Immunomodulatory Agents and Risk of Postpartum Multiple Sclerosis Relapses

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Abstract

Objective: To determine whether treatment with an interferon beta or glatiramer acetate shortly after delivery reduces the otherwise increased risk of postpartum relapses of multiple sclerosis.

Methods: In a retrospective cohort of 112 women with multiple sclerosis and live births from Kaiser Permanente Southern California, complete medical and pharmacy records of the mothers and infants were reviewed. Propensity score-adjusted hazard ratios (HR) of time to first postpartum relapse were calculated.

Results: Of 80 women who breastfed little or not at all, 55 (69%) resumed treatment within 1 year postpartum, of whom 26 (47%) relapsed within 6 months postpartum. Resuming treatment within 2 weeks postpartum did not decrease the risk of relapse in the 2 years postpartum compared with women who resumed treatment later in the postpartum year (propensity score-adjusted HR = 1.3, 95% confidence interval = 0.5-3.4, p = 0.6). There was no difference in relapse rates between the groups in the first 6 months postpartum. However, later in the postpartum year those who resumed treatment early had fewer relapses (p = 0.08, Poisson regression).

Conclusions: Among women who breastfeed little or not at all, starting treatment with interferon beta or glatiramer acetate within two weeks postpartum does not reduce the risk of postpartum relapse of multiple sclerosis but may reduce the risk of subsequent relapses in the postpartum year.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the brain and spinal cord, which predominantly affects women of childbearing age. Often MS is inactive during pregnancy (approximately 70% reduction in attacks during the third trimester) but causes frequent attacks in the postpartum period.[1] Current immunomodulatory agents for treatment of MS, including glatiramer acetate, interferon beta, and second-line agents are not recommended during lactation because of safety concerns, so women are often untreated during this period.[2,3]

Multiple prior studies have demonstrated that women with more aggressive disease are less likely to breastfeed,[2,3] partly because of the desire to restart treatment with immunomodulatory agents. However, no study has proved the efficacy of immunomodulatory agents in the early postpartum period.

Because a diagnosis of MS portends a major risk of disability over time, and because breastfeeding has multiple proven benefits for infants, it is important for neurologists to give informed, evidence-based advice on lactation. This is especially true given that glatiramer acetate and interferon beta reduce the risk of relapses by only approximately 25%[4,5] and may take several months to take effect,[4,5] and postpartum attacks often occur very early after delivery.[1] This study aimed to evaluate the efficacy of early resumption of immunomodulatory agents in preventing postpartum relapses in women with MS. We focused on women who chose not to breastfeed exclusively because this behavior may reduce the risk of postpartum relapses,[2] and including these women could lead to erroneous conclusions that resuming immunomodulatory agents is potentially harmful because these women rarely breastfeed exclusively.

Methods

Study Design and Subjects

The institutional review board of Kaiser Permanente Southern California (KPSC) approved this study. Informed consent was waived because this was only a database and chart review study.

For this retrospective cohort study, we identified 112 women with clinically definite MS[6] and their 114 live infants born in the KPSC Region between 2004 and 2010. KPSC is a large prepaid health maintenance organization with more than 3.2 million members, including more than 2500 women with MS. It provides comprehensive health care coverage to approximately 20% of the population in the geographic area it serves. The costs of specialist consultations, hospitalizations, magnetic resonance images, other diagnostic tests, and medications are fully covered. The KPSC membership is representative of the general population in Southern California regarding ethnicity/race, age, sex, and socioeconomic status.[7] After exclusion of 2 patients who had no KPSC encounters after delivery, the final cohort for data analysis included 112 deliveries.

To identify women with MS who delivered live infants in KPSC, we searched electronic databases for any mention of the International Classification of Diseases, Ninth Revision diagnostic codes for MS (340) and live birth (V30-39) (N = 122). An MS diagnosis was confirmed, and disability, relapses, and additional clinical details were extracted from full medical records, including all inpatient and outpatient records, computed tomographic scans and magnetic resonance images, and other laboratory diagnostic test results ordered through June 2011 by 2 neurologists (BEB or SMB and ALG).

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

Information about breastfeeding, formula feeding, and introduction of solid food was abstracted from the infant records by a research professional (MDC) blinded to the mother's clinical history. This information is routinely recorded as part of 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.

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 regression method. Estimates of early treatment with immunomodulatory agents were adjusted, both singly and in combination, for disease duration (in years), relapse frequency in the 2 years before conception (0-1 or ≥ 2), treatment with immunomodulatory agents in the 6 months before pregnancy (yes/no), and age at the onset of pregnancy (in years). The independent effects of these factors were also tested.

