Breastfeeding is not related to postpartum relapses in multiple sclerosis

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ABSTRACT

Objective: To assess the relationship between breastfeeding and risk of puerperal relapses in a large cohort of patients with multiple sclerosis (MS).

Methods: We prospectively followed-up pregnancies occurring between 2002 and 2008 in women with MS, recruited from 21 Italian MS centers, and gathered data on breastfeeding through a standardized interview. The risk of relapses after delivery was assessed using the Cox regression analysis.

Results: A total of 302 out of 423 pregnancies in 298 women resulted in full-term deliveries. Patients were followed up for at least 1 year after delivery. The time-dependent profile of the relapse rate before, during, and after pregnancy did not differ between patients who breastfed and patients who did not. In the multivariate analysis, adjusting for age at onset, age at pregnancy, disease duration, disability level, and relapses in the year prior to pregnancy and during pregnancy, treatment with disease-modifying drugs (DMDs), and exposure to toxics, the only significant predictors of postpartum relapses were relapses in the year before pregnancy (hazard ratio [HR] = 1.5; 95% confidence interval [CI] 1.3–1.9; $p < 0.001$) and during pregnancy (HR = 2.2; 95% CI 1.5–3.3; $p < 0.001$).

Conclusions: In our sample, postpartum relapses were predicted only by relapses before and during pregnancy. Therefore, the reported association between breastfeeding and a lower risk of postpartum relapses may simply reflect different patient behavior, biased by the disease activity. Our results can assist neurologists facing the breastfeeding issue in mother counseling and shared decision-making. Especially, among patients with high risk of postpartum relapses, breastfeeding may not be feasible and early postpartum treatment should be an option.
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GLOSSARY

BG = breastfeeding group; **CI** = confidence interval; **DMD** = disease-modifying drug; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **MS** = multiple sclerosis; **NBG** = not breastfeeding group; **PS** = propensity score; **PRIMS** = Pregnancy in MS study.

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Issues of conception, pregnancy, and delivery are receiving renewed interest in multiple sclerosis (MS). There is consistent evidence that the 12-month period after delivery, and particularly the first trimester, is characterized by a significant increase in the relapse rate and represents a critical phase for patient counseling and therapeutical decision-making, since available disease-modifying drugs (DMDs) are contraindicated during breastfeeding.[1] Conversely, there is limited information on the impact of breastfeeding on disease course. The large European Pregnancy in MS (PRIMS) study[1,2] reported no association between breastfeeding and postpartum relapses. These results are in line with findings from a more recent study,[3] whereas another group has suggested a protective role of breastfeeding,[4] possibly mediated through immuno-

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logic mechanisms related to the lactational amenorrhea.[5] To date, there is no definitive consensus on whether breastfeeding should be advised against in order to start or resume therapy soon after delivery, due to the risk of postpartum relapses. In the absence of evidence-based recommendations that can solve the mother's dilemma, the final decision between the 2 mutually exclusive options is often left to the patient herself.[6]

In a previous multicentric, prospective study we addressed the issue of DMD safety during pregnancy in MS.[7] The study dataset also gathered detailed follow-up information, including breastfeeding choice and disease course after delivery. In this further analysis of the same cohort of patients, we aimed to assess the impact of breastfeeding on the postpartum relapse rate, taking into account possible confounders.

METHODS Between 2002 and 2008, all pregnancies occurring in patients with MS, diagnosed according to MacDonald et al.[8] criteria and referred to the participating centers, were identified and tracked over the whole gestational period. The 21 participating sites represented the main Italian MS Centers located throughout the entire country. In the present study, we included all pregnancies resulting in full-term deliveries and having a postpartum follow-up duration of at least 1 year. All the patients were regularly followed up every 6 months and in the case of relapse. Clinical and therapeutic data were gathered by the neurologist using a standardized information form. After delivery, the neurologist administered a semi-structured interview to each patient dealing with pregnancy outcomes, breastfeeding, and potential confounders (see below). Pregnancy outcomes focused on in utero exposure to toxins, smoke, alcohol, pharmacologic therapies, and timing of therapy suspension in relation to conception.[7] Follow-up data on the babies were also gathered and updated every 6 months on the basis of a standardized questionnaire aimed at the parents.[7] Breastfeeding was classified according to the WHO's definition of exclusive or predominant breastfeeding (the infant received breast milk only, with liquid supplementation allowed), complementary breastfeeding (the infant received breast milk, with liquid and food supplementation allowed, including nonhuman milk), and not breastfeeding (the infant did not receive any breast milk).[9-11] As for disease activity, the date of onset and number of relapses in the year prior to conception, during pregnancy, and in the year after delivery were recorded. A relapse was defined as the appearance or reappearance of one or more symptoms attributable to MS, accompanied by objective deterioration, as shown by neurologic examination, lasting at least 24 hours, in the absence of fever and preceded by neurologic stability for at least 30 days.[8] Disability was also recorded on the Functional Systems and Expanded Disability Status Scale (EDSS)[12] in the case of relapse and over the follow-up period.

