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► To cite this version:

Lucile Lescot, Mathilde Lefort, Soizic Leguy, Emmanuelle Le Page, Sandra Vukusic, et al.. Disease modifying therapies and disease activity during pregnancy and postpartum in a contemporary cohort of relapsing Multiple Sclerosis patients. *Multiple Sclerosis and Related Disorders*, 2022, 68, pp.104122. 10.1016/j.msard.2022.104122 . hal-03776859

HAL Id: hal-03776859

<https://hal.science/hal-03776859>

Submitted on 20 Oct 2022

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Disease modifying therapies and disease activity during pregnancy and postpartum in a contemporary cohort of relapsing Multiple Sclerosis patients

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ABSTRACT

Background: In Multiple Sclerosis (MS) women, therapeutic management for pregnancy planification and during pregnancy still represents a challenge regarding timing of disease-modifying therapies (DMT) stop, risk of disease reactivation and potential fetal toxicity. The objective of this study was to describe disease activity during pregnancy and postpartum depending on treatment status before conception in women with MS.

Methods: 339 MS patients who have achieved a pregnancy between 2007 and 2017 were included. Women were classified according to their exposure to DMT in the 18 months period prior to pregnancy (untreated / first- / second/third-line treatment).

Results: 122 women were not exposed to DMT prior to conception, whereas 147 were exposed to first-line DMT and 70 to second/third line DMT (73% to natalizumab and 23% to fingolimod) before conception. In the first-line group, the ARR decreased from 0.39 during the year before conception to 0.21 during pregnancy, whereas it increased in the second/third-line group from 0.59 to 0.78. 47.1% of the second/third-line group faced at least one relapse during pregnancy and the time from conception to first relapse was significantly shorter in this group ($p < 10^{-4}$). The risk of relapse during pregnancy and postpartum was associated with occurrence of pre-conception relapses and second/third line DMT exposure before pregnancy.

Conclusion: Careful consideration should be given to natalizumab and fingolimod exposed patients before conception as they are at higher risk of reactivation of MS during pregnancy.

Keywords: multiple sclerosis; post-partum; relapses; Disease Modifying Therapies.

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INTRODUCTION

1
2 Multiple Sclerosis (MS) predominantly affects young women, and especially those of
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4 childbearing age (1,2). During pregnancy and postpartum, a typical pattern of clinical activity
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6 evolution was reported in 1998 with a continuous decrease of the annualized relapse rate (ARR)
7
8 during pregnancy, then an increase during the first 3 months of postpartum before returning to
9
10 the pre-pregnancy rate (3). Several other studies confirmed these data (4–6) Nevertheless, they
11
12 were conducted in MS women either untreated or treated by first-line disease-modifying
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14 therapies (DMT) before conception. This does not accurately reflect current clinical practice.
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16 Indeed, in more recent studies, between 61% and 92% of Relapsing-Remitting MS (RRMS)
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18 patients were on first- or second-line DMT in the year before conception(7–10). Although there
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20 are no controlled data, it is currently admitted to discontinue most of DMTs before conception
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22 or at pregnancy onset to minimize risk of fetal harm (11). However, discontinuation can lead to
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24 disease reactivation, in particular after second-line DMTs withdrawal in pregnant women (12–
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31 18).

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34 Therapeutic management for pregnancy planification and during pregnancy still represents a
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36 challenge regarding timing of DMT stop, risk of disease reactivation and potential fetal toxicity.
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39 More data are needed to better understand the impact of DMT use before conception on disease
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41 activity during pregnancy and postpartum.

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44 The objectives of our study were, in a large contemporary cohort, (1) to describe the course of
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46 the clinical disease activity during pregnancy planification, pregnancy and postpartum periods
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48 depending on treatment status and type before pregnancy; (2) to compare the time from
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50 conception to first relapse, first disability progression and first MRI activity, depending on
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52 treatment status and type before pregnancy; and (3) to identify factors associated with disease
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54 activity during the period from conception to 3 months postpartum.
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METHODS

The OFSEP cohort and participating centers

OFSEP is a French multimodal nationwide MS registry supplemented by neurologists from MS centres and regional networks(19). Data are collected retrospectively at the first visit and then prospectively during follow-up on a standardized clinical form in the European Database for MS (EDMUS) software (20). For this study, we used data from five OFSEP centers.

Standard protocol approvals, registrations, and patient consents

All patients included in the OFSEP cohort signed an informed consent to allow the registration of their medical data in the database and its use after anonymization for research. For the present study, approval of the Comité de Protection des Personnes has been obtained on 16th April 2019 (registration number SI: 19.03.05.63609). All patients received an information letter and a non-consent form that they could return in case of refusal to participate.

