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► To cite this version:

Soizic Leguy, Mathilde Lefort, Lucile Lescot, Audrey Michaud, Sandra Vukusic, et al.. COPP-MS: COrticosteroids during the Post-Partum in relapsing Multiple Sclerosis patients. *Journal of Neurology*, 2022, 269 (269), pp.5571-5581. 10.1007/s00415-022-11215-7 . hal-03704177

HAL Id: hal-03704177

<https://ehesp.hal.science/hal-03704177>

Submitted on 12 Oct 2022

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COPP-MS: Corticosteroids during the Post-Partum in relapsing Multiple Sclerosis patients

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Keywords: multiple sclerosis; post-partum; relapses; disability; preventive corticosteroids.

Wordcount:

Article: 3282

Abstract: 209

Character count for the title: 79

Number of references: 36

Number of figures: 4

Number of tables: 2

Statements and Declarations

Competing interests: 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 no conflict of interest regarding this work.

Study funding: This work has been granted by the Eugene Devic EDMUS Foundation against Multiple Sclerosis and by the Aide à la Recherche sur la Sclérose en Plaques (ARSEP) foundation.

Acknowledgments: The present study is supported by a grant from the ARSEP. 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. The authors thank the technicians of participating centers for their help (Mr Leport from Rennes, Mrs Moyon from Nantes, Mrs Callier from Nice, Mrs Berthe from Strasbourg). The authors also thank Merck Serono for partly supporting this study.

ABSTRACT:

Background: No specific treatment has demonstrated its effectiveness to prevent post-partum relapses for multiple sclerosis (MS) women.

Objective: To assess the effectiveness of preventive high-dose corticosteroids in the post-partum period by comparing two strategies: (1) no preventive treatment and (2) standardized preventive treatment.

Methods: We selected 5 French Multiple Sclerosis centers using the same post-partum strategy for their patients – either high-dose steroids (treating centers TC) or no treatment (non-treating centers NTC). We included relapsing-remitting multiple sclerosis women who delivered between January 2007 and January 2017. Our primary outcomes were the time from delivery to first relapse, EDSS progression and MRI activity between patients of treating centers and non-treating centers, after propensity-score weighting.

Results: 350 patients were included (116 from treating centers, 234 from non-treating centers). For both groups, the annualized relapse rate decreased during pregnancy (0.28 in treating centers and 0.34 in non-treating centers during the third trimester) and increased during the first post-partum trimester (0.45 and 0.69 respectively) with 11% and 14% (NS) of patients facing at least one relapse respectively. Our primary outcomes were not statistically different between both groups.

Conclusion: This study provides class III evidence that systematic high-dose corticosteroids are not associated with a reduced inflammatory activity during the post-partum period in multiple sclerosis patients.

INTRODUCTION

Multiple sclerosis (MS) is a common inflammatory demyelinating disease of the central nervous system which affects preferentially young women.

Pregnancy influences the clinical course with a decrease of the annualized relapse rate (ARR) during pregnancy, especially during the third trimester, and an increase during the post-partum (PP) period, with 13% to 30% of women facing a relapse [1–12].

Recent studies suggest that the proportion of patients having a relapse in PP is currently decreasing, probably due to a better control of the disease activity before and during pregnancy with disease modifying drugs (DMDs) [4–15]. However, this risk of disease reactivation still exists and the therapeutic management of MS patients in PP is a matter of debate. Several strategies have already been assessed (corticosteroids, intravenous immunoglobulin, hormonal treatment or early DMDs restart [3, 5, 8, 9, 13, 14, 16–23, 15]). Among them, the effectiveness of preventive high-dose corticosteroids (CTCs) has been evaluated in two retrospective clinical studies suggesting a beneficial effect [16, 17]. Limited level of evidence leads to heterogeneous practices between MS centers and between patients.

In this context, using the French MS Registry (Observatoire Français de la Sclérose En Plaques–OFSEP) [24], we aimed to assess the real-life effectiveness of high-dose corticosteroids in prevention of PP relapses in relapsing-remitting MS (RRMS) patients, comparing two different strategies: (1) systematic preventive treatment by high-dose CTCs (2) versus no preventive treatment by high-dose CTCs.

1. Patients and Methods

The OFSEP cohort and participating centers

OFSEP is a French multimodal nationwide MS registry [24]. Data are prospectively collected during follow-up in the European Database for MS (EDMUS) software [24,

25]. For the current study, five French MS centers were selected according to their systematic strategies in PP. Two of them, defined as “treating centers” (TC), propose a systematic standardized intravenous corticotherapy after delivery contrary to the three others, defined as “non-treating centers” (NTC).

Standard protocol approvals, registrations, and patient consents

All patients signed an informed consent to allow the registration of their medical data in the OFSEP database. The present study received approval from the Comité de Protection des Personnes on April 16th 2019 (registration number SI: 19.03.05.63609) and was declared to the Agence Nationale de Sécurité du Médicament et des produits de santé (ID RCB:2019-A00567-50). The study was also registered in clinicaltrials.gov (NCT03917589). All patients received an information letter and a non-consent form.

Study cohort: the COPP-MS cohort

The inclusion criteria were: (1) women with RRMS defined by the 2010 revised MacDonald criteria[26], non-opposed to participation, (2) aged from 15 to 49 years at pregnancy onset, (3) having at least one pregnancy with live birth after MS onset from January 1, 2007 to January 1, 2017, (4) having at least one neurological visit per year within two years preceding the pregnancy and within two years after the delivery. In case of several pregnancies in the period, only the last one was analyzed.

Preventive treatment in PP

The systematic preventive treatment protocol was one gram of intravenous methylprednisolone (IVMP) per month, started the day after delivery at maternity and given for 3 to 6 months.

Data collection

Following variables were collected using extraction from EDMUS database (from 2 years before pregnancy onset to 2 years after delivery): age and MS duration at delivery, clinical activity (ARR, relapses, EDSS), radiological activity and DMDs exposure (considering first-line therapies (interferon, glatiramer acetate, teriflunomide, dimethyl-fumarate), second-line therapies (natalizumab, fingolimod), third-line therapy (mitoxantrone, alemtuzumab) and off-label therapies (azathioprine, cyclophosphamide, laquinimod, methotrexate, mycophenolate mofetil, rituximab)). Missing data were collected directly on site by two neurologists (SL, LL) and data (as relapses, EDSS, MRI parameters) were checked using MS patients' files in each center. A questionnaire about breastfeeding (exclusivity/duration), vitamin D supplementation and smoking habits before/during/after pregnancy was sent to patients.