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethics committee of the University of Florence, and written consent was obtained from all patients.

Statistical analysis. Baseline characteristics were reported as frequency (%) and mean ± SD, and compared with Pearson χ^2, Student *t*, and Mann-Whitney *U* test when appropriate.

For comparison with previous studies,[3,4] patients were divided into 2 groups: those who breastfed their infants for at least 2 months consecutively and exclusively (breastfeeding group [BG]) and those who breastfed their infants for less than 2 months or did not breastfeed at all (not breastfeeding group [NBG]). Breastfeeding for a period of at least 6 months was also taken into account in the analysis. An annualized relapse rate was calculated for each trimester in the year before conception, during pregnancy, and in the year after delivery. The relapse frequency in terms of annualized relapse rate in each trimester before, during, and after pregnancy in the BG was compared with that observed in the NBG using a 2 (group: BG and NBG) × 11 (time: 4 trimesters before conception, 3 trimesters during pregnancy, 4 trimesters after delivery) mixed factorial design, with repeated measures on the second factor. This allows evaluation of differences between the 2 groups (effect for group), within each group over time (effect for time), and the interaction between group and time (effect for group × time).

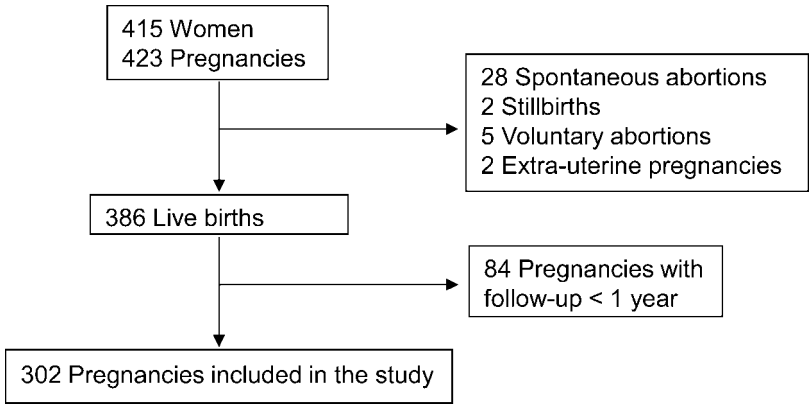
Moreover, the patients were grouped as patients with at least one relapse and patients with no relapse in the year after delivery. The impact of breastfeeding and other possible predictors of postpartum relapse was assessed through a multivariate survival analysis (Cox regression model). Together with breastfeeding, the following covariates were entered into the model: age at MS onset, age, disease duration and EDSS at conception (determined as 14 days after the mother's last menstrual period), DMDs before pregnancy, number of relapses in the year before pregnancy and during pregnancy, smoking, alcohol intake, and toxin exposure during pregnancy.

Propensity score (PS)–adjusted Cox regression model was also assessed. PS methodology is a common device used to reduce bias in treatment comparisons in observational studies.[13-15] Separate pairwise logistic regression models were first used to predict the probability (PS) to be assigned to one specific treatment group (BG) vs the control group (NBG). These models included as covariates the same confounders entered in the multivariate model. PS pairwise logistic models were selected in a stepwise fashion, and model building stopped when adequate covariate balance was reached.[14] Overlapping of PS between treatment and control groups was checked, and nonoverlapping subjects were excluded from the analyses. Finally, PS quintiles derived from the definitive logistic model were introduced in the Cox regression model, to allow an adjusted comparison between treatment groups for the endpoint at issue.