Study cohort

Inclusion criteria were: (a) RRMS patients according to McDonald criteria 2017 (21) non-opposed to participation to the study, (b) aged 15 to 49 at conception, (c) having at least one pregnancy with live birth after MS onset from January 1, 2007 to January 1, 2017, (d) having at least one neurological visit per year in the 24 months preceding the pregnancy and one neurological visit within 12 months after delivery. In case of several pregnancies per woman, only the last one fulfilling the criteria was analyzed.

Data extraction from EDMUS database was performed in January 2020.

Treatment status

A patient was considered as “treated” if she fulfilled one of the following cases:

(1) treated at least 6 months with the same first- or second-line DMT continuously over a period of 18 months before conception;

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(2) treated with mitoxantrone for a minimum of 3 cures over a period of 18 months before conception;

(3) treated with alemtuzumab for a minimum of one cycle over a period of 18 months before conception.

These definitions were applied to DMT started before conception and which could be continued during pregnancy.

Interferon, glatiramer acetate, teriflunomide and dimethyl fumarate were classified as first-line DMT, while natalizumab and fingolimod were classified as second-line DMT and mitoxantrone and alemtuzumab as third-line DMT. Patients were classified according to the last DMT received before conception.

Patients not fulfilling this definition were considered as “untreated” before conception.

The washout period was defined as the period from DMT stop to conception and did not exceed one year.

Data collection and protocol

Following variables were collected using EDMUS database (from 18 months before conception to 12 months after delivery): age and MS duration at conception, clinical activity (number of relapses, EDSS), radiological activity (new T2-lesions and gadolinium enhancing lesions on MRI) and DMTs exposure.

Missing or incomplete data were collected directly using MS patients’ files in each centre by two neurologists (SL, LL). Information about Assisted Reproductive Techniques (ART), delivery, breastfeeding, vitamin D supplementation and smoking habits were collected through an auto-questionnaire or medical file when available.

Outcomes

The following outcomes were considered and compared between groups according to DMT exposure before conception:

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(1) The ARR over several periods of interest.

(2) The time from conception to first relapse, first disability progression and first MRI activity up to 12 months of postpartum.

Disability progression was defined as follows: an increase of 1.5 point on EDSS if baseline EDSS was 0, of 1 point if it was ≥ 1 and < 5.5 or of 0.5 if the baseline EDSS was ≥ 5.5 .

MRI activity was defined as either a gadolinium enhancing lesion or a new T2-lesion over the period of interest. Cerebral and medullar MRI were grouped together.

(3) Risk factors of disease activity during the period from conception to 3 months postpartum were assessed among: age at MS onset and at conception, MS duration at conception, status of treatment during pregnancy (ongoing vs stopped), relapse occurrence over one year before conception, EDSS at conception, MRI activity over one year before conception, use of ART, smoking and vitamin D exposure before conception.

Statistical analysis

Demographic characteristics and MS disease activity parameters at conception were described overall and by treatment groups. Treated and untreated patients were compared on baseline characteristics using Student's t-tests for continuous variables or Fisher's exact tests for categorical variables. For comparison of measures over two periods, paired-tests were used. Treatment exposure before conception and washout duration were described. Patients with ongoing treatment at conception were described by treatment exposure and the time of stop was reported. For each group, ARR were computed, every 3 months, from the 12 months preceding pregnancy to 12 months postpartum. Trends of ARR were compared using linear regression. For comparison of mean ARR, by group, at each trimester, one-way analysis of variance (ANOVA) was used. Time before reaching each outcome of interest was studied using Kaplan-Meier estimates. Restricted mean survival time (RMST) were computed to describe each outcome of interest in each group. Factors associated with MS activity over the 12 months from

1 conception to 3 months postpartum were studied using a logistic regression analysis. The level
2 of significance was 5%, except for the variable selection process with univariate logistic
3 regression models where the level of significance was 20%. Statistical analysis was performed
4 using R 4.0.3 software.
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RESULTS

Characteristics of the cohort at conception

Among the 350 patients fulfilling inclusion criteria(22), 11 were treated by an off-label treatment (azathioprine, mycophenolate mofetil, methotrexate, rituximab and cyclophosphamide) before pregnancy and were excluded of the analysis. Characteristics at conception for the 339 patients are presented in *Table 1*. Overall, 217 women (64.0%) were treated in the 18 months period before conception, most of them (147 (67.7%)) by a first-line DMT.

Untreated women were older at MS onset and at conception with a lower EDSS at conception compared to treated ones. They presented a more active disease with 46.7% of them who had at least one relapse in the 12 months before conception, *versus* 35.0% in the treated group.

Second/third-line treated patients were younger at MS onset and presented a higher EDSS at conception compared to first-line treated patients.

Proportion of smokers as well as proportion of vitamin D supplementation before conception were comparable between the groups. The proportion of children conceived through ART were similar between the groups.

