Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort

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Abstract

Objective

To determine whether women with multiple sclerosis (MS) diagnosed according to current criteria are at an increased risk of postpartum relapses and to assess whether this risk is modified by breastfeeding or MS disease-modifying therapies (DMTs), we examined the electronic health records (EHRs) of 466 pregnancies among 375 women with MS and their infants.

Methods

We used prospectively collected information from the EHR at Kaiser Permanente Southern and Northern California between 2008 and 2016 of the mother and infant to identify treatment history, breastfeeding, and relapses. Multivariable models accounting for measures of disease severity were used.

Results

In the postpartum year, 26.4% relapsed, 87% breastfed, 36% breastfed exclusively for at least 2 months, and 58.8% did not use DMTs. At pregnancy onset, 67.2% had suboptimally controlled disease. Annualized relapse rates (ARRs) declined from 0.37 before pregnancy to 0.14–0.07 ($p < 0.0001$) during pregnancy, but in the postpartum period, we did not observe any rebound disease activity. The ARR was 0.27 in the first 3 months postpartum, returning to prepregnancy rates at 4–6 months (0.37). Exclusive breastfeeding reduced the risk of early postpartum relapses (adjusted hazard ratio = 0.37, $p = 0.009$), measures of disease severity increased the risk, and resuming modestly effective DMTs had no effect (time-dependent covariate, $p = 0.62$).

Conclusion

Most women diagnosed with MS today can have children without incurring an increased risk of relapses. Women with suboptimal disease control before pregnancy may benefit from highly effective DMTs that are compatible with pregnancy and lactation. Women with MS should be encouraged to breastfeed exclusively.

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Glossary

ARR = annualized relapse rate; **cEHR** = complete electronic health record; **CI** = confidence interval; **CIS** = clinically isolated syndrome; **DMT** = disease-modifying therapy; **EHR** = electronic health record; **GLAT** = glatiramer acetate; **HR** = hazard ratio; **IFN- β** = interferon-beta; **IQR** = interquartile range; **KPNC** = Kaiser Permanente Northern California; **KPSC** = Kaiser Permanente Southern California; **MS** = multiple sclerosis; **OR** = odds ratio; **PS** = propensity score; **RRMS** = relapsing-remitting MS.

Women with multiple sclerosis (MS) are widely counseled that their risk of relapse will decline during pregnancy only to rebound in the early postpartum period before returning to their prepregnancy risk later in the postpartum year. These counseling recommendations are based on the findings from a study of women recruited from multiple referral centers over 24 years ago.¹ Since then, MS diagnostic criteria have been revised to allow for earlier diagnosis and diagnosis of milder cases, calling into question the generalizability of these findings in contemporary MS populations.

The fear of postpartum relapses affects family planning, treatment, and breastfeeding choices. Women must choose whether to forego breastfeeding, forego MS disease-modifying therapies (DMTs), or accept the uncertain risks of breastfeeding while on a DMT. Although the infant and maternal health benefits of prolonged breastfeeding are well established, whether resuming DMTs reduces the risk of postpartum MS relapses has yet to be demonstrated.^{2–4}

Previous studies that have attempted to address these controversies have significant methodological limitations including selection bias,^{2,4–8} referral center bias,^{2,4–8} small sample,^{6,7} and incomplete or poor measures^{1,5,7,8} of breastfeeding and yielded mixed results. For example, breastfeeding exclusively for at least 2 months has been associated with a reduced risk of postpartum relapses,^{4,6} some breastfeeding with no effect^{1,5,8} or marginal benefit,⁹ and more formula feedings among breastfeeding women with an increased risk of postpartum relapses.¹⁰ A meta-analysis of breastfeeding and postpartum MS relapse risk showed a potentially protective effect but raised questions about incompletely controlling for confounding by indication,¹¹ particularly since resuming DMTs while breastfeeding were mutually exclusive events because women with more active disease before pregnancy were being counseled to forego breastfeeding to resume medications.⁷ Resuming DMTs within 2 weeks,³ 2⁴ or 3 months,² or sometime during the postpartum year⁸ has failed to demonstrate benefit.

The objective of this study was to assess the risk of pregnancy-associated MS relapses in a contemporary, population-based cohort and to identify whether breastfeeding or treatment choices modify these risks.

Methods

Study population

Pregnant women with MS or its precursor, clinically isolated syndrome (CIS), were identified through the membership of

Kaiser Permanente Southern California (KPSC) and Kaiser Permanente Northern California (KPNC). We searched electronic databases to identify members with MS or CIS with live births between January 2008 and April 2016 using a combination of *International Classification of Diseases, Ninth Revision* or *Tenth Revision* codes for MS or CIS and pregnancy.³ The complete electronic health records (cEHRs) were reviewed to determine eligibility by an MS expert (A.L.-G.). All KPSC and KPNC members who met the 2010 McDonald criteria for MS,¹² regardless of subtype, or CIS¹³ during or at the onset of pregnancy were included.

