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ARTICLE CLASSIFICATION OF EVIDENCE

Pregnancy decision-making in women with multiple sclerosis treated with natalizumab

II: Maternal risks

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Abstract

Objective

To assess the risk of disease reactivation during pregnancy after natalizumab suspension in women with multiple sclerosis (MS).

Methods

Data of all pregnancies occurring between 2009 and 2015 in patients with MS treated with natalizumab and referring to 19 participating sites were collected and compared with those of pregnancies in untreated patients and patients treated with injectable immunomodulatory agents through a 2-factor repeated measures analysis. Predictors of disease activity were assessed through stepwise multivariable logistic regression models.

Results

A total of 92 pregnancies were tracked in 83 women receiving natalizumab. Among these pregnancies, 74 in 70 women resulted in live births, with a postpartum follow-up of at least 1 year, and were compared with 350 previously published pregnancies. Relapse rate during and after pregnancy was higher in women treated with natalizumab ($p < 0.001$). In multivariable analysis, longer natalizumab washout period was the only predictor of relapse occurrence during pregnancy ($p = 0.001$). Relapses in the postpartum year were related to relapses during pregnancy ($p = 0.019$) and early reintroduction of disease-modifying drugs (DMD; $p = 0.021$). Disability progression occurred in 16.2% of patients and was reduced by early reintroduction of DMD ($p = 0.024$).

Conclusions

Taken as a whole, our findings indicate that the combination of avoiding natalizumab washout and the early resumption of DMD after delivery could be the best option in the perspective of maternal risk. This approach must take into account possible fetal risks that need to be discussed with the mother and require further investigation.

Classification of evidence

This study provides Class IV evidence that in women with MS, the risk of relapses during pregnancy is higher in those who had been using natalizumab as compared to those who had been using interferon-β or no treatment.

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Glossary

CI = confidence interval; **CP** = control pregnancies; **DMD** = disease-modifying drugs; **EDSS** = Expanded Disability Status Scale; **IFN-β** = interferon-β; **MS** = multiple sclerosis; **noWOP** = no washout pregnancies; **NP** = natalizumab pregnancies; **ONP** = other natalizumab pregnancy; **OR** = odds ratio; **WOP** = washout pregnancies.

The European multicentric Pregnancy in Multiple Sclerosis study[1] documented for the first time the protective role of pregnancy against disease activity in women with multiple sclerosis (MS), with possible activity restart after delivery, a finding confirmed in subsequent observations.[2] A similar profile was observed in pregnant women with MS treated with interferon-β and glatiramer acetate: the relapse rate progressively declined over the gestational trimesters, and peaked early after the delivery, particularly in patients who did not resume disease-modifying drugs (DMD).[3] Recently, the introduction of sequestrating DMDs such as natalizumab raised new challenges for neurologists and patients facing pregnancy planning. Based on preclinical information, regulatory agencies recommended to avoid pregnancy during treatment and to respect a 3-month washout period before conception.[4] However, disease reactivation after natalizumab suspension is reported in nearly one-third of patients within 2–6 months.[5–7] In hypothesis, the gestational period might protect patients against the risk of disease reactivation after drug suspension. However, this hypothesis is challenged by the publication of case series that reported severe disease reactivation after natalizumab suspension for pregnancy planning.[8–10] This missing piece of information is critically important for the counseling of women with MS contemplating a pregnancy program.

Recently, the Italian Pregnancy Network[3,11–13] collected data on pregnancies occurring in patients with MS receiving natalizumab. The objective of this study was to assess the risk of disease reactivation during pregnancy after natalizumab suspension, compared with that observed in patients receiving interferon-β (IFN-β) and in untreated patients.[11]

Methods

All pregnancies occurring in patients with MS, diagnosed according to McDonald criteria,[14–16] treated with natalizumab between 2009 and 2015 were collected. The 19 participating sites represented the main Italian MS Centers located throughout the country. We included pregnancies ending in live births and with a postpartum follow-up of at least 1 year. All the patients were prospectively followed up every 6 months and in the case of relapse. Data were gathered by the neurologist using a standardized semi-structured interview dealing with pregnancy outcomes, breastfeeding, and potential confounders (details are reported in previous publications[11–13]). A specific section focused on in utero exposure to toxins, smoke, alcohol, pharmacologic therapies, and timing of suspension in relationship with conception.[11–13]

