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Disease Activity And Its Association With Breastfeeding In Multiple Sclerosis Patients During Postpartum Period

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Abstract

Background: The post-partum period may represent a difficult phase in multiple sclerosis (MS) course, as during the first three months after delivery, a disease worsening is possible, particularly in women with a more active disease and multiple relapses that occurred prior to the pregnancy.
Aim of the work: This study aimed to investigate the association between breastfeeding and disease activity of MS during postpartum period.
Patients and methods: A retrospective observational study was conducted on 113 MS women following 136 pregnancies occurred after MS diagnosis and with history of at least one pregnancy during the last seven years. The archived files and a self-administrating questionnaire were used for data collection.
Results: Disease modifying therapy (DMT) usage and disease duration did not show any significant association with disease activity. While, number of postpartum relapses was significantly related to exclusive breastfeeding (OR=0.31, 95%CI: 0.12–0.67, P=0.02). Furthermore, the pregnancy and pre-pregnancy relapses were significant predictors for postpartum relapses (OR=3.09, 95%CI: 1.68–5.67, P<0.001, and OR=2.21, 95%CI: 1.23–3.69, P=0.005, respectively).
Conclusions**:** Postpartum reactivation of the disease occurs from the third month after labor rather than the early postpartum period. Exclusive breastfeeding for at least two months decreased the risk of postpartum relapse.

Keywords: Pregnancy; Multiple Sclerosis; Breastfeeding; DMT.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disorder of the central nervous system that is characterized by neurological relapses and frequent progressive neurological dysfunction and disability[1]. Its prevalence is two to three times more common in women than in men, with a mean age of onset of 30 years[2]. A population-based study showed that 126 669 people in the UK were living with MS in 2010 and the prevalence among women was 285.8 per 100 000[1]. More than half of women with MS will develop the disease during their reproductive years[3]. This makes pregnancy and its related issues, like lactation, very important issue to be studied and analyzed to know the relationship between pregnancy and lactation.

Women with MS appeared to have fewer relapses during pregnancy, but relapse during the first three to four months postpartum is not uncommon (20–30% of female patients)[4]. However, the risk of postpartum relapse steadily increases during the few months after delivery than the pre-pregnancy period[5]. The exact mechanism of this increase in the post-partum relapsing rate is not well established[6,7]. Many theories have been proposed for that assumption; including the decrease in the decrease in humoral immunity and increase in the cellular immunity in addition to shifting from Th2 to Th1 causing increase in the disease activity[6,7]. This assumption was introduced many years ago based on some studies which included patients who were known to have MS at that time[6]. However, the criteria for MS diagnosis at that time was not yet upgraded to include many patients with minor conditions[6]. Therefore, after the update and inclusion of many milder cases, this concept may be affected or may changes.

Interestingly, a recent study showed that the annualized relapsing rate after pregnancy did not increase during the first three months after delivery[5]. Instead, it increased from the fourth moth to the last month of the postpartum year[5]. This may be influenced by many factors including the clinical status of the patient, the-pregnancy disease activity and breast feeding[8-10]. Several studies have found that breastfeeding has beneficial effects on MS relapse[11]. Exclusive breastfeeding for at least the first two months postpartum has shown to reduce relapse in the immediate postnatal period as it leads to a distinct hormonal state in which luteinizing hormone (LH) and pulsatile gonadotrophin-releasing hormone (GnRH) are suppressed and prolactin levels are high[12]. This results in anovulation, lactational amenorrhoea and a reduction of tumor necrosis factor-alpha (TNF-α)-producing CD4 cells. This immunological effect is believed to reduce postpartum relapse by four-fold[13]. A previous meta-analysis by demonstrated that breastfeeding halves the risk of MS relapse[14].

This work aims to study the relationship between breastfeeding and disease activity after delivery in MS women, taking into account the role of disease severity and activity before and during the pregnancy period and patient exposure to disease modifying drugs (DMDs).

PATIENT AND METHODS

This study was conducted as a retrospective observational study on pregnant women with MS diagnosis and with a history of at least one pregnancy during the last seven years, through which the archived files of the eligible participants were used for data extraction. Moreover, a self-administrated questionnaire was filled by each participant. This study was conducted at MS units in Al- Hussein University hospital, Bab-Elshaarya University hospital, and Cairo Fatemic hospital. We performed this study under the umbrella of the Helsinki's declarations and each female patient signed informed consent before the enrollment. The institutional review board approval was obtained from the ethical committee of the Faculty of Medicine for boys, Al-Azhar University, Cairo.

In this study we included Any female patient with MS which was clinically definite CDMS) and with child bearing-potential (15-45 years old) with at least one successful pregnancy during the last seven years was included in the study. The diagnosis of MS should be established at least one year before the conception. Moreover, patients with other demyelinating diseases or any other autoimmune diseases were also excluded. Patients with EDSS score more than 6 at the enrolled time were also were omitted.

All selected women included in this study were subjected to the following: Demographic data including age, BMI, maternal MS clinical history was extracted from medical records, including time duration since MS diagnosis, comorbidities rather than MS, number of pregnancies, and abortions before and after MS diagnosis (in the last seven years) were considered, Expanded Disability Status Scale (EDSS) score, clinical relapses, and DMT use preconception and after delivery or pregnancy loss. Furthermore, the data about pregnancy and its outcomes with or without treatment were considered.

Any new neurological symptom or worsening in the neurological symptoms for at least one day without evidence of infection or fever was considered as relapse. Any use of steroids as prophylaxis during this pregnancy or postpartum was also recorded. In addition, the data about labor and postpartum period including the anesthesia, delivery associated complications, neonatal outcomes immediately after delivery, postpartum RR, and DMT usage were collected. The postpartum outcomes including the RR, steroids usage as prophylaxis, breastfeeding, and DMT usage were collected. The breastfeeding status (exclusive, nonexclusive, or not at all) up to 12 months after delivery was recorded. Exclusive breastfeeding was considered when the mother exclusively fed her baby for at least two months.

The disease activity assessment was conducted through calculating the annualized relapsing rate (ARR) which was assessed two years before pregnancy, every three months during pregnancy, and every three months postpartum. In the case of more than one pregnancy, the ARR was found by dividing all relapses that occurred on the time per year (0.33) then we divided them by the number of pregnancies.

Results were collected, tabulated, statistically analyzed by IBM personal computer and statistical package SPSS version 25 (Armonk, NY: IBM Corp, 2013). Descriptive statistics included Percentage (%), mean (x), and standard deviation (SD) or median and interquartile range (IQR) according to its normality. Furthermore, analytic statistics included chi-square test ($\chi 2$), t-test, Mann-Whitney U test, and regression analysis was conducted to investigate the predictor factors of relapse either during pregnancy or postpartum with odds ratio (OR) and 25% confidence interval (CI). P-value <0.05 was considered statistically significant.

RESULTS

We included into this study 113 MS women with 136 postpartum years following 136 pregnancies that occurred after MS diagnosis. The mean age of these women was 32.14 ± 4.98 years with median of the disease duration till the time of screening 4.45 years with interquartile range from 1.91 to 8.96 years. Despite most of the included women had RRMS, seven women had progressive relapsing MS at the time of enrollment. Among these women, one patient had prior data of postpartum period before development of progressive stage. As regard the clinical characteristics of the included patients, only three women were unilaterally supported or wheelchair bound with EDSS ≥ 4. Despite most women did not use DMT, interferon beta was the most used DMT (Table 1)

Characteristic	Value
Age (mean, SD), y	32.14 ± 4.98
Disease duration, median (IQR), y	4.45 (1.91-8.96)
MS subtype at onset of pregnancy, no. (%)	
RRMS	127 (93.38%)
Progressive, relapsing MS	9 (6.62%)
Relapses during 2 years before pregnancy [a]	
0	61 (44.85%)
1	52 (38.23%)

≥2	23 (16.92%)
MS-related disability, no. (%)	
No disability	84 (61.76%)
Some disability but fully ambulatory	41 (30.15%)
Some ambulatory impairment	8 (5.88%)
Cane required	2 (1.47%)
Wheelchair required	1 (0.74%)
EDSS score before pregnancy, no. (%)	
0-0.5	66 (48.53%)
1-1.5	47 (34.56%)
2-2.5	15 (11.03%)
3-3.5	5 (3.68%)
≥ 4	3 (2.21%)
DMT use during postpartum year, no. (%)	
None	71 (52.21%)
Interferon-beta	32 (23.53%)
Dimethyl fumarate	9 (6.62%)
Natalizumab	4 (2.94%)
Rituximab	5 (3.68%)
Fingolimod	12 (8.82%)
ocrelizumab	3 (2.20%)
Time to restart DMT after delivery [c] (median, IQR), d	86 (29-201)

Table 1. Demographic characteristics of the included 113 MS women with 136 postpartum period. Abbreviations: DMT = disease-modifying therapy; IQR = interquartile range; MS = multiple sclerosis; RRMS = relapsing-remitting MS; EDSS= Expanded Disability Status Scale.[a] One case with deep venous thrombosis

As regard the annualized relapsing rate during the postpartum period, it was significantly decreased during the first and last quarters of the postpartum year when compared to the two years before the pregnancy (P = 0.037 and 0.023, respectively). Furthermore, when comparing this relapsing rate with the annualized relapsing rate before the pregnancy, there was only significant increase during the two middle quarters (P =0.041). However, there was no difference between these two quarters and the two years before the pregnancy (Table 2 and Figure 1))

	No. relapses	Rate of relapse/ pregnancies/y [a]	P Value*
2 years before pregnancy	101	0.37 (0.32-0.41)	—
Year after pregnancy			
Months 1–3	9	0.27 (0.16-0.39)	0.037
Months 4–6	13	0.38 (0.26-0.52)	0.990
Months 7–9	13	0.38 (0.26-0.52)	0.751
Months 10–12	8	0.24 (0.17-0.38)	**0.023**

Table 2. relapse rates during first year postpartum

[a]Mean and 95% confidence intervals.