KPSC and KPNC provide care to over 7 million members in California. Approximately 20% and 30% of the general population in the geographic areas served belong to the health plans in Southern and Northern California, respectively. The sociodemographic characteristics of KPSC and KPNC members are generally representative of the underlying population.¹⁴

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the KPSC and KPNC institutional review board.

Data collection

Symptom onset, relapses, and disability level were abstracted from the mother's cEHR by an MS expert (A.L.-G.) blinded to treatment history and breastfeeding. Relapses were defined as the occurrence, reappearance, or worsening of symptoms of neurologic dysfunction lasting for 48 hours or more and needed to be documented by a treating physician during a physical examination. Symptoms that occurred within 1 month of each other were part of the same relapse. No MS-related disability was defined as documentation of a normal/near-normal neurologic examination, no fatiguing limb weakness, or significant visual or bladder impairment. Treatment history was collected through electronic searches and verified via cEHR review conducted by a research professional.

Breastfeeding, formula feeding, and introduction of solid food were abstracted from the infant's medical record by a research professional blinded to the mother's clinical history. This information is routinely recorded via a standard questionnaire administered by nursing staff at the infant well-baby/immunization visits at 2 days, 2 weeks, and 2, 4, 6, 9, and 12 months of age. After the 2-month visit, if an infant was noted to be breastfeeding one visit but had stopped by the

subsequent visit, the mother's cEHR was reviewed for mention of breastfeeding, and the last recorded date of breastfeeding was chosen as the stop date.

Statistical analyses

To describe the natural history of MS, we calculated annualized relapse rates (ARRs) for the 2 years before pregnancy, each trimester during pregnancy, and each 3-month interval during the postpartum year. The relapse rate was calculated in each period by using the annualized relapses (calculated by dividing the actual relapses in the period by time in years, 0.33 for most) divided by the total pregnancies in that period (or women at risk for the 2 years before pregnancy). The 95% confidence interval (CI) and values comparing pregnancy and postpartum trimesters to the prepregnancy period were calculated by Poisson regression. Generalized estimation equations were used to account for women with multiple pregnancies.

Breastfeeding was defined a priori as exclusive (no formula feedings for at least the first 2 months postpartum) as in previous studies,^{4,6} nonexclusive (breast and formula feedings within 2 months), or none (reference group). The 2-month mark was chosen in this and previous studies^{4,6} because it is when milk supply becomes well established (i.e., the hardest months to get through) and attainable. In accordance with intention to treat, women who stopped breastfeeding within 2 months postpartum after an MS relapse ($n = 2$) were classified as breastfeeding exclusively.

The association between breastfeeding and use of DMT in the postpartum period and the time to onset of the first postpartum relapse was determined by survival analysis. Adjusted and unadjusted hazard ratios (HRs) were calculated by using the Cox proportional hazards regression. Primary analyses assessed the associations with the time to onset within the first 6 months postpartum because this is when postpartum rebound disease activity has been reported and when exclusive breastfeeding ends naturally with introduction of solids.⁴ Exclusive breastfeeding was modeled as a fixed covariate, and DMT use was modeled as a time-dependent covariate in the data analysis. To allow for comparison, estimates of breastfeeding and postpartum DMT use were adjusted, both singly and in combination, for age and disease duration at the onset of pregnancy (in years), relapse frequency in the 2 years before conception (0–1 or ≥ 2), treatment with DMTs in the year before pregnancy (yes/no), MS-related disability (yes/no), and relapses during pregnancy (yes/no). The independent effects of these factors were also tested. The robust sandwich covariance matrix estimate was used in all models to account for women with multiple pregnancies. All models were hypothesis driven and defined based on a priori knowledge of potential measures of disease severity (age, relapse frequency, relapses during pregnancy, disability, and disease duration). Prepregnancy DMT use was included because it has been associated with decision to breastfeed or resume DMTs in previous studies.⁴

Because interferon-beta (IFN-beta) and glatiramer acetate (GLAT), the most commonly used postpartum DMTs, have a delayed onset of action as previously suggested,² we conducted secondary analyses examining DMT use over the entire postpartum year and whether early postpartum DMT use (within 2 months postpartum and before a relapse) reduced the risk of subsequent postpartum relapses.

To determine whether the effect of breastfeeding or DMT use varies by disease severity, we conducted sensitivity analyses in women with suboptimally controlled disease at pregnancy onset defined as 1 or more relapses in the 2 years before pregnancy and/or neurologic disability. To explore whether the continued lack of rebound disease activity we observed was due to exclusive breastfeeding, we restricted ARR calculations to only those women who did not breastfeed exclusively and had suboptimally controlled disease at pregnancy onset.