All analyses were performed using SPSS 18.0 (SPSS, Chicago, IL).

RESULTS During the study period, a total of 423 pregnancies were tracked in 415 women. The last pregnancy included took place in January 2008. Among these, 302 pregnancies resulted in full-term deliveries, with a postpartum follow-up of at least 1 year (figure 1). Table 1 shows the main demographic and clinical characteristics of the study cohort. No woman was lost to follow-up. On the whole, 213

Figure 1 Flow chart of the pregnancies enrolled in the study



patients (70.5%) breastfed their infant for a mean period of 5.6 ± 4.3 months. A total of 104 (34.4%) patients breastfed for at least 2 months and were assigned to the BG group: among these, 84 (27.8%) breastfed for at least 6 months. The remaining 198 (65.6%) patients who breastfed for less than 2 months or did not breastfeed at all were included in the NBG group. Differences between BG and NBG subjects are reported in table 1. As compared with the NBG group, patients in the BG group had significantly lower EDSS scores at conception (1.3 ± 1.0 vs 1.6 ± 1.0; $p = 0.004$), were less frequently treated with DMDs before pregnancy (36.5% vs 51.5%; $p = 0.011$), and experienced a lower number of relapses both during pregnancy (0.06 ± 0.3 vs 0.14 ± 0.4; $p = 0.041$) and in the 12-month period after delivery (0.35 ± 0.5 vs 0.66 ± 0.9; $p = 0.001$).

As for the relationships between clinical characteristics and the duration/status of breastfeeding, not breastfeeding and shorter duration of breastfeeding were both associated with higher frequency of treatment with DMDs before pregnancy; not breastfeeding was also associated with higher EDSS scores.

Table 1 Characteristics of the study cohort

	Total sample (n = 302)	BG (n = 104)	NBG (n = 198)	p
Age at conception, y, mean (SD)	31.5 (4.7)	31.6 (5.0)	31.5 (4.6)	0.314
Age at onset, y, mean (SD)	24.5 (5.7)	24.1 (6.0)	24.7 (5.6)	0.391
Disease duration at conception, y, mean (SD)	7.1 (4.9)	7.6 (5.5)	7.0 (4.6)	0.872
EDSS at conception, mean (SD)	1.5 (1.0)	1.3 (1.0)	1.6 (1.0)	0.004
Treated with DMDs before pregnancy, n (%)	140 (46.4)	38 (36.5)	102 (51.5)	0.011
Relapses in the year prior to pregnancy, mean (SD)	0.4 (0.7)	0.3 (0.7)	0.4 (0.7)	0.539
Relapses during pregnancy, mean (SD)	0.12 (0.4)	0.06 (0.3)	0.14 (0.4)	0.041
Relapses in the year after the delivery, mean (SD)	0.55 (0.7)	0.35 (0.5)	0.66 (0.9)	0.001

Abbreviations: BG = breastfeeding group; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; NBG = not breastfeeding group.

Breastfeeding duration ≥6 months was associated with lower number of postpartum relapses ($p < 0.001$) (tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org).