Consistently with previous articles,[12,17] substance exposure status was defined as exposed (any exposure to any substance in any trimester) and never exposed (no substance exposure). Maternal smoking status was defined as never smoked (no smoking in any trimester) and smoked (smoking in any trimester). Alcohol exposure status was defined as exposed (drinking more than 1 unit per day) and not exposed (drinking less than 1 unit per day).[12,17]

Data of pregnancies in patients treated with natalizumab (natalizumab pregnancies [NP]) were compared with those of pregnancies in untreated patients and patients treated with injectable immunomodulatory agents reported in previous publications by the same network. Since the disease activity around pregnancy in untreated and immunomodulatory-treated patients was comparable, these 2 groups were merged (control pregnancies [CP]).

Moreover, in order to assess the effect of the length of washout period, NP were arbitrarily divided into 2 groups: pregnancies in patients who received last natalizumab infusion before the onset of the last menstrual period (washout pregnancies [WOP]) and pregnancies in patients who received last natalizumab infusion after the onset of the last menstrual period (no washout pregnancies [noWOP]).

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. An annualized relapse rate for each trimester in the year before pregnancy, during pregnancy, and in the year after delivery was calculated. Moreover, disability was recorded on the Functional Systems and Expanded Disability Status Scale (EDSS)[18] at follow-up visits and in the case of relapse. Baseline EDSS was measured within 1 month from conception (defined as 14 days after the mother's last menstrual period). Disability progression was defined as a worsening of at least 1.5 points on the EDSS for patients with baseline EDSS = 0, at least 1 point for patients with baseline EDSS 1–5.5, and 0.5 point for patients with baseline EDSS = 6.0, evaluated outside relapse periods and confirmed without any significant recovery at 12 months.

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. Comparisons of baseline data were assessed through Pearson χ^2, Student *t*, and Mann-Whitney *U* tests when appropriate.

The relapse frequency in terms of annualized relapse rate in each trimester before, during, and after pregnancy in the NP was compared with that observed in the CP using a 2-factor group (NP and CP) × time (4 trimesters before conception, 3 trimesters during pregnancy, 4 trimesters after delivery) mixed analysis of variance, 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).

The annualized relapse rate in each trimester before, during, and after pregnancy in the WOP, noWOP, and CP were compared using a 2-factor group (WOP, noWOP and CP) × time (4 trimesters before conception, 3 trimesters during pregnancy, 4 trimesters after delivery) mixed analysis of variance, with repeated measures on the second factor.

Possible predictors of relapse occurrence during the pregnancy and the year after the delivery were assessed through stepwise multivariable logistic regression models. For relapse occurrence during the pregnancy (dependent variable), the following covariates were entered: current age, disease duration and EDSS at conception, number of relapses in the year before pregnancy, smoking (yes vs no), alcohol and toxin exposure during pregnancy (yes vs no), and natalizumab washout period (noWOP vs WOP).

For the occurrence of relapses in the postpartum year (dependent variable), the following covariates were entered: current age, disease duration and EDSS at conception, number of relapses in the year before pregnancy, smoking (yes vs no), alcohol and toxin exposure during pregnancy (yes vs no), relapses during pregnancy, breastfeeding (yes vs no), natalizumab washout period (noWOP vs WOP), DMD restart after delivery (within 1 month vs beyond 1 month/untreated), and an interaction variable washout period × DMD. Model assumptions and goodness of fit were assessed through the Hosmer-Lemeshow goodness of fit test. All analyses were performed using the SPSS 23.0 software running on Windows (SPSS, Chicago, IL).