Outcomes

Primary outcomes were the (1) time to first relapse, (2) time to first EDSS progression and (3) time to first new MRI activity, from delivery over two years. EDSS progression was defined as follows: +1.5 point if baseline EDSS=0, +1 if $1 \leq \text{EDSS} < 5.5$, +0.5 if $\text{EDSS} \geq 5.5$. New MRI activity was defined as either Gadolinium enhancing lesion or a new T2-lesion. Delays were censored at the earliest of: secondary progressive MS date, end of follow-up date or end of study date (i.e. delivery +2 years).

Secondary binary outcomes were the risk of occurrence of at least one relapse in the first six months, the first year and the first two years PP, and at least one EDSS progression and one MRI activity after delivery and until two years.

In a first descriptive step, before propensity-score weighting, we described characteristics at baseline and calculated the ARR before, during and after pregnancy.

Statistical analysis

Demographics and clinical characteristics were described and compared using Student test for continuous variables and Fisher test for categorical ones (level of significance: 5%). ARR were defined as the total number of relapses divided by the follow-up duration in each period of interest.

In the main analysis, we defined two cohorts, patients from TC and patients from NTC, independently of IVMP status, to compare centers practicing or not preventive corticosteroids strategy. A secondary analysis was performed with a per protocol method (exact treatment received), defining a cohort of patients actually treated and a cohort of patients who did not, independently of their origin center. Both analyses followed a similar modeling strategy.

Our study was not randomized, so in order to improve group balancing, a propensity score (PS) was used. Using PS, we want to balance between the both groups to make them comparable at therapeutic decision. This therapeutic decision should reflect the decision of the neurologist based on the risk to reach the outcome, for instance, the risk of relapse. Thus, PS was obtained from a multivariate logistic regression including variables statistically associated with each specific outcome (Cox model, level of significance: 20%) [27–29] For each outcome, following variables were considered potentially associated with: age at delivery, MS duration at delivery, ARR over the two years before pregnancy, number of relapse during pregnancy, EDSS at pregnancy onset, MRI within the two years before pregnancy, breastfeeding, DMD within the year before pregnancy and DMD during pregnancy. The association of each variable with each outcome were studied using Cox model (level of significance: 20%). Then, outcomes were studied using Kaplan-Meier methods weighting by the stabilized inverse probability of treatment weights (IPTW), a weight obtained from PS and the corresponding log-rank test. In each balanced group, we reported and compared the

weighted restricted mean time (RMST) before reaching outcomes [30] (significance level: 5%). RMST were restricted at six months, one year and two years of PP. Binary outcomes were assessed using IPTW weighted logistic regression. Confidence interval were obtained by bootstrap (k=1000).

Analysis was performed using R software (R4.0.3), the weighted Kaplan-Meier estimators were obtained using the package RISCA [31].

2. Results

Characteristics at baseline and at delivery

Database extraction identified 390 eligible patients. Inclusion process led to 350 patients retained for the analysis (*Figure 1*).

Characteristics at baseline are presented in Table 1.A for the main analysis and available in supplementary for the secondary analysis (*eTable 1.A*). Overall, 116 (33.1%) patients were followed in TC and 234 (66.9%) in NTC, and 71 (20.3%) patients were actually treated with IVMP in the PP period (69 from TC, 2 from NTC). Clinical data (ARR, EDSS), radiological activity and DMDs use were similar between patients of TC and NTC within the two years before pregnancy. Overall, 150 patients were exposed to DMDs during pregnancy (72.7% with first line, 25.3% with second line and 2% with off-label therapy), with a mean duration of 2.4 (± 3) months and no difference between TC and NTC. Comparison of treated (N=69) and untreated patients (N=47) in TC showed no statistical difference for characteristics at baseline (*data not shown*).

Characteristics at delivery and in PP are presented in Table 1.B for the main analysis (in supplementary for the secondary analysis, *eTable 1.B*). Breastfeeding was more frequent in TC (66.2%) compared to NTC (42.6%) ($p < 0.001$). Among breastfeeding mothers, exclusive breastfeeding (only breast-milk used for at least two months)

included 32% of patients from TC and 22% of patients from NTC ($p=0.088$). Mean breastfeeding duration was 4.8 months (± 4.3) in TC and 6.4 months (± 9.2) in NTC. On average, treated patients received monthly IVMP during 4.56 (± 1.8) months after delivery. Median delay before DMDs resumption was not different between TC and NTC ($p=0.700$). Indeed, 41% of patients from TC and 46% from NTC have resumed their DMDs in the first three months of PP. Considering treated patients, during the preventive corticotherapy, 71.7% breastfed and 68% resumed a DMD before the end of the month following the last infusion (*eTable 1.B*).

ARR before pregnancy, during pregnancy and over two years of PP every 3 months for patients of TC and NTC.

As shown in *Figure 2*, ARR were similar in the two groups before pregnancy ($p=0.841$). Regarding the whole cohort, ARR decreased during pregnancy compared to pre-pregnancy rates and increased during the first trimester of PP compared to pregnancy rates. At one year, ARR remain slightly lower than pre-pregnancy rate.

Comparison of ARR along time using linear regression between TC and NTC showed no difference between curves, in main analysis ($p=0.404$). Overall, 11% of patients from TC and 14% from NTC faced at least one relapse during the first PP trimester ($p=0.505$).

Time to first relapse in PP: No difference in both analyses

Regarding this outcome, PS model included: ARR over the two years before pregnancy, number of relapses during pregnancy and DMDs during pregnancy (*Table 2*). No statistical difference was found comparing the Kaplan-Meier estimates for the time to first relapse from delivery ($p=0.691$, *Figure 3*), as well as the restricted mean time (RMST) before reaching the first relapse in PP at six months, one year and two years between groups (*Figure 4*). Odds-Ratio (OR) associated with the proportion of patients

facing at least one relapse in each group was 0.99 [0.53; 1.63] in the first six months after delivery, 0.87 [0.41; 1.53] in the first year and 0.85 [0.44; 1.42] in the first two years. In the TC group, PP relapse rates were not different between treated and untreated patients ($p>0.05$). Results were confirmed in the secondary analysis without statistical difference between the two curves ($p=0.537$) (*Figure 3*), and no difference between RMST at the three time-points (*Figure 4*).