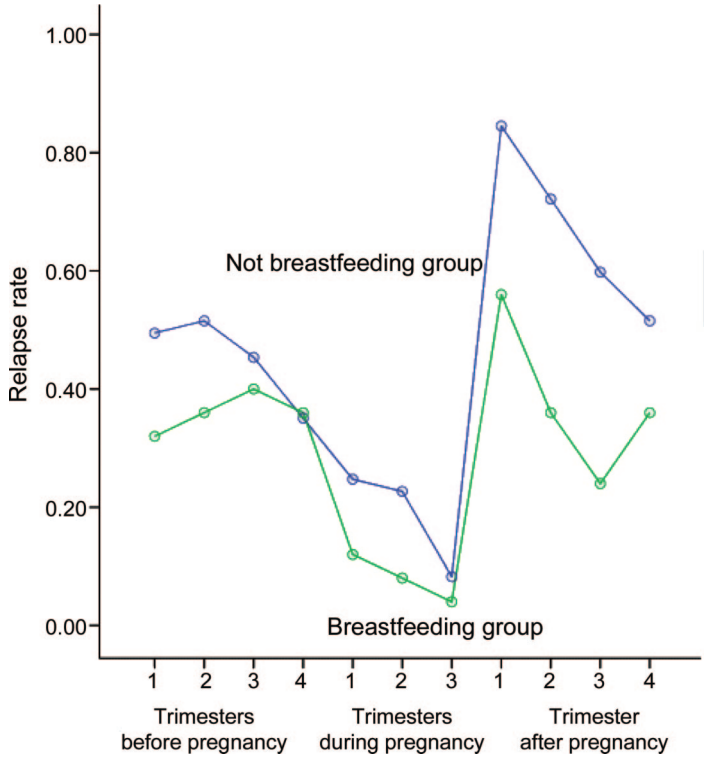
The annualized relapse rate in the year before conception, during pregnancy, and after delivery is illustrated in figure 2. In both the BG and NBG groups, relapse rate significantly decreased during pregnancy, particularly in the third trimester, and increased in the postpartum, particularly in the first trimester (effect for time $F = 6.162$, $p < 0.001$), without differences in the time-dependent profile of the relapse rate (effect for group × time $F = 0.695$, $p = 0.730$). The mean relapse rate before, during, and after pregnancy was significantly lower in the BG group than in the NBG group (effect for group $F = 8.297$, $p = 0.004$). In particular, the difference was significant in the first 2 trimesters of pregnancy (0.12 ± 0.7 and 0.08 ± 0.6 vs 0.25 ± 0.9 and 0.23 ± 0.9, respectively), and in the first 3 trimesters after delivery (0.56 ± 1.4, 0.36 ± 1.2 and 0.24 ± 1.0 vs 0.85 ± 1.8, 0.72 ± 1.5 and 0.60 ± 1.5, respectively).

In the year after the delivery, 112 patients (37.1%) experienced one relapse; 20, 2 or more relapses (6.6%) (table 2). Patients with relapses in the postpartum period experienced a higher number of relapses in the year prior to pregnancy (0.55 ± 0.8 vs 0.24 ± 0.58: $p < 0.001$) and during pregnancy (0.21 ± 0.5 vs 0.04 ± 0.2; $p < 0.001$), and were less likely to breastfeed their infants (26.5% vs 40.0%; $p = 0.014$). As for the relationship between the timing of relapses and breastfeeding behavior, relapses occurring within 1 month after delivery prevented breastfeeding in 17 women; those occurring between the second and third month led to stopping breastfeeding in 22 women. The Cox regression model (table 3) confirmed that the only significant predictors of relapses in the 12-month period after delivery were a higher number of relapses in the year before pregnancy (HR = 1.5, 95% CI 1.3–1.9, $p < 0.001$) and during pregnancy (HR = 2.2, 95% CI 1.5–3.3, $p < 0.001$). These findings were confirmed in the PS-adjusted analysis (table 3).

Finally, the same variables predicted the risk of relapses occurring within 3 and 6 months after delivery (table e-3).

DISCUSSION There is conflicting evidence on the relationship between breastfeeding and the risk of postpartum relapses in patients with MS. As first demonstrated in the PRIMS study,[1] it is now well-acknowledged that relapse rate significantly declines during pregnancy and resumes in the first trimester after delivery. However, both the PRIMS study and

Figure 2 Annualized relapse rate for each 3-month period before, during, and after pregnancy in patients who breastfed and patients who did not



2 (group) × 11 (time) mixed factorial design, with repeated measures on the second factor. In both the breastfeeding and not breastfeeding groups, the relapse rate significantly decreased during pregnancy and increased in the postpartum (effect for time $F = 6.162$, $p < 0.001$), without differences in the time-dependent profile of the relapse rate (effect for group × time $F = 0.695$, $p = 0.730$). The mean relapse rate during and after pregnancy was significantly lower in the breastfeeding group than in the not breastfeeding group (effect for group $F = 8.297$, $p = 0.004$).

its 2-year follow-up failed to find an association between breastfeeding and postpartum relapses.[1,2] On the contrary, a recent study[4] on 32 Californian patients with MS reported a reduction in the postpartum relapse risk up to approximately one-fifth in the exclusive breastfeeding patients. In a following article,[5] the same authors suggested that the protective role of breastfeeding may be due to the increase in interferon-γ–producing CD4+ T cells, related to lactational amenorrhea. Conversely, in another study on 61 Finnish patients with MS,[3] breastfeeding was not confirmed to be protective and the choice to breastfeed was essentially associated with mild disease activity in the year before conception. These 2 studies, however, are clearly limited by the small sample size. In particular, since relapses during pregnancy are relatively rare events, group differences in the relapse rate associated with breastfeeding are difficult to compare in such small cohorts.