Treatment status before conception and during pregnancy

Table 2 reports the last DMT received in the 18 months before conception in the whole cohort and in the treated group.

Over the 147 first-line treated patients, 42.8% stopped their treatment at a median time of 3.8 months (IQR: 1.9-7.1) before conception. In the second-line DMT group, 21 (41.1%) patients stopped natalizumab before pregnancy with a median time of wash out duration of 3.6 months (IQR: 1.1-5.6) and 12 (75.0%) stopped fingolimod before pregnancy with a median time of wash out duration of 3.1 months (IQR: 1.2-3.9).

1 Among treated patients, 57.2% continued their DMT for a median duration of 4.9 weeks (IQR:
2 2.7 - 12.3) during the pregnancy. Most of them were on interferon (48%), glatiramer acetate
3 (24%) or natalizumab (24%). Among patients who continued DMT during pregnancy, 78%
4 stopped it during the first trimester of pregnancy.
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8 **ARR before conception, during pregnancy and over 12 months after delivery**

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10 For untreated and first-line treated patients, we observed a similar evolution of the mean ARR
11 with a decrease during pregnancy and a moderate increase in the 3 months postpartum period
12 (*Figure 1*). During pregnancy, 15.6% of untreated patients and 14.3% of first-line treated
13 patients presented at least one relapse and they were respectively 12.3% and 10.9% during the
14 3 months of postpartum (*Table S2*).
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23 The course of clinical disease activity was different for patients treated by second/third-line
24 DMT before conception (*Figure 1*). During pregnancy, mean ARR increased from 0.60 on the
25 year before conception to 0.91 and 0.84 during the second and third trimester respectively, with
26 47.1% of the patients facing at least one relapse during pregnancy. Mean ARR remained high
27 during the first three months postpartum (ARR = 0.80) with 18.6% of the patients facing at least
28 one relapse before returning to the pre-pregnancy rate (*Table S3*). During pregnancy, 49% of
29 patients on natalizumab before pregnancy and 43.7% of patients on fingolimod before
30 pregnancy had at least one relapse.
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43 Mean ARR for the second/third-line group was significantly different compared to the untreated
44 and first-line group for each trimester of pregnancy, and concerning the whole post conception
45 period we observed a significant difference of the mean ARR between the first-line DMT group
46 and second/third-line DMT group.
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53 **Time to first relapse from conception**

54 The restricted mean time (RMST) before first relapse from conception to 12 months postpartum
55 were 12.2 (95% Confidence Interval (CI): [10.3; 14]) months for second/third-line *versus* 16.5
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(95% CI: [15.4; 17.5]) and 16.8 (95% CI: [15.7; 17.9]) months for first-line and untreated, respectively. Comparisons of Kaplan-Meier estimates showed a significant difference (log-rank test $p < 10^{-4}$) (Figure 2A). Median time to the first relapse was 10 months after conception for patients treated with a second/third-line while the median was not reached for patients treated with a first-line or untreated. From conception to 3 months postpartum, the probability of being free from relapse was 77% (95% CI: [69%; 85%]) for untreated patients and 75% (95%CI: [68%; 82%]) for first-line treated patients and only 47% (95%CI: [37%; 60%]) for patients treated with second/third-line treatment before conception.

Time to first disability progression from conception

From conception to 12 months postpartum, the RMST before first disability progression in the three groups were 19.9 (95% CI: [19.1; 20.7]) months for second/third-line *versus* 20.6 (95% CI: [20.3; 20.9]) and 20.9 (95% CI: [20.7; 21.0]) months for first-line and untreated, respectively. Comparisons of Kaplan-Meier estimates showed a significant difference (log-rank test $p = 0.020$) (Figure 2B). From conception to 3 months postpartum, the probability of being free from disability progression was 99% (95%CI: [98%; 100%]) for untreated patients, 96% (95%CI: [93%; 99%]) for first-line treated patients and 91% (95%CI: [85%; 98%]) for patients treated with second/third-line treatment.

For untreated patients, mean EDSS didn't change significantly from pre-pregnancy compared to the end of the first postpartum year (1.08 *vs* 1.05, $p = 0.950$). For treated patients, however, the mean pre-pregnancy EDSS and at the end of post-partum year were statistically different (1.50 *vs* 1.72, $p = 0.021$).

Time to first MRI activity from conception

This analysis was conducted on patients with available MRI over the outcome study period (N = 176, 50%). The RMST before first MRI activity from conception to 12 months postpartum, were 11.9 (95% CI: [10.4; 13.5]) months for second/third-line *versus* 14.1 (95% CI: [12.9;

15.2]) and 15.3 (95% CI: [13.6; 17.1]) months for first-line and untreated, respectively. Comparisons of Kaplan-Meier estimates showed a significant difference (log-rank test $p=0.002$) (figure 2C). From conception to 3 months postpartum, the probability of being free from MRI activity was 77% (95%CI: [67%; 89%]) for untreated patients, 60% (95%CI: [50%; 72%]) for first-line treated patients and 38% (95%CI: [26%; 55%]) for patients treated with second/third-line treatment.