Classification of evidence

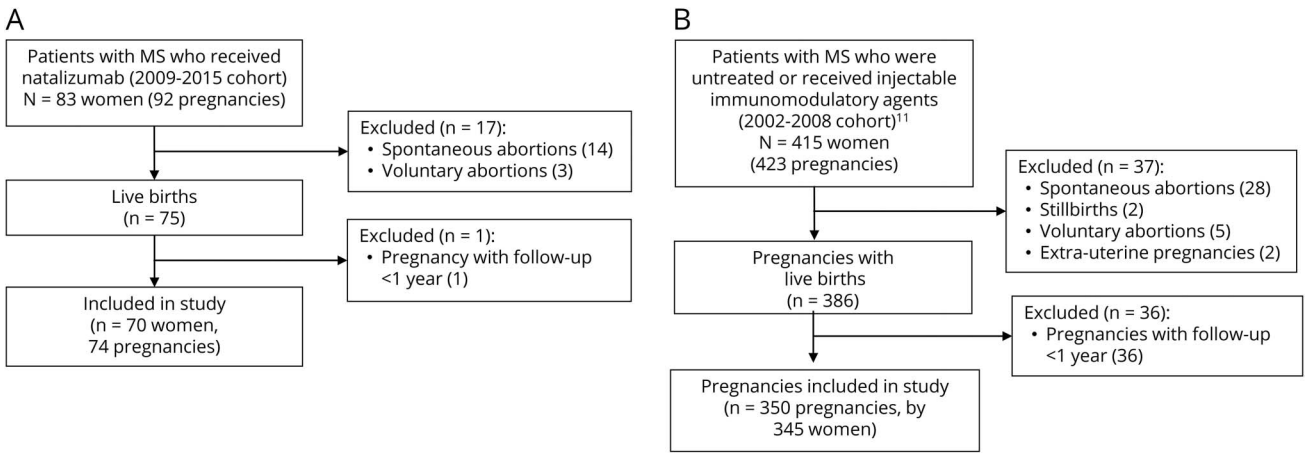
This study provides Class IV evidence that in women with MS, the risk of relapses during pregnancy is higher in those who had been using natalizumab as compared to those who had been using IFN-β or no treatment.

Results

Study population

During the study period, a total of 92 pregnancies were tracked in 83 women receiving natalizumab. All patients had relapsing-remitting MS course. Among these pregnancies, 74 in 70 women resulted in live births, with a postpartum follow-up of at least 1 year, and were compared with 350 previously published pregnancies in women receiving injectable immumodulatory agents or untreated (figure 1). The table shows the main demographic and clinical characteristics of the study cohort. In 27 out of 74 (36.5%) pregnancies, women received glucocorticoid treatment for relapses. Thirteen women received steroids in the first trimester, 12 in the second trimester, 9 in the third trimester. Seven women received 2 pulses of steroids.

Figure 1 Flowcharts of the pregnancies enrolled in the study



(A) Patients with multiple sclerosis (MS) who had received natalizumab (2009–2015 cohort). (B) Patients with MS who were untreated or had received injectable immunomodulatory agents (2002–2008 cohort).[11]

