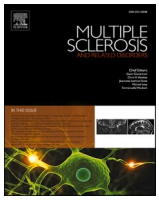
Multiple Sclerosis and Related Disorders 48 (2021) 102682

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Pregnancy outcomes in women with Multiple Sclerosis

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ARTICLE INFO

Keywords:
Pregnancy
Pregnancy outcomes
Multiple Sclerosis

ABSTRACT

Introduction: Women represent two-thirds of the MS population and are usually diagnosed during childbearing age. Collection of local information about pregnancy outcomes is fundamental to support individual decision-making.

Objective: To explore the trends in pregnancy decision making and pregnancy outcomes before (PreMS) and after (PostMS) MS diagnosis.

Methods: We developed a questionnaire for retrospective assessment of pregnancy outcomes in PreMS and PostMS patients under regular care at the Programa de Esclerosis Multiple UC in Chile.

Results: From the 218 women who responded to the questionnaire, 67 women did not have pregnancies. The total number of pregnancies registered was 299, 223 were PreMS (97 women, mean 2.5 ± 1.3 per/woman), and 76 PostMS (59 women, mean 1.9 ± 1.1 per/woman, $p = 0.003$). Mean age at first pregnancy was 27.6 ± 6.2 in PreMS, and 32.6 ± 4.6 years in PostMS women ($p < 0.001$). Significant differences between PreMS and PostMS pregnancy outcomes were cesarean section (37% vs. 66%; OR 2.74 95%CI(1.5-52), p=0.002), suspected relapse during 6 months after birth (7% vs. 18%, $p<0.001$), and breastfeeding (83% vs 67%, p=0.005). Gestational age, weight/size at birth, were not different between groups. Major malformations were observed similarly in both groups.

Conclusions: Changes in pregnancy decision-making after MS diagnosis occur, having fewer children and at an older age. It also changes obstetrician decisions for cesarean sections, with a 3 fold increase. Regarding newborn outcomes, there were no differences between groups.

Introduction

Multiple sclerosis (MS) is three times more common in women than men (Houtchens et al., 2018). The clinical average age of onset is about 30 years old (Alroughani et al., 2016), which implies a substantial and growing burden among women in childbearing age. The increased MS risk in women suggests differences in the immune system or central nervous system between women and men, which may be caused by genetic dissimilarities, sex hormones, and environmental exposures (Filippi et al., 2018). Non-hormonal factors may include smoking, history of Epstein-Barr virus infection, vitamin D deficiency, high body mass index, and high sodium intake (Belbasis et al., 2015; Kavak et al., 2015; Fitzgerald et al., 2017), among others. Considering the hormonal factor, a recent study from Zuluaga et al. (2019) demonstrates that menarche, pregnancies, and breastfeeding did not substantially modify the risk of MS or disability accrual using a multivariable and time-dependent approach (Zuluaga et al., 2019).

Family planning is a major life event in a woman with MS, because of the risk of future physical and cognitive disability, and the social burden imposed on their partner and their children (Moberg et al., 2019; Confavreux et al., 1998). From the perspective of the treating neurologist, an added complication is managing the disease-modifying therapies (DMTs) carefully in relation to family planning, pregnancy outcomes and the postpartum period (Confavreux et al., 1998). Therefore, it is necessary to develop evidence to support patients and their families decision-making.

Pregnancy outcomes of women with MS have been evaluated in several studies, however, there is no information in Chilean patients. Our objective was to conduct a retrospective study assessing the pregnancy outcomes in patients before (PreMS) or after MS (PostMS)

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https://doi.org/10.1016/j.msard.2020.102682
Received 24 September 2020; Received in revised form 23 November 2020; Accepted 6 December 2020
Available online 9 December 2020

diagnosis, and in patients PostMS with or without DMT.

2.-METHODS

2.1. Study design

We conducted a retrospective study based on the prospectively collected database of patients under regular care at the Programa de Esclerosis Múltiple UC between 2008 and April 2018. We developed a questionnaire for the retrospective assessment of pregnancy outcomes in PreMS and PostMS diagnosis patients. After an extensive review of the literature (Jesus-Ribeiro et al., 2017; Fong et al., 2018; Houtchens et al., 2018; Amato et al., 2017; Portaccio et al., 2018; Sandberg-Wollheim et al., 2018), a questionnaire consisting of 23 questions including characteristics of the patient, treatment during conception, pregnancy outcomes, and the disease evolution through the pregnancy was developed (Supplementary Material 1). A phone-call was performed in order to fill out the questions, and clinical data were obtained from the prospective database.