Indeed, data from the large PRIMS study showed that patients who chose to breastfeed, in comparison with patients who did not, had milder disability and fewer relapses both in the year before pregnancy and during pregnancy.[1,2]

Our results, obtained in a large cohort of patients with MS, showed that the time-dependent profile of the relapse rate before, during, and after pregnancy did not differ between patients who breastfed their babies and patients who did not. The main difference between the 2 groups was lower disease activity in the BG subjects. Indeed, lower risk of postpartum relapses was not associated with breastfeeding, but with the number of relapses before and during pregnancy. This finding was also confirmed in the PS-adjusted analysis that provides a less biased comparison of the 2 study groups. In this respect, our findings are consistent with the large PRIMS study and the recent Finnish study.

In interpreting our findings in the context of previous evidence, a few issues should be discussed. In our cohort, the proportion of exclusive breastfeeding subjects (34.4%) was slightly lower than that reported in the Italian population (40%–50%).[16,17] Also, the proportion of maternal breastfeeding of any duration was slightly lower in the patients (70.4% vs 81.1%).[16,17] It is noteworthy that in our country breastfeeding is generally encouraged due to its benefits for both the child and the mother,[18-20] although there are no published national guidelines. The lower breastfeeding rate in our MS cohort can be due, at

Table 2 Characteristics of patients with and without postpartum relapses

	Relapsing (n = 132)	Not relapsing (n = 170)	p
Age at conception, y, mean (SD)	31.2 (4.9)	31.7 (4.5)	0.419
Age at onset, y, mean (SD)	25.0 (6.0)	24.2 (5.5)	0.225
Disease duration at conception, y, mean (SD)	6.4 (4.3)	7.7 (5.2)	0.063
EDSS at conception, mean (SD)	1.6 (1.1)	1.4 (0.9)	0.270
Treated with DMDs prior to pregnancy, n (%)	67 (50.8)	73 (42.9)	0.177
Relapses in the year prior to pregnancy, mean (SD)	0.55 (0.8)	0.24 (0.58)	<0.001
Relapses during pregnancy, mean (SD)	0.21 (0.5)	0.04 (0.2)	<0.001
Breastfeeding, n (%)	35 (26.5%)	68 (40.0%)	0.014

Abbreviations: DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale.

Table 3 Predictors of postpartum relapses

	HR	95% CI	p
Relapses in the year prior to pregnancy	1.5	1.3–1.9	<0.001
Relapses during pregnancy	2.2	1.5–3.3	<0.001
PS-adjusted Cox regression model			
Relapses in the year prior to pregnancy	1.8	1.4–2.3	<0.001
Relapses during pregnancy	4.9	2.6–9.0	0.001

Abbreviations: CI = confidence interval; HR = hazard ratio; PS = propensity score.

least in part, to the higher prevalence of preterm deliveries.[7,17] In particular, the proportion of preterm deliveries was 18.2% among patients who breastfed and 37.9% among those who did not ($p < 0.001$). Moreover, the occurrence of relapses during the first trimester after delivery may require the introduction of treatments (steroids, DMDs) and the prevention/suspension of breastfeeding, as documented in 13% of our patients. In this regard, it is worth noting that a relapse within the first 2 months after delivery may cause discontinuation of breastfeeding, thus preventing a patient from being included in the BG group. In previous studies, this may have led to overestimating the protective role of exclusive breastfeeding.