Propensity score (PS)-adjusted Cox regression models were also examined. Predicted probability of exclusive breastfeeding or resuming DMTs within 2 months postpartum was modeled using the logistic regression model. This included the same covariates as in the standard multivariable models for DMT use. Because the decision to breastfeed precedes postpartum DMT use, this variable was not included in the propensity to breastfeed exclusively. The Cox regression models were then adjusted for the PS quintiles derived from the logistic regression model.

The 5 cases in which MS onset occurred during pregnancy were classified as no relapses before pregnancy but did not contribute to ARRs before symptom onset. One woman who did not breastfeed was excluded from early resumption of DMT analyses because she left Kaiser Permanente within 2 months postpartum.

The mean values and SDs of normally distributed variables were compared using 2-sample *t* tests; for variables with nonnormal distributions, the Wilcoxon rank-sum test was used; and for binary or categorical variables, the χ^2 with the Fisher exact test was used. Statistical significance was set at $p = 0.05$. No adjustment for multiple comparisons was made. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Data availability

Due to review boards' policies, data would be available upon reasonable request.

Results

Patient characteristics and disease course during pregnancy and postpartum period

Four hundred sixty-six pregnancies occurred among 375 women during the study period. General characteristics of the women at the onset of each pregnancy are presented in table

1. Most women had relapsing-remitting MS (RRMS, 83.5%), 54.7% had at least 1 relapse within 2 years before pregnancy, 39.9% had MS-related disability, and 67.2% had suboptimally controlled disease at pregnancy onset. The majority (70.1%) had been treated with a DMT at some point since diagnosis, but 48.4% had discontinued treatment at least 1 year before pregnancy. Of those pregnancies exposed to DMT in the year before pregnancy, the majority (93.7%) used IFN-beta or GLAT. Only 13 women were treated with highly effective DMTs before pregnancy. Of the 51.6% of women who used DMTs in the year before pregnancy, half ($n = 119$, 25.8%) conceived while on treatment.

The average ARR declined during pregnancy compared with the 2 years before conception and returned to prepregnancy rates 4–6 months postpartum (table 2 and figure). There was no increase in the rate of relapse in the first 3 months postpartum in the entire cohort (figure) or in women with suboptimally controlled disease before pregnancy (figure). Even when women who breastfed exclusively were excluded from the suboptimally controlled disease analysis, no rebound increase in the ARR was observed in the first 3 months postpartum (0.56 and 0.47, $p = 0.33$, 2 years before pregnancy and 0–3 months postpartum, respectively). Most pregnancies ($n = 343$, 73.6%) were followed by a relapse-free postpartum year. However, 103 women experienced 1 relapse (22.1%), and 20 women (4.3%) experienced multiple relapses in the 12 months postpartum (table 3). Only 40 relapses occurred during pregnancy (table 3), 15 (37.5%) of which occurred in women who had stopped their DMT in the first/early second trimester or within 3 months before conception.

Predictors of postpartum relapses

Table 4 shows the crude and adjusted HRs of predictors of relapses within the first 6 months postpartum. MS-related disability on neurologic examination before pregnancy and younger age was associated with an increased risk of relapses in the first 6 months postpartum and throughout the postpartum year (adjusted HR = 1.79, 95% CI = 1.22–2.60, $p = 0.0026$ for disability). Relapsing during pregnancy was associated with an increased risk of early postpartum relapses, but the effect was not statistically significant through 12 months postpartum (adjusted HR = 1.68, 95% CI = 0.90–3.14, $p = 0.1023$ for pregnancy relapse). A high relapse frequency preceding pregnancy was associated with relapse throughout the postpartum year (adjusted HR = 1.64, 95% CI = 1.07–2.51, $p = 0.0227$) but not within the first 6 months (table 4).

Breastfeeding

Most (87.3%) women breastfed their infants, and 35.8% breastfed exclusively for at least 2 months. The total duration of breastfeeding was significantly shorter in women who introduced supplemental feedings within the first 2 months postpartum compared with those who breastfed exclusively (median 2.3 months, interquartile range [IQR] = 0.7–6.1 vs 9.2 months, IQR = 6.0–12.4 months; $p < 0.0001$,

respectively). The introduction of supplemental feedings occurred very early in this group compared with those who breastfed exclusively (median 0.0 months, IQR = 0.0–0.5 vs 6.0 months, IQR = 4.0–6.2 months; $p < 0.0001$, respectively).