This study was performed with the approval of the Ethics Committee of Pontificia Universidad Católica de Chile and all patients signed written informed consent.

2.2. Statistical analysis

Descriptive statistics were obtained for the demographic, clinical, and specific reproductive information (i.e. pregnancies, and breast-feeding), baseline characteristics were reported as frequency (%), mean ± standard deviation (SD), median ± range, odds ratio ± confidence interval (CI). Comparisons between groups were performed with the Chi-square or Fisher's Exact test (differences between categorical variables), Student's t-test (continuous variables when normally distributed), and Mann-Whitney U test (non-normally distributed continuous variables) when appropriate. For matched samples, the Wilcoxon test was used. A multivariate binary logistic regression was used to assess the risk for cesarean section. For statistical analysis IBM SPSS Statistics 21 was used, P values <0.05 were considered statically significant.

Results

From a total of 663 patients with MS recorded in the database, there was a female to male ratio of 1.5: 1 (433 women). There were 223 women in regular control at the MS program (at least twice a year), and 218 of them agreed to participate in a survey, and respond to the questionnaire (Fig. 1). No statistically significant differences were observed between respondent and non-respondent patients, except for disease duration (respondent 8.4±5.4 years vs. non-respondent 11.5±7.7 years, $p<0.001$) (Supplementary Material 2: Table 1).

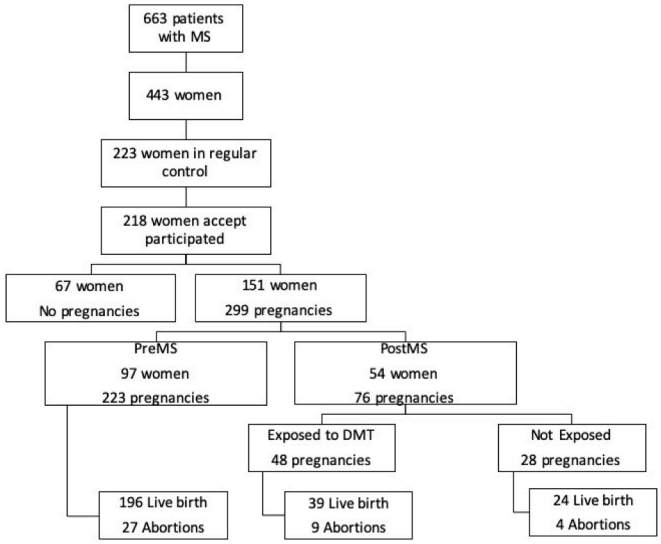

Fig. 1. Flowchart of included and excluded patients

Patients characteristic

The survey showed that 151 women had pregnancies, and a total of 299 pregnancies outcomes were registered. No statistically significant differences were observed between respondent women with or without pregnancies, except for current age (women with pregnancies 45.2±11.4 years. vs women without pregnancies 36.9±9.7 years, $p<0.001$) (Supplementary Material 2: Table 2). PreMS patients were significantly older at MS diagnosis compared to postMS (preMS 40.6±8.7 years vs 28.7±5.5 in PostMS, $p<0.001$). Demographic and clinical characteristics of PreMS and PostMS women are shown in Table 1.

Pregnancy trends of included patients

PostMS patients had significantly fewer pregnancies (54 women with 76 pregnancies, mean 1.9 ± 1.1 pregnancies/woman,) compared to PreMS patients (97 women with 223 pregnancies, mean 2.5 ± 1.3 Pregnancies /woman), ($p = 0.003$). PostMS patients were significantly older than the PreMS patients at the first pregnancy (mean age at pregnancy was 27.6 ± 6.2 years for the PreMS patients, and 32.6 ± 4.6