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

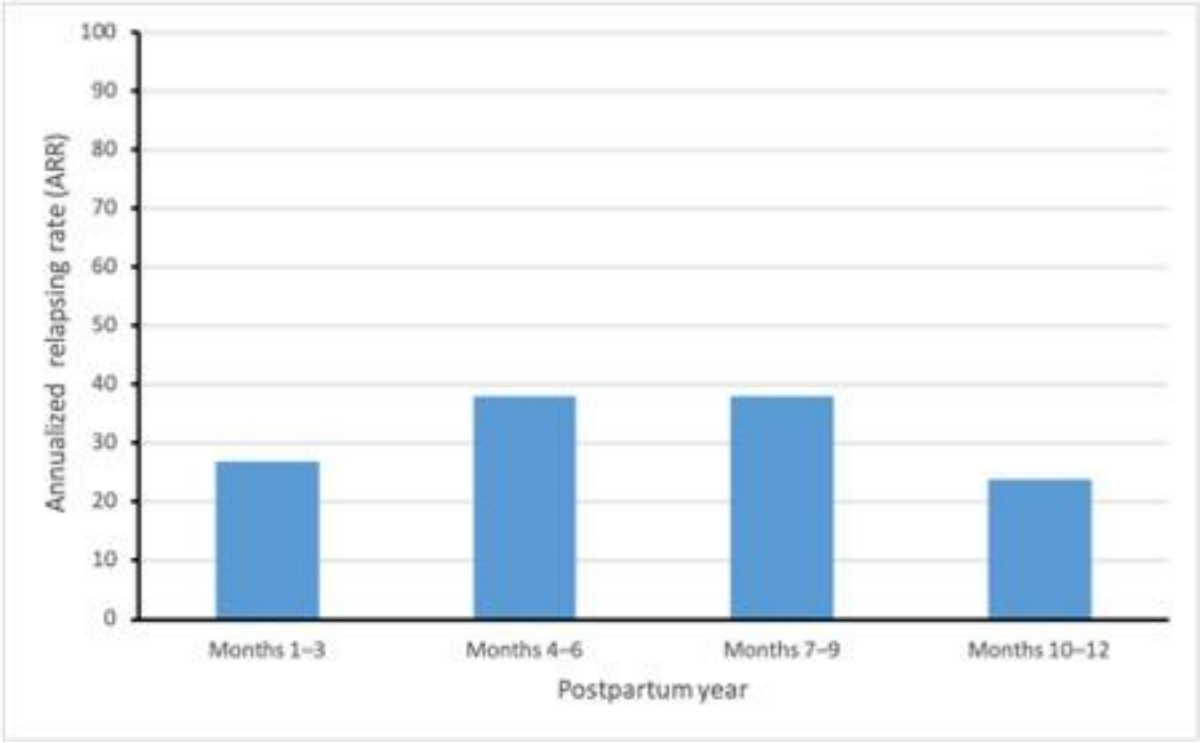

Figure 1. the annualized relapsing rate during each quarter of the postpartum year.

Having the factor that affected the postpartum relapsing rate with no breastfeeding as a reference, the exclusive breastfeeding for four months was shown to be associated with decrease the MS relapse, while the non-exclusive breastfeeding was not reported to be associated with a decrease in the MS relapse (HR = 0.31, 95% CI, 0.12–0.67, P =0.002 vs HR = 0.59, 95% CI, 0.31–1.16, P=0.126). On the other hand, the pre-pregnancy and pregnancy relapses were associated with the increase of the risk of postpartum relapse (HR = 2.21, 95% CI, 1.23–3.69, P =0.005 vs HR = 0. 3.09, 95% CI, 1.68–5.67, P<0.001). `Furthermore, the disability of the patient was associated with increased relapsing risks (HR = 2.08, 95% CI, 1.72–3.41, P = 0.002). Other factors including the disease duration and use of DMT were reported to have no effect on the relapsing rate (Table 3).

	Hazard ratio (95% CI) [a]	p Value
No breastfeeding	1.0 (ref)	
Exclusive breastfeeding [b]	0.31 (0.12–0.67)	0.002
Nonexclusive breastfeeding [b]	0.59 (0.31–1.16)	0.126
Pre-pregnancy relapses [c]	2.21 (1.23–3.69)	0.005
Use of DMT before pregnancy by 1 year	1.46 (0.90–2.38)	0.130
Pregnancy relapse	3.09 (1.68–5.67)	<0.001
Use of postpartum DMT [d]	1.41 (0.71–2.58)	0.340

Age, (years)	0.92 (0.89-0.99)	0.016
Disease duration, (years)	1.12 (0.96–1.23)	0.437
Disability [e]	2.08 (1.72–3.41)	0.002

Table 3. Regression analysis of factors associated with increase the risk of MS relapse.
Abbreviations: CI = confidence interval; DMT = disease-modifying therapy; MS = multiple sclerosis.
[a] Cox proportional hazards model.
[b] Reference group no breastfeeding.
[c] Reference group 0–1 relapse in 2 years before pregnancy.
[d] Time-dependent covariate.
[e] Reference group no MS-related disability at pregnancy onset

DISCUSSION

A definitive ascertainment of possible relationships between breastfeeding and disease course in MS has critical practical implications for women's counseling and clinical decision-making, yet evidence in this area is and remains controversial[15]. The post-partum period may represent a difficult phase in the MS course: as described above, during the first 3 months after delivery, a disease worsening is possible, particularly in women with the more active disease before and during the pregnancy period[16]. Thus, this study was conducted to include MS women with a history of at least one pregnancy during the last seven years. A self- administrating questionnaire in addition to the archived files of the patients was used for data collection.

Our reported percentage of exclusive breastfeeding was higher than that was reported by a previous study which found the proportion of exclusive breastfeeding subjects was (34.4%)15. It is noteworthy that breastfeeding is generally encouraged due to its benefits for both the child and the mother. In line with current findings, a previous series of four pregnant women showed increased disability and MRI activity on stopping treatment, and a further case involving a young woman with increased disease activity after discontinuing a clinical trial of natalizumab to plan a pregnancy[17]. Similar results were reported with fingolimod[18,19]. Other findings concluded that intensive breastfeeding reduced the frequency of attacks only in the first 6 months after birth and could not demonstrate a relationship between pre-pregnancy disease severity and the choice to forego exclusive breastfeeding[12].

As regards breastfeeding, pour results support the results of a previous meta-analysis which evaluated 12 studies and concluded that breastfeeding has a decreasing effect on disease activity in MS[14]. Furthermore, another study reported that mothers who did not breastfeed in the postpartum period or who breastfed for less than three months had more attacks[20]. It also, revealed that most of their patients used DMT while they were pregnant, and they found that there was no relationship between DMT use and fetal development problems. Supportingly, another study revealed that patients who chose to breastfeed, in comparison with patients who did not, had a milder disability and fewer relapses both in the year before pregnancy and during pregnancy[15]. Breast feeding could increase the CD4 T-cells which produce interferon; therefore, it deceases the disease activity. After, delivery, women with increased disease activity were more likely to stop breastfeeding or even forego it in order to resume the DMT; therefore, breastfeeding was used only in women with milder disease activity. This could explain that why breastfeeding protects from MS relapses[21,22]. On the other hand, the previous two studies failed to find an association between breastfeeding and postpartum relapses[23,24]. Other studies showed no relationship between the breastfeeding, age at onset of the disease, the number of pregnancies, the total number of outbreaks prior to pregnancy, or sex of the newborn and the disease activity[25,26]. As regards the use of postpartum DMT, our results showed no effect on the disease activity; however, Hallwig et al revealed that 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[12]. This

indicates that exclusive breastfeeding has the upper hand over nonexclusive breastfeeding or even DMT. The usage of interferon beta or glatiramer acetate by most included women postpartum indicates that more potent DMTs may be protected or have beneficial effect on the disease activity rather than the breastfeeding. These studies, however, are clearly limited by the small sample size.

Using DMT during pregnancy could affect postpartum breastfeeding but not postpartum disease activity. These findings are consistent with those reported by Portaccio et al who reported that DMT at any time before pregnancy did not alter the postpartum risk of relapse[15]. Furthermore, they found that pre-pregnancy 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 postpartum underscores the importance of studying these issues in their cohort. Another study reported in its univariable analyses that the odds of having at least one clinical relapse during the first trimester postpartum was increased with the occurrence of ≥1 relapse during pregnancy and reduced with exclusive breastfeeding for three months compared with nonexclusive breastfeeding[27]. Postpartum relapses were not significantly related to DMT use preconception, possibly because of broader clinical trends toward avoiding long periods off DMT and mitigating rebound risk after fingolimod and natalizumab[28]. In contrast, Hughes et al found DMT use before pregnancy to be associated with a reduced risk of relapse postpartum[29].

Despite our study showed many advantages, it has some pitfalls including the selection bias of the included MS women. This bias was due to the increased number of MS participants who were receiving DMT. Therefore, it was out of our hands to avoid it. Furthermore, the relationship between breastfeeding and postpartum disease activity may be underestimated due to selection bias.

CONCLUSION

In our study, it was observed that exclusive breastfeeding for three months or more reduced the frequency of attacks in the postpartum period. Relapse in postpartum may be diminished by exclusive breastfeeding. Breastfeeding should be encouraged for all MS patients who are planning for pregnancy. Pre-pregnancy counseling and careful planning will allow women with MS to have a favorable pregnancy outcome. Reassurance and health education are needed for all MS women during their childbearing potential.

Conflict of interest

The author declares that there was no conflict of interest.

Author's Contribution

AHE hypothesized the idea, wrote the protocol, collected the data, performed the analysis, and wrote the manuscript.

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