Early resumption of immunomodulatory therapy was defined a priori as resuming treatment with interferon beta or glatiramer acetate within 15 days of delivery because it is well-known that most postpartum relapses occur in the first 3 to 4 months postpartum and that the immunomodulatory agents have a delayed onset of action. For the primary analyses, we chose to compare this group with those women who started regimens of immunomodulatory agents later in the postpartum year. We did so because we found that some women did not resume receiving immunomodulatory agents until they had a relapse and that the small group of women who resumed treatment after the first year postpartum or not at all had a very low risk of relapse. This could lead to the erroneous conclusion that early immunomodulatory treatment increases the risk of relapses. Sensitivity analyses were conducted to examine the effect of resuming immunomodulatory agents within 30 days of delivery vs later in the postpartum year and to compare women who received immunomodulatory treatment within 15 days of delivery with the women who resumed treatment later or not at all.

Exclusive breastfeeding was defined a priori as no regular formula feedings (at least one bottle a day) for the first two months postpartum. Nonexclusive breastfeeding was defined as either not breastfeeding at all, breastfeeding for less than two months, or starting regular supplemental formula feedings in the first two months postpartum.

Propensity score-adjusted Cox regression models were also examined. Predicted probability of resuming early treatment was modeled using a hypothesis-driven logistic regression model. This included the same covariates as in the standard multivariable models as well as breastfeeding (yes/no) and non-Hispanic, white race/ethnicity (yes/no). The Cox regression models were then adjusted for the propensity score quintiles derived from the logistic regression model.

An annualized relapse rate for each 6-month postpartum period was calculated until 24 months postpartum. The relapse rate was calculated in each time period by using the annualized relapses (calculated by dividing the actual relapses in the period by the time in years, which is 0.5 in our study) divided by the total number of patients in that period. The 95% confidence interval (CI) was calculated by assuming that the relapses were Poisson distributed. The p values of comparing 2 groups in each period were then calculated by Poisson regression.

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, 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 9.2 (SAS Institute Inc, Cary, NC).

Table 1. Characteristics of women with multiple sclerosis at onset of pregnancy

Characteristic	Resumed IMAs 0-15 days postpartum (n = 17)	Resumed IMAs 16-365 days postpartum (n = 38)	p value
Mean disease duration, years (SD)	7.1 (5.1)	5.4 (4.4)	0.22
Mean age, years (SD)	33.6 (5.3)	31.5 (4.2)	0.12
Relapses 2 years before pregnancy, no. (%)			
0	7 (41)	8 (21)	0.19
1	3 (18)	17 (45)	
2	6 (35)	8 (21)	
3	1 (6)	3 (8)	
≥ 4	0 (0)	2 (5)	
Use of MS immunotherapies, no. (%)			
Ever	17 (100)	36 (95)	> 0.5
≤ 6 months before pregnancy	15 (88)	15 (39)	0.002
EDSS ≥ 4.0, no. (%)	0 (0)	6 (16)	0.16

EDSS = Expanded Disability Status Scale; IMAs = immunomodulatory agents: interferon beta and glatiramer acetate; MS = multiple sclerosis; SD = standard deviation.

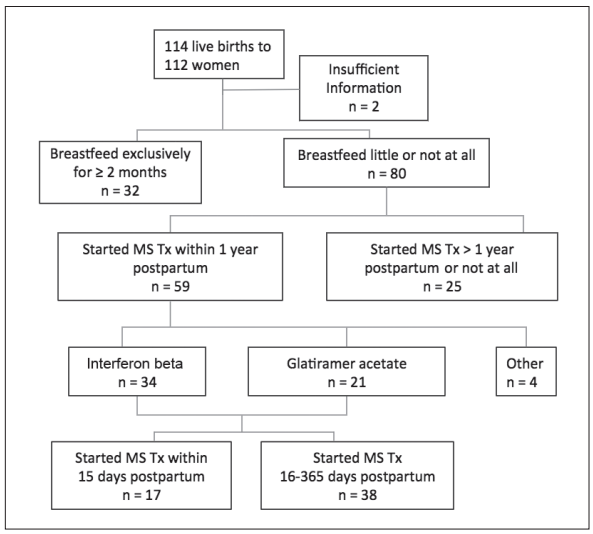

Figure 1. Breastfeeding and treatment outcomes in women with multiple sclerosis included in the study.

MS = multiple sclerosis; Tx = treatment.

