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Maternal and fetal outcomes in an Italian multicentric cohort of women with multiple sclerosis exposed to dimethyl fumarate during pregnancy

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Abstract

Background: Evidence on the impact of dimethyl fumarate (DMF) during pregnancy in women with multiple sclerosis (MS) is limited.

Objectives: To investigate disease activity and pregnancy outcomes in a retrospective cohort of women exposed to DMF in early pregnancy.

Methods: Women discontinuing DMF after pregnancy confirmation were identified from 29 Italian MS Centers. Disease activity 12 months before conception, during pregnancy, and 12 months postpartum were recorded, exploring reactivation predictors. Pregnancy and fetal outcomes were assessed.

Results: The study analyzed 137 pregnancies (12 pregnancy losses, 125 live births) from 137 women (mean age 32.9 ± 4.7 years), discontinuing DMF within a median (interquartile range (IQR)) interval of 4.9 (3.7–5.7) weeks from conception. In live birth pregnancies, annualized relapse rate (ARR) significantly decreased during pregnancy (ARR = 0.07, 95% confidence interval (CI): 0.03–0.14, $p = 0.021$) compared to pre-conception (ARR = 0.21 (95% CI: 0.14–0.30)) and increased postpartum ((ARR = 0.22 (95% CI: 0.15–0.32), $p = 0.006$). Median time to first relapse (TTFR) was 3.16 (IQR: 1:87–5.42) months. Higher pre-conception relapse number (hazard ratio (HR) = 2.33, 95% CI: 1.08–5.02) and Expanded Disability Status Scale (EDSS; HR = 1.81, 95% CI: 1.17-2.74) were associated with shorter TTFR, while treatment resumption with longer TTFR (HR = 0.29, 95% CI: 0.11–0.74). Fetal outcomes were unaffected by DMF exposure.

Conclusion: DMF discontinuation does not increase relapse risk during pregnancy. Early therapy restart prevents postpartum relapses. Early DMF exposure shows no adverse fetal outcomes.

Keywords: Multiple sclerosis, dimethyl fumarate, pregnancy

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Introduction

Early studies in pregnant women with multiple sclerosis (MS) have established that pregnancy protects from relapses, while a rebound of disease activity has been reported in 10%–30% of women in the initial 6 months after delivery[1–4]. Several studies have consistently demonstrated that treatment with disease-modifying therapies (DMTs) in the pre-conception

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period is associated with lower number of relapses in the postpartum[4]. Nevertheless, these studies mainly included patients treated pre-conceptionally with platform injectables. More recently, evidence has shown that sudden interruption of highly efficacious drugs, like natalizumab[5,6] and fingolimod[7,8], may increase the risk of relapses during both pregnancy and postpartum. In this scenario, limited data are available about maternal and newborn outcomes in women treated with dimethyl fumarate (DMF) who interrupt the treatment during early pregnancy. Analysis of pregnancy outcomes after exposure to DMF collected through an international registry[9] (TecGistry; NCT01911767) reassured about the safety of DMF exposure as no evidence of increased risk of fetal abnormalities or adverse pregnancy outcomes were found, confirming previous observations coming from clinical trials[10].

The UK consensus on pregnancy in MS (2019)[11] has stated that women of childbearing age, diagnosed with MS and undergoing DMF, are recommended to use contraception or to switch to an alternative therapy if they are considering having children, being DMF not labeled for use during pregnancy. Conversely, the most recent guidelines have softened their stance, recommending the suspension of DMF only upon a positive pregnancy test[12,13]. This strategy relies on the mechanism of action of DMF[14] and its short half-life (about 1 hour for monomethyl fumarate, its main active metabolite[15]), allowing a minimization of fetal exposure after treatment suspension, as well as on reassuring results from the final analysis of TecGistry.[9]

Considering that DMF is commonly prescribed to women of childbearing age[16], there is a need to provide new real-life evidence on the safety of DMF discontinuation in the mothers and of early pregnancy exposure to DMF in newborns.

To this aim, we have designed a retrospective multicenter study, enrolling Italian women who got pregnant while on treatment with DMF in order to evaluate the maternal, pregnancy, and fetal outcomes.