Table 1
Demographic and clinical characteristics of included patients

	PreMS	PostMS	OR 95% (CI)	*p value*
Patients N	97	54		
Current age years mean (± SD)	49.6 (±10.4)	37.1 (±7.39)		p<0.001
Age at diagnosis years mean (± SD)	40.6 (±8.75)	28.7 (±5.5)		p<0.001
Age at pregnancy, years mean (± SD)	27.6 (±6.2)	32.6 (±4.6)		p<0.001
Disease duration at pregnancy, years mean (± SD)		4 (±3.6)		
Pregnancies N	223	76		
Mean Pg/woman (± SD)	2.5±1.3	1.9±1.1		p=0.003
Median (range)	2 (1-8)	2 (1-6)		p=0.019
Treatment at pregnancy N(%)				
-No treatment		28 (36.84)		
-IFNβ		28 (36.84)		
-Glatiramer Acetate		9 (11.84)		
-Teriflunomide		3 (3.95)		
-Natalizumab		1 (1.32)		
-Fingolimod		1 (1.32)		
-Rituximab		6 (7.89)		
Current EDSS Median (range)	2 (0-7.5)	1 (0-7.5)	2.32 (0.9-5.9)	p=0.069
0-3 N (%)	66 (68)	44 (81.5)		
3.5-6 N (%)	16 (16.5)	3 (5.5)		
>6 N (%)	7 (7.2)	4 (7.4)		
unknown	8 (8.2)	3 (5.5)		
Current MS Phenotype N(%)			2.545 (0.9-7.2)	p=0.072
-CIS	2 (2)	2 (3.7)		
-RR	75 (77.3)	47 (87)		
-SP	13 (13)	5 (9.3)		
-PP	6 (6)	0 (0)		

EDSS: Expanded disability Status Scale, Pg: Pregnancies, CIS: clinical isolated syndrome, RR: relapsin-remitting, SP: secundary progressive, PP: primary progressive. N: Number, %: Percentage, SD: Standard deviations,OR: Odds ratio, CI: confidence interval Mann Whitney, Chi square

years for the PostMS) ($p < 0.001$), with a mean disease duration at the pregnancy of 4 ± 3.6 years in the PostMS patient. From this cohort, 10 women had pregnancies both pre and post MS diagnosis, while 87 women had only preMS pregnancies, and 44 had only pregnancies post MS.

Three patients were exposed to assisted reproductive therapy; 1 PreMS patient and 2 PostMS patients. Only one PostMS patient reported the name and the type of assisted reproductive therapy (Recombinant follicle-stimulating hormone Puregon®).

Disease Modifying Treatment and pregnancy

From the 76 pregnancies conceived after MS diagnosis, 28 (36.84%) women were not receiving any disease-modifying treatment, 28 (36.84 %) were receiving interferon beta (IFNβ), 9 (11.84%) glatiramer acetate, 3 (3.95%) teriflunomide, 1 (1.32%) natalizumab, 1 (1.32%) fingolimod, and 6 (7.89%) with rituximab. All patients discontinued DMT by the time of pregnancy diagnosis (first missed period/positive pregnancy test). No reliable information about DMT exposure before pregnancy was obtained. The patient receiving teriflunomide performed accelerated elimination with cholestyramine according to current guidelines (Table 1).

Obstetrical information and pregnancy outcomes

Reported deliveries outcomes showed only a significant difference in the delivery type between preMS and postMS patients. From 259 full term delivered, pregnancy outcomes of PreMS and PostMS respectively: Newborns 196 (88%) vs 63 (83%). Spontaneous abortions were observed in 40 pregnancies, 27 (12%) in preMS patients vs 13 (17%) (p=0.27) in postMs patients. Vaginal delivery was observed in 124 (63%) vs 22 (34%); cesarean section was observed in 72 (37%) of the preMS patients vs 41 (66%) of PostMS patients (OR 3.2 95%CI(1.8-5.9, p<0.001). In the binary logistic regression adjusting for age at pregnancy, this increased risk was still statistically significant (OR 2.74 95% CI(1.45-5.18) p=0.002) (Table 2). When assessing risk for cesarean section in each group, age at pregnancy was associated with a slightly higher probability of cesarean section in preMS women (OR 1.06 95%CI (1.0-1.12) p=0.041) but not in postMS (OR 0.99 85%CI(0.89-1.12) p=0.99). While in the postMS group, disease duration at pregnancy was associated with a slightly higher probability of cesarean section (OR 1.33 95%CI(1.05-1.70) p=0.02) adjusted for age at pregnancy and treatment (no EDSS at pregnancy was reliably obtainable). Emergency cesarean section was observed in 15 (7%) of PreMS patients versus 10 (13%) in PostMS patients (Supplementary Material 2: Table 3).