Time to first EDSS progression in PP: No difference in both analyses

PS model for this outcome included: year of pregnancy (*Table 2*). No statistical difference was found comparing the curves representing time to first EDSS progression ($p=0.840$, *Figure 3*) as well as RMST after delivery at six months, one year and two years (*Figure 4*). OR associated to the proportion of patients facing at least one EDSS progression was 0.93 [0.52; 1.54]. The secondary analysis was consistent with these results, with no difference between Kaplan-Meier curves ($p=0.453$, *Figure 3*) and no difference between RMST at the three timepoints (*Figure 4*).

Time to first MRI activity in PP: No difference in main analysis

PS model for this outcome included age and MS duration at delivery, number of relapses during pregnancy, MRI activity within the year before pregnancy, breastfeeding at delivery, DMDs over the two years before pregnancy and DMDs during pregnancy (*Table 2*). MRI was available for 284 patients, 105 (37%) were done within the 6-months PP, 39 (14%) between 6- and 12-months PP and 140 (49.2%) after 12-months PP.

No difference was found between the two groups comparing Kaplan-Meier estimates ($p=0.093$) and RMST at six months, one year and two years (*Figure 4*). OR associated to the proportion of patients with a new MRI activity was 1.40 [0.67; 2.45]. In the secondary analysis, a difference between treated and untreated groups was observed, in

favor of untreated group ($p=0.042$) (*Figure 3*). Although, differences of RMST were not different at six months, a difference at one year and two years of PP was observed, in favor of untreated group (-0.012 [-0.21 ; -0.01] at one year and -0.26 [-0.48 ; -0.03] at two years) (*Figure 4*).

3. **Discussion**

Our main objective was to assess, in a large cohort of MS patients, the effectiveness of preventive IVMP in the PP period on disease activity by comparing two strategies: (1) Systematic preventive treatment and (2) No preventive treatment. Using two complementary statistical analyses, time to first relapse and to first EDSS progression were not statistically different between patients of TC and NTC and between treated and untreated patients.

Until now, only two retrospective observational studies of small size [16, 17] have assessed this question, showing a decreased risk of PP relapses with preventive corticotherapy, and motivating some teams to apply a standardized protocol. In the first one, the ARR of 22 untreated MS women appeared higher in the first PP trimester (2 ± 0.66) than the ARR of 20 MS women treated by one gram of IVMP monthly during six months in PP (0.8 ± 0.41) [16]. In the second study, 17.9% of 39 MS patients treated directly after delivery with one gram of IVMP faced a relapse in PP compared to 46.2% of 13 untreated MS patients [17]. In these two uncontrolled studies, the groups were small, and the untreated groups were particularly active in the 3 months PP with ARR of 2 in the French study (1.2 in PRIMS), and 46.2% of patients facing a relapse in the American one (28% in PRIMS) [1, 2]. Moreover, critical variables could have influenced disease activity in the PP: DMDs exposure before pregnancy was not

described in the French study and appeared substantially different, although not statistically, in the American one (89.7% and 69.2% patients on DMDs respectively in treated and untreated group). Considering breastfeeding, no difference between the two groups was reported in the American study, but data were not available for the French one. Considering the statistical analysis, the authors did not balance their treated/not treated groups that were not comparable and they did not consider the indication bias especially in the American study.

In our study, we retrospectively included 350 patients of five French MS centers with a prospective follow-up. Our findings were consistent with recent literature, confirming an increase of ARR in PP but lower than the ARR firstly described in historical cohorts, with 13% of patients presenting a relapse during the 3 months PP [4, 7, 8, 10–12, 15, 32]. These data confirmed a decrease of the risk of inflammatory disease reactivation in PP. Unlike the two previous studies, we found no benefit for a preventive corticotherapy in our cohort on clinical parameters [16, 17], maybe partly explained by the difference in term of disease activity before pregnancy between our contemporary cohort and these two older cohorts (ARR of 0.5 in the year before pregnancy in our cohort compared to 0.6 and 1 in the two groups of the French study), but also during the PP (with 11% and 14% of patients relapsing in the 3 months PP in our cohort compared to 17.9 and 46.2% in the two groups of the American study). Indeed, changes in the therapeutic management of MS have led to a significant reduction of the disease activity over the last decade and especially during the PP [4–15].

Concerning the time to first MRI activity, no statistical difference was found with the main analysis, but the secondary analysis found a difference at one year and two years after delivery with an earlier occurrence of MRI activity for treated patients compared

to untreated patients. It was not explained by the time before resuming DMDs in PP which was not delayed for treated patients ($p=0.600$). However, comparison of MRI activity has to be interpreted cautiously due to missing data, and to a substantial variability of delay between delivery and MRI acquisition between patients with probably more frequent control MRIs for patients with active disease.

In our cohort, breastfeeding was more frequent in TC (66.2%) compared to NTC (42.6%) ($p<0.001$), but not statistically different considering exclusive breastfeeding ($p=0.088$). Some studies showed a potential protective effect of breastfeeding that could influence the risk of disease reactivation in this period [6, 12, 15, 33, 34]. This variable, considered at baseline, was not included in the PS because not associated with the outcome in the model. Characteristics of breastfeeding such as exclusivity or duration, assessed after baseline, could thus be influenced by that occurs after baseline, such as disease activity, preventing their inclusion in the PS.

Early DMD resumption after delivery could reduce the risk of disease reactivation [8, 9, 13, 14, 23]. In our study, no difference for delay of DMD resumption was found between TC and NTC and did not influence our results.