Although the 21 participating sites represented the largest Italian MS centers, the study population may not be entirely representative of the general population of patients with MS. It also has to be noted that 84 patients were not included in the present study and are being followed up for further analyses. The characteristics of these patients were not different from those of patients included in the study, with the exception of older age (33.0 ± 4.3 years; $p = 0.008$) and higher frequency of treatment with DMDs before pregnancy (76.2%; $p < 0.001$). Moreover, although the interview was performed soon after delivery, we cannot exclude that recall bias in reporting breastfeeding behavior and supplementation with formula feedings may have occurred to some extent. However, this should have occurred for both the BG and NBG groups, thus not affecting the main study conclusions. Finally, in our study neither lactational amenorrhea nor immunologic changes were assessed.

On the whole, our findings, in line with other cohorts presented in the literature,[1-3] did not confirm a protective role of exclusive breastfeeding. They rather indicate that the reported association between breastfeeding and a lower risk of postpartum relapses may simply reflect different patient behavior, biased by the disease activity.

Our results can assist neurologists facing the breastfeeding issue in mother counseling and shared decision-making. Breastfeeding should not be encouraged as a protective factor. Especially, among patients with high disease activity and high risk of postpartum relapses, breastfeeding may not be feasible and early postpartum treatment should be an option.

AUTHOR CONTRIBUTIONS

Dr. Portaccio: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Ghezzi: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Hakiki: study concept or design, acquisition of data. Dr. Martinelli: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Moiola: analysis or interpretation of data, acquisition of data. Dr. Patti: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. La Mantia: drafting/revising the manuscript, acquisition of data. Dr. Mancardi: study concept or design, acquisition of data. Dr. Solaro: analysis or interpretation of data, study supervision. Dr. Tola: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Pozzilli: drafting/revising the manuscript, study supervision. Dr. De Giglio: analysis or interpretation of data, acquisition of data. Dr. Totaro: drafting/revising the manuscript, acquisition of data. Dr. Lugaresi: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. De Luca: drafting/revising the manuscript, contribution of vital reagents/tools/patients, acquisition of data. Dr. Paolicelli: analysis or interpretation of data, acquisition of data. Dr. Marrosu: drafting/revising the manuscript, acquisition of data. Dr. Comi: drafting/revising the manuscript, study supervision. Dr. Trojano: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Amato: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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DISCLOSURE

Dr. Portaccio serves on a scientific advisory board for Biogen Idec and receives research support from Merck Serono, Biogen Idec, Bayer Schering Pharma, and sanofi-aventis. Dr. Ghezzi serves on scientific advisory boards for Merck Serono and Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Merck Serono, Biogen Idec, Bayer Schering Pharma, and Novartis; serves as a consultant for Novartis; and receives research support from Sanofi-aventis, Biogen Idec, and Merck Serono. Dr. Hakiki reports no disclosures. Dr. Martinelli has received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, Bayer Schering Pharma, Novartis, and sanofi-aventis; and has served as a consultant to Bayer Schering Pharma, sanofi-aventis, and Teva Pharmaceutical Industries Ltd. Dr. Moiola reports no disclosures. Dr. Patti has served on scientific advisory boards for Merck Serono, Bayer Schering Pharma, Novartis, and Biogen Idec; has received speaker honoraria from Biogen Idec, Bayer Schering Pharma, sanofi-aventis, and Novartis; and has received research support from the University of Catania and FISM. Dr. La Mantia has received funding for travel from Biogen Idec and Bayer Schering Pharma. Dr. Mancardi has received funding for travel from Biogen Idec, Merck Serono, and Bayer Schering Pharma; serves on the editorial board of *Neurological Sciences*; and has received speaker honoraria from Biogen Idec and Bayer Schering Pharma. Dr. Solaro reports no disclosures. Dr. Tola has served on scientific advisory boards for and received speaker honoraria from Biogen Idec, sanofi-aventis, Merck Serono, and Novartis; and has received research support from sanofi-aventis. Dr. Pozzilli serves on scientific advisory boards for and has received speaker honoraria from Novartis, Merck Serono, Biogen Idec, Bayer Schering Pharma, and