Table Characteristics of the study cohort

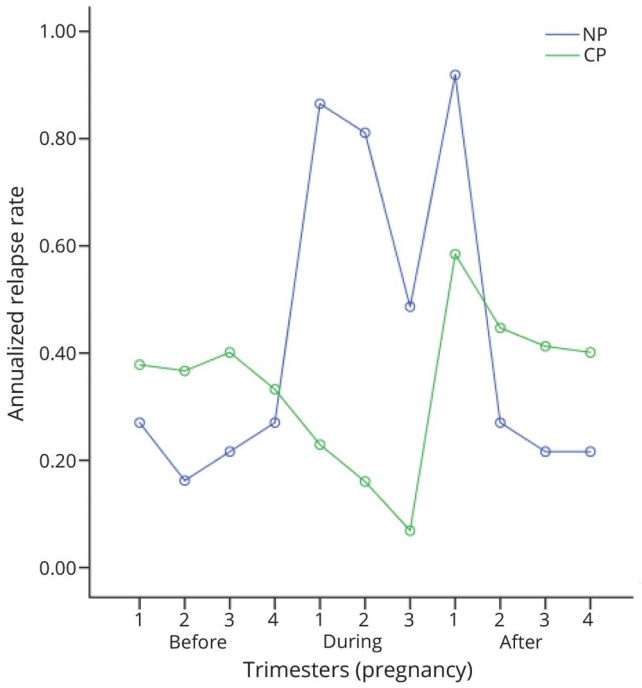
	Natalizumab pregnancies		Control pregnancies		*p* Values
	Women (n = 70)	Pregnancies (n = 74)	Women (n = 345)	Pregnancies (n = 350)	
Age at conception, y, mean (SD)	31.2 (4.9)	—	31.8 (4.7)	—	0.325
Age at onset, y, mean (SD)	22.1 (5.6)	—	24.7 (5.8)	—	<0.001
Disease duration at conception, y, mean (SD)	9.1 (4.5)	—	7.2 (4.8)	—	0.001
EDSS at conception, median (IQR)	2.4 (1.5–3.5)	—	1.5 (1.0–2.0)	—	<0.001
Smoking during pregnancy, n (%)	—	10 (13.5)	—	25 (7.1)	0.070
Relapses in the year prior to pregnancy, mean (SD)	—	0.2 (0.6)	—	0.37 (0.7)	0.135
Relapses during pregnancy, mean (SD)	—	0.5 (0.9)	—	0.1 (0.4)	<0.001
Relapses in the year after delivery, mean (SD)	—	0.4 (0.7)	—	0.4 (0.7)	0.474
Exclusive breastfeeding, n (%)	—	16 (21.6)	—	121 (34.6)	0.044
Disability progression on the EDSS in the year after delivery, n (%)	—	12 (16.2)	—	46 (13.1)	0.467

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range.
No patient reported alcohol or substance exposure.

Disease activity before, during, and after pregnancy in NP and CP groups

The annualized relapse rate in the year before conception, during pregnancy, and after delivery in NP and CP is illustrated in figure 2. While in the CP group, the expected temporal profile of disease activity was observed (decrease of relapse rate during pregnancy, increase of relapse rate after delivery), in the NP group, relapse rate increased both during pregnancy (with a peak in the first trimester) and after delivery. The difference between the 2 groups was significant (effect for group × time $F_{9,3789.052} = 5.782$, $p < 0.001$). In particular, during 27 (36.5%) pregnancies in women receiving natalizumab, at least one relapse occurred (1 relapse in 18 patients, 2 in 5 patients, 3 in 4 patients), whereas the same occurred in 35 (10%) CP (1 relapse in 31 participants, 2 relapses in 4 patients; $p < 0.001$). After delivery, the occurrence of relapses peaked in the first trimester in both groups (16 [21.7%] NP and 48 [13.7%] CP; $p = 0.084$).

Figure 2 Annualized relapse rate in the year before, during, and after pregnancy in natalizumab pregnancies (NP) and control pregnancies (CP)

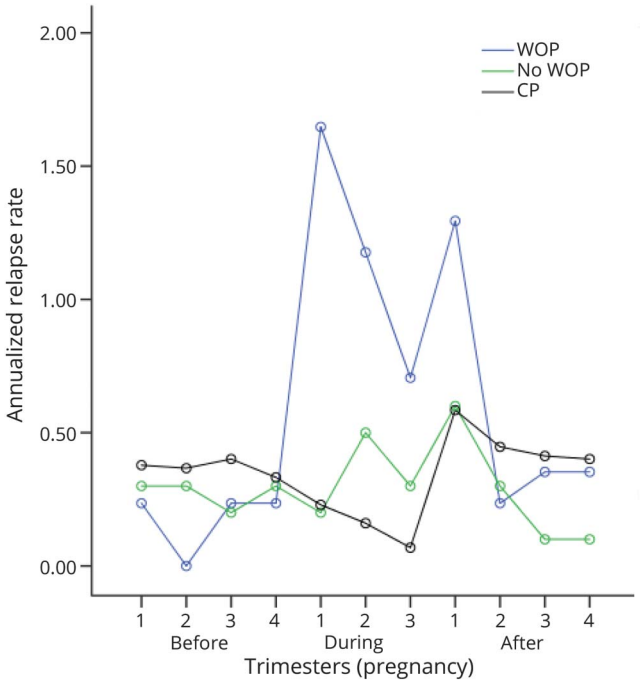


Effect of natalizumab washout on disease activity before, during, and after pregnancy

Thirty-four pregnancies occurred in patients who received last natalizumab infusion before the onset of the last menstrual period (WOP), whereas the remaining 40 pregnancies occurred in patients who received last natalizumab infusion after the onset of the last menstrual period (noWOP).