One of the main strengths of our study is the large sample of MS patients with a prospective follow up, composing a representative cohort. There were very few missing data concerning our clinical endpoints, thanks to the use of EDMUS database, on-site data control and additional data collected with questionnaires. Regarding methodological choices, all women of TC did not receive IVMP (40% of patients from TC remained untreated). We cannot exclude that this high proportion of patients could be explained by unobserved or unknown confounders. A consequence of such unobserved data is a potential selection bias if we perform a direct comparison between treated patients and untreated patients [35]. Similar to randomized clinical trial

analyses, the intention-to-treat (ITT) principle was applied whereby the results were based on the practice of the center, and not on the treatment actually given. That point led us to perform two complementary statistical methods. The main analysis, equivalent to an ITT analysis, is a conservative method considering all patients as having received the treatment's strategy of their own center. The secondary analysis, equivalent to a per-protocol analysis, investigates the real exposure considering each patient according to the treatment actually received. To ensure comparability of our two populations, already very closed, we used a PS. Our conclusions are strengthened by concordance of both analyses and comforted by data of literature as the monthly high dose methylprednisolone benefit for controlling disease activity has never been clearly documented in MS, especially in very active MS [36].

Currently, no preventive treatment has demonstrated its benefit to prevent PP relapses. Studies assessing intravenous immunoglobulins effect showed conflicting results [18–21]. No protective effect was reported with hormonal treatments analyzed in a large randomized controlled study[3]. An interesting lead could be an early reintroduction of DMDs in the PP, which could reduce the risk of rebound [8, 9, 13, 14, 23], that will be analyzed in a second study on the same cohort of patients.

Main limitations of our study are classical ones in such retrospective studies, linked to the challenge of data collection. We ensured quality of our collected data using a national database, on sites files' checking and questionnaires. However, a selection bias could exist as we included patients followed exclusively in MS expert centers whose representativeness may be questionable. Only 71 patients of the entire cohort were actually treated, among which 69 patients of TC. The quite low proportion of treated patients in TC could be explained by different management strategies in PP according to neurologist. Moreover, even in a systematic approach, several patients

may have declined the proposal of a preventive corticotherapy administered monthly. Despite these limitations, collected data remains of great interest as no randomized study would be easily achievable on this purpose on a cohort of MS patients.

Thanks to our large cohort and robust statistical methods, we assess in this study the absence of benefit of high dose corticosteroids in PP period, providing class III evidence that IVMP do not prevent clinical activity during the PP period in women with MS.

Statements and Declarations

Competing interests: 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 no conflict of interest regarding this work.

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Acknowledgments: The present study is supported by a grant from the ARSEP. 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. The authors thank the technicians of participating centers for their help (Mr Leport from Rennes, Mrs Moyon from Nantes, Mrs Callier from Nice, Mrs Berthe from Strasbourg). The authors also thank Merck Serono for partly supporting this study.

References :

1. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med*. 1998;339:285–91.
2. Vukusic S, Hutchinson M, Hours M, Moreau T, Cortinovis-Tourniaire P, Adeleine P, et al. Pregnancy and multiple sclerosis (the PRIMIS study): clinical predictors of post-partum relapse. *Brain*. 2004;127 Pt 6:1353–60.
3. Vukusic S, Ionescu I, Cornu C, Bossard N, Durand-Dubief F, Cotton F, et al. Oral nomegestrol acetate and transdermal 17-beta-estradiol for preventing post-partum relapses in multiple sclerosis: The POPARTMUS study. *Mult Scler*. 2020;:1352458520978218.
4. Hughes SE, Spelman T, Gray OM, Boz C, Trojano M, Lugaesi A, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Mult Scler*. 2014;20:739–46.
5. Fragoso YD, Boggild M, Macias-Islas MA, Carra A, Schaerer KD, Aguayo A, et al. The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis. *Clin Neurol Neurosurg*. 2013;115:154–9.
6. Hellwig K, Haghighi A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord*. 2012;5:247–53.
7. Alroughani R, Alowayesh MS, Ahmed SF, Behbehani R, Al-Hashel J. Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. *Neurology*. 2018;90:e840–6.
8. Bsteh G, Algrang L, Hegen H, Auer M, Wurth S, Di Pauli F, et al. Pregnancy and multiple sclerosis in the DMT era: A cohort study in Western Austria. *Mult Scler*. 2020;26:69–78.
9. Berenguer-Ruiz L, Gimenez-Martinez J, Palazón-Bru A, Sempere AP. Relapses and obstetric outcomes in women with multiple sclerosis planning pregnancy. *J Neurol*. 2019;266:2512–7.
10. Finkelsztejn A, Fragoso YD, Ferreira MLB, Lana-Peixoto MA, Alves-Leon SV, Gomes S, et al. The Brazilian database on pregnancy in multiple sclerosis. *Clin Neurol Neurosurg*. 2011;113:277–80.
11. Jesus-Ribeiro J, Correia I, Martins AI, Fonseca M, Marques I, Batista S, et al. Pregnancy in Multiple Sclerosis: A Portuguese cohort study. *Multiple Sclerosis and Related Disorders*. 2017;17:63–8.
12. Langer-Gould A, Smith JB, Albers KB, Xiang AH, Wu J, Kerezsi EH, et al. Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort. *Neurology*. 2020;94:e1939–49.
13. Vukusic S, Durand-Dubief F, Benoit A, Marignier R, Frangoulis B, Confavreux C. Natalizumab for the prevention of post-partum relapses in women with multiple sclerosis. *Mult Scler*. 2015;21:953–5.
14. Portaccio E, Moiola L, Martinelli V, Annovazzi P, Ghezzi A, Zaffaroni M, et al. Pregnancy decision-making in women with multiple sclerosis treated with natalizumab:

II: Maternal risks. *Neurology*. 2018;90:e832–9.

15. Canibañó B, Deleu D, Mesraoua B, Melikyan G, Ibrahim F, Hanssens Y. Pregnancy-related issues in women with multiple sclerosis: an evidence-based review with practical recommendations. *J Drug Assess*. 2020;9:20–36.

16. de Seze J, Chapelotte M, Delalande S, Ferriby D, Stojkovic T, Vermersch P. Intravenous corticosteroids in the postpartum period for reduction of acute exacerbations in multiple sclerosis. *Multiple Sclerosis Journal*. 2004;10:596–7.

17. Avila-Ornelas J, Avila M, Stosic M, Robles L, Prieto PG, Hutton GJ, et al. The Role of Postpartum Intravenous Corticosteroids in the Prevention of Relapses in Multiple Sclerosis. *International Journal of MS Care*. 2011;13:91–3.

18. Hellwig K, Beste C, Schimrigk S, Chan A. Immunomodulation and postpartum relapses in patients with multiple sclerosis. *Ther Adv Neurol Disord*. 2009;2:7–11.