Results

Of the 114 live births (112 women), 80 babies (70%) were breastfed little or not at all, 32 (28%) were breastfed exclusively for at least the first 2 months postpartum, and 2 (2%) had insufficient documentation in their medical records to determine the exposures or outcomes of interest (Figure 1). Of the 80 women who breastfed little or not at all, 55 (69%) resumed treatment with interferon beta (n = 34) or glatiramer acetate (n = 21) within 1 year postpartum, whereas the remainder resumed treatment either much later or not at all (Figure 1). Seventeen (31%) of the 55 women who resumed treatment continued with interferon beta or glatiramer acetate within 15 days postpartum, 29 women (53%) between 16 and 180 days, and 9 (16%) between 181 and 365 days. Thirty-seven (67%) of these 55 treated women relapsed within 2 years, most of whom (n = 26) relapsed within 6 months postpartum. Fourteen women waited until they had their first postpartum relapse before resuming treatment.

The baseline characteristics of women with MS who did not breastfeed exclusively and resumed immunomodulatory agents within the first 2 weeks postpartum and those who resumed treatment later in the postpartum year are presented in Table 1. Women who resumed treatment within the first 2 weeks postpartum were older, had longer disease duration, had slightly fewer relapses in the 2 years before pregnancy, were less likely to have clinically significant disability (Expanded Disability Status Scale score ≥ 4.0), and were more likely to have been treated in the 6 months before pregnancy. Only treatment within 6 months of pregnancy reached statistical significance (Table 1). Only 2 women in each group had relapses during pregnancy, and development of clinically significant disability progression during the 2 years postpartum was rare in both groups (Table 2).

Women who started treatment with interferon beta or glatiramer acetate even as early as 2 weeks postpartum had a similar risk of return of relapses in the 2 years postpartum and relapsed around the same time (unadjusted HR = 1.1, 95% CI = 0.56-2.2, p = 0.7) as did women with MS who resumed treatment with interferon beta or glatiramer acetate later in the postpartum year (Figure 2; Table 2). The lack of a robust protective effect of early treatment with interferon beta or glatiramer acetate remained even after adjusting for age, disease duration, prepregnancy relapse frequency, and prepregnancy treatment (standard multivariable adjustment HR = 1.2, 95% CI = 0.60-2.5, p = 0.6 and propensity score-adjusted HR = 1.3, 95% CI = 0.47-3.4, p = 0.6).

Among the 25 women who resumed immunomodulatory agents during the second year postpartum or not at all, only 8 (32%) relapsed during the 2 years postpartum. Inclusion of these women in the analyses still failed to show a protective effect of early immunomodulatory treatment on return of relapses (standard adjustment HR = 1.5, 95% CI = 0.74-3.1, p = 0.3). Additional sensitivity analyses comparing immunomodulatory treatment within 30 days postpartum vs later in the postpartum year also

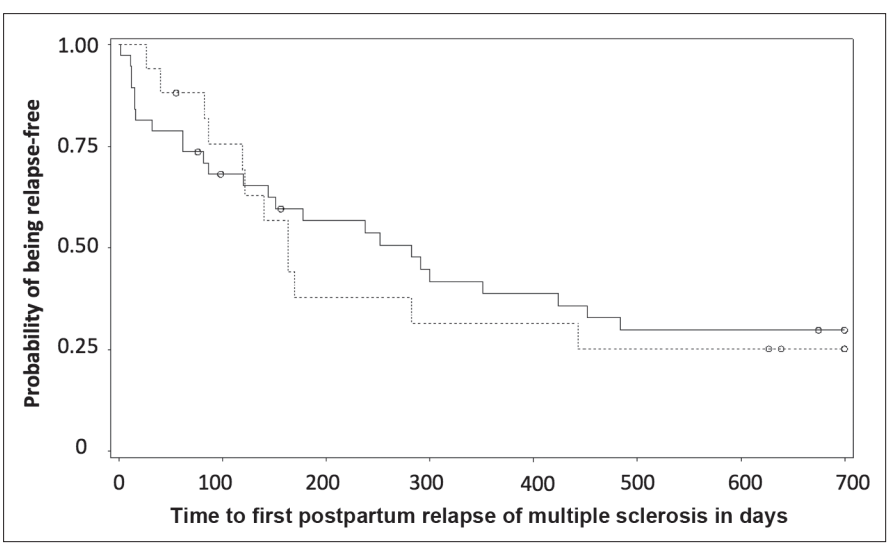

Figure 2. Kaplan-Meier curve for multiple sclerosis relapses in the postpartum period among women who breastfed little or not at all and started immunomodulatory treatment within one postpartum year.