Women who breastfed exclusively had fewer relapses ($n = 15$, 8.98%) in the first 6 months postpartum compared with those who breastfed nonexclusively ($n = 41$, 17.1%) or not at all ($n = 15$, 25.4%, $p = 0.0054$). Exclusive breastfeeding significantly reduced the risk of postpartum relapses (table 4, PS-adjusted HR = 0.33, 95% CI = 0.15–0.69, $p = 0.0032$) but not non-exclusive breastfeeding (PS-adjusted HR = 0.62, 95% CI = 0.34–1.14; $p = 0.1243$) compared with no breastfeeding (reference group). Exclusive breastfeeding was similarly protective in women with suboptimally controlled disease activity at pregnancy onset (adjusted HR = 0.38, 95% CI = 0.18–0.83, $p = 0.0154$; p trend = 0.0424), and breastfeeding non-exclusively was not (adjusted HR = 0.70, 95% CI = 0.35–1.40, $p = 0.3115$) compared with no breastfeeding (reference group).

During the second half of the postpartum year, the proportion of women who had their first postpartum relapse was very similar among women who breastfed exclusively for at least the first 2 months postpartum ($n = 17$, 10.2%), those who breastfed nonexclusively ($n = 29$, 12.1%), and those who did not breastfeed ($n = 6$, 10.2%).

The only significant predictor of breastfeeding choices was use of DMT in the year before pregnancy. These women were less likely to breastfeed exclusively (crude odds ratio [OR] = 0.61, 95% CI = 0.41–0.89, $p = 0.0105$; adjusted OR = 0.63, 95% CI = 0.43 to 0.94, $p = 0.0242$) but not less likely to have postpartum relapses (table 4) compared with those not using DMTs. Age, disease duration, disability, prepregnancy relapse frequency, and relapses during pregnancy were not associated with breastfeeding choices (table 5).

MS DMT use

MS DMTs were resumed during the postpartum year in 41.2% of pregnancies (table 3). Of the women with postpartum relapses, 45 (36.6%) waited until after their first postpartum relapse to resume DMTs. DMT use and breastfeeding were not mutually exclusive. Sixty women resumed DMTs while breastfeeding, 11 within the first 2 months postpartum while breastfeeding exclusively, and an additional 35 women who breastfed exclusively resumed DMTs later in the postpartum year.

DMT use during the postpartum year, modeled as a time-dependent covariate, had no effect on the risk of postpartum relapses during the first 6 months (table 4) or the entire postpartum year (adjusted HR = 0.89, 95% CI = 0.56–1.43, $p = 0.63$).

Seventy-eight (16.7%) women resumed DMTs within 2 months postpartum, but 2 did not until after their first postpartum relapse. Twelve women (15.8%) who resumed DMTs

Table 1 Characteristics of women with MS at the onset of pregnancy

Characteristic	Total, n = 466	
Age (mean, SD), y	31.89	4.73
Disease duration, median (IQR), y	5.46	2.85–9.04
Race/ethnicity		
White	253	54.29
Hispanic	130	27.90
Black	56	12.02
Asian/other	27	5.79
MS subtype at onset of pregnancy, no. (%)		
RRMS	389	83.48
Progressive, relapsing MS	4	0.86
Clinically isolated syndrome	68	14.59
Symptom onset during pregnancy	5	1.07
Relapses during 2 years before pregnancy ^a		
0	209	45.34
1	184	39.91
≥2	68	14.75
MS-related disability, no. (%)		
No disability	280	60.09
Some disability but fully ambulatory	150	32.19
Some ambulatory impairment	29	6.22
Cane required	5	1.07
Wheelchair required	2	0.43
DMT use before pregnancy, no. (%) ^a		
Never	138	29.93
At the time of conception ^b	119	25.81
Within 1 year prior	238	51.62
Type used within 1 year prior		
Interferon-beta	110	46.22
Glatiramer acetate	113	47.48
Dimethyl fumarate	2	0.84
Natalizumab	9	3.78
Rituximab	4	1.68
Fingolimod	0	0.00

Abbreviations: DMT = disease-modifying therapy; IQR = interquartile range; MS = multiple sclerosis; RRMS = relapsing-remitting MS.

^a Does not include 5 women with onset during pregnancy.

^b Last menstrual period.

within 2 months relapsed within 6 months and 25 (32.9%) within 12 months postpartum compared with 15.2% and 25.1%, respectively, among those who did not.

Most women who resumed a DMT within 2 months postpartum were on a DMT in the year before pregnancy (n = 74, 94.9%) and many at the time of conception (n = 43, 55.1%).