sanofi-aventis. Dr. De Giglio reports no disclosures. Dr. Totaro has received honoraria for consultancy or speaking from sanofi-aventis, Biogen Idec, Bayer Schering Pharma, and Merck Serono. Dr. Lugaresi received honoraria for speaking from Bayer Schering, Biogen Dompé, Novartis Pharma, and sanofi-aventis, and research grants from sanofi-aventis, Novartis Pharma, Merck Serono, Biogen Dompé, and Bayer Schering. Dr. Lugaresi has served on scientific advisory boards for Biogen Idec, Merck Serono, and Bayer Schering Pharma; has received funding for travel and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, sanofi-aventis, and Teva Pharmaceutical Industries Ltd.; serves as a consultant for Fondazione "Cesare Serono"; and has received research support from Fondazione Italiana Sclerosi Multipla, Bayer Schering Pharma, Biogen Idec, Merck Serono, sanofi-aventis, Novartis, and AISM (Associazione Italiana Sclerosi Multipla). Dr. De Luca receives research support from Merck Serono. Dr. Paolicelli serves as a consultant for Merck Serono and Bayer Schering Pharma. Dr. Marrosu serves on scientific advisory boards for Merck Serono, Biogen Idec, and Bayer Schering Pharma; has received funding for travel from Biogen Idec, Merck Serono, Bayer Schering Pharma, and sanofi-aventis; serves on the editorial board of *Neurological Sciences*; has received speaker honoraria from Biogen Idec and Merck Serono; and has received research support from Merck Serono, Biogen Idec, and Fondazione Banco di Sardegna. Dr. Comi serves on scientific advisory boards for Bayer Schering Pharma, Merck Serono, Teva Pharmaceutical Industries Ltd., sanofi-aventis, Novartis, and Biogen Idec; and has received speaker honoraria from Teva Pharmaceutical Industries Ltd., sanofi-aventis, Serono Symposia International Foundation, Biogen Idec, Merck Serono, Novartis, and Bayer Schering Pharma. Dr. Trojano has received speaker honoraria from Merck Serono, Bayer Schering Pharma, sanofi-aventis, and Biogen Idec; and has received research support from Biogen Idec and Merck Serono. Dr. Amato serves on scientific advisory boards for and has received speaker honoraria and research support from Biogen Idec, Merck Serono, Bayer Schering Pharma, and sanofi-aventis; and serves on the editorial board of *BMC Neurology*.

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REFERENCES

1. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis: Pregnancy in Multiple Sclerosis Group. N Engl J Med 1998;339:285–291.
2. Vukusic S, Confavreux C. Pregnancy and multiple sclerosis: the children of PRIMS. Clin Neurol Neurosurg 2006; 108:266–270.
3. Airas L, Jalkanen A, Alanen A, Pirttila T, Marttila RJ. Breast-feeding, postpartum and prepregnancy disease activity in multiple sclerosis. Neurology 75:474–476.
4. Langer-Gould A, Huang SM, Gupta R, et al. Exclusive breastfeeding and the risk of postpartum relapses in women with multiple sclerosis. Arch Neurol 2009;66:958–963.
5. Langer-Gould A, Gupta R, Huang S, et al. Interferon-gamma-producing T cells, pregnancy, and postpartum relapses of multiple sclerosis. Arch Neurol 67:51–57.
6. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. Mult Scler 2004;10:582–588.
7. Amato MP, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. Neurology 75:1794–1802.
8. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–127.
9. WHO: Division of Diarrhoeal and Acute Respiratory Disease Control. Indicators for Assessing Breastfeeding Practice. Geneva: WHO; 1991.
10. WHO: Global Data Bank on Breastfeeding. Breastfeeding: The Best Start. Geneva: WHO; 1996.
11. WHO. Nutrition Database System. Copenhagen: WHO; 1998.
12. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
13. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–2281.
14. Yanovitzky I, Zanutto E, Hornik R. Estimating causal effects of public health education campaigns using propensity score methodology. Eval Program Plann 2005; 209–220.
15. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757–763.
16. Giovannini M, Riva E, Banderali G, et al. Feeding practices of infants through the first year of life in Italy. Acta Paediatr 2004;93:492–497.
17. ISTAT. Gravidanza, parto, allattamento al seno 2004–2005 [online]. Available at: http://www.istat.it/salastampa/comunicati/non_calendario/20060605_00/testointegrale.pdf. Accessed December 15, 2010.
18. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database Syst Rev 2002; CD003517.
19. Ip S, Chung M, Raman G, et al. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess 2007;1–186.
20. Oddy WH. The impact of breastmilk on infant and child health. Breastfeed Rev 2002;10:5–18.