Women who started treatment in the first 15 days (n = 17; dashed line) did not experience a delay in the time to the first postpartum relapse and had the same risk of having a postpartum relapse as women who started treatment later in the postpartum year (Days 16-365; n = 38; solid line; p value = 0.75 by log-rank test).

failed to show a protective effect of early treatment (standard adjustment HR = 0.95, 95% CI = 0.48-1.9, p = 0.9).

The annualized relapse rates and proportion of women with relapse in the 2 years after delivery are presented in Table 3. Relapse rates were significantly higher in the first year postpartum compared with the second year regardless of when immunomodulatory treatment was resumed. Overall, 26 women (47%) suffered 31 relapses in the first 6 months postpartum. However, there was no difference in the relapse rates of the 2 groups during this period. The women who resumed immunomodulatory agents in the first 2 weeks postpartum did appear to have a lower risk of relapse later in the postpartum year (unadjusted p = 0.08; Table 3), although this did not reach statistical significance even after adjusting for measures of disease severity (adjusted p = 0.08, Poisson regression). This difference was not sustained into the second postpartum year.

Discussion

In this study, we found that starting treatment with interferon beta or glatiramer acetate as early as two weeks after delivery did not decrease the risk of a postpartum relapse. This was true even after taking into account the prepregnancy disease severity and reducing the potential for confounding by excluding women who chose to breastfeed exclusively or those who chose not to resume treatment at all. We also found a nonsignificant trend toward fewer relapses in the second half of the postpartum year among those women who resumed treatment early vs later in the postpartum year. Our findings suggest that among women who breastfeed little or not at all, starting treatment with interferon beta or glatiramer acetate even within two weeks postpartum does not dramatically reduce the risk of having a first postpartum relapse but may reduce the risk of subsequent relapses in the postpartum year.

No previous studies have examined whether forgoing breastfeeding in order to resume immunomodulatory agents reduces the risk of postpartum relapses—despite the clinical importance of the question. In fact, most studies of MS and pregnancy were conducted before the widespread use of immunomodulatory agents.[1,8] However, our findings are not surprising because both interferon beta and glatiramer acetate have demonstrated a delayed onset of action in reducing time to first relapse,[4,5] and the highest risk period for postpartum MS relapses is the first 4 months postpartum.[1] In addition, the effect of interferon beta and glatiramer acetate in reducing the risk of relapse is modest at best, with no more than 25% reduction over 2 years.[4,5] Another, less likely explanation for our findings is that the overwhelming immunologic changes of pregnancy[9] may make the pathophysiology of postpartum relapses unlike relapses that occur during other phases of life and therefore resistant to treatment with immunomodulatory agents.

We set stringent criteria for the timing of resuming immunomodulatory agents postpartum and defining the comparison group to maximize the possibility of detecting a benefit of resuming immunomodulatory agents in preventing postpartum relapses. Because of the well-known delayed onset of action of interferon beta and glatiramer acetate, we required that immunomodulatory agents be resumed within 2 weeks postpartum. Because of the potential protective effects of exclusive breastfeeding, which could, in comparison, make resuming immunomodulatory agents look harmful, we excluded women who chose to breastfeed exclusively. Finally, some women seem to wait to resume immunomodulatory agents until after they have their first postpartum relapse, which may not occur until the second postpartum year or later. To avoid obscuring a treatment effect by including these women with relatively benign disease, we excluded those who did not breastfeed and did not

Table 2. Clinical characteristics of women with multiple sclerosis during pregnancy and postpartum Years 1 and 2

Characteristic	Resumed IMAs 0-15 days postpartum (n = 17)	Resumed IMAs 16-365 days postpartum (n = 38)	p value
Pregnancy			
Women with relapses, no. (%)	2 (12)	2 (5)	> 0.5
Postpartum Years 1 and 2			
Women with relapses, no. (%)	12 (71)	25 (66)	> 0.5
Time to first postpartum relapse, days			> 0.5
Range	26-443	1-484	
Median	163	282	
First quartile	119	61	
EDSS ≥ 4.0, no. (%)	3 (17)	6 (16)	> 0.5
Disability progression,[a] no. (%)	3 (17)	2 (5)	0.17

[a] Defined as progression from Expanded Disability Status Scale (EDSS) of < 4.0 to ≥ 4.0; or progression from EDSS of 4.0 to EDSS ≥ 6.0; or progression from EDSS of 6.0 to EDSS ≥ 7.0.
IMAs = immunomodulatory agents: interferon beta and glatiramer acetate.