Table 2
Obstetrical data of included patients

Delivery outcomes	PreMS (223)	PostMS (76)	OR 95% (CI)	*p value*
Newborns N (%)	196 (88)	63 (83)	0.66 (0.3-1.4)	p=0.269
Vaginal delivery	124 (63)	22 (35)	3.2 (1.8-5.9)	p<0.001
			2.74 (1.5-5.2)	p=0.002[b]
Cesarean section[a]	72 (37)	41 (65)		
Gestational age weeks median (range)	38 (25-42)	38 (25-40)		p=0.372
Birth weight gr median (range)	3400 (750-4800)	3345(750-4485)	p=0.91	
Birth height cm median (range)	50 (30-56)	49 (30-53)		p=0.051
Major malformation N (%)	5 (2.6)	1 (2)	0.66 (0.3-1.4)	
Abortion n (%)	27 (12)	13 (17)	0.66 (0.3-1.4)	p=0.27
Disease course pregnancy-postpartum				
-Relapses during Pg N (%)	7 (4)	3 (5)	0.95 (0.2-3.9)	p=0.006
-Relapse 6 month after birth N (%)	13 (7)	14 (18.4)	0.27 (0.1-0.6)	p<0.001
-Breastfeeding (%)	163 (83)	42 (67)	2.59 (1.4-4.9)	p=0.005

N: Number, %: Percentage, SD: Standard deviations,OR: Odds ratio, CI: confidence interval Mann Whitney, Chi square. [a]Patients with an indication for cesarean section because of two previous interventions were excluded from this analysis.[b]Binary logistic regression adjusted for age at pregnancy.

Median gestational age was 38 (25-42) weeks in patients PreMS, 38 (25-40) weeks in patients PostMS; median birth weight was 3400 (750-4800) grams in newborns of PreMS patients vs 3345 (750-4485) grams in newborns of PostMS patients; the median birth length was 50 (30-56) cm in newborns of PreMS patients vs 49 (30-53) cm in newborns of PostMS patient. Furthermore, there was no significant difference in the number of spontaneous abortions between groups (p=0.27) (Table 2). The frequency of complications during pregnancy was similar in both groups (10%). Details of reported complications is shown in Supplementary Material 2: Table 4.

Disease course during pregnancy, postpartum and breastfeeding

There were 7 (4%) of suspected relapse *during pregnancy* in PreMS patients vs 3 (5%) in PostMS patients (p=0.006), none of them was receiving DMT before or during pregnancy, and 2 received corticosteroids.

There was a suspected relapse *during 6 months after birth* in 13 (7%) of PreMS patients vs. 14 (18%) in PostMS patients ($p < 0.001$) (Table 2). From the PostMS patients, 8 received corticosteroids, of which 3 were receiving glatiramer acetate until pregnancy and 1 was receiving fingolimod until pregnancy. One patient was previously on interferon beta 1a IM and received immunoglobulin for her relapse, 1 resumed natalizumab and one resumed rituximab.

The group of PreMS report 83% of breastfeeding vs 67% in the PostMSgroup (p=0.005). All patients that had a relapse during postpartum were breastfeeding and not receiving DMT. After the relapse, they suspended breastfeeding, and started DMT, except for 2 patients who did not start immunomodulatory treatment.

Discussion

In this retrospective questionnaire-based study, we found that women after MS diagnosis have fewer pregnancies, at an older age, and have a 3-fold risk of being performed a C-Section compared to women that conceived before MS diagnosis. Also, a lower frequency of breastfeeding is seen after MS diagnosis.

Previously to the Pregnancy in Multiple Sclerosis (PRIMS) study conducted by Confavreux in 1998 which showed no long-term adverse effects from pregnancy on the course of MS, women with MS were advised by physicians not to have children due to the concern of worsening their MS disease course (Zuluaga et al., 2019; Moberg et al., 2019; Confavreux et al., 1998; Fabian et al., 2016; Langer-Gould et al., 2019). This recommendation is still a common practice for neurologists not specialized in MS, and evidence-based information is needed in order to improve counseling regarding pregnancy.