Factors associated with the risk of relapse during the period including pregnancy and the 3 months postpartum

In the multivariate analysis (Table 3), the risk of relapse during pregnancy and 3 months postpartum was significantly associated with occurrence of pre-conception relapses and exposition to second or third-line treatment before pregnancy. Then, focusing on the first-line treated patients (Table S4), we showed that to continue treatment during a part of pregnancy was significantly associated with lower risk of relapse in pregnancy and 3 months postpartum period (OR = 0.31 95%CI: [0.13; 0.72], $p = 0.006$). In contrast, for the second/third-line treated patients (Table S5), no significant association between the occurrence of relapse during pregnancy and 3 months postpartum period and the maintenance of treatment or not during a part of pregnancy ($p = 0.817$) was demonstrated.

Resumption of DMT after delivery

The majority of untreated patients before pregnancy remained without DMT after delivery (64%). Among first-line treated patients, 75% resumed or continued first-line DMT. In the second/third-line group, 81% resumed or continued the same DMT.

The RMST from delivery to DMT resumption over 12 months, were statistically different with 3.5 months (95%CI: [2.9; 4.0]) for treated patients and 9.4 months (95%CI: [8.6; 10.1]) for untreated patients ($p < 10^{-4}$). Among treated patients, the second/third-line patients resumed their DMT earlier than those treated with first-line (RMST: 2.3 months 95%CI: [1.6; 3.1] vs 3.8

1 months 95% CI: [3.2; 4.5], $p = 0.003$). At one year after delivery, the probability of being treated
2 was 88% (95% CI: [83%; 92%]) for treated patients before conception and 36% (95% CI: [27%;
3 44%]) for the untreated patients.
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6 **Breastfeeding**

7 Breastfeeding was more frequent for untreated patients (66.7%) compared to first-line treated
8 patients (45.1%) and second/third-line patients (28.1%) ($p < 10^{-4}$). Mean breastfeeding duration
9 was 7.3 months (± 10.5) for untreated patients, 4.2 months (± 3.5) for first-line treated patients
10 and 6.0 months (± 8.8) for second/third-line patients, and was not statistically different between
11 the different groups ($p = 0.147$).
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DISCUSSION

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3 Therapeutic management of pregnancy has been considerably challenged these last years.
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5 Timing of DMT stop, risk of disease reactivation during and after pregnancy and potential fetal
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7 toxicity are some of the practical issues that are not fully resolved. In this study, we aimed to
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9 describe the influence of DMT before pregnancy onset on disease activity during pregnancy
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11 and early postpartum in a large prospective national cohort.
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15 We first observed that 13% of the patients presented a relapse in the 3 months postpartum period
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17 in the whole cohort with a mean ARR of 0.61. These data confirm the decreased risk of disease
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19 reactivation described these last years during the postpartum period. Indeed, ARR in the 3
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21 months postpartum was estimated at 1.2 in PRIMIS in 1998 (3) whereas it was estimated
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23 between 0.27 and 0.94 in more recent cohorts(8,10,23,24). In the same way, between 23% and
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25 43% of the patients had a relapse on this postpartum period in the historical cohorts(3,25,26)
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27 compared to 7% to 22 % in more recent studies (7,23,27). These current results are probably
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29 explained by a better control of the disease activity before pregnancy with an increasing
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31 proportion of treated patients and the availability of highly effective DMTs. Indeed, the mean
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33 ARR before pregnancy is lower in the recent studies (8,10,23,24) (between 0.09 and 0.64) and
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35 in our study (0.48) than in PRIMIS (0.7).
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42 The second important observation we made in our cohort was on the risk of disease reactivation
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44 during pregnancy in MS patients treated by second-line DMT before pregnancy with 47 % of
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46 those patients that had at least one relapse during pregnancy. Importantly, in our cohort, the
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48 second/third-line group was composed of 73% (n=51) of patients treated with natalizumab and
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50 23% (n=16) of patients treated with fingolimod before conception. It is now well known that
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52 patients who discontinue natalizumab, especially in a context of pregnancy, are at high risk of
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54 disease reactivation(18,28,29). In the situation of fingolimod discontinuation associated to
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56 pregnancy within the year, disease reactivation has also been described with increased ARR
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1 during pregnancy (from 0.49 to 0.7)(9,29,30). Our results give insight to the attitude suggested
2 to maintain natalizumab for at least one or two trimesters during pregnancy (6,9,10,18,31) but
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4 also to be careful with the use of fingolimod in patients with pregnancy desire.
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7 Concerning the disease activity during post-partum, we didn't show significant differences
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9 comparing ARR of the groups. One explanation could be that patients in the second/third line
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11 DMT group resumed their DMT faster after delivery decreasing the risk of disease reactivation
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13 (8,32).
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16 The strength of our study is firstly the quality of our data. This study was based on five French
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18 centers dataset with a prospective follow-up. There were very few missing data concerning our
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20 clinical endpoints, thanks to the use of EDMUS database and a checking of medical records on
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22 sites. Moreover, questionnaires allowed us to collect additional information. Despite substantial
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24 missing data (only 50% of patients had undergone MRI during the period of interest in our
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26 study), this study included MRI data that are rarely described in similar studies. Data were
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28 collected over a substantial period of time: 24 months before conception, during pregnancy and
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30 12 months after delivery.
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36 However, despite a population of 350 women, we did not have sufficient numbers of patients
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38 to evaluate the specific effects of each treatment during pregnancy and early postpartum. As
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40 such, we decided to group treatments by line status and pooled second- and third-lines in a same
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42 group. However, conclusions concerning the course of ARR before, during and after pregnancy
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44 were similar when third-line patients were excluded (N=3) (data not shown).
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48 To conclude, this study provides reassuring data on the course of pregnancy and postpartum in
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50 a contemporary MS cohort with more than 85% of MS patients who were relapse-free during
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52 the 3 months postpartum period. However, a peculiar attention should be paid to women treated
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54 with natalizumab or fingolimod before conception who are at higher risk of disease reactivation
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56 after treatment stop, especially during pregnancy.
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ACKNOWLEDGMENTS