Table 3. Relapse during the 2 years postpartum in women with multiple sclerosis

Months postpartum	Resumed IMAs 0-15 days postpartum			Resumed IMAs 16-365 days postpartum			Total			p[b] value
	Number (%) of women with relapse[a]	Number of relapses	Rate of relapse per woman per year, mean (95% CI)	Number (%) of women with relapse[a]	Number of relapses	Rate of relapse per woman per year, mean (95% CI)	Number (%) of women with relapse[a]	Number of relapses	Rate of relapse per woman per year, mean (95% CI)	
1-6	10 (58.8)	10	1.18 (0.72-1.82)	16 (42.1)	21	1.11 (0.80-1.49)	26 (47.3)	31	1.13 (0.86-1.45)	> 0.5
7-12	3 (20.0)	3	0.4 (0.15-0.87)	16 (45.7)	21	1.20 (0.86-1.62)	19 (38.0)	24	0.96 (0.71-1.27)	0.08
13-18	2 (13.3)	2	0.26 (0.07-0.68)	7 (20.0)	7	0.4 (0.22-0.67)	9 (18.0)	9	0.36 (0.21-0.57)	> 0.5
19-22	1 (6.7)	1	0.13 (0.02-0.48)	4 (12.1)	5	0.30 (0.15-0.56)	5 (10.4)	6	0.25 (0.13-0.44)	> 0.5

[a] Seven women were lost to follow-up over the 2-year period: 2 who were treated 0 to 15 days postpartum and 5 who resumed treatment later.
[b] p value compares the relapse rate of those who resumed immunomodulatory treatment earlier vs later in the postpartum year.
CI = confidence interval; IMAs = immunomodulatory agents: interferon beta and glatiramer acetate.

resume immunomodulatory agents within the first postpartum year. Despite this, we were unable to detect a significantly decreased risk of postpartum relapses in women who resume immunomodulatory agents shortly after delivery.

The nonsignificant trend toward fewer relapses in the second half of the first postpartum year in women who started interferon beta or glatiramer acetate treatment earlier rather than later may be the result of the delayed effect of glatiramer acetate and interferon beta. However, it is difficult to draw conclusions from such a small number of patients, and these findings need to be confirmed in a larger study.

Limitations of this study include the small sample size and reliance on routine medical records to identify relapses. This study does not exclude the possibility of a very small treatment effect; larger sample sizes are needed to address this issue. It is possible that women may not have sought care for minor relapses, although it seems unlikely that this would differ by exposure group. Furthermore, we observed a very similar annualized relapse rate and proportion of women with relapses during the first 6 months postpartum compared with the Pregnancy in Multiple Sclerosis (PRIMS) study[10] (47.3% and 48%, respectively).

Strengths of this study are the complete and accurate pharmacy and health care records of mother and offspring in addition to the population-based source and clinical relevance of the question.

This study failed to demonstrate that resuming interferon beta or glatiramer acetate even as early as within the first 2 weeks postpartum could significantly decrease the risk of first postpartum relapse among women who choose not to breastfeed. However, the trend toward a decreased risk of relapse later in the postpartum year warrants further study. A larger collaborative study between KPSC and Kaiser Permanente Northern California funded by the National Multiple Sclerosis Society, New York, NY, is currently under way to confirm findings from this study. ❖

Disclosure Statement

Dr Langer-Gould is the site principal investigator for 2 industry-sponsored Phase 3 clinical trials (Biogen Idec, Weston, MA; Hoffman-La-Roche; Basel, Switzerland) and 1 industry-sponsored diagnostic assay observational study (Biogen Idec). She is also the principal investigator of an MS susceptibility study funded by the National Institutes of Health, Bethesda, MD, and a research grant from the National Multiple Sclerosis Society, New York, NY. The other authors have no potential conflicts of interests to disclose.

Authors' Contributions

Brandon Emet Baeber, MD, contributed to the collection of the data as well as drafting and revising the manuscript. Margaret D Chi, MPH, and Sonu Malik Brara, MD, contributed to the collection of the data as well as critical review of the manuscript. Jian Liang Zhang, MS, made substantial contributions to the data analysis and interpretation of the data. He contributed to drafting and revising the manuscript. Annette M Langer-Gould, MD, PhD, made substantial contributions to the conceptualization and design of the study; contributed to data collection, analysis, and interpretation; helped draft and revise the manuscript; and supervised the study.

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Sound of Gnawing

Even as I sit and write, millions of bacteria are gnawing away my precious spinal cord, and if you put your ear to my back the sound of the gnawing I dare say could be heard.

—*The Journal of a Disappointed Man,* Wilhelm Nero Pilatus Barbellion (Bruce Frederick Cummings), 1889-1919, English diarist