The annualized relapse rate in the year before conception, during pregnancy, and after delivery in WOP, noWOP, and CP is illustrated in figure 3. Again, in women who received natalizumab, the relapse rate increased both during pregnancy and after the delivery (effect for group × time $F_{17.991,3778.015} = 4.654$, $p < 0.001$). However, the increase was clearly more prominent in the WOP than in the other 2 groups (pairwise comparisons effect for groups $p < 0.021$), whereas the noWOP and CP did not differ (pairwise comparisons effect for groups $p > 0.9$). On the whole, 19 (55.9%) WOP pregnancies experienced at least 1 relapse (1 relapse in 11 patients, 2 in 5 patients, 3 in 4 patients), whereas relapses occurred in 8 (20%) noWOP pregnancies (1 relapse in 7 patients, 3 relapses

Figure 3 Annualized relapse rate in the year before, during, and after pregnancy in washout pregnancies (WOP), no washout pregnancies (noWOP), and control pregnancies (CP)



in 1 patient) and in 35 (10%) CP pregnancies (1 relapse in 31 patients, 2 relapses in 4 patients; $p < 0.001$).

In the stepwise multivariable logistic regression analysis, WOP was the only predictor of relapse occurrence during the pregnancy (odds ratio [OR] 6.01; 95% confidence interval [CI] 2.06–17.56; $p = 0.001$). The Hosmer-Lemeshow goodness of fit test was not significant ($p = 0.186$).

Focusing on the postpartum period, 56 (75.7%) patients resumed a DMD within 1 month after the delivery (49 natalizumab, 6 fingolimod, 1 IFN-β-1a 44 μg), 10 (13.5%) did so beyond 1 month after the delivery (6 natalizumab, 4 fingolimod), and 8 (10.8%) remained untreated. In the stepwise multivariable logistic regression analysis, significant predictors of postpartum relapses were higher number of relapses during pregnancy (OR 2.14; 95% CI 1.12–4.08; $p = 0.019$) and DMD restart beyond 1 month or no treatment after delivery (OR 4.40; 95% CI 1.28–15.16; $p = 0.021$). The Hosmer-Lemeshow goodness of fit test was not significant ($p = 0.123$). All the other possible covariates were not retained in the final models.

Relapse-related disability accumulation and role of DMD resumption after delivery

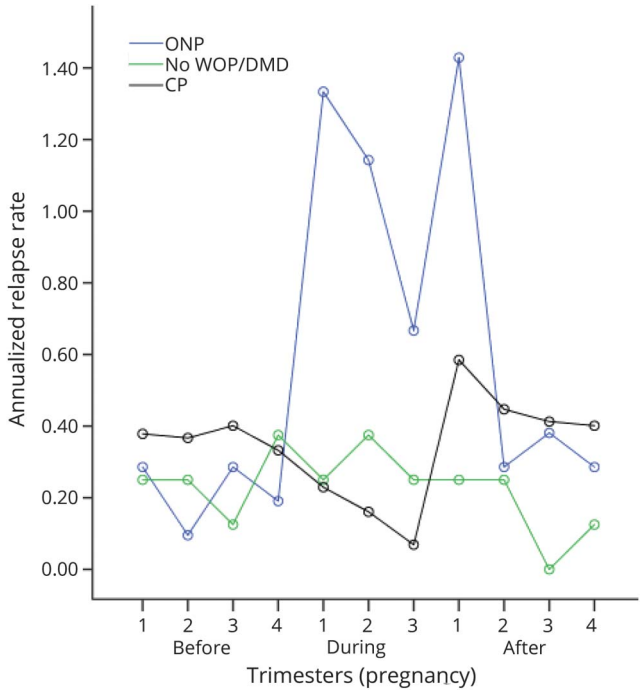
Twelve (16.2%) patients worsened on the EDSS at the end of the 1-year follow-up period. In almost all the cases (11 out of 12, 91.7%), disability accumulation was due to the occurrence of relapses during the pregnancy or after the delivery. Indeed, relapse occurrence was related to disability worsening in 32.4% of women (11 out of 34). As for the risk of postpartum relapses, the risk of disability accrual was lower in patients who resumed DMD within 1 month (10.7% vs 33.3%; $p = 0.024$).