1
2 This work has been done with data from the OFSEP (<http://www.ofsep.org/fr/>). The authors
3
4 [thank the technicians of participating centers for their help \(Mr Leport from Rennes, Mrs](#)
5
6 [Moyon from Nantes, Mrs Callier from Nice, Mrs Berthe from Strasbourg\).](#)
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FIGURE LEGENDS:

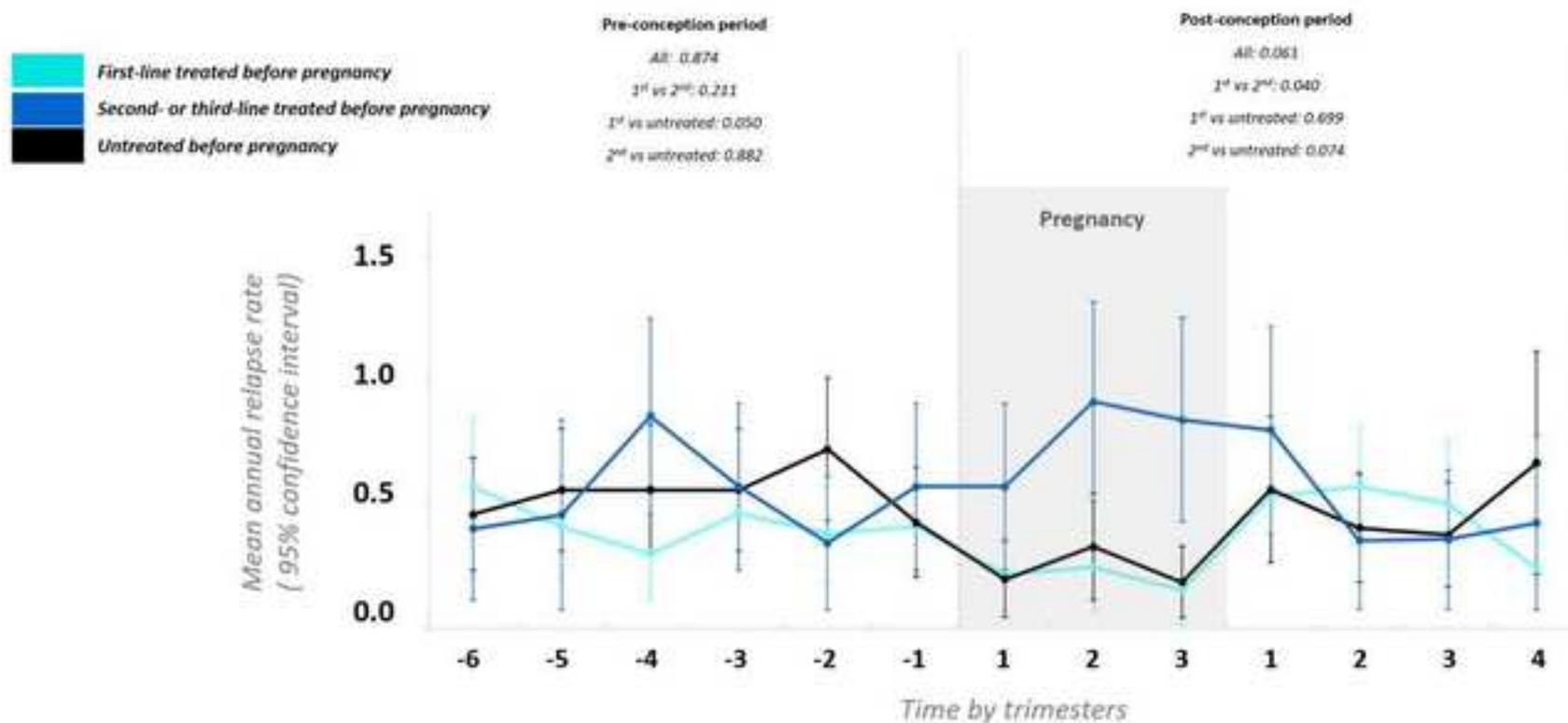
Figure 1: Mean annual relapse rate 12 months before, during and after pregnancy by trimesters, according to last treatment status before pregnancy: first-line, second/third-line treated or untreated.