Table 2 Pregnancy-related multiple sclerosis relapses

	No. available pregnancies ^a	No. pregnancies w/relapse	No. relapses	Rate of relapse/pregnancies/y ^b	p Value ^c
2 years before pregnancy	461	252	342	0.37 (0.33, 0.41)	—
Pregnancy					
First trimester	461	10	10	0.08 (0.04, 0.16)	<0.0001
Second trimester	461	9	9	0.07 (0.04, 0.15)	<0.0001
Third trimester	461	16	16	0.14 (0.09, 0.23)	<0.0001
Year after pregnancy					
Months 1–3	465	31	31	0.27 (0.19, 0.38)	0.0389
Months 4–6	462	43	43	0.37 (0.28, 0.49)	0.9902
Months 7–9	460	41	45	0.39 (0.29, 0.52)	0.7513
Months 10–12	452	29	29	0.26 (0.18, 0.37)	0.0230

^a Only the number of pregnancies observed for the full 3-month intervals is shown.

^b Mean and 95% confidence intervals.

^c Compared with 2 years before pregnancy, generalized estimation equations were used to account for women with multiple pregnancies.

Other factors that predicted early DMT use were relapses during pregnancy and disability at pregnancy onset, whereas intent to breastfeed reduced the likelihood of early DMT use (data not shown). DMT use within 2 months postpartum was not associated with a reduced risk of postpartum relapses during the 12 months postpartum even after taking into account these factors (PS-adjusted HR = 1.07, 95% CI = 0.65–1.76, $p = 0.81$, data not shown).

Discussion

For the past 20 years, women with MS have been counseled that the risk of relapse declines during pregnancy yet increases during the first few months postpartum before returning to prepregnancy rates later in the postpartum year. How to minimize this risk of postpartum relapses has been the subject of much debate. Until recently, all MS DMTs were considered incompatible with pregnancy and breastfeeding, and women with MS often chose to forego breastfeeding and resume DMTs or breastfeed and remain untreated. This clinical dilemma intensified as the evidence has mounted that prolonged and exclusive breastfeeding has significant infant and maternal health benefits, including studies suggesting that exclusive breastfeeding may reduce the risk of postpartum MS relapses.^{4,6}

In our large contemporary, population-based cohort, we found a decreased relapse rate during pregnancy but no increased rate during the postpartum year compared with the prepregnancy period. Most women were relapse-free during the postpartum year, although most breastfed and less than half used DMTs. The increase in breastfeeding rates, including women with more severe MS disease activity before pregnancy, coincides with system-wide efforts to encourage

all women to breastfeed their babies exclusively. Breastfeeding exclusively was associated with a reduced risk of postpartum relapses in the first 6 months postpartum even in women with suboptimally controlled disease before pregnancy. Breastfeeding choices were not significantly influenced by prepregnancy disease severity or pregnancy relapses. In contrast, postpartum use of the modestly effective DMTs, IFN-beta or GLAT, had no effect on risk of relapse in the postpartum year, even if treatment was started within 2 months. The finding from our study indicates that the fear of an increased risk of postpartum relapse no longer applies to most women with MS today, particularly in women who breastfeed exclusively.

Despite this absence of rebound disease activity postpartum, we were surprised to see that 67% of women had suboptimally controlled disease entering pregnancy and concerned that very few had been treated with highly effective DMTs. This is particularly troubling because this and previous studies^{1,2,15,16} have shown that measures of disease severity including prepregnancy relapse rate, MS-related disability, and relapses during pregnancy are independent predictors of postpartum relapses. In addition, MS-related disability is a measure of incomplete relapse recovery in this population, a predictor of poor long-term prognosis.¹⁷ Thus, although exclusive breastfeeding reduced the risk of postpartum relapses in these women with active MS before pregnancy and should be encouraged for multiple reasons, optimizing disease control before and after pregnancy is also essential. These findings led to the development and implementation of a pregnancy-specific MS treatment algorithm in KPSC described in detail elsewhere.¹⁸ Briefly, we now treat women with active disease and/or neurologic disability with a highly effective DMT with a prolonged duration of action (rituximab) before pregnancy,

Table 3 Clinical characteristics of women with MS during pregnancy and the postpartum period

Characteristic	Total, n = 466	
Pregnancy		
Relapse during pregnancy, no. (%)	40	8.58
DMT use during pregnancy ^a , no. (%)	22	4.72
DMT type used		
Interferon-beta	7	31.82
Glatiramer acetate	14	63.64
Natalizumab	1	4.55
Postpartum period		
No. of postpartum relapses, no. (%)		
0	343	73.61
1	103	22.10
2	15	3.22
≥3	5	1.07
Time to first postpartum relapse ^b , median (IQR), d	168	(82, 230)
DMT use during postpartum year, no. (%)		
None	274	58.80
Interferon-beta	77	16.52
Glatiramer acetate	90	19.31
Dimethyl fumarate	10	2.15
Natalizumab	10	2.15
Rituximab	4	0.86
Fingolimod	1	0.21
Time to restart DMT ^c (median, IQR), d	88.5	(32, 197.5)
Breastfeeding, no. (%)		
None	59	12.66
Nonexclusively	240	51.50
Exclusively for 2 mo or more	167	35.84

Abbreviations: DMT = disease-modifying therapy; IQR = interquartile range; MS = multiple sclerosis.

^a During the second and/or third trimester.

^b Of those who relapse.

^c Of those who resumed DMTs.

hold infusions during pregnancy, and resume infusions typically 6–12 months postpartum or sooner if indicated or desired by the mother. We consider rituximab and other monoclonal antibody DMTs, along with IFN-beta and GLAT, to be compatible with lactation¹⁸ and encourage women to breastfeed exclusively for 6 months and continue breastfeeding thereafter per their preferences.

Our recommendation that women with MS breastfeed exclusively extends beyond the potential beneficial effects of

reducing postpartum MS relapse risk. There is extensive evidence pointing to a plethora of infant and maternal health benefits with breastfeeding, particularly prolonged or exclusive breastfeeding. These benefits include a decreased risk of infections, lower infectious mortality, and improved intelligence in the offspring compared with infants with short duration of breastfeeding or those who are not breastfed at all.¹⁹ These effects create inequalities that persist into adulthood. Maternal health benefits include a decreased risk of breast and ovarian cancers, type 2 diabetes, and metabolic

Figure Average annualized relapse rate before, during, and after pregnancy

syndrome.^{20,21} It is these benefits and others not listed here that have led the World Health Organization and American Academy of Pediatrics to recommend exclusive breastfeeding for 6 months. A recent meta-analysis¹⁹ concluded that “the scaling up of breastfeeding to a near universal level could prevent 823,000 annual deaths in children younger than 5 years and 20,000 annual deaths from breast cancer.”

We contrast these striking benefits of breastfeeding with the common practice of telling women with MS to forego exclusive/prolonged breastfeeding to resume DMTs, although there is no evidence that breastfeeding harms them, even in previous studies in which breastfeeding, particularly exclusively, meant foregoing DMTs.^{4–6} Our study provides additional evidence that exclusive breastfeeding may even reduce the risk of postpartum MS relapses (with or without resuming DMTs). Thus, we reason that continuing to recommend that women with MS forego exclusive breastfeeding to resume MS DMTs that are incompatible with lactation is overly conservative and likely harmful to the infant’s and mother’s health.

The findings from this study are consistent with our previously reported findings that exclusive breastfeeding seems to reduce the risk of postpartum relapse^{4,6} in the first but not second half of the postpartum year, acting like a treatment with a natural end date when the infant begins regular supplemental feedings,⁴ typically between 4 and 8 months of age. Our findings are also consistent with previous studies that examined some but not necessarily exclusive breastfeeding and found no association with postpartum relapse risk^{1,5} or marginal benefit⁹ when considering the entire postpartum year.

We found no evidence that confounding by indication (women with higher disease activity are less likely to breast-feed exclusively and have a higher risk of postpartum relapses) is a better explanation of our findings. There was no significant association between breastfeeding choices and measures of disease severity. We found consistent protective associations using multiple statistical methods and found that exclusive breastfeeding was also highly protective in women with suboptimally controlled disease at pregnancy onset,

Table 4 Modifiable and nonmodifiable factors and MS relapses within the first 6 months postpartum

	Hazard ratio (95% CI) ^a			
	Unadjusted	p Value	Adjusted ^b	p Value
No breastfeeding	1.0 (ref)		1.0 (ref)	
Nonexclusive breastfeeding ^c	0.62 (0.34–1.14)	0.1258	0.69 (0.36–1.31)	0.2543
Exclusive breastfeeding ^c	0.32 (0.16–0.64)	0.0014	0.37 (0.18–0.78)	0.0093
Postpartum DMT use ^d	1.37 (0.72–2.62)	0.3403	0.83 (0.40–1.72)	0.6230
Prepregnancy relapses ^e	2.17 (1.26–3.74)	0.0051	1.37 (0.78–2.38)	0.2714
Disability ^f	2.10 (1.30–3.39)	0.0023	1.79 (1.10–2.91)	0.0189
1 year prepregnancy DMT use	1.46 (0.90–2.38)	0.1300	1.17 (0.68–2.02)	0.5747
Pregnancy relapse	3.11 (1.71–5.65)	0.0002	2.68 (1.41–5.08)	0.0027
Age, y	0.94 (0.90–0.99)	0.0162	0.95 (0.90–1.00)	0.0445
Disease duration, y	1.02 (0.97–1.08)	0.4368	1.04 (0.98–1.10)	0.2204

Abbreviations: CI = confidence interval; DMT = disease-modifying therapy; MS = multiple sclerosis.

^a Cox proportional hazards model.

^b Mutually adjusted for all of the covariates listed.

^c Reference group no breastfeeding.

^d Time-dependent covariate.

^e Reference group 0–1 relapses in 2 years before pregnancy.

^f Reference group no MS-related disability at pregnancy onset.

whose prepregnancy ARR approached that of the historical cohort (ARR 95% CI = 0.60–0.80¹). In addition, the magnitude of effect is large enough that it is unlikely to be explained by residual or unmeasured confounding.²² Only the behavioral choice of using DMTs in the year before pregnancy, which had no impact on the risk of postpartum relapses, was associated with a decreased likelihood of breastfeeding exclusively and an increased likelihood of resuming DMTs. PS-

adjusted models taking this nonconfounding association into account continued to show a benefit of exclusive breastfeeding. Like other studies, we found no increased risk of postpartum relapses in women who breastfed even in lieu of resuming DMTs.

In contrast, we found no evidence that starting modestly effective DMTs during the postpartum year, even within 2 months after delivery, reduces the risk of postpartum relapses. Previous

Table 5 Breastfeeding choices stratified by measures of disease severity

	No BF, n (%)	Some but not exBF, n (%)	exBF, n (%)	p Value
≥2 relapses ^a	10 (14.7)	39 (57.4)	19 (27.9)	0.3367
0–1 relapses ^a	49 (12.3)	201 (50.5)	148 (37.2)	
At least some disability	27 (14.5)	96 (51.6)	63 (33.9)	0.5554
No disability	32 (11.4)	144 (51.4)	104 (37.1)	
Pregnancy relapse	6 (15.0)	20 (50.0)	14 (35.0)	0.8973
Pregnancy relapse-free	53 (12.4)	220 (51.6)	153 (35.9)	
Suboptimally controlled disease ^b	45 (14.4)	158 (50.5)	110 (35.1)	0.281
Clinically silent disease	14 (9.2)	82 (53.6)	57 (37.3)	
Very high disease activity ^c	5 (11.6)	28 (65.1)	10 (23.3)	0.1468
Moderate/low disease activity	54 (12.8)	212 (50.1)	157 (37.1)	

Abbreviations: BF = breastfeeding; exBF = exclusive breastfeeding

^a In the 2 years before pregnancy.

^b At least 1 relapse in the 2 years before pregnancy and/or some disability at pregnancy onset.

^c Women with at least 2 relapses and some disability at pregnancy onset.

studies of postpartum DMT use and relapses found either no effect when resumed within 2 weeks³ or 1 month⁴ or a non-significant reduction later in the postpartum years when resumed within 3 months.² These studies were limited by selection^{2,4} and referral center bias^{2,4} and did not include patients with CIS,²⁻⁴ resulting in participants with more active disease before, during, and after pregnancy than seen in our population. All studies, including this one, are limited by relatively few women resuming DMTs early in the postpartum year.

Our population was more mildly affected when compared with historical studies.^{1,23} The women in our study had significantly lower ARRs before and after pregnancy (0.37) compared with the historical MS and pregnancy cohort (0.7¹) from which the counseling recommendations stem. Women in our study also had fewer relapses during pregnancy and in the postpartum period compared with more recent referral center^{2,7,8} and registry⁴ studies. These differences are most likely due to changes in MS diagnostic criteria and lack of referral center bias in our population.

The historical cohort¹ was recruited from referral centers at a time when MS diagnostic criteria required 2 clinical relapses and breastfeeding rates were low. Since then, MS diagnostic criteria have been revised to require only 1 clinical relapse and rely heavily on MRI findings. The 2017 criteria classify many patients previously designated as CIS, including all of those included in this study, as MS. These changes have led to earlier MS diagnosis and diagnosis of milder cases. This is reflected nicely in the marked decline in ARRs observed in the placebo arms of randomized controlled trials from 0.84²³ to 0.36²⁴ when using the revised diagnostic criteria. Thus, it is not surprising that our patients had fewer prepregnancy relapses than the historical cohort¹ or other cohorts that excluded patients with CIS.^{2,4}

Another change is the now common use of MS DMTs and availability of highly effective DMTs. However, we believe that DMT use alone is an unsatisfactory explanation for our more mildly affected population, as the prepregnancy relapse rates we observed are very similar to the placebo arms of contemporary RRMS RCTs.²⁴ In addition, very few women were treated with highly effective DMTs, and many women were untreated before pregnancy.