Taking into account the main findings of the present study, patients with noWOP and early DMD resumption (noWOP/DMD) appeared to be at lower risk of disease activity during the pregnancy and after the delivery. Figure 4 depicts the annualized relapse rate in the year before conception, during pregnancy, and after delivery in noWOP/DMD, other natalizumab pregnancy (ONP), and CP. Similar to what is illustrated in figure 3, ONP patients experienced a higher relapse rate both during the pregnancy and after the delivery (pairwise comparisons effect for group $p < 0.006$). The absence of postpartum relapse peak in noWOP/DMD patients has to be noted. Moreover, the risk of disability progression was lower in noWOP/DMD than in ONP (3.1% vs 26.2% $p = 0.008$).

Discussion

Several prospective and retrospective studies in women with MS who were untreated or had received injectable immunomodulatory drugs (interferons and glatiramer acetate) consistently showed that relapse rate was reduced over the

Figure 4 Annualized relapse rate in the year before, during, and after pregnancy in no washout pregnancies (noWOP) and early disease-modifying drug resumption (DMD), other natalizumab pregnancies (ONP), and control pregnancies (CP)



gestational period and peaked early after the delivery.[2,3] Moreover, there is mounting evidence on the safety of exposure of conception and first trimester of the pregnancy to injectable immunomodulatory drugs, which can be continued until the beginning of the gestation.[11,19] Therefore, main concerns of patients and physicians were focused on the postpartum period, particularly on the first trimester after the delivery, and the main issue to manage was the decision to (re)start a DMD or to breastfeed postponing treatment (re) introduction.

More recently, the use of natalizumab raised new challenges for neurologists and patients facing pregnancy planning. After the withdrawal of this drug, a disease reactivation is expected in approximately one-third of the patients within a period of 2–6 months that may overlap with the time required for the women to become pregnant.[5–7] Therefore, pregnancy planning in women treated with natalizumab represents a paradigmatic scenario in which physicians and patients must share the decision weighing possible exposure-related fetal harms against the risk of disease reactivation during pregnancy for the mother. In hypothesis, the gestational period could protect patients against the risk of disease reactivation or rebound syndrome after drug suspension. The results of this collaborative, prospective study based on the Italian pregnancy dataset clearly showed that the pregnancy failed to prevent clinical disease activity in women who received natalizumab before conception. It is noteworthy that this dataset is representative of the major Italian MS centers where the prescription of second-line DMDs and natalizumab is authorized. One or more relapses occurred in 36.5% of the patients, a 3.5-fold increase in comparison to what was observed in the historical control group (women with MS who were untreated or had received injectable immunomodulatory drugs).[11] Although we did not gather data attempting to measure the severity of relapses, in our cohort relapses were associated with irreversible disability accrual in one-third of cases. Splitting our sample on the basis of length of washout period, we found that receiving the last natalizumab infusion after the onset of the last menstrual period led to an approximately 3-fold reduction of the risk of relapses during the pregnancy. Moreover, early resumption of natalizumab after the delivery (within 1 month) lowered to the same extent the risk of postpartum relapses. These findings were independent of differences in disease activity between NP and CP, such as disease duration and EDSS score at conception, since they were not associated with relapse-rate in the analysis of variance (data not shown) and logistic models. As for breastfeeding, it was not retained in the final models. It has to be noted, however, that the proportion of breastfeeding is significantly lower in women receiving natalizumab, due to the higher proportion of early DMD restart after delivery.