Methods

Study design

This retrospective, observational study, analyzed data collected from MS women identified from a data set of 29 Italian MS Centers, treated with DMF, who experienced pregnancy during therapy with DMF.

Data about maternal outcomes were collected from 12 months before pregnancy to 12 months after delivery. Pregnancy and fetal outcomes (congenital anomalies and fetal diseases/infectious complications) were also evaluated.

Inclusion criteria were the following: diagnosis of relapsing-remitting MS (RRMS)[17], treatment with DMF pre-conception for at least 3 months, history of pregnancy during DMF therapy and discontinuation of DMF during pregnancy.

Women were excluded from the analysis if postpartum follow-up was shorter than 12 months (only for pregnancies with live births). This study was approved by the Ethics Committee of the Tor Vergata University Hospital (no. of approval 108/2023). The local ethics committee waived the need for informed consent, as per Italian regulation for retrospective analysis of anonymized medical record-derived data.

Maternal and fetal outcomes

The following variables were collected from included women: demographic and medical information (including previous pregnancies number and outcome), age at conception, MS history (year of MS diagnosis, past use of MS therapies), start date of DMF therapy, previous pregnancies number and outcome, date of last menstrual period (LMP), date of DMF interruption during pregnancy, number and date of MS relapses experienced in the 12 months before pregnancy and after delivery and during pregnancy, total Gd+ and new T2 lesions at magnetic resonance imaging (MRI) performed in the 12 months postpartum as per clinical practice, type of postpartum MS therapy and date of resumption.

As regards pregnancy and newborn variables, we collected pregnancy outcome (live birth, abortion, still birth), gestational age (weeks), weight (g) and length (cm) at birth, congenital anomalies, and fetal diseases/infectious complications at birth.

In accordance with the European Surveillance of Congenital Anomalies (EUROCAT)[18], abortion was defined as pregnancy loss at <22 weeks of gestation, still birth as death of a fetus prior to complete expulsion or extraction from its mother at or after 22 weeks of gestation. As fetal diseases/infections complications, we included only events identified as clinically relevant by neonatologists at newborns hospital discharge.

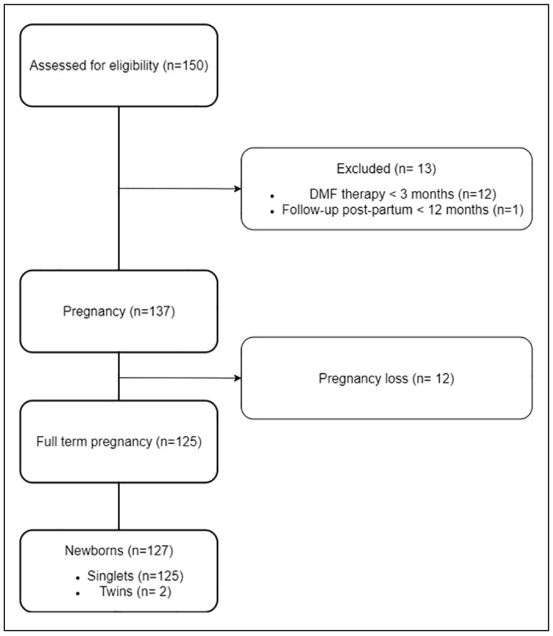

Figure 1. Flow-chart showing case disposition.

Statistical analysis

Categorical variables were characterized using counts and percentages. Continuous variables were described using either the median (interquartile range (IQR)) or the mean (±standard deviation (SD)), depending on their distribution, unless stated otherwise.

Annualized relapse rate (ARR) was defined as the total number of relapses divided by the total number of person-years. ARR in the year before conception, during pregnancy and in the 12 months after delivery were compared by a mixed-effect negative binomial model accounting for the repeated measure analysis, with *p* values adjusted for multiple testing (Tukey correction).

A time-dependent Cox regression modeling was employed to assess the effect of treatment, fitted as time-varying covariate, on the time to first relapse (TTFR) and presence of GD+ lesions in the year after delivery, both in univariable analysis and with adjustment for age at conception, disease duration, Expanded Disability Status Scale (EDSS) score, the number of relapses and MRI activity in the year before conception, and breastfeeding (fixed effects). The results were presented as hazard ratios (HRs) along with their corresponding 95% confidence intervals (CIs).

