

# Exclusive Breastfeeding and the Risk of Postpartum Relapses in Women With Multiple Sclerosis

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**Objective:** To determine if exclusive breastfeeding protects against postpartum relapses of multiple sclerosis (MS) and, if so, whether this protection is related to prolonged lactational amenorrhea.

**Design:** We conducted structured interviews to assess clinical, menstrual, and breastfeeding history during each trimester and 2, 4, 6, 9, and 12 months postpartum and collected neurological examination findings from the treating physicians of women with MS. Hazards ratios (HRs) were adjusted for measures of disease severity and age.

**Setting:** Kaiser Permanente Northern California and Stanford University.

**Participants:** We prospectively enrolled 32 pregnant women with MS and 29 age-matched, pregnant controls.

**Main Outcome Measure:** Postpartum relapse.

**Results:** Of the 52% of women with MS who did not breastfeed or began regular supplemental feedings within 2 months postpartum, 87% had a postpartum relapse, compared with 36% of the women with MS who breastfed exclusively for at least 2 months postpartum (unadjusted HR, 5.0; 95% confidence interval, 1.7-14.2;  $P = .003$ ; adjusted HR, 7.1; 95% confidence interval, 2.1-24.3;  $P = .002$ ). Sixty percent reported that the primary reason for foregoing exclusive breastfeeding was to resume MS therapies. Women who breastfed exclusively had a later return of menses ( $P = .001$ ) than women who did not, and lactational amenorrhea was associated with a reduced risk of postpartum relapses ( $P = .01$ ).

**Conclusions:** Our findings suggest that exclusive breastfeeding and concomitant suppression of menses significantly reduce the risk of postpartum relapses in MS. Our findings call into question the benefit of foregoing breastfeeding to start MS therapies and should be confirmed in a larger study.


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**M**ULTIPLE SCLEROSIS (MS) is a chronic inflammatory disease of the central nervous system that predominantly affects women in their childbearing years. It is well known that women with MS have fewer relapses during pregnancy and a high risk of relapse in the postpartum period.<sup>1</sup> Whether breastfeeding is beneficial or harmful in MS is not certain.

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Multiple sclerosis immunomodulatory agents (IMAs), including interferon beta, glatiramer acetate, and natalizumab, are not recommended for use during pregnancy or lactation and their effect on postpartum relapses has never been studied. Thus, patients need to choose whether to forego nursing (and the health benefits to the infant) and resume treatment or nurse and remain untreated, without clear evidence to

support either practice. Previous studies of the influence of breastfeeding on postpartum relapse activity in MS found either no<sup>2</sup> or marginal benefit,<sup>1</sup> but none of the studies examined exclusive breastfeeding. One study evaluated the effect of formula feedings and found that more formula feedings increased the risk of early postpartum relapses among women who breastfed at all,<sup>3</sup> suggesting that exclusive vs nonexclusive breastfeeding might be an important distinction.

Studies of healthy women have shown that exclusive breastfeeding results in prolonged lactational amenorrhea and ovarian suppression.<sup>4</sup> Once supplemental infant feedings are introduced, maternal ovarian activity and menses return.<sup>5</sup> Therefore, breastfeeding combined with early supplemental feeding may not have the same effect as exclusive breastfeeding in women with autoimmune diseases and may in fact be more similar to not breastfeeding at all.

The objective of our study was to determine if exclusive breastfeeding pro-

fects against postpartum relapses of MS and, if so, whether this protection is related to prolonged lactational amenorrhea.

## METHODS

### STUDY SUBJECTS

We recruited 32 women with clinically definite MS<sup>6</sup> and 29 healthy pregnant controls matched on age and parity from Kaiser Permanente Northern California and Stanford University between June 2002 and July 2005. Subjects were eligible if they were less than 35 weeks' pregnant or planning to become pregnant. Details of the study and testing procedures were explained to each subject, and a written informed consent was obtained. The institutional review boards at Stanford University and Kaiser Foundation Research Institute approved this study.

### STUDY DESIGN

Study subjects completed a structured, interviewer-administered questionnaire on study entry and during the remaining trimesters of pregnancy, as well as at 2, 4, 6, 9, and 12 months postpartum. The study entry questionnaire captured detailed medical and reproductive history and the follow-up questionnaires collected information about changes in neurological status, breastfeeding and supplemental feeding behaviors, menstrual history, medical history, and medication use. Follow-up questionnaires were obtained outside of the regularly scheduled visits if women had a relapse or prior to restarting MS medications. Women who reported worsening MS on the questionnaire were referred to their treating physician if they had not already been evaluated.