The p-value was computed using a linear regression for testing trends. The number of patients currently treated in each trimester is reported for each group defined according to treatment before conception (as specifically defined in the methodology). The asterisk indicates significant difference between Annual Relapses Rates (ARR) by trimester.

Figure 2: Kaplan-Meier estimates of the time to first relapse (A) to first disability progression (B), to first MRI activity (C) from conception to one-year postpartum according to last treatment status before pregnancy: first-line treated, second/third line treated or untreated.

Disclosure: LM received honoraria as speaker from Biogen, Merck Serono, BMS Celgene, Sanofi Genzyme, Roche, and Novartis. SV reports consulting and lecture fees, travel grants and research support from Biogen, Celgène, Novartis, Merck, Roche, Sanofi Genzyme and Teva Pharm. DAL has received consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck, Roche, Sanofi, Medday, Teva Pharma and BMS. SW received honoraria as speaker or consultant from Alexion, Biogen, Merck Serono, Roche, and Novartis. ELP received honoraria for lectures or consulting from Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, TEVA, Roche, Alexion. SL, ML, LL, AM, GE, AK, JDS, CLF, EL have no disclosure regarding this work.

Funding statement: This work has been done with data from the OFSEP (<http://www.ofsep.org/fr/>), which is supported by a grant provided by the French State and handled by the Agence Nationale de la Recherche within the framework of the Investments for the Future program under the reference ANR-10-COHO-002 OFSEP and by the Eugene Devic Foundation Against Multiple Sclerosis.



Number of patients

First-line treated before pregnancy	147	147	147	147	147	147	147	147	147	146	140	136	134
Currently treated	96	109	118	127	128	113	94	22	27	23	76	103	109
Second- or third-line treated before pregnancy	70	70	70	70	70	70	70	70	70	70	68	67	66
Currently treated	64	62	61	54	61	52	41	7	5	7	50	58	59
Untreated before pregnancy	122	122	122	122	122	122	122	122	122	122	119	117	115
Currently treated	8	8	8	9	10	7	8	0	2	2	15	26	34