Information about the impact of MS on pregnancy outcomes includes that the rate of spontaneous abortions and ectopic pregnancies among women with MS seems similar to the general population (Moberg et al., 2019; Van Der Walt et al., 2019). The study from Roux et al, showed a similar rate of spontaneous pregnancies per woman, time to pregnancy, and spontaneous miscarriage rates compared with the general population (Roux et al., 2015). However, in the same cohort, the mean number of children per woman was lower in the group with MS (1.33 children per woman) compared with the general population (1.99 children per woman) (Roux et al., 2015). A similar result was published in the Danish

population where women with MS had fewer children with an incidence rate ratio of 0.63 than matched reference women (Moberg et al., 2019). These results were consistent with what was observed in our cohort where postMS women presented with a statistically significant lower number of pregnancies per woman compared with preMS. When evaluating the perspective of the patients in a Canadian survey regarding the choice of parenthood after a diagnosis of MS, 72.5% of Canadian pwMS and 75.2% of American pwMS responded that they had no preference about having any/more children (Alwan et al., 2013). This preference was reported even in a time when DMTs were available for most of the respondents since the survey was conducted in 2007–2008 (Sandberg-Wollheim et al., 2018) (Portaccio et al., 2018). Furthermore, the rates of pregnancies in the women with MS in the United States has increased from 2006 to 2014 from 7.91% to 9.47%, while the rate of women without MS decreased from 8.83% to 7.75% (Houtchens et al., 2018).

Considering age, postMS women had their children at 33 years old, and the fecundity rate in 2016 in Chile was 1.7, while preMS women had their children at 28 years old, and fecundity rate in 1998 was 2.17 (Instituto Nacional de Estadísticas, 2018; GUIA PERINATAL, 2015). We propose that the number of pregnancies per woman could be also explained by social epoch, and not by the disease itself.

PostMS patients were older by the time of their first child compared to preMS patients, this finding is consistent with other previous research of Houtchens et al, where the average of the first pregnancy in PostMS was 32.6 (±4.6) years old compared with 27.6 (±6.2) years in preMS (Houtchens et al., 2018). Concerns about the family, neurologic symptoms, issues regarding the appropriate time to discontinue DMT, and the need to stabilize a newly diagnosed patient can all delay pregnancy in women with MS (Houtchens et al., 2018; Amato et al., 2017; Bove et al., 2014). In this cohort, PostMS patients had a mean disease duration at the pregnancy of 4 ±3.6 years, and most with accepted treatment or with suspended treatment in search of becoming pregnant.

In our cohort, the mean age at diagnosis of MS was 41 years in PreMS, and 29 in PostMS ($p < 0.001$). The retrospective cohort study from Nguyen et al. (2020) showed that women with previous pregnancies and childbirths had a later onset CIS compared with women who had never been pregnant and those who had never given birth with a delayed time to CIS by a median of 3.3 years in women with pregnancies and 3.4 years in women with previous childbirths (Nguyen et al., 2020). The study from Zuluaga et al (2019) showed a similar result where the mean age from diagnosis in preMS women was 37 years compared with 27 years in postMS women. Their univariate analysis revealed that pregnancy prior to the clinically isolated syndrome was protective for MS diagnosis, however, this effect was lost in the multivariate analysis when adjusting for age at clinically isolated syndrome, topography, oligoclonal bands, imaging and disease modifying treatment (Zuluaga et al., 2019), as a reflection in the change in the diagnostic criteria in recent years and the increasing incorporation of paraclinical assessments, especially the magnetic resonance, to supplement clinical findings allowing an earlier, more specific, and more sensitive diagnosis.

A relevant finding in our study was the number of births by caesarean section, although it is described in the literature that patients diagnosed with MS have a greater chance of having a cesarean delivery. Gianini et al. describe 45% of deliveries by caesarean section, while in our study there were 66 % of patients with cesarean delivery which is higher than described in the literature, and higher compared to the group of PreMS patients and to the Chilean registry (25-40%) (GUIA PERINATAL, 2015). This is an important finding to evaluate recommendations made and the possible risks involved in cesarean delivery without obvious clinical indication (Giannini et al., 2012).

Women with MS are twice as likely to be re-hospitalized 3 months after delivery compared with women without MS (Kelly et al., 2009). Also, MS it's been shown to be associated with mildly increased odds of antenatal hospitalization, intrauterine growth restriction, and cesarean delivery (Houtchens et al., 2018). Fong et al. (2018) used 2001–2009 hospital discharge data from California and found that rates of urinary tract infection, cesarean delivery, and induction of labour were slightly increased in patients with MS; however, antepartum and peripartum morbidities were not increased (Fong et al., 2018).The study of Nguyen et al. 2019, shows a higher number of induced abortions on FDA pregnancy class C/D drugs compared with pregnancy class B and no DMT ($p=0.010$); but no differences in spontaneous abortions, term or preterm births (Nguyen et al., 2019).