Taken as a whole, our findings indicate that the combination of avoiding natalizumab washout before conception and the early resumption of natalizumab after delivery could be the best option in the perspective of maternal risk. Indeed, these patients had an 8.5-fold reduction of the risk of disability progression over the 1-year follow-up period. These findings have both positive and negative implications. On the one hand, the efficacy of this option is straightforward. Only 8 (25%) patients had relapses during pregnancy or after the delivery, and only 1 (3.1%) patient progressed on the EDSS. Moreover, the absence of postpartum relapse peak after early natalizumab reintroduction is worth noting. This is in line with a recent observation in which natalizumab redosing immediately after delivery prevented postpartum relapses in a clinical series.[20] These data suggest a proactive approach, maintaining natalizumab until conception and, perhaps, in very active cases, during the whole pregnancy. Moreover, natalizumab becomes a valuable option also for prevention of postpartum relapses in other patients with MS who are at high risk of postpartum relapses.

On the other hand, there are several safety implications for pregnancy and fetal outcomes that must be taken into account. Natalizumab binds α4 integrins that play an active role in fertilization, implantation, and placental and cardiac development. In preclinical studies, exposure to natalizumab was related to reduced fetus survival and an increased risk of hematologic effects (anemia, thrombocytopenia), increased spleen weight, and reduced liver and thymus weights.[4] Available evidence on pregnancy exposure to natalizumab in women with MS is still limited and provides conflicting figures on the risk of spontaneous abortion, whereas the risk of birth defects requires further surveillance.[21,22] As for the use of natalizumab during the gestational period, mild to moderate hematologic alterations (mainly thrombocytopenia and anemia) were reported in 10 of 13 babies whose mothers received natalizumab during the third trimester of pregnancy.[23] Conversely, in women who appear to be at low risk of reactivation, the prevention of potential fetal harms could be favored, respecting the required washout period before conception.

One possible limitation of the study is that the assessments of length of washout periods and the reintroduction of DMD after delivery were performed using an arbitrary definition of time cutoffs without information on magnetic resonance disease activity. Despite this, our findings shed more light on the pattern of disease activity in women with MS suspending natalizumab for a pregnancy. In these patients, the considerable risk of disease reactivation during pregnancy and after delivery can be reduced, maintaining natalizumab until conception and resuming the drug early postpartum. This approach must take into account possible fetal risks that need to be thoroughly discussed with the mother and require further investigation in future research.

Author contributions

Emilio Portaccio: study concept and design, analysis and interpretation of data, critical revision of manuscript for intellectual content. Lucia Moiola: acquisition of data, critical revision of manuscript for intellectual content. Vittorio Martinelli: acquisition of data, critical revision of manuscript for

intellectual content. Pietro Annovazzi: acquisition of data, critical revision of manuscript for intellectual content. Angelo Ghezzi: study concept and design, critical revision of manuscript for intellectual content. Mauro Zaffaroni: acquisition of data, critical revision of manuscript for intellectual content. Roberta Lanzillo: acquisition of data, critical revision of manuscript for intellectual content. Vincenzo Brescia Morra: acquisition of data, critical revision of manuscript for intellectual content. Francesca Rinaldi: acquisition of data, critical revision of manuscript for intellectual content. Paolo Gallo: acquisition of data, critical revision of manuscript for intellectual content. Carla Tortorella: acquisition of data, critical revision of manuscript for intellectual content. Damiano Paolicelli: acquisition of data, critical revision of manuscript for intellectual content. Carlo Pozzilli: analysis and interpretation of data, critical revision of manuscript for intellectual content. Laura De Giglio: acquisition of data, critical revision of manuscript for intellectual content. Paola Cavalla: acquisition of data, critical revision of manuscript for intellectual content. Eleonora Cocco: acquisition of data, critical revision of manuscript for intellectual content. Maria Giovanna Marrosu: analysis and interpretation of data, critical revision of manuscript for intellectual content. Claudio Solaro: acquisition of data, critical revision of manuscript for intellectual content. Antonio Uccelli: acquisition of data, critical revision of manuscript for intellectual content. Alice Laroni: acquisition of data, critical revision of manuscript for intellectual content. Luisa Pastò: acquisition of data, critical revision of manuscript for intellectual content. Marta Giannini: acquisition of data, critical revision of manuscript for intellectual content. Maria Trojano: analysis and interpretation of data, critical revision of manuscript for intellectual content. Giancarlo Comi: analysis and interpretation of data, critical revision of manuscript for intellectual content. Maria Pia Amato: study concept and design, analysis and interpretation of data, critical revision of manuscript for intellectual content.

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Disclosure

E. Portaccio served on scientific advisory boards for Biogen Idec and Merck Serono; received honoraria for speaking and funding for traveling from Biogen, Genzyme, Novartis, Merck, and Teva; and received research support from Merck Serono. L. Moiola received honoraria for speaking or for advisory board from Sanofi-Genzyme, Biogen, Novartis, and Teva. V. Martinelli served on scientific advisory boards for Merck Serono and Genzyme and received honoraria for speaking, consultancy, or support for participation in national and international congresses from Bayer Schering, Biogen-Dompè, Merck Serono, Novartis, Genzyme, and Teva Pharmaceuticals. P. Annovazzi served on advisory boards for Biogen, Merck Serono, Teva, Novartis, and Genzyme; received funding for traveling and honoraria for speaking or writing from Biogen, Teva, Novartis, and Genzyme; and is involved as a principal investigator in clinical trials for Genzyme. A. Ghezzi received honoraria for speaking from Biogen-Idec, Merck-Serono, Novartis, Genzyme, Teva, and Allergan, and for consultancy from Merck-Serono, Teva, Novartis, and Biogen-Idec; and received support for participation in national and international congresses from Schering, Biogen-Idec, Merck-Serono, Novartis, Genzyme, and Teva. M. Zaffaroni received honoraria for speaking or for serving in advisory boards and received funding for traveling from Almirall, Biogen, Genzyme, Merck Serono, Novartis, and Teva; and is involved as a principal investigator in clinical trials promoted by Biogen, Genzyme, Novartis, Roche, and Chugai. R. Lanzillo received personal compensation from Merck Serono, Novartis, Almirall, Genzyme, Bayer, and Teva for public speaking, editorial work, and advisory boards. V. Brescia Morra received personal compensation from Merck Serono, Novartis, Almirall, Genzyme, Bayer, and Teva for public speaking, editorial work, and advisory boards. F. Rinaldi served on an advisory board for Biogen-Idec and received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva, and Bayer Schering Pharma. P. Gallo has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono, and Novartis; received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma, Bayer-Schering Pharma, and Teva; received research support from Bayer, Biogen Idec/Elan, Merck Serono, Genzyme, and Teva; and received research grants from the University of Padova, Veneto Region of Italy, the Italian Association for Multiple Sclerosis, and the Italian Ministry of Public Health. C. Tortorella received honoraria for speaking from Biogen-Idec, Sanofi-Aventis, Merck Serono, Novartis, Bayer-Schering, and Teva Pharmaceutical. D. Paolicelli received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Bayer-Schering, Sanofi-Aventis, Teva, Novartis and Genzyme. C. Pozzilli received consulting and/or lecture fees and/or research funding and travel grant from Almirall, Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva. L. De Giglio received travel grants from Biogen, Novartis, and Teva. P. Cavalla reports no disclosures relevant to the manuscript. E. Cocco served on scientific advisory boards and received honoraria for speaking from Almirall Bayer, Biogen, Merck Serono, Novartis, Sanofi-Genzyme, and Teva. M. Marrosu received speaker honoraria and honoraria for serving on advisory board activities from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Genzyme, Sanofi-Aventis, and Teva, and research grants from Merck Serono and Novartis. C. Solaro served on advisory boards for Biogen Idec and Merck Serono; received speaking honoraria from Bayer Schering, Biogen Idec, Merck Serono, Almirall, Teva, and Genzyme; and received research grants and support by the Fondazione Italiana Sclerosi Multipla (FISM). A. Uccelli received consultancy fees and support for travel expenses and participation in congresses from Sanofi-Aventis, Biogen, Merck-Serono, Novartis, and Roche. A. Laroni received lecturing honoraria from Biogen-Dompé, Biogen Idec, and Novartis and funding for travel from Bayer-Schering, Novartis, Biogen-Dompé, Biogen Idec, Merck Serono, and

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