Comparison of ARR by trimester

-	-	-	-	-	-	0.030	0.001	<10 ⁻⁴	0.508	0.438	0.679	0.156
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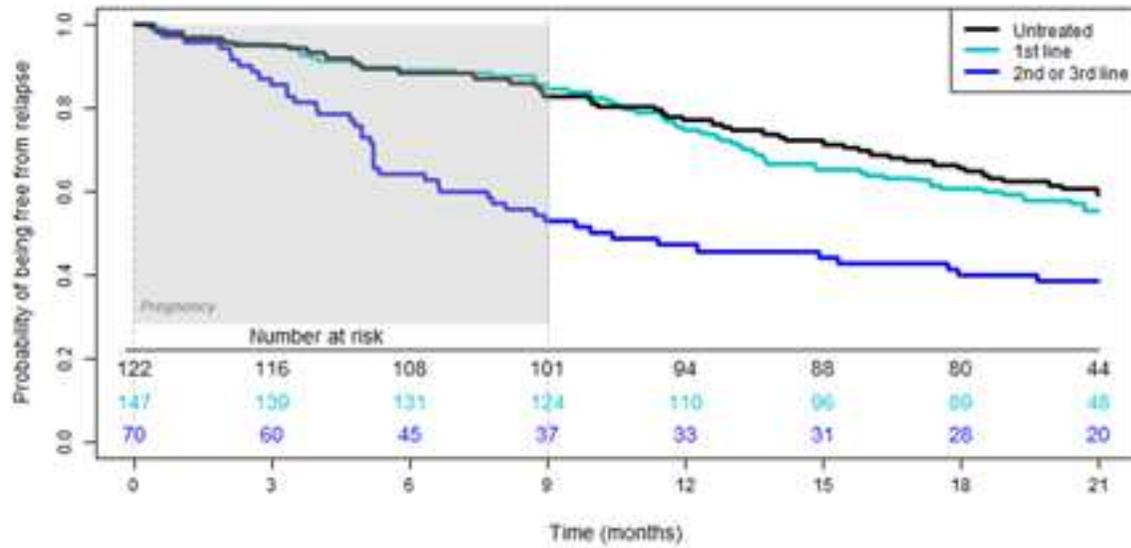
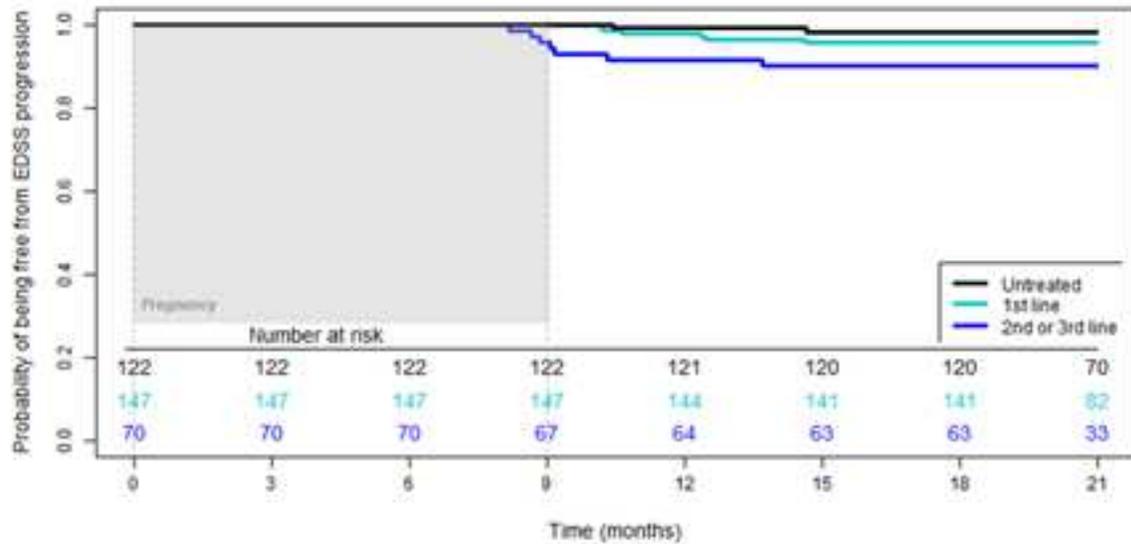
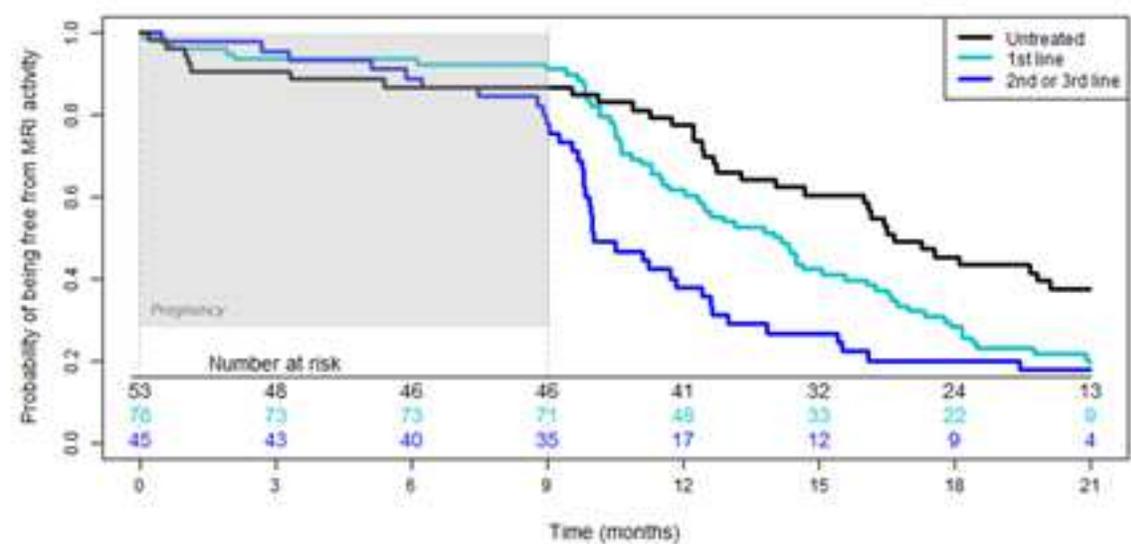
A - Time to first relapse from conception**B - Time to first EDSS progression from conception****C - Time to first MRI activity from conception**

Table 1: Demographic and clinical/MRI patients' characteristics before conception
overall and according to (1) treatment status before conception: treated and untreated and (2) last treatment line before conception for treated patients: first-line or second/third-line treated.