A relapse was defined as the occurrence, reappearance, or worsening of symptoms of neurological dysfunction that lasted for more than 48 hours. Transient, fever-related worsening of symptoms or fatigue alone were not considered relapses. Symptoms that occurred within 1 month of each other were considered to be part of the same attack. All relapses were confirmed by the treating physician. The medical records were abstracted for documentation of relapses and progression of disability.

Three women with MS (2 moved out of the study area) and 1 healthy woman dropped out before breastfeeding status was assessed and were not included in the postpartum analysis. Seven healthy women and 5 women with MS missed some postpartum study visits.

### STATISTICAL ANALYSES

The time to onset of the first postpartum relapse was determined by using the Kaplan-Meier method. Adjusted and unadjusted hazard ratios (HRs) were calculated by using the Cox proportional hazards method. Estimates of exclusive breastfeeding were adjusted, both singly and in combination, for disease duration (in years), relapse frequency in the 2 years prior to conception (0-1 or  $\geq 2$ ), prepregnancy treatment with IMAs (yes/no), and age at the onset of pregnancy (in years). The independent effects of these factors were also tested. To account for the potentially time-dependent nature of breastfeeding and relapse, sensitivity analyses were conducted by excluding women who reported that their breastfeeding habits were influenced by worsening MS symptoms.

Exclusive breastfeeding was defined a priori as no regular formula feedings (at least 1 bottle a day) for the first 2 months postpartum. Nonexclusive breastfeeding was defined as either

**Table 1. Characteristics of Participants With MS at Onset of Pregnancy**

	Breastfed Exclusively (n=14)	Did Not Breastfeed Exclusively (n=15)	P Value
Disease duration, y, median (range)	4.63 (1.62-20.83)	5.50 (2.08-15.24)	>.2
Age, y, mean (SD)	32.97 (3.50)	32.59 (4.57)	>.2
Relapses over previous 2 y, No. (%)			
0	4 (28.6)	4 (26.7)	>.2
1	5 (35.7)	3 (20.0)	
2	4 (28.6)	5 (33.3)	
3	1 (7.1)	2 (13.3)	
6	0	1 (6.7)	
Use of MS immunotherapies, No. (%)			
Ever	8 (57.1)	14 (93.3)	.04
Within 2 mo	2 (14.2)	2 (13.3)	>.2

Abbreviation: MS, multiple sclerosis.

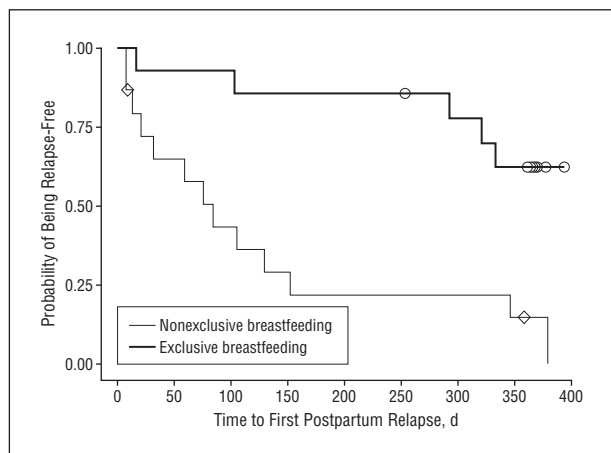
not breastfeeding at all, breastfeeding for less than 2 months, or starting regular supplemental formula feedings within the first 2 months postpartum.

The means and standard deviations of normally distributed variables were compared using 2-sample *t* tests; for variables with nonparametric distributions, the Wilcoxon rank sum test was used and for binary or categorical variables,  $\chi^2$  with Fisher exact test. Statistical significance was set at  $P=.05$ . No adjustment for multiple comparisons was made. All statistical analyses were performed using SAS version 9 (SAS, Cary, North Carolina).

