeeding exclusively, the magnitude of effect was similar and statistically significant (adjusted HR, 1.70; 95% CI, 1.02-2.85; P = .04) (Figure 1). With the propensity score method, the odds ratio was 1.78 (95% CI, 1.02-3.08; P = .04). Women who did not breastfeed exclusively experienced nearly the same risk for a postpartum relapse within the first 6 months as did those who did not breastfeed (adjusted HR, 0.96; 95% CI, 0.45-2.03; P = .91). The return of menses within the first 4 months post partum (a surrogate marker of lower breastfeeding duration and intensity) was independently associated with a trend toward higher risk for relapse during the first 6 months post partum (adjusted HR, 1.46; 95% CI, 0.94-2.26; P = .09).

Among the 81 women who chose to include supplemental feedings with breastfeeding or to not breastfeed, 29 (35.8%) resumed DMT within the first 30 days post partum (9 [11.1%] had received glatiramer acetate; 14 [17.3%] had received interferon beta; and 6 [7.4%] had received natalizumab). These women had a similar risk of postpartum relapse within the first 6 months compared with the 52 women who did not breastfeed exclusively and did not resume DMT (34.6% vs 44.8%; P = .36; unadjusted HR, 1.37; 95% CI, 0.46-2.80; P = .38; adjusted HR, 1.36; 95% CI, 0.63-2.94; P = .42). Compared with women who breastfed exclusively, those who resumed DMT early had a higher risk of postpartum relapse (unadjusted HR, 2.20; 95% CI, 1.14-4.23; P = .02 and adjusted HR, 2.02; 95% CI, 1.03-3.99; P = .04).

Introduction of Supplemental Feedings
Most women who intended to breastfeed exclusively introduced supplemental infant feedings in the second half of the...
Discussion

In this large, prospective contemporary cohort study of pregnant women with MS, those who intended to breastfeed their infants exclusively for at least 2 months had a significantly lower risk of relapse during the first 6 months postpartum compared with those who did not breastfeed exclusively. The effect of exclusive breastfeeding seems to be plausible, since disease activity returned in the second half of the postpartum year in exclusively breastfeeding women, corresponding to the introduction of supplemental feedings and the return of menstrual cycles. Taken together, our findings suggest that exclusive breastfeeding acts like a modestly effective treatment with a natural end date. There is a strong biological rationale to carefully distinguish between exclusive and nonexclusive breastfeeding rather than breastfeeding with supplemental feeding vs not breastfeeding as was done in most previous MS studies. The introduction of regular formula feedings or solid food leads to a distinct change in the women’s hormonal status resulting in the return of ovulation. During exclusive breastfeeding, the pulsatile release of gonadotropin-releasing hormone and luteinizing hormone is suppressed with a corresponding suppression of the growth of ovarian follicles resulting in lactational amenorrhea and anovulation. Shortly after the breastfeeding frequency is reduced (1 or 2 regularly replaced breastfeeding meals are sufficient to interrupt this cycle), the ovarian activity resumes with the return of menses. Therefore, the effect of exclusively breastfeeding on MS relapse was potentially masked by combining exclusively with nonexclusively breastfeeding women into 1 group.

The health benefits of breastfeeding for the child are well recognized in Western societies. It is therefore important to collect breastfeeding information prospectively since women may be likely to more favorably recall how long and exclusively they breastfed their infants when data are ascertained prospectively. For this reason, it is also important to examine neutral indicators of the frequency and intensity of breastfeeding, such as the return of menses and introduction of supplemental feedings, as we did. This difference in data collection methods may explain the discrepancy between the findings from the present study and those of a large Italian study in which exclusive breastfeeding information was obtained retrospectively and no information on the return of menses or introduction of supplemental feedings was reported.

Confounding by indication (women with higher disease activity are more likely to forego breastfeeding and therefore have a higher risk for postpartum relapse) has been discussed as a possible explanation for the reduced risk of relapse in women who breastfeed. We think this is an unlikely explanation for our findings because we were not able to demonstrate a relationship between prepregnancy disease severity and the choice to forego exclusive breastfeeding. In addition, our cohort consisted almost entirely of women who received DMT before pregnancy, implying more active disease than in previous cohorts. If confounding by indication was the explanation for the differing findings between previous studies and ours, the selection bias for women with more severe disease included in our study should have led to no effect of breastfeeding. Finally, to control for confounding by indication, we used 2 well-recognized statistical methods (standard multivariable adjustment and propensity score matching), both of which indicate a modest beneficial effect of exclusive breastfeeding on reducing the risk of MS relapse in the first 6 months postpartum.