	All	Treated	Untreated	P	Treated by 1 st line	Treated by 2 nd / 3 rd line	P
	N = 339	N = 217	N = 122		N = 147	N = 70	
Demographic characteristics							
Age at MS onset [†]	24.4 ± 5.3	23.5 ± 5.1	26 ± 5.4	<10 ⁻⁴	24.1 ± 4.9	22.3 ± 5.1	0.016
Age at conception [†]	31.5 ± 4.3	31.1 ± 4.1	32.2 ± 4.6	0.034	31.2 ± 4	30.9 ± 4.5	0.619
Clinical/MRI characteristics							
MS duration at conception (years) [†]	7.1 ± 4.2	7.6 ± 4.1	6.2 ± 4.3	0.004	7.1 ± 4.1	8.6 ± 4.1	0.014
At least one relapse during the year before conception [‡]	133 (39.2%)	76 (35.0%)	57 (46.7%)	0.037	46 (31.2%)	30 (42.8%)	0.123
ARR during the year before conception ^{‡, §}	0.49 ± 0.69	0.45 ± 0.7	0.57 ± 0.67	0.139	0.39 ± 0.65	0.59 ± 0.79	0.070
EDSS at conception (±3 months) [†]	1.2 ± 1.5	1.4 ± 1.5	1 ± 1.4	0.011	1.1 ± 1.3	2 ± 1.7	0.001
At least one available MRI during the year before conception ^{‡, ¶}	199 (58.7%)	134 (61.8%)	65 (53.3%)	0.136	81 (55.1%)	53 (75.7%)	0.004
MRI activity ^{‡, ¶} during the year before conception	94 (47.2%)	58 (41.8%)	38 (58.5%)	0.034	37 (45.7%)	19 (35.8%)	0.286

[†]mean ± standard deviation; [‡]N(%); [§]ARR: Annual Relapse Rate; [¶] computed on available data

Table 2: Descriptive of the last treatment received in the 18 months period before conception

	All	Treated
	N = 339	N = 217
None	122 (35.9%)	
First-line DMT[†]		
Interferon	96 (28.3%)	96 (44.2%)
Glatiramer acetate	48 (14.1%)	48 (22.1%)
Dimethyl fumarate	2 (0.6%)	2 (0.9%)
Teriflunomide	1 (0.3%)	1 (0.5%)
Second/third-line DMT[†]		
Natalizumab	51 (15.0%)	51 (23.5%)
Fingolimod	16 (4.7%)	16 (7.3%)
Mitoxantrone	2 (0.6%)	2 (0.9%)
Alemtuzumab	1 (0.3%)	1 (0.5%)

[†]DMT : Disease Modifying Treatment

Table 3: Multivariate logistic regression of the variables that may predispose to relapses in pregnancy and 3 first months of postpartum

	Univariate analysis			Multivariate analysis		
	Odd ratio	95% Confidence Interval	p	Odd ratio	95% Confidence Interval	p
Age at MS onset (<i>> 25 versus ≤ 25</i>)	0.65	[0.40; 1.04]	0.077	1.01	[0.53; 1.89]	0.983
Age at conception (<i>> 35 versus ≤ 35</i>)	0.86	[0.47 ; 1.52]	0.605	-		
MS duration at conception (<i>> 7 versus ≤ 7</i>)	1.14	[0.72 ; 1.82]	0.577	-		
Line (<i>versus Untreated</i>)						
First-line	1.13	[0.64; 1.99]	0.672	0.90	[0.43; 1.93]	0.793
Second/third-line	3.76	[2.02; 7.15]	<10⁻⁴	3.39	[1.52; 7.79]	0.003
Relapse one year before conception (<i>Yes versus No</i>)	2.24	[1.41; 3.57]	0.001	2.43	[1.29; 4.61]	0.006
EDSS at conception (±3 months) (<i>< 3 versus ≥ 3</i>)	2.50	[1.33; 4.67]	0.004	1.43	[0.62; 3.20]	0.393
MRI activity - one year before pregnancy (<i>Yes versus No</i>)	1.38	[0.83; 2.28]	0.213	-		
Use of ART † (<i>Yes versus No</i>)	1.50	[0.64; 3.39]	0.335	-		
Smoker before conception (<i>Yes versus No</i>)	1.54	[0.88; 2.69]	0.132	1.69	[0.90; 3.14]	0.097
Vitamin D before conception (<i>Yes versus No</i>)	0.91	[0.51; 1.63]	0.762	-		

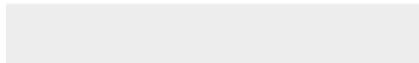
†ART: assisted reproductive technology

For the multivariate analysis, variable selection process of univariate logistic regression was based on a level of significance at 20%.



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