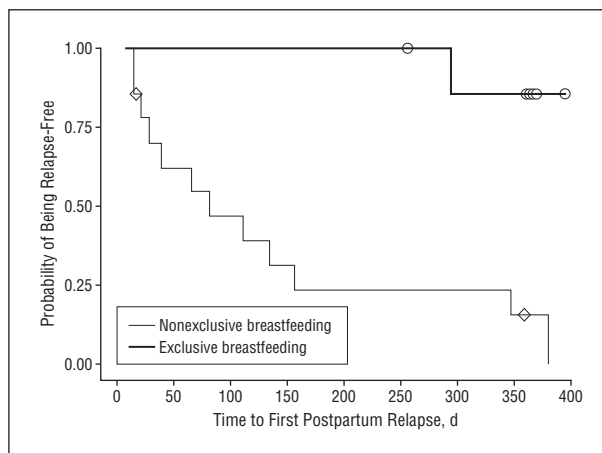
## RESULTS

There was no difference in the mean (SD) age for women with MS (32.5 [4.3] years) compared with healthy women (32.6 [4.7] years), but only 69% of women with MS breastfed compared with 96% of healthy women. Of the women who breastfed, more women with MS began daily formula feedings within the first 2 months postpartum (30%) compared with healthy women (18%). Among women with MS, 11 (73%) reported that the primary reason for forgoing breastfeeding or starting early formula feedings was to take medications for MS, 8 (53%) resumed MS medications within the first 2 months postpartum, and 2 of these women reported that worsening MS symptoms influenced their decision to resume treatment.

The baseline characteristics of women with MS who breastfed exclusively for at least the first 2 months and those who did not are presented in **Table 1**. More women who chose not to breastfeed exclusively had been treated with IMAs prior to conception, but age, disease duration, and clinical measures of disease severity were similar in the 2 groups. Only 2 women had clinically significant disability prior to conception (Expanded Disability Status Scale score  $\geq 4.0$ ) and at 1 year postpartum, 1 of whom breastfed exclusively. Most



**Figure 1.** Kaplan-Meier curve for multiple sclerosis relapses in the postpartum period among women who did or did not breastfeed exclusively. Women who did not breastfeed exclusively ( $n=14$ ) were more likely to relapse in the postpartum period and did so sooner than women who breastfed exclusively for at least the first 2 months postpartum ( $n=15$ ;  $P$  value = .001 by log-rank test).



**Figure 2.** The effect of breastfeeding exclusively or not in the subgroup of women who had received immunomodulatory agents prior to pregnancy. Among the 22 women who had received immunomodulatory agents prior to pregnancy, those who did not breastfeed exclusively ( $n=14$ ; 86% relapsed; median time to relapse, 2.2 months) were significantly more likely to relapse in the postpartum period and did so sooner than women who breastfed exclusively for at least the first 2 months postpartum ( $n=8$ ; 13% relapsed; median time to relapse, >12 months;  $P$  value = .001 by log-rank test).

**Table 2. Clinical Characteristics of Participants With MS During Pregnancy and the Postpartum Period**

	Breastfed Exclusively (n=14)	Did Not Breastfeed Exclusively (n=15)	P Value
<b>Pregnancy</b>			
Women with relapses, No. (%)	2 (14.3)	2 (13.3)	>.02
<b>Postpartum Year</b>			
Breastfeeding duration, mo, median (range)	8.5 (4.0-13.0)	1.8 (1.5-4.0) <sup>a</sup>	.001
Return of menses, mo, median (range)	5.9 (1.7-13.2)	2.2 (1.4-4.9)	.001
Women treated with IMAs, <sup>b</sup> No. (%)	6 (42.9)	12 (80.0)	.04
Time to MS treatment initiation, mo, median (range)	8.47 (4.8-12)	1.23 (0-10.6)	.002
Women with relapses, No. (%)	5 (35.6)	13 (86.7)	.008
Time to relapse, mo			
Median	<sup>c</sup>	2.8	<.001
First quartile	10.7	0.7	

Abbreviations: IMA, immunomodulatory agent; MS, multiple sclerosis.

<sup>a</sup> Among the women who breastfed some but not exclusively for the first 2 months postpartum.

<sup>b</sup> Interferon beta or glatiramer acetate.

<sup>c</sup> Only 25% had relapse by 10.7 months in women who breastfed exclusively so a median time is not reportable.