The most important independent predictors of forgoing exclusive breastfeeding were DMT before pregnancy and continued DMT until conception. However, neither of these factors predicted the likelihood to experience a postpartum...
relapse. To our knowledge, these findings are novel. The decision to continue medication into pregnancy seems to represent a behavior that influences another behavior (breastfeeding), without having an effect of the postpartum risk of relapse. These findings are consistent with those of an Italian study in which DMT at any time before pregnancy did not alter the postpartum risk of relapse but are in contrast with those of a study that found DMT use before pregnancy to be associated with a reduced risk of relapse post partum. However, since most women in the latter study stopped DMT during the first trimester, a sustained benefit for 9 to 12 months after the last dose does not seem plausible and is likely a chance finding.

Our findings that prepartum relapse was not predictive of postpartum relapse and that MS treatment at the time of conception is strongly associated with the decision to forgo breastfeeding and resume DMT post partum underscores the importance of studying these issues in a contemporary cohort. In contrast to previous studies, approximately 90% of the women in the present study received DMT agents before pregnancy, which is nearly twice the number than reported from recent cohorts. Therefore, it is not surprising that the prepregnancy relapse rate in our study is lower than the one reported in the landmark Pregnancy in Multiple Sclerosis study and that the rate is no longer an important predictor of postpartum relapse in women receiving DMT before pregnancy, although the retrospective assessment of relapse before the cohort entry is a limitation in our study similar to that of previous studies.

We speculate that, as a putative mechanism for the reduced risk of relapse, hormonal changes leading to anovulation might play a key role since women with MS are less likely to receive the diagnosis during their anovulatory years (childhood or after menopause) and women with MS were found to be more likely to experience relapse shortly before menstruation. Healthy ovulating women experience cytokine changes related to the menstrual (ovulatory) cycle, with fluctuation of tumor necrosis factor, a proinflammatory cytokine in MS. In a pilot study of postpartum women with MS, the return of menses was associated with a rise in tumor necrosis factor levels. In the present study, we observed that an earlier return of menses was associated with a higher risk of relapse in the first 6 months post partum. This earlier return, combined with our finding that relapse activity returned after introduction of regular supplemental feedings in the exclusively breastfeeding group, strongly suggests that exclusive breastfeeding acts like a treatment with a natural end date.

In contrast, women who resumed treatment with DMT within 1 month after delivery appeared to have a trend toward a higher risk of postpartum relapse compared with women who breastfed exclusively. We think this finding is driven by the potentially beneficial effects of exclusive breastfeeding rather than a harmful effect of DMT medications, since women who did not breastfeed exclusively or resume DMT early had a similar risk of relapse compared with women who resumed DMT. Most women used interferon beta or glatiramer acetate post partum; thus, we cannot exclude the possibility that treatment with natalizumab or fingolimod, agents that demonstrated clear superiority over injectable DMT medications, has the potential to reduce the risk of postpartum relapse compared with exclusive breastfeeding.

The main limitation of this study is selection bias inherent to voluntary registries. This bias is reflected in the high proportion of women receiving DMT. Thus, the magnitude of effect in this study likely represents an underestimation of the relationship between nonexclusive breastfeeding and the risk of postpartum relapse.

The strengths of our study include the large sample size, prospective design, frequent follow-up intervals, and carefully collected information on the intention to breastfeed with exact dates of the introduction of supplemental feeding and return of menses.

Our results are important for clinical practice since breastfeeding is highly promoted for the first 6 months of life owing to various well-known beneficial effects for the mother and child. One small study suggested that breastfeeding may decrease the risk to develop MS in infants.

Conclusions

Taken together, our findings indicate that women with MS should be supported if they choose to breastfeed exclusively since it clearly does not increase the risk of postpartum relapse. Relapse in the first 6 months post partum may be diminished by exclusive breastfeeding, but once regular feedings are introduced, disease activity is likely to return.
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**REFERENCES**