As mentioned above, previous studies show a rate of spontaneous abortions and ectopic pregnancies among women with MS seems to be comparable with that of the general population (Houtchens et al., 2018; Mueller et al., 2002). We found similar rates regarding spontaneous abortions and ectopic pregnancies when comparing women with PreMS with PostMS. These findings are supported by other studies, even when the mother and fetus might have been exposed to DMT, for example, IFNβ, glatiramer acetate, in our cohort the number of pregnancies with other DMT treatments is too small to make any conclusion. The frequency of spontaneous abortion is difficult to specify in the general population. It is estimated that approximately 15% of clinical pregnancies end in spontaneous abortion, however, if subclinical pregnancies are considered, the frequency of spontaneous abortion ranges from 30-50% of gestations (Donoso S et al., 2016). These was important to our group of patients because the group PreMS have a 12% of spontaneous abortions, but the group PostMS have a 17%. This difference might be explained because of the use of DMT or because of the rigorous clinical control in patients of childbearing age in search of the option of pregnancy. The anthropometric parameters of the newborns from PreMS and PostMS were in the range of Chilean statistics of anthropometric curves. A similar result with respect major malformations were observed in both groups 5 (3%) vs 1 (2%), and compared to the prevalence of congenital malformation in Chilean newborns (Nazer et al., 2014).

Increased frequency of postpartum relapse in this cohort may be explained because of recall bias in previously undiagnosed patients. The short-term effect of pregnancy has been studied previously; results demonstrate that relapse risk decreases during pregnancy, but increases during the postpartum period due to hormonal changes occurring during these periods (Tisovic et al., 2019). However, the role of pregnancy and breastfeeding in the long- term prognosis of MS remains controversial (Zuluaga et al., 2019).

In our study, we found statistical differences in breastfeeding between PreMS and PostMS groups. The group of PreMS patients 83% report breastfeeding vs 67% patients in the PostMS group ($p=0.005$). This could be associated with the divergent evidence regarding breastfeeding and the risk of postpartum relapses. With some studies suggesting that breastfeeding modestly reduces the risk of postpartum relapses (Zuluaga et al., 2019; Hellwig et al., 2015), nevertheless, other studies have reported that relapse rates before or during pregnancy were the main factors that determined the risk of relapse during the postpartum period (Portaccio et al., 2011). In this context, our group suggests that patients with highly active disease start DMT early after postpartum (only 1-3 months of breastfeeding), while in patients with low disease activity and platform treatments before pregnancy (such as interferon beta or glatiramer acetate), are encouraged to breastfeed for 6 months. Decisions about treatment maintenance, especially with interferon beta and glatiramer acetate during pregnancy and breastfeeding according to recent changes in labelling, probably will be incorporated as the evidence continues to show that this is a safe recommendation.

Our study has several limitations including the small sample size, single-centre study, and retrospective collection of data regarding pregnancy outcomes, so we cannot exclude recall bias in reporting data. As this was a retrospective questionnaire and not all patients were pregnant during their clinical follow-up in our center, unfortunately we do not have reliable information about the duration of DMT exposure before pregnancy, or a reliable EDSS by the time of pregnancy.

Conclusions

Changes in pregnancy decision-making after MS diagnosis occur, having fewer children and at an older age, and with a lower rate of breastfeeding. Although this finding could be associated with generational trends, a 3-fold increase in cesarean section might reflect the need for more education not only for neurologists, but also including the obstetrical care team, patients and families.

More evidence is needed in order to support decision-making and to improve the care of women with MS who are of childbearing age

Author contribution

Category 1 Conception and design of study: Bernardita Soler, Ethel Ciampi, Reinaldo Uribe-San-Martín, Claudia Cárcamo

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Declaration Of Conflicting Interest

EC received the ECTRIMS Clinical Fellowship (2013-2014), ECTRIMS travel grant awards, and academic travel support from Novartis, Genzyme, Merck, Biogen and Roche, has been a member of advisory boards at Genzyme, Biogen, Merck and Novartis, has received sub-investigator fees from the ISS “Social Cognition in MS” project at Teva.

RUSM received academic travel support from Novartis, Genzyme, Merck, Biogen and

Roche, has been a