19. Brandt-Wouters E, Gerlach OHH, Hupperts RMM. The effect of postpartum intravenous immunoglobulins on the relapse rate among patients with multiple sclerosis. *Int J Gynaecol Obstet*. 2016;134:194–6.

20. Rosa GR, O'Brien AT, Nogueira E de AG, Carvalho VM de, Paz SC, Fragoso YD. There is no benefit in the use of postnatal intravenous immunoglobulin for the prevention of relapses of multiple sclerosis: findings from a systematic review and meta-analysis. *Arquivos de Neuro-Psiquiatria*. 2018;76:361–6.

21. Horvat Ledinek A, Brecl Jakob G, Jerše J, Ruška B, Pavičić T, Gabelić T, et al. Intravenous immunoglobulins for the prevention of postpartum relapses in multiple sclerosis. *Mult Scler Relat Disord*. 2020;38:101519.

22. Winkelmann A, Rommer PS, Hecker M, Zettl UK. Intravenous immunoglobulin treatment in multiple sclerosis: A prospective, rater-blinded analysis of relapse rates during pregnancy and the postnatal period. *CNS Neurosci Ther*. 2018;25:78–85.

23. Portaccio E, Ghezzi A, Hakiki B, Sturchio A, Martinelli V, Moiola L, et al. Postpartum relapses increase the risk of disability progression in multiple sclerosis: the role of disease modifying drugs. *J Neurol Neurosurg Psychiatry*. 2014;85:845–50.

24. Vukusic S, Casey R, Rollot F, Brochet B, Pelletier J, Laplaud D-A, et al. Observatoire Français de la Sclérose en Plaques (OFSEP): A unique multimodal nationwide MS registry in France. *Mult Scler*. 2020;26:118–22.

25. Confavreux C, Compston DA, Hommes OR, McDonald WI, Thompson AJ. EDMUS, a European database for multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 1992;55:671–6.

26. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69:292–302.

27. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163:1149–56.

28. Karim ME, Pellegrini F, Platt RW, Simoneau G, Rouette J, de Moor C. The use and quality of reporting of propensity score methods in multiple sclerosis literature: A review. *Mult Scler*. 2020;1352458520972557.

29. Simoneau G, Pellegrini F, Debray TP, Rouette J, Muñoz J, Platt RW, et al. Recommendations for the use of propensity score methods in multiple sclerosis

research. *Mult Scler*. 2022;:13524585221085732.

30. Zhao L, Claggett B, Tian L, Uno H, Pfeffer MA, Solomon SD, et al. On the restricted mean survival time curve in survival analysis. *Biometrics*. 2016;72:215–21.
31. RISCA: Causal Inference and Prediction in Cohort-Based Analyses version 0.9 from CRAN. <https://rdr.io/cran/RISCA/>. Accessed 26 Feb 2021.
32. Voskuhl RR, Wang H, Wu TCJ, Sicotte NL, Nakamura K, Kurth F, et al. Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15:35–46.
33. Hellwig K, Rockhoff M, Herbstritt S, Borisow N, Haghighia A, Elias-Hamp B, et al. Exclusive Breastfeeding and the Effect on Postpartum Multiple Sclerosis Relapses. *JAMA Neurol*. 2015;72:1132–8.
34. Krysko KM, Rutatangwa A, Graves J, Lazar A, Waubant E. Association Between Breastfeeding and Postpartum Multiple Sclerosis Relapses: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2020;77:327–38.
35. Couvrat-Desvergnès G, Foucher Y, Le Borgne F, Dion A, Mourad G, Garrigue V, et al. Comparison of graft and patient survival according to the transplantation centre policy for 1-year screening biopsy among stable kidney recipients: a propensity score-based study. *Nephrol Dial Transplant*. 2019;34:703–11.
36. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry*. 1997;62:112–8.

Table 1: Patients' characteristics (A) before pregnancy, (B) at delivery and during the post-partum (main analysis).

| Table 1: Characteristics in each cohort | | | | |
|--|--------------|------------------|----------------------|---------|
| | Total Cohort | Treating Centers | Non-Treating Centers | p-value |
| | N = 350 | N = 116 | N = 234 | |
| A) At baseline | | | | |
| CLINICAL CHARACTERISTICS | | | | |
| Age at MS onset (years) ^b | 24.3 ± 5.3 | 24.1 ± 5.6 | 24.4 ± 5.1 | 0.673 |
| MS duration at conception (years) ^b | 7.2 ± 4.2 | 7 ± 4.6 | 7.3 ± 4.1 | 0.548 |
| Relapses over the two years before pregnancy | | | | |
| At least one relapse ^a | 219 (62.6%) | 66 (56.9%) | 153 (65.4%) | 0.129 |
| ARR ^{b,c} | 0.62 ± 0.71 | 0.61 ± 0.82 | 0.63 ± 0.66 | 0.841 |
| Relapses During Pregnancy | | | | |
| At least one relapse ^a | 77 (22%) | 27 (23.3%) | 50 (21.4%) | 0.683 |
| ARR ² | 0.35 ± 0.71 | 0.35 ± 0.68 | 0.35 ± 0.73 | 0.944 |
| EDSS at pregnancy onset (±3 months) ^{b,a} | 1.3 ± 1.5 | 1.1 ± 1.4 | 1.3 ± 1.5 | 0.241 |
| <3 | 270 (83.6%) | 88 (86.3%) | 182 (82.4%) | 0.799 |
| [3;6[| 49 (15.2%) | 13 (12.7%) | 36 (16.3%) | |
| >6 | 4 (1.2%) | 1 (1.0%) | 3 (1.4%) | |
| NA | 27 | 14 | 13 | |
| MRI within the two years before pregnancy | | | | |
| At least one available MRI ^{a,c} | 266 (76%) | 72 (62.1%) | 194 (82.9%) | |
| At least one MRI activity ^{a,c} | 171 (64.3%) | 47 (65.3%) | 124 (63.9%) | 0.886 |
| TREATMENT EXPOSURE | | | | |
| Mean DMD duration before pregnancy (years) | 3.8 ± 3.2 | 3.9 ± 3.6 | 3.7 ± 3 | 0.552 |
| DMD within the year before pregnancy | | | | |
| None | 109 (31.2%) | 40 (34.5%) | 69 (29.5%) | 0.391 |
| First line | 167 (47.7%) | 57 (49.1%) | 110 (47.0%) | |
| Other DMDs (2 nd and 3 rd line, off label) | 74 (21.1) | 19 (16.4%) | 55 (23.5%) | |
| DMD exposure during pregnancy | 150 (42.9%) | 54 (46.6%) | 96 (41.0%) | 0.359 |
| ENVIRONMENT | | | | |
| Smoker | | | | |
| before pregnancy ^{a,c} | 92 (35.8%) | 19 (35.8%) | 73 (35.8%) | 1.000 |
| NA | 75 | 47 | 28 | |
| during pregnancy ^{a,c} | 49 (19.2%) | 13 (25%) | 36 (17.7%) | 0.241 |
| NA | 77 | 48 | 29 | |
| Vitamin D | | | | |
| before pregnancy ^{a,c} | 90 (38.3%) | 18 (35.3%) | 72 (39.1%) | 0.745 |
| NA | 97 | 49 | 48 | |
| during pregnancy ^{a,c} | 127 (54%) | 27 (52.9%) | 100 (54.3%) | 0.875 |
| NA | 97 | 49 | 48 | |
| B) At delivery and in post-partum | | | | |
| CIRCUMSTANCES OF DELIVERY | | | | |
| Age at delivery (years) ^b | 32.2 ± 4.3 | 31.9 ± 4.6 | 32.4 ± 4.2 | 0.264 |
| Term of pregnancy (months) ^b | 9.0 ± 0.5 | 8.9 ± 0.6 | 9.0 ± 0.4 | 0.043 |
| EDSS at delivery (±3 months) ^{b,a,c} | 1.3 ± 1.5 | 1.3 ± 1.6 | 1.3 ± 1.5 | 0.947 |
| Breastfeeding | | | | |
| Yes ^{a,c} | 141 (48.6%) | 49 (66.2%) | 92 (42.6%) | <0.001 |
| NA | 42 | 26 | 16 | |
| Duration (months) ^b | 5.9 ± 8.1 | 4.8 ± 4.3 | 6.4 ± 9.2 | |
| TIME TO DMD START FROM DELIVERY ¹ | | | | |