SAS 9.4 (Institute Inc., Cary, NC, USA) and *R* (v 4.1.3) were used for the computation.

Results

The whole data set comprised 150 women, among those 12 were excluded due to short DMF treatment (<3 months), and 1 was excluded due to short post-partum follow-up (<12 months), as per inclusion and exclusion criteria applied for the analysis (Figure 1). Among the remaining 137 women, pregnancy was prematurely interrupted in 12 cases and resulted in live births in 125 cases (Figure 1). Demographic and clinical characteristics of both groups are summarized in Table 1. In the whole population the mean age at conception was 32.9 (SD: ±4.7) years, the median duration of DMF treatment at conception was 19.0 (IQR: 10.1–34.3) months and the median exposure to DMF during pregnancy was 4.9 (IQR: 3.9–5.7) weeks. During pregnancy, eight women experienced non-serious infections; specifically, four had urinary tract infections, two COVID-19, one upper respiratory tract infection, and one acariasis.

Out of 117/137 women who restarted a therapy within 12 month after the delivery/abortion, 96 (82.05%) resumed DMF in the year after delivery after a median interval of 1.4 (0.6–3.2) months, while 21 (17.9%) women switched to another DMT after a median interval of 4.9 (2.3–7.5) months. Seven women switched to Natalizumab, four to Ocrelizumab, four to Cladribine, two to Interferon beta, two to fingolimod, and two to glatiramer acetate.

In the group of women with full-term pregnancies 37/123 (30.1%) mothers breastfed exclusively and 35/123 (28.4%) breastfed not exclusively and the remaining 51/123 (41.5%) did not breastfeed.

In the group of 65 women for which information on the date of breastfeeding cessation was available, the median duration of breastfeeding was 131 (IQR: 61–207) days. The median interval between breastfeeding cessation and therapy resumption was 17 (IQR: 1-64) days.

In our cohort, only four women resumed DMF during breastfeeding, with a median duration of breastfeeding during therapy of 137 (IQR: 93–167) days.

Disease activity before, during, and after pregnancy

The ARR in the year before conception, during pregnancy and in the 12 months after delivery was analyzed only for the 125 women who had a live newborn. In this group, 25 women (20%) had at least one relapse in the

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Table 1. Maternal baseline characteristics of the study cohort relative to each pregnancy.

	Whole population	Live birth	Pregnancy loss
N	137	125	12
Age at conception (years), mean (SD)	32.88 (4.72)	32.94 (4.66)	32.30 (5.50)
Presence of comorbidities, *n* (%)	28 (20.44)	25 (20.00)	3 (25.00)
Number of relapses in the year before conception, median (range)	0.00 (0.00–2.00)	0.00 (0.00–2.00)	0.00 (0.00–2.00)
Interval between LPM and delivery (months), mean (SD)	8.52 (2.18)	9.12 (1.00)	2.30 (1.03)
Disease duration -(years), mean (SD)	11.09 (6.09)	10.91 (6.08)	13.00 (6.15)
EDSS in year prior to conception, median (range)	1.50 (0.00–4.50)	1.50 (0.00–4.50)	2.00 (1.00–4.00)
Previous pregnancy, *n* (%)	57 (41.61)	51 (40.80)	6 (50.00)
Previous abortion, *n* (%)	3/57 (5.26)	3/51 (5.88)	0/6 (0.00)
Last DMT prior to DMF, *n* (%)	80 (58.39)	74 (59.20)	6 (50.00)
Fingolimod, *n* (%)	6 (7.50)	5 (6.76)	1 (16.67)
GA, *n* (%)	11 (13.75)	10 (13.51)	1 (16.67)
Interferon, *n* (%)	47 (58.75)	44 (59.46)	3 (50.00)
Natalizumab, *n* (%)	9 (11.25)	9 (12.16)	0 (0.00)
Other, *n* (%)	7 (8.75)	6 (8.11)	1 (16.67)
Duration of DMF treatment at conception (months), median (IQR)	19.04 (10.06–34.29)	19.23 (11.54–35.51)	11.92 (6.39–20.47)
Interval between LMP and last DMF (weeks), median (IQR)	4.86 (3.86–5.71)	4.86 (4.00–5.71)	4.21 (3.21–5.71)
Patients switched to another therapy after delivery, *n* (%)	21/117 (17.95)	20/107 (18.69)	1/10 (10.00)
Time to switch to another therapy after delivery (months), median (IQR)	4.93 (2.27–7.46) *N*=21	5.13 (1.77–8.19) *N*=20	2.99 *N*=1
Time to DMF restart after delivery (months), median (IQR)	1.38 (0.61–3.22) *N*=96	1.48 (0.62–3.55) *N*=87	0.54 (0.39–0.92) *N*=9
Patients resuming DMF after delivery			
• In the first month, *n* (%)	41/96 (42.7)	33/87 (37.9)	8/9 (88.9)
• Between 2 and 3 month, *n* (%)	14/96 (14.6)	13/87 (14.9)	1/9 (11.1)
• Between 4 and 6 month, *n* (%)	30/96 (31.2)	30/87 (34.5)	
• >6 months, *n* (%)	11/96 (11.5)	11/87 (12.6)	
Breastfeeding, *n* (%)			
- Exclusive	37/123 (30.1)	37/123 (30.1)	
- Artificial	35/123 (28.4)	35/123 (28.4)	
- Mixed	51/123 (41.5)	51/123 (41.5)	