The lack of an increased relapse rate and even slight suppression in the first 3 months postpartum we observed is most likely due to the high rates of breastfeeding, particularly exclusive breastfeeding. This is supported by the multiple sensitivity analyses we conducted that continue to demonstrate a lack of postpartum rebound relapses and a beneficial effect of breastfeeding exclusively even in women with more active disease before pregnancy. However, even when we focused on the women with suboptimally controlled disease at pregnancy onset and excluded those who breastfed exclusively for 2 months or more, we still did not observe any early postpartum rebound disease activity. This could be due to a time-dependent beneficial effect of breastfeeding or differences in

capturing postpartum relapses. The historical cohort study¹ collected prepregnancy relapses from routine medical records like we did, but prospectively collected postpartum relapses, while we relied on routine medical records, a method that is likely to underreport mild relapses. These limitations are currently under investigation in a prospective cohort study.

Our findings also differ from a recently published database study¹⁶ and a referral center study,⁸ which reported rebound disease activity in the postpartum period. The database study reported prepregnancy relapse rates similar to ours,¹⁶ but the results of both studies are difficult to interpret because of large amounts of missing data,¹⁶ selection and referral center bias,^{8,16} inability to account for breastfeeding choices,¹⁶ and pregnancies spanning 1967–2010¹⁶ or 1993–2015.⁸ Other recent MS and pregnancy studies did not report relapse rates,^{2,4} making it unclear whether rebound postpartum disease activity was observed.

Few women in our study were treated with natalizumab or fingolimod before pregnancy; therefore, this study does not address the potential harms of drug cessation or benefits of breastfeeding on postpartum MS relapses, if any, in these patients. Future studies to address this subgroup of women are needed as severe drug cessation relapses during pregnancy have been reported.^{25,26} Other limitations of this study include reliance on routinely collected medical records to assess relapses and disease activity. This undercounting of mild relapses before, during, and after pregnancy and misclassifying patients as optimally controlled because MRIs were rarely ordered postpartum and usually only when relapses occurred. In addition, we could not examine exclusive breastfeeding as a time-dependent covariate, as precise breastfeeding stop dates after 2 months postpartum are rarely recorded. We cannot exclude a small, delayed benefit of IFN-beta or GLAT treatment, particularly in women who concomitantly breastfeed. These limitations should be addressed in future studies.

Strengths of this study are a large, population-based sample, representative of women diagnosed with MS now and comprehensive medical records of the mother and infant, allowing unbiased assessment of clinical variables, breast and formula feeding. Unlike previous studies,⁴⁻⁶ breastfeeding and DMT use were not mutually exclusive, allowing us to examine these factors simultaneously.

Taken together, our findings indicate that most women diagnosed with MS today can have children and breastfeed without incurring an increased risk of relapses during the postpartum period. Women with MS should be encouraged to breastfeed exclusively, and those with active disease before pregnancy and/or incomplete recovery from previous relapses should optimize their MS DMT before conception. Women who are considering foregoing breastfeeding to resume modestly effective DMTs should be informed that there is no evidence that these DMTs will reduce the risk of postpartum relapses and counseled about the general health benefits of breastfeeding.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Annette Langer-Gould, MD, PhD	Los Angeles Medical Center, Department of Neurology, Southern California Permanente Medical Group	Designed and conceptualized the study; collected and interpreted the data; drafted and revised the manuscript for intellectual content; had full access to all the data; and takes responsibility for the integrity of the data and accuracy of the data analysis
Jessica B. Smith, MPH	Kaiser Permanente Southern California, Pasadena	Collected, analyzed, and interpreted the data and revised the manuscript for content
Kathleen B. Albers, MPH	Kaiser Permanente Northern California, Oakland	Collected and analyzed data and revised the manuscript for content
Anny H. Xiang, PhD	Kaiser Permanente Southern California, Pasadena	Contributed to study design and data analysis plan; interpreted the data; and revised the manuscript for content
Jun Wu, MD, MS	Kaiser Permanente Southern California, Pasadena	Analyzed and interpreted the data and drafted and revised the manuscript for content
Erica H. Kerezsi, MS	Kaiser Permanente Northern California, Oakland	Collected data and revised the manuscript for content
Keeli McClearn, BA	Kaiser Permanente Northern California, Oakland	Collected data and revised the manuscript for content
Edlin G. Gonzales, MA	Kaiser Permanente Southern California, Pasadena	Collected data and revised the manuscript for content

Appendix (continued)

Name	Location	Contribution
Amethyst D. Leimpeter, MS	Kaiser Permanente Northern California, Oakland	Collected data and revised the manuscript for content
Stephen K. Van Den Eeden, PhD	Kaiser Permanente Northern California, Oakland	Contributed to study design and data analysis plan; interpreted the data; and revised the manuscript for content

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