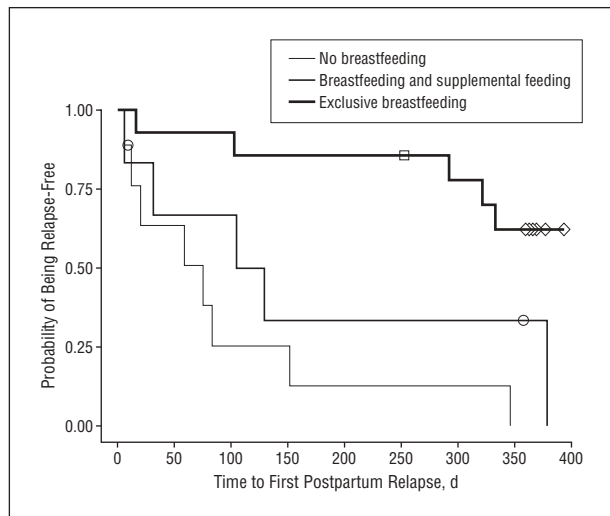
women had no clinically significant disability at study entry or exit (Expanded Disability Status Scale score  $\leq 2.0$ ;  $n=27$ ).

Women who did not breastfeed or started regular supplemental feedings within the first 2 months postpartum had a significantly higher risk of postpartum relapses during the year following delivery and relapsed earlier (unadjusted HR, 5.0; 95% confidence interval [CI], 1.7-14.2;  $P=.003$ ) than women with MS who breastfed exclusively (**Figure 1**) (**Table 2**). This protective effect

of exclusive breastfeeding was not diminished after adjusting for age, disease duration, prepregnancy relapse frequency, and prepregnancy treatment (adjusted HR, 7.1; 95% CI, 2.1-24.3;  $P=.002$ ; eTable, <http://www.archneurology.com>) nor was it diminished when the 2 subjects whose relapse symptoms influenced their breastfeeding choices were removed from the analysis (adjusted HR, 6.2; 95% CI, 1.7-23.4;  $P=.007$ ). Exclusive breastfeeding was similarly protective in the subgroup of 22 women who had used IMAs prior to pregnancy, a group that potentially had more severe disease (adjusted HR, 17.7; 95% CI, 2.2-144.5;  $P=.007$ ) (**Figure 2**).

Additional analyses restricted to the subgroup of women who had 2 or more relapses in the 2 years preceding pregnancy ( $n=13$ ) and the subgroup of women with the most aggressive disease prior to pregnancy—those who were treated with IMAs prior to pregnancy and had 2 or more relapses in the 2 years prior to pregnancy ( $n=10$ )—showed that even among these women, exclusive breastfeeding significantly reduced the risk of postpartum relapses ( $P=.02$  and  $P=.02$  by log-rank test, respectively). The frequency and timing of postpartum relapses among women with MS who breastfed some, but not exclusively, was similar to the women with MS who did not breastfeed at all (**Figure 3**). Age, disease duration, prepregnancy relapse frequency, and prepregnancy treatment were not associated with the risk of postpartum relapses (**Table 3**).

Women with MS who breastfed exclusively for at least the first 2 months breastfed longer and had a significantly later return of menses (median, 5.9 months) compared with the women who did not breastfeed exclusively (median return of menses, 2.2 months) (**Table 2**). Women with MS who breastfed some, but not exclusively, resumed menses only marginally later (median, 3.1 months; range, 1.4-4.9 months) than the women who did not breastfeed at all (median, 2.0 months; range, 1.5-3.2 months;  $P=.14$ ). In healthy women, exclusive breast-



**Figure 3.** Kaplan-Meier curve for multiple sclerosis relapses in the postpartum period comparing women with different breastfeeding choices. The frequency and timing of postpartum relapses in women who did not breastfeed at all (n=9; 88% relapsed; median time to relapse, 2.5 months) and the women who breastfed some but not exclusively during the first 2 months postpartum (n=6; 83% relapsed; median time to relapse, 3.9 months) were similar ( $P$  value = .21, log-rank comparing these 2 groups only). Both of these groups had a higher risk of relapsing in the postpartum period than the women who breastfed exclusively for at least the first 2 months postpartum (n=14; median time to relapse, >12 months;  $P$  value < .001, log-rank test for all 3 groups).

feeding was also associated with a later return of menses (median, 8.2 months; range, 1.5-13.1 months) compared with those who began supplemental formula feedings within 2 months (median, 1.6 months; range, 1.0-3.6 months). Like not breastfeeding exclusively, an early return of menses (before 4 months) was associated with an increased risk of postpartum relapse in women with MS (adjusted HR, 4.0; 95% CI, 1.3-12.5;  $P$  = .01).

### COMMENT

In this prospective cohort study, we found that women with MS who breastfed exclusively for the first 2 months postpartum were approximately 5 times less likely to relapse in the postpartum year than women who did not breastfeed or began supplemental formula feedings during that time. Fewer women with MS breastfed exclusively compared with healthy women; the principal reason for not breastfeeding exclusively was a desire to resume MS immunotherapies. Women with MS and healthy women who breastfed exclusively had significantly prolonged lactational amenorrhea, which was associated with a decreased risk of relapse in women with MS.

That exclusive breastfeeding may have significantly different maternal effects than a combination of breastfeeding and supplement feeding is supported by biological studies of breastfeeding in healthy women.<sup>5</sup> Exclusive breastfeeding results in high prolactin levels, low and nonpulsatile luteinizing hormone levels, and ovarian suppression (lack of ovulation and postmenopausal levels of estradiol and progesterone). High frequency and intense suckling maintain high prolactin levels, low luteinizing hormone levels, and lactational amenorrhea.<sup>7,8</sup>

**Table 3. Independent Association Between Measures of Disease Severity and the Risk of Postpartum Relapse**

Independent Predictor	HR (95% CI)	$P$ Value
Age <sup>a</sup>	1.0 (0.9-1.1)	.80
Disease duration <sup>a</sup>	1.0 (0.9-1.1)	.71
Relapse frequency (continuous)	1.0 (0.7-1.4)	.95
Relapse frequency (binary) <sup>b</sup>	1.3 (0.5-3.5)	.54
IMA use prior to pregnancy (ever/never)	0.9 (0.3-2.6)	.89
First postpartum period within 4 mo	3.9 (2.3-12.0)	.02
Not breastfeeding exclusively	5.0 (1.7-14.2)	.003

Abbreviations: CI, confidence interval; HR, hazard ratio; IMA, immunomodulatory agent approved for multiple sclerosis.

<sup>a</sup>In years.

<sup>b</sup>In the 2 years prior to pregnancy (0-1 or  $\geq 2$ ).

Once regular supplemental infant feedings are introduced, the frequency and total duration of suckling episodes typically decline and, similar to complete weaning, prolactin levels drop, ovarian activity resumes, and menses returns.<sup>5</sup>

Our findings suggest that the beneficial effects of exclusive breastfeeding on MS relapses are related to prolonged lactational amenorrhea. Our study shows that the duration of lactational amenorrhea in the women who began early formula feedings is similar to those women who did not breastfeed at all and significantly shorter than women who breastfed exclusively, consistent with studies in healthy women.<sup>4</sup>

Previous studies of the effect of breastfeeding on postpartum MS relapses were conducted at a time or in cultures where healthy women were less likely to breastfeed<sup>1,2</sup> and supplementation with formula feedings was more common than it is now.<sup>9</sup> Only 1 study examined the effect of early formula feedings and reported that more formula feedings increased the risk of early postpartum relapses among women who breastfed at all,<sup>3</sup> but this study did not compare these women with nonbreastfeeding women and allowed subjects to join the study after parturition, thereby potentially biasing their sample to include women who were more likely to breastfeed and had milder MS. In our study (where women were recruited during pregnancy), the risk of relapse in women who began early formula feedings was significantly higher than women who breastfed exclusively and comparable with that of nonbreastfeeding women. Thus, it is not surprising that the previous studies that grouped women with MS who began early formula feedings with women who breastfed exclusively (rather than with nonbreastfeeding women) found either no difference or only a slight decrease in postpartum relapse rates compared with nonbreastfeeding women.