LPM: last menstrual period; EDSS: Expanded Disability Status Scale; DMD: disease-modifying drug; DMF: dimethyl fumarate; GA: glatiramer acetate; IQR: interquartile range.

year postpartum, 17/25 (68%) had the relapse before restarting therapy and the remaining eight after a median of 2.3 range 0.7–10.4) months from DMF restart.

The ARR was 0.21 (95% CI: 0.14–0.30) in the year before conception. It decreased to 0.07 (95% CI: 0.03–0.14) ($p=0.021$) during pregnancy but it significantly increased in the year postpartum compared to pregnancy ((ARR = 0.22 (95% CI: 0.15–0.32), $p=0.006$), returning to values similar to those observed before pregnancy ($p=0.944$) (Figure 2). Median TTFR was 3.16 (IQR: 1:87%–%.42) months.

Factors associated with the TTFR in the year after delivery at univariable and multivariable analyses for the analyzed cohort are reported in Table 2.

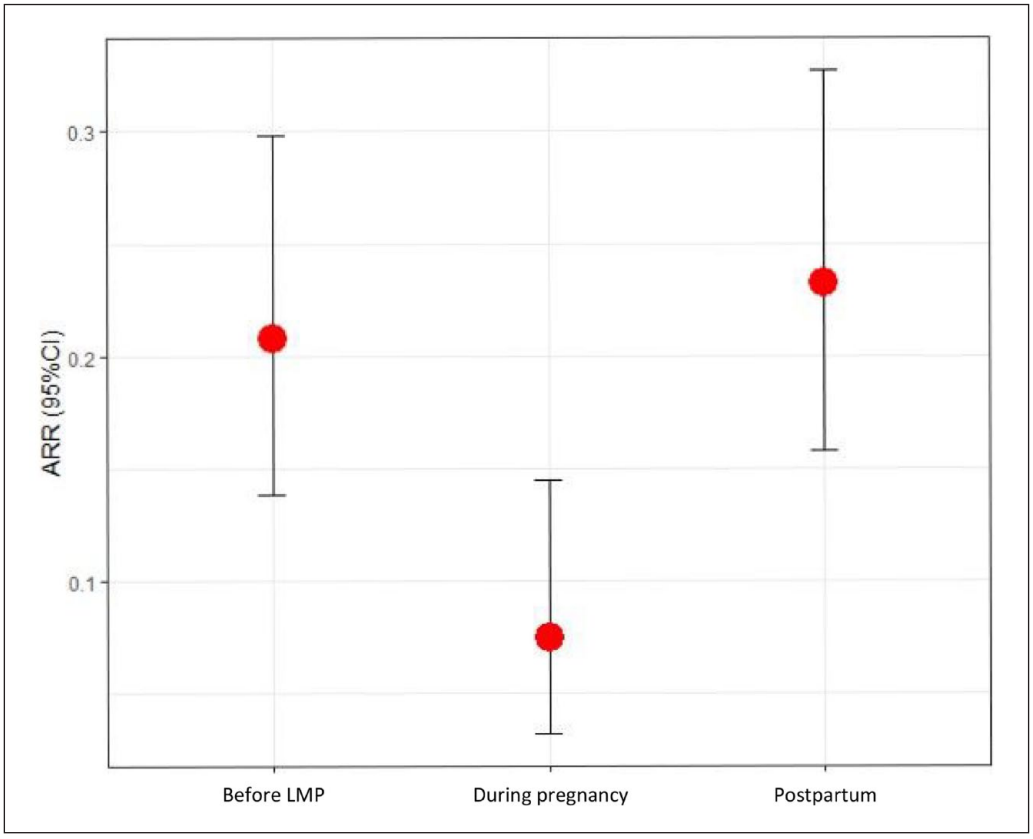

Figure 2. Annualized relapse rate (ARR) in the 12 months before conception, during pregnancy and in the 12 months after delivery. The ARR in the year before conception was 0.21 (95% CI: 0.14–0.30), it decreased during pregnancy to 0.07 (95% CI: 0.03–0.14) ($p = 0.021$) and significantly increased ($p = 0.006$) in the year postpartum (ARR = 0.22 (95% CI: 0.15–0.32)).

After adjusting for confounders, our results indicate that a higher number of relapses pre-conception (HR = 2.33, 95% CI: 1.08–5.01) and a higher EDSS score pre-conception (HR = 1.80, 95% CI: 1.17–2.74) were risk factors for a shorter TTFR from delivery (Table 2).

Conversely, treatment after delivery was associated with a significantly longer TTFR (HR = 0.29, 95% CI: 0.11–0.74). Exclusive breastfeeding also showed a trend toward a longer TTFR (HR = 0.41, 95% CI: 0.15–1.16), but this effect did not reach statistical significance ($p = 0.094$).

In a sensitivity analysis excluding those women starting other treatments or untreated during the 12 months post-partum or assuming DMF while breastfeeding, the results of the multivariable analysis remained consistent (Supplementary Table 1).

MRI activity

The median time of last MRI before conception was 3.65 (IQR: 1.87–6.57) months. Among the 113 women with MRI contrast agent (Gd) available, 8 (7.1%) exhibited a median of 1 Gd+ lesion (IQR: 1–1), and 16 out of 123 (13.0%) had a median of 1 T2 lesion (IQR: 1–2) in the last MRI before conception. In the year after delivery, MRI was available for 123/125 (98.4%) women, and it was performed after a median time of 2.70 (IQR: 1.28–4.83) months; 110/123 MRI were done with Gd. Among the 123 patients for whom MRI data were accessible, 46/123 (37.4%) had a median of two new T2 lesions (IQR: 1–3 lesions) and 23/110 (20.9%) a median of 1 Gd+ lesion (IQR: 1–2 lesions).

Factors associated with the presence of new GD+ lesions in the year after delivery, as determined by univariable and multivariable analyses for the

Table 2. Time-dependent Cox proportional hazard regression models for independent predictors of time to first relapse (TTFR) and presence of new GD+ lesions.

	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	TTFR *N*=125		TTFR *N*=123		GD+ lesion *N*=110		GD+ lesion *N*=108	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at conception	0.96 (0.88–1.04)	0.319	0.93 (0.84–1.03)	0.152	0.93 (0.85–1.03)	0.169	0.84 (0.73–0.98)	0.026
Disease duration	0.97 (0.91–1.04)	0.445	0.99 (0.91–1.08)	0.883	0.95 (0.8–1.03)	0.218	0.98 (0.90–1.08)	0.705
Baseline EDSS	1.80 (1.21–2.67)	0.003	1.80 (1.17–2.74)	0.007	1.81 (1.20–2.74)	0.005	2.35 (1.42–3.88)	0.001
Number of relapses 1 year before conception	2.47 (1.34–4.58)	0.004	2.33 (1.08–5.01)	0.030	1.87 (0.94–3.73)	0.076	2.18 (1.03–4.60)	0.042
MRI activity in the year before conception*	1.26 (0.43–3.68)	0.669	1.35 (0.44–4.18)	0.598	1.71 (0.40–7.32)	0.466	1.35 (0.30–6.11)	0.695
Therapy restart	0.36 (0.15–0.89)	0.026	0.29 (0.11–0.74)	0.009	0.32 (0.11–0.93)	0.037	0.26 (0.08–0.85)	0.026
Exclusive breastfeeding (*N*=123)	0.53 (0.20–1.42)	0.207	0.41 (0.15–1.16)	0.094	1.12 (0.46–2.72)	0.806	0.91 (0.35–2.38)	0.846

*defined as the presence of new T2 lesions and/or new GD+ lesions.

analyzed cohort, are presented in Table 2. Our results indicate that a higher number of pre-conception relapses (HR=2.18, 95% CI: 1.03–4.60) and a higher pre-conception EDSS score (HR=2.35, 95% CI: 1.42–3.88) were risk factors for the presence of new GD+ lesions in the postpartum period (Table 2). Conversely, older age at conception (HR=0.84, 95% CI: 0.73–0.98) and resumption of treatment after delivery were associated with a significant reduction in the presence of GD+ lesions (HR=0.26, 95% CI: 0.08–0.85).

Pregnancy and fetal outcomes

Out of 137 pregnancies, 11 (8.0%) resulted in abortion (<22 weeks) and 1 (0.7%) in fetal death (>22 weeks), while the remaining 125 (91.2%) ended with live births (125 singlets and 1 set of twins). Fetal and obstetric outcomes were analyzed for 127 live births from 125 women. In the whole group, the mean gestational age was 39.6 (SD; 4.3) weeks with 12/127 infants born prematurely. Mean birth weight and length are reported in Table 3.

Of 127 live-birth 5 (3.9%) had congenital anomalies: 3 major (2.3%) (2 labiopalatoschisis and 1 trisomy 18 syndrome) and 2 minor (1.6%) (1 craniomegaly, 1 patent foramen ovale). In 2/127 (1.657%) cases, jaundice due to hyperbilirubinemia was reported. In one case (0.8%), an infectious complication (bronchiolitis) occurred 1 week after delivery.

Discussion

In this study, we investigated disease activity and pregnancy outcomes in a retrospective cohort of women exposed to DMF in early pregnancy.

Exposure to DMF may be either accidental, as in the case of unintentional pregnancy or reflect a new approach to the management of DMF in women planning a pregnancy by treating neurologists. In the last few years, in fact, building on accumulating data showing no signal of adverse fetal outcomes in exposed pregnancies and according to the latest guidelines, MS neurologists might have decided to advise women to maintain DMF until conception and interrupt the treatment only after confirmation of pregnancy. Indeed, independently from the reason for the exposure, our study fills the gap of knowledge regarding the maternal and fetal safety of interrupting treatment at early pregnancy stage. In particular, our study provides evidence that this approach is not associated with an increased relapse risk during gestation in women with MS. Our data confirm in an independent group the preliminary observations by Yeh et al., showing that DMF washout was not associated with a significantly increased ARR in a smaller cohort

Table 3. Fetal outcomes.

	Whole population
N	127
Preterm birth (<37 weeks), *n* (%)	12 (9.45)
Birth weight (g), mean (SD)	3125.18 (450.30) *N*=125
Birth length (cm), mean (SD)	49.67 (2.59) *N*=120
Head circumference (cm), mean (SD)	34.90 (3.14) *N*=41
Newborns with congenital anomalies, *n* (%)	5 (3.94)
Newborns with fetal diseases[a], *n* (%)	2 (1.57)
Newborns with infections, *n* (%)	1 (0.79)

[a]Fetal diseases: two cases of jaundice due to hyperbilirubinemia.

of women (*N*=57) who discontinued DMF either at conception or within 3 months prior to conception.[10]

Therefore, based on our data, we can assume that hormonal driven immunomodulation occurring during pregnancy may adequately replace the effect of DMF treatment. Nevertheless, hypothetically we cannot exclude a synergic interaction between previous treatment with DMF and the pregnancy-dependent immunomodulation. Although DMF mainly acts by regulating proteins with antioxidant and/or anti-inflammatory properties, it is also known that it can also impact on the survival of lymphocytes leading to various degrees of lymphocytopenia[14] which is a common side effect of treatment[19–21]. Moreover, DMF seems to have a larger impact on T cells, particularly CD8+ lymphocytes[22], which are also implicated in the pregnancy-associated improvement of MS[23]. Lymphocyte count may take a long time to fully recover[24] after DMF discontinuation, possibly contributing to prolonged therapeutic effect[25]. On the contrary, occasionally, it has been reported a rebound of disease activity after DMF suspension[26], even in patients with prolonged lymphocytopenia[27]. Considering the retrospective design of this study, we were unable to collect sufficient data on lymphocyte count before and during gestation after DMF discontinuation, in order to explore the correlation with clinical outcomes; however, also taking into account potential risk of prolonged lymphopenia, we believe that lymphocyte dynamics in pregnant women with MS should be closely monitored in future studies. Meanwhile, our results, in addition to the short-half-life of DMF[15], support its continuation until pregnancy confirmation and can be usefully incorporated in the counseling of women treated with DMF planning a pregnancy.

Our study further corroborates previous evidence showing a significant increase of ARR and radiological activity after delivery, with a higher risk in women with higher EDSS and number of relapses in the pre-conception year[2,4,28]. Interestingly, this risk appeared to be mitigated by treatment resumption after delivery. Also, our findings underline the importance of initiating treatment earlier, considering that the median TTFR was 3.16 months and that starting treatment within the first-month postpartum significantly reduced the occurrence of Gd+ lesions.

These results strengthen the notion that also in women with mild disability and treated with platform therapies until early pregnancy, postpartum disease reactivation is still an issue, despite the optimization of pre-conception management, thus supporting the resumption of tailored effective treatment strategies soon after delivery.

About 60% of women in our cohort breastfed exclusively or not exclusively; albeit not statistically significant, exclusive breastfeeding was associated with a trend toward longer TTFR, suggesting a possible protective effect on disease reactivation. However, we believe that these results should be interpreted cautiously, and they need to be confirmed in larger cohorts. In our cohort, the duration of breastfeeding (exclusive or mixed) was known for 65/72, and covered a median period of around 5 months, moreover only four women restarted DMF while breastfeeding. These data suggest that breastfeeding and treatment restart are still considered mutually exclusive with potential impact on women's health, in agreement with recent guidelines that do not support its use while breastfeeding[12]. Currently, evidence on the safety of the use of DMF in lactating women is still scarce. The calculated relative infant dose of DMF in the milk from two lactating women was found to be far lower than 10%, indicating a limited exposure of the newborns to treatment[29]. Building on these considerations, it would be important to establish the safety of breastfeeding in women restarting DMF in the first trimester after delivery, which could not be assessed in this study.

Our study also showed that early fetal exposure to DMF does not increase the rate of adverse pregnancy or fetal outcomes, confirming the results of the analysis of the international pregnancy registry (TecGistry)[9].

Mean duration of the exposure in our cohort was 4.9 weeks, and it was comparable to the women enrolled in the TecGistry[9]. Compared to the TecGistry cohort, we recorded a slightly higher incidence of spontaneous abortions (8% versus 3.5%) and birth defects (3.9% versus 2.2%), that in any case did not exceed the rate observed in the general population[30,31]. Although it is known from studies in female rabbits and rats that DMF crosses the placental membrane into fetal blood, no fetal malformations were noted at therapeutic doses in animals, and all in vitro mutagenicity and clastogenicity tests were negative[15]. At higher doses (11-fold the recommended human therapeutic dose), reduced fetal body weight was observed in rats and rabbits; although expected considering the preclinical data, our data confirm that there was no difference in mean newborns' body weight compared to the standard reference values[32].

In addition, it is worth underlining that we did not detect a significant incidence of infectious complications in both in mothers and newborns, suggesting that the immunological action of DMF seems not to have an impact on maternal and fetal immunocompetence, although these results should be interpreted cautiously and further investigated. In fact, due to the retrospective observational study design, we could only collect information on clinically relevant findings reported by neonatologists upon hospital discharge with potential underreporting of minor clinical events, which represents a limitation of the study. In conclusion this study shows that in women with MS: (1) discontinuing DMF at early pregnancy is not associated with disease reactivation during gestation; (2) a rapid resumption of treatment after delivery is advisable in order to prevent postpartum reactivation, particularly in women with worse baseline prognostic factors after appropriate discussion around the risk/benefit of breastfeeding; (3) a short fetal exposure to DMF does not affect pregnancy or fetal outcomes as defined above. These preliminary reassuring results need to be replicated and expanded encouraging the collection of more data regarding pregnancies exposed to DMF.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: D.L. received travel funding from Biogen, Merck-Serono, Sanofi-Genzyme, Teva, Bristol-Myers Squibb, Mylan, Novartis, Roche, Horizon, Alexion speaking or consultation fees from Sanofi-Genzyme, Merck-Serono, Teva, Biogen, Roche, Novartis, Bristol-Myers Squibb, Bayer-Schering. S.B. received travel funding from Biogen and Bristol-Myers Squibb. F.B. reported receiving teaching honoraria from Novartis and personal fees from Eisai, Biogen, and Chiesi outside the submitted work. M.P.A. has received research grants honoraria as a speaker and member of Advisory Boards from Biogen, Bayer, Novartis, Roche, Teva, Sanofi-Genzyme, Merck, Roche Celgene BMS, Janssen, Horizon. S.B. speaker honoraria and/or travel/congress grant from: Novartis, Merck-Serono, Alexion, BMS, Biogen, Roche, Janssen-Cilag. Research grant from Roche. G.B. received honoraria for speaking or consultation fee from Almirall, Biogen, Merck, Novartis, Sanofi, Teva, Roche. M.B. declares fees from Biogen, Sanofi-Genzyme, Roche, and Novartis. S.B. has been founded for advisory board, academic purposes and speech honoraria by Genzyme, Roche, Biogen, Merck-Serono, Novartis and Almirall. P.C. received honoraria for speaking and/or for consultancy and support for participation to scientific congresses from Almirall, Biogen, Merck-Serono, Novartis, Sanofi-Genzyme, Roche, Teva, Alexion, Celgene BMS, Janssen, Horizon. M.C. received personal compensations for public speaking from Novartis, Sanofi-Genzyme, Teva and consulting fees from Roche and Zambon. D.C. is an Advisory Board member of Almirall, Bayer-Schering, Biogen, GW Pharmaceutical, Merck-Serono, Novartis, Roche, Sanofi-Genzyme and Teva and received honoraria for speaking or consultation fee from Almirall, Bayer-Schering, Biogen, GW Pharmaceuticals, Merck-Serono, Novartis, Roche, Sanofi-Genzyme and Teva. He is also the principal investigator in clinical trials for Bayer-Schering, Biogen, Merck-Serono, Novartis, Roche, Sanofi-Genzyme. E.C. received travel grant, speaker fee and consultancy from Biogen Idec, Teva, Genzyme, Merck-Serono, Novartis, Roche and Admirall. A.C. has served on scientific advisory boards for Merck-Serono, Sanofi-Genzyme, Biogen, Novartis, Almirall. She has received institutional research support from Roche and Biogen. A.C. received speaker honoraria from Biogen, Sanofi-Genzyme, Teva and travel grants from Biogen, Merck, Sanofi-Genzyme, Teva; advisory boards member honoraria from Biogen, Merck, Novartis, Teva. E.D.A. received speaking honoraria from Biogen, Merck-Serono, Novartis, Sanofi-Genzyme, Bayer-Schering. M.D.F. participated on advisory boards and steering committees for and received speaker or writing honoraria, research support and funding for traveling from Alexion, BMS, Bayer, Biogen Idec, Genzyme, Horizon, Merck, Mylan, Novartis, Roche,

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Supplemental Material

Supplemental material for this article is available online.

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