| | | | | |
|--|-------------------|--------------------|-------------------|-------|
| DMDs resumption^a | | | | |
| At 3 months | 155 (44%) | 48 (41%) | 107 (46%) | |
| At 6 months | 209 (60%) | 68 (59%) | 141 (60%) | |
| At two years | 270 (77%) | 87 (75%) | 183 (78%) | |
| Median time before DMD resumption (years) [95%CI] | 0.33 [0.27; 0.40] | 0.34 [0.25; 0.51] | 0.32 [0.22; 0.41] | |
| RMST before DMD resumption [95%CI] | 0.72 [0.64; 0.81] | 0.75 [0.60; 0.89] | 0.71 [0.61; 0.81] | 0.700 |
| Difference RMST | | 0.03 [-0.21; 0.21] | | |
| Proba.* at 3 months PP | 44% [39%; 50%] | 42% [33%; 51%] | 47% [29%; 53%] | |
| Type of DMD | | | | |
| None | 80 (23%) | 29 (25%) | 51 (22%) | |
| First line | 178 (51%) | 58 (50%) | 120 (51%) | |
| Other DMDs (2 nd and 3 rd line, off label) | 92 (26%) | 29 (25%) | 63 (27%) | |

^aN(%); ^bmean ± standard deviation; ^ccomputed on available data; *probability of being newly treated
MS: Multiple Sclerosis; ARR: Annual Relapse Rate; EDSS: Expanded Disability Status Scale; DMD: disease-modifying drug; MRI: Magnetic Resonance Imaging; PP: post-partum
First line: interferon, glatiramer acetate, teriflunomide, dimethyl fumarate; Second line: natalizumab, fingolimod; Third line: mitoxantrone, alemtuzumab; Off-label: azathioprine, cyclophosphamide, laquinimod, methotrexate, mycophenolate mofetil, rituximab

Table 2: Variables included in the propensity score models for each outcome of the COPP-MS study

| Table 2. Variables included in the propensity score models for each outcome of the COPP-MS study | | | |
|--|--|---|---|
| Variables | Time to first relapse from delivery over two years | Time to first EDSS progression from delivery over two years | Time to first new MRI activity from delivery over two years |
| Year of pregnancy | 0.293 | 0.176 | 0.404 |
| Age at delivery | 0.998 | 0.448 | 0.360 |
| MS duration at delivery | 0.283 | 0.317 | 0.009 |
| ARR over the two years before pregnancy | 0.005 | 0.611 | 0.755 |
| Number of relapses during pregnancy | 0.021 | 0.356 | 0.057 |
| EDSS at pregnancy onset (±3 months) | 0.586 | 0.547 | 0.279 |
| MRI within the two years before pregnancy | 0.393 | 0.507 | 0.010 |
| Breastfeeding | 0.569 | 0.636 | 0.274 |
| DMD within the year before pregnancy | 0.243 | 0.787 | 0.001 |
| DMD exposure during pregnancy | 0.025 | 0.602 | 0.007 |

*bold p means <20% i.e. included in the propensity score corresponding to the outcome.
Note: for each outcome, a Cox model was built included the pool of variables potentially associated with the treatment decision. The table presents the p value relating to this association. A level of 20% was considered to decide if the variables was included in the propensity score model corresponding to the outcome.

FIGURE LEGENDS:

Figure 1: Flowchart of the study population.

RRMS: Relapsing-Remitting Multiple Sclerosis; OFSEP: Observatoire Français de la Sclérose en Plaques; TC: Treating Centers; NTC: Non-Treating Centers.

Figure 2: Mean annual relapse rate (main analysis)

2-years before, during and 2-years after pregnancy, computed by trimesters every 3 months in treating centers (TC) and non-treating centers (NTC).

Figure 3: Propensity score weighted Kaplan-Meier estimates of the time before reaching outcomes (main and secondary analysis).

A: first relapse, B: first EDSS progression, C: first new MRI activity, from delivery in treating (TC) and non-treating centers (NTC).

D: first relapse, E: first EDSS progression, F: First new MRI activity, from delivery for treated and untreated patients.

For all of the subfigures, the blue line represents the curve for the patients from the TC or the treated patients; the gray line represents the curve for the patients from the NTC of the untreated patients. The dotted lines represent the 95% confidence interval in each group according to the same color legend. The weighted number of at risk patients is indicated in blue for the patients from the TC/treated patients and in gray for the patients from the NTC/untreated patients. The p-value was computed using the propensity score weighted log-rank statistical test.

Figure 4: Restricted mean time before reaching outcomes (main and secondary analysis).

A: first relapse, B: first EDSS progression, C: first new MRI activity from delivery over six months, one year and two years of post-partum.

(1) Main analysis comparing treating centers (TC) to non-treating centers (NTC). (2)

Secondary analysis comparing treated patients to untreated patients,

For all of the subfigures, the blue bar represents RMST for patients from TC (main analysis, left column) or treated patients (secondary analysis, right column); the gray line represents the RMST for patients from NTC or the untreated patients. The difference of RMST is indicated in the table for each corresponding pair of bars.

Figure 1:

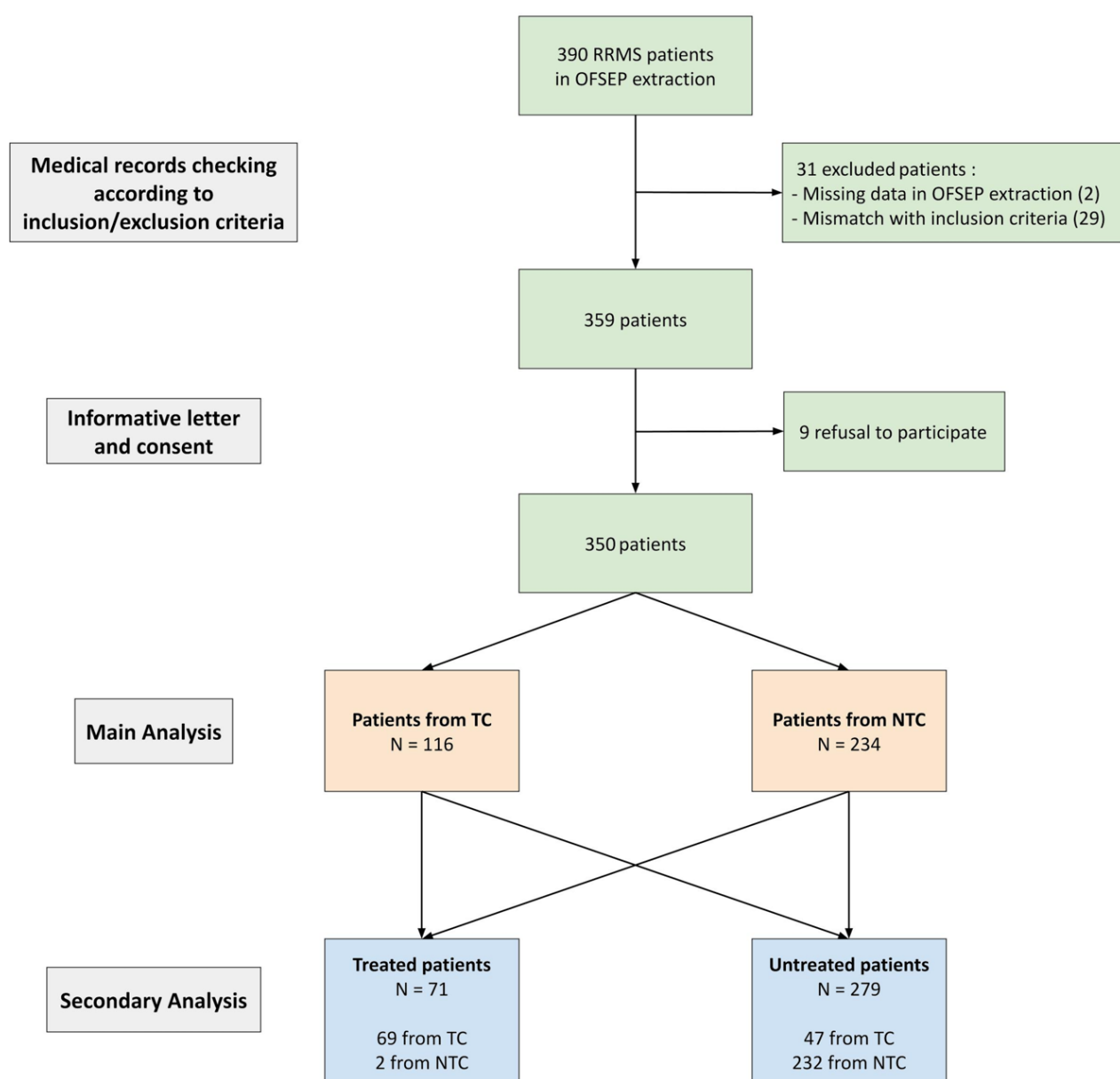
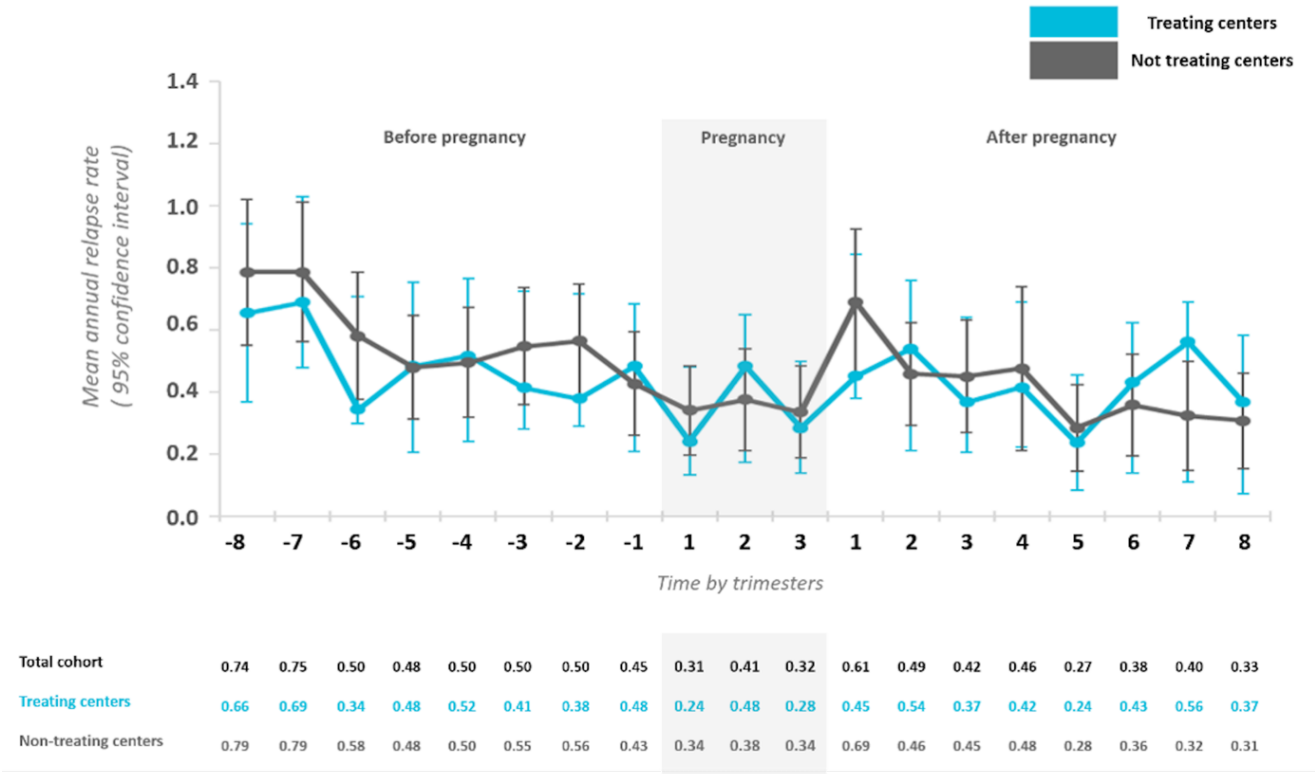
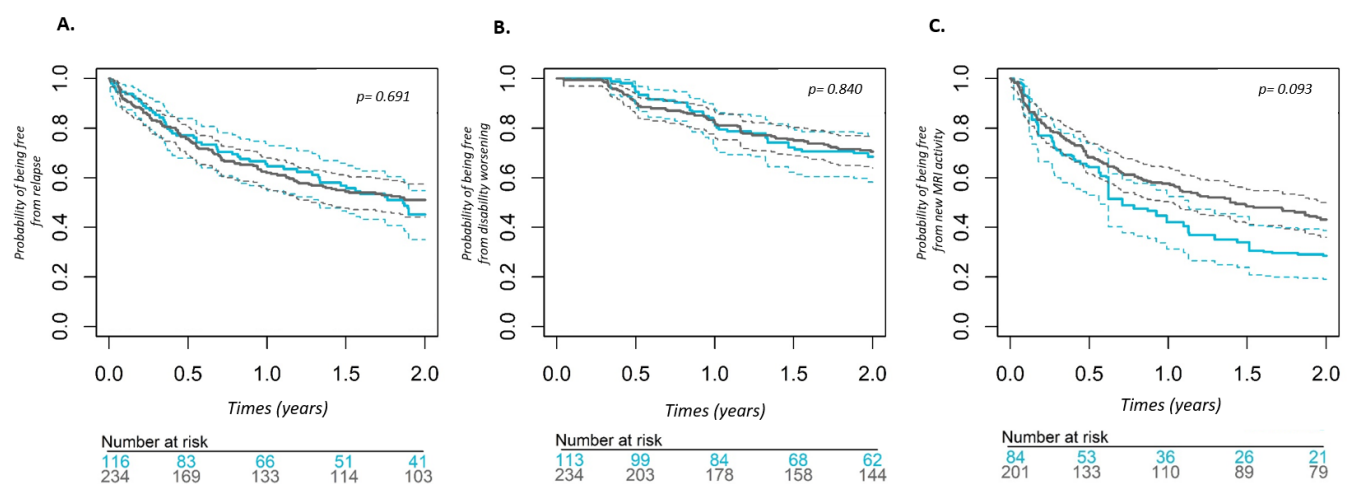


Figure 2:



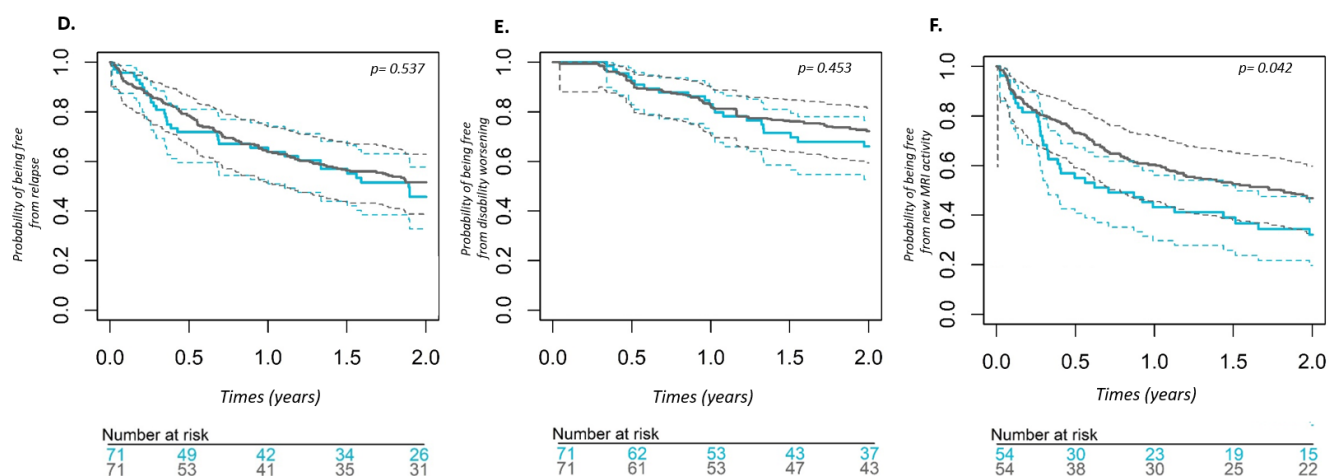
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Figure 3:



*Number at risk are weighted

■ Treating centers ■ Not treating centers



*Number at risk are weighted

■ Treated ■ Untreated

Figure 4:

