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ORIGINAL COMMUNICATION

Relapses and obstetric outcomes in women with multiple sclerosis planning pregnancy

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Abstract

Objective To evaluate the effect of discontinuation of different disease-modifying therapies (DMTs) before pregnancy with respect to the occurrence of relapses and pregnancy outcomes.

Methods Women with multiple sclerosis who desire to bear children were followed prospectively. Demographic data, clinical characteristics, and the information on the use of DMTs were collected. A multivariate analysis was used to assess the relationship between relapses and the prior use of different DMTs.

Results The present study assessed 75 consecutive pregnancy plans (66 women), 65 of which resulted in pregnancy. The mean age of the participants was 32.1 ± 4.2 years, and the mean disease duration was 6.1 ± 4.2 years. No relapses before pregnancy were reported in the group of women who maintained their DMT until pregnancy confirmation, while 14 relapses were reported in 12/42 women (29%) who discontinued DMT before pregnancy. During pregnancy, patients on natalizumab or fingolimod before pregnancy had a higher rate of relapses. Most women restarted their previous DMT after delivery within the first trimester. The relapse rate in postpartum was 0.07.

Conclusions Disease-modifying therapies received influences the risk of relapse and disease progression from women who are planning pregnancy. The risk of relapse during pregnancy was significantly higher in the group of women treated with natalizumab or fingolimod compared to the group of women treated with interferon beta or glatiramer acetate. The postpartum risk of relapses was lower than that found in previous reports.

Keywords Multiple sclerosis · Pregnancy · Relapse · Disability · Therapy · Disease-modifying treatment

Introduction

Women with multiple sclerosis (MS) considering pregnancy face a dilemma regarding their treatment. Since there are no drugs for MS completely safe for use during pregnancy; they must weigh the possible risks of exposing the unborn fetus to disease-modifying therapies (DMTs) against the maternal risk of relapses and disease progression if they discontinue DMT [1]. Women are often advised to discontinue DMT for MS prior to conception, since pregnancy has an immunomodulating effect on MS considered to be greater than that of any of the first-line DMTs [2]. However, there is increasing evidence of the risk of a rebound of disease activity after withdrawal of natalizumab or fingolimod for pregnancy planning [3–5].

In a large prospective study of the natural history of multiple sclerosis in pregnant women, the rate of relapse declined during pregnancy, particularly in the third trimester, and increased during the first 3 months postpartum before returning to the pre-pregnancy rate [6]. However, since 1995, MS has entered a 'treatment era': a growing number of drugs have emerged on the market, rendering it is necessary to evaluate the risk of relapse before, during, and after pregnancy in a population in which different DMTs are used [7].

Considering the fact that no prospective, randomized, double-blind clinical trial of the effect of DMT on pregnancy can be performed, the best evidence-based data can only be achieved via non-biased comprehensive observational

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studies [8, 9]. The present study sought to evaluate the effect of discontinuation of different DMTs before pregnancy with respect to the occurrence of relapses and pregnancy outcomes.

Methods

Study population

Our study was performed in two health areas in the province of Alicante, Marina Baixa and Alicante; both are situated in the southeast of Spain and contain a combined population of 500,000. Patients with MS were attended by MS clinics in both health areas. The healthcare system in Spain is universal and free to access.

Study design and participants

In this study, all women with MS and desire to attain motherhood were followed prospectively from the time of expressing pregnancy desire (basal visit). Information from the relapses and MRI lesions presented in the year preceding the basal visit was obtained from the patient's records. The patients underwent routine follow-up that included clinical visits at approximately 6-month intervals. Recruitment of the patients began in May 2009 and ended in June 2018. Only women with relapsing–remitting MS (RRMS) as defined by McDonald's diagnostic criteria were included [10]. Pregnancy planning was discussed considering the patient's condition, and updated information including the risk of relapses and the potential impact of the drugs on fetal outcomes were provided to the potential mothers; the ultimate decision concerning the time of discontinuing DMT was made by the patient.

Variables and measurements

A relapse was defined as a new or recurrent symptoms and objective typical findings of MS with a duration of at least 24 h in the absence of fever or infection [10]. All EDSS assessments were performed by trained and certified examiners (www.neurostatus.net). Disability progression was defined as an increase of at least 1 point between baseline EDSS and 6 months postpartum EDSS if the baseline EDSS was lower than 5.5 points and at least 0.5 points if the baseline EDSS was above of 5.5 points, or at least a rise of 1.5 points if baseline EDSS was 0 points [11].

Demographic data (age) and clinical characteristics (EDSS, disease duration, smoking or alcohol exposure during pregnancy, number of relapses in the preceding year and during pregnancy and postpartum, use of DMTs before and during pregnancy and the moment of its withdrawal before conception or after pregnancy confirmation) were collected from all patients. Smoking was defined as "not exposed" (no smoking during pregnancy) or "exposed" (smoking during pregnancy). Alcohol exposure was defined as "exposed" (any alcohol consumption during pregnancy) or "not exposed" (no alcohol consumption during pregnancy). MRI activity was assessed for the presence of new or newly enlarged lesions T2-weighted MRI or T1 Gd-enhancing lesions T1-weighted MRI. All newborns, as a part of routine care, were evaluated by a pediatrician. Low birth weight was defined as 2.499 g or less, regardless of gestational age [12].

Statistical analysis

Qualitative variables were reported as frequency (percentage) and were compared with Pearson's test in case of normal distribution. Quantitative variables were reported as mean ± SD and were compared with Student test or Mann–Whitney *U* depending on parametric or non-parametric conditions. To determine if there were differences in the relapse rate between the different lines of treatment, the number of relapses were considered as a Poisson distribution and log-linear models were estimated; with them, we also calculated the rate ratios, both raw and adjusted for possible confounding variables (washout period, age at which they began to desire pregnancy and disease duration). To determine the goodness-of-fit of the model, our results were compared with the null model through the likelihood ratio test. With the multivariate models, the relapse rate was estimated and then used in Cartesian graphics to help analyze the results. All calculations were performed with a statistical significance of 5% and for every relevant parameter, we calculated the confidence interval (CI) of 95%. The statistical package used was the IBM SPSS Statistics 25.

Standard protocol approvals, registrations, and patient consents

The institutional ethics committee of the Hospital Marina Baixa approved the study and all research was completed in accordance with the declaration of Helsinki guidelines for research practice. Informed consent was obtained from all patients.

Results

During the study period, 75 consecutive pregnancy plans (66 women) were assessed, 65 of which resulted in pregnancy (Fig. 1). The other ten pregnancy plans that did not result in pregnancy were from women who experienced relapses after discontinuing DMT and then stopped trying to get pregnant. One woman had an unintended pregnancy

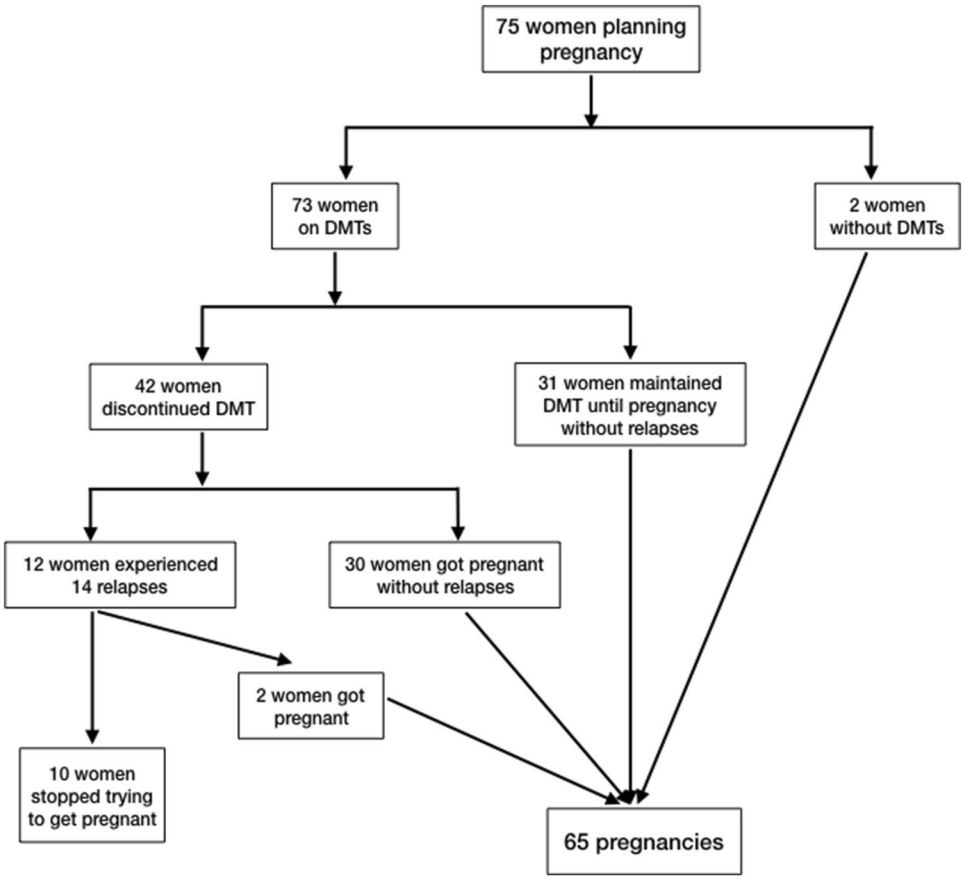

Fig. 1 Flow-chart of the women included in the study

under treatment with natalizumab and chose to abort and was not included in this study. The mean age of the study participants was 32.1 ± 4.2 years, the mean disease duration was 6.1 ± 4.2 years, and the mean basal EDSS was 1.2 ± 1. Seven relapses from seven women were reported in the year preceding the basal visit (annualized relapse rate: 0.09); six were treated with interferon beta (IFN-β) and one was treated with glatiramer acetate. Brain MRI in the year preceding the basal visit was available in 62/75 women (83%) and showed disease activity (new T2 lesions or Gd-T1 lesions) in 3 patients. Taking into account the treatment received by patients in the study, only 2/75 pregnancy plans were from women who did not receive DMTs, 42/73 (58%) were from women who discontinued DMT before pregnancy and 31/73 (42%) continued DMT until the confirmation of pregnancy. In the group of women who discontinued DMTs before pregnancy, 27 were treated with IFN-β (64%), 7 with fingolimod (17%), 4 with glatiramer acetate (10%), 2 with dimethyl fumarate (5%) and 2 with natalizumab (5%). In the group of women who continued DMT until the confirmation of pregnancy, 18 were treated with IFN-β (58%), 8 with natalizumab (26%), 3 with glatiramer acetate (10%) and 2 with rituximab (6%).

No relapses before pregnancy were reported in the group of women who maintained their DMT until pregnancy confirmation, while 14 relapses were reported in 12/42 women (29%) who discontinued DMT before conception ($p < 0.001$). Ten of the 12 women who experienced relapses after discontinuing DMT resumed their previous DMT. The mean washout time until pregnancy was 4.5 ± 3.5 months.

Most pregnancies (96.9%) occurred among the patients who were received DMT in the year before pregnancy. Only two women reported alcohol or tobacco use during pregnancy. Four women became pregnant with assisted reproduction techniques (6.2%). Women treated with fingolimod or natalizumab exhibited a longer disease duration than women who received IFN-β or glatiramer acetate (7.9 ± 4.1 vs 5 ± 3.4 years, $p = 0.01$); no significant differences in age or basal EDSS were observed between these two groups.

Six patients (9.2%) experienced 11 relapses during pregnancy, 3 patients received natalizumab, 2 patients received fingolimod and 1 patient received IFN-β. None of the patients with natalizumab or fingolimod experienced any relapse in the year preceding the basal visit. However, its relapse rate increased to 0.71 during pregnancy. The annualized relapse rate among patients who were treated with glatiramer acetate or IFN-β was 0.11 in the year preceding the basal visit and decreased to 0.02 during pregnancy. No relapse was reported in the 4 patients who became pregnant with assisted reproduction techniques. All relapses during

pregnancy after the first trimester were treated with IV methyl prednisolone (IVMP) of 500 mg or 1000 mg doses for 3–5 days, depending on the severity of relapse. Of the six women who experienced relapses during pregnancy, information about the EDSS 6 months after delivery was available for five patients, and disability progression was confirmed in four of the five patients. On the whole, EDSS data 6 months post-delivery was available for 55/59 patients; disability progression occurred in 2/50 patients without relapses and in 4/5 patients with relapses during pregnancy ($p < 0.001$).

During pregnancy, patients who were on natalizumab or fingolimod compared to those who were treated with IFN-β or glatiramer acetate, featured a higher relapse rate (rate ratio = 0.031, $p < 0.001$). After adjusting the results for the washout period, disease duration, and age at which pregnancy was desired, this relationship remained significant (rate ratio = 0.038, $p = 0.003$). The associations are presented in Fig. 2. In our series, three of seven women on fingolimod ceased their pregnancy attempts because of severe relapses; and two of the remaining four women who became pregnant experienced relapses during pregnancy with disability worsening.

There were 59 live newborns, one ectopic pregnancy and 5 spontaneous abortions. There was only one malformation; one infant, with in-utero exposure to IFN-β, was born with anal atresia and unilateral renal agenesis. One patient of our series became pregnant 1 month after rituximab infusion (500 mg); she did not experience any relapses or medical complications during pregnancy, and she delivered a term-healthy newborn. Cesarean sections were performed in 36% of the women. Mean birth weight was 3040 ± 659 g; there were nine newborns with low birth weight (15.3%). Birth weight in pregnancies exposed to DMTs did not differ significantly from pregnancies not exposed to DMTs ($p = 0.38$). Women exposed to DMTs were older than women not exposed to DMTs (33.5 years vs 31.2 years, $p = 0.02$).

With the exception of two women, all restarted their previous DMT after delivery: 36 within 1 month (61%) and 48 in the first trimester (81.4%). Women who suffered an abortion were not included in the post-partum analysis. Four patients experienced four relapses in the first trimester post-partum (relapse rate: 0.07); three of them had not restarted their DMT at the time of relapse.

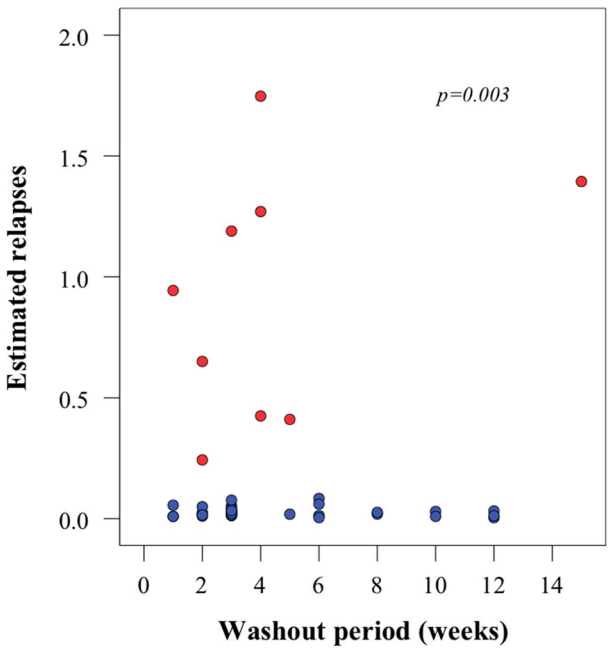

Fig. 2 Estimated relapses during pregnancy according to washout period and DMT. Legend: red, women receiving natalizumab/fingolimod; blue, women receiving interferon-beta/glatiramer acetates

Discussion

MS has little effect on pregnancy or fetal status and pregnancy does not increase the risk of relapses. However, in the treatment era, women should consider the risk of relapse and disease progression upon discontinuation of treatment depending on the DMT they receive for treatment. Our study shows the considerable influence of the type of DMT on the risk of relapses and disease progression of women who are planning pregnancy. The risk of relapse during pregnancy was significantly higher in the group of women treated with natalizumab or fingolimod relative to those who were treated with first-line injectable drugs.

The natural history of MS reveals a reduced risk of relapse during pregnancy. Recent data from an administrative claim database support this observation, but the use of DMTs before pregnancy was only 20% [13]; this contrasts with the 89.9% rate of use reported by a recent study from Kuwait [14] and the 97.3% rate of our series. The increase in the rate of relapses during pregnancy observed by both studies suggests that the formerly common knowledge regarding the reduced risk of relapses during pregnancy may not remain valid in the treatment era. The increase in relapse occurrence during pregnancy was mostly accounted for by patients who had received natalizumab and fingolimod prior to pregnancy; indeed, there are clinical evidences for a fingolimod rebound [3, 4, 15]. Since a 2-month washout period is mandatory to prevent teratogenicity, there is a risk of relapses even before pregnancy. In our series, only two of the seven women on fingolimod became pregnant without relapses before or during pregnancy. In the case of natalizumab, there are also clinical evidences for disease activity and disability progression during pregnancy due to its discontinuation [5]. Continuation of treatment until conception may thus be a

preferred strategy to prevent relapses before pregnancy but may not prevent relapses during pregnancy. In our series, two of the eight women who discontinued natalizumab after pregnancy confirmation suffered relapses during the second trimester as well as disability progression. Continuing natalizumab during pregnancy may better prevent relapses, but exposure to natalizumab during the third trimester is associated with a high incidence of hematologic alterations such as thrombocytopenia and anemia in the newborns [16].

Discontinuation of first-line injectable DMTs, glatiramer acetate, and IFN-β were associated with a 29% risk of relapse before achieving pregnancy. Considering that no safety concerns have been identified with glatiramer acetate and IFN-β, both DMTs can be safely administrated until pregnancy was confirmed to prevent early relapses before pregnancy [17, 18]. Rituximab, a monoclonal anti-CD20 antibody, is frequently used off-label for treating MS. The biological effect (B cell depletion) of rituximab is longer than its pharmacokinetic effect and theoretically could be used in women with MS who are planning a pregnancy [19]. Since its safety is not well known, effective contraception is advised by manufacturers during and for 12 months after treatment [20]. In a case series of 11 pregnancies in women with demyelinating diseases treated with rituximab within 6 months of conception, none of the patients experienced a relapse before conception or during pregnancy. All children were reported to be healthy at birth and remained healthy at follow-up [21]. One patient of our series became pregnant 1 month after the rituximab infusion (500 mg) and was followed prospectively; she did not experience any relapse or medical complications during pregnancy and delivered a term-healthy newborn. The available data provide some preliminary reassurance that rituximab may prevent relapses without evidence of major adverse effects during pregnancy, although more experience is needed to determine the safety of rituximab and other B cell-depleting agents, such as ocrelizumab, during pregnancy in women with MS.

Data from several studies confirmed an increase in the relapse risk during postpartum [13, 14, 22–24]; however, we did not observe a higher risk of relapses in the first trimester postpartum. There are several factors that may decrease this risk. Pre-conception DMT exposure and low relapse rates were independent protective factors against relapses in the postpartum [23]. There is some evidence that early DMT resumption may reduce the risk of postpartum relapses [24]. An Italian study reported that the proportion of women who resumed DMTs in the first month and the first trimester following delivery were 11% and 21.1%, respectively [24]; according to the aforementioned US database, these proportions were 8.3% and 12.9%, respectively [13]. In our series, these proportions were much higher, 61% and 81.4%, respectively. The high pre-conception DMT exposure and early DMT resumption in our series might account for the low relapse rate in postpartum.

Our study is subject to the limitation of a reduced number of patients receiving different DMTs. Most of the women in our study received DMTs before pregnancy, which may limit the generalizability of our findings to women who do not receive DMTs. On the other hand, the study was conducted in a general hospital with universal healthcare access, eliminating the bias of a tertiary center or non-uniform access to healthcare or DMTs. In addition, this study featured a high proportion of women with early resumption of DMT postpartum.

The findings of this study suggest that women with multiple sclerosis should not stop treatment with glatiramer acetate or interferon before pregnancy, and that early resumption of DMT may prevent postpartum relapses. Women receiving natalizumab or fingolimod who plan pregnancy represent a high-risk population; the management of their condition, therefore, warrants more careful evaluation.

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Compliance with ethical standards

Conflicts of interest Leticia Berenguer-Ruiz has received personal compensation for consulting, serving on a scientific advisory board or speaking with Almirall, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis and Teva. Juana Gimenez-Martinez has received speaker honoraria from Almirall, Biogen Idec and Sanofi-Aventis. Antonio Palazón-Bru reports no disclosures. Angel P. Sempere has received personal compensation for consulting, serving on a scientific advisory board or speaking with Almirall, Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Roche, Sanofi-Aventis and Teva.

Ethical standard The authors confirm that this article complies with ethical standards.

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