While it may be tempting to attribute our findings to confounding by disease severity (that is, women with more severe disease are less likely to breastfeed and more likely to resume medications in the early postpartum period and more likely to relapse in the postpartum period), we could find no evidence of this. A confounder must be related to both the predictor (breastfeeding) and the outcome (postpartum relapses). However, we found that measures of more severe disease prior to pregnancy were not

independent predictors of postpartum relapses. Additionally, the beneficial effect of exclusive breastfeeding was unaffected by adjustment for multiple measures of disease severity (including treatment with IMAs prior to pregnancy). Furthermore, women's perceptions of disease severity were not significantly related to breastfeeding choice. Only 2 women cited worsening MS symptoms as a reason to forgo breastfeeding, and excluding these subjects did not diminish the effect of exclusive breastfeeding. Also, the magnitude of the effect is large enough that it is unlikely that it could be explained by unmeasured or residual confounding.<sup>10</sup>

There was an imbalance in prior IMA use between women who breastfed exclusively and women who did not. However, this imbalance does not explain our finding, because we found that exclusive breastfeeding was highly protective even among the subgroup of women who had all received IMAs prior to pregnancy. In addition, exclusive breastfeeding was also highly protective among the subgroup of women with the most aggressive disease prior to pregnancy (those with frequent relapses who also received IMA therapy). This indicates that the protective effect of exclusive breastfeeding in this study is robust and that prepregnancy treatment, a potential marker of more severe disease, was not an important confounder.

Unlike the PRIMS study,<sup>1,11</sup> we did not find that a high prepregnancy relapse frequency was a predictor of postpartum relapses. There are several important differences in study design that might explain this discrepancy. The PRIMS study<sup>1</sup> enrolled women with MS at referral centers in France in an era prior to the widespread use of IMAs. In contrast, we recruited participants from both community and tertiary care settings, and the majority of our patients had been treated with IMAs. Thus, it is possible that in a modern day-treated community-based population of women with MS, relapse frequency is not an important predictor of postpartum relapses. A larger study comparing predictors of postpartum relapse in community and tertiary care settings is needed to resolve this discrepancy.

Why breastfeeding might be beneficial in humans with an autoimmune disease like MS has not been studied. Studies of immunity and breastfeeding, while plentiful, are predominantly focused on breast milk content and health benefits to the infant.<sup>9,12</sup> Little is known about maternal immunity during breastfeeding.

While a few studies have examined the effect of prolactin in animal models, the results are conflicting. A study in the animal model of MS suggests that prolactin worsens disease through proinflammatory mechanisms.<sup>13</sup> However, in an animal model of demyelination, pregnancy, the postpartum period, and exogenous prolactin administration were associated with enhanced myelination and myelin repair.<sup>14</sup>

Some researchers have hypothesized that high-estrogen states are protective against MS relapse,<sup>15-17</sup> which would seem contradictory to our findings because lactational amenorrhea reflects a low-estrogen state. However, the evidence supporting a link between a high estrogen level and MS disease activity is not clear cut. Estrogen levels during pregnancy are extremely high and

MS relapse rates are low<sup>1</sup> and estrogen treatment is protective in the animal model of MS.<sup>18</sup> On the other hand, the onset of MS is rare prior to menarche or after menopause, and MS is less common in men than women.<sup>19</sup> A unifying hypothesis is that anovulation (common to all of these states) is protective in MS rather than estrogen levels per se. Furthermore, breastfeeding is not simply a low-estrogen state or high-prolactin state but is associated with multiple hormonal changes, and it is plausible that other hormonal factors could account for the apparent reduction in relapses we observed.

Our study is limited by the small sample as well as our inability to fully separate out the effects of postpartum MS treatment from nonexclusive breastfeeding on postpartum relapses. Thus, our findings should be confirmed in a larger study.

To our knowledge, our study is the first prospective cohort study to address this question and fills an important gap in knowledge that cannot be addressed in a randomized trial. Other strengths are the inclusion of healthy controls, the long duration of follow-up, and the rigorous statistical methods used. In addition, we distinguished between exclusive and nonexclusive breastfeeding, recorded return of menses, and examined the impact of these factors on MS disease activity. To our knowledge, it is the first study to examine the potential maternal health benefits of exclusive breastfeeding in any autoimmune disease.

Our findings show that exclusive breastfeeding (and prolonged lactational amenorrhea) significantly reduces the risk of postpartum relapses of MS. Ongoing and future studies of postpartum disease activity in MS, particularly treatment trials, should distinguish between exclusive and nonexclusive breastfeeding and account for it in their analysis.

Our findings also suggest that women with MS should be encouraged to breastfeed exclusively for at least the first 2 months postpartum in lieu of starting IMA treatment shortly after delivery. These findings highlight the need to critically evaluate the efficacy of early postpartum treatments in MS, especially if they are not compatible with lactation.

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**Additional Information**: The eTable is available at <http://www.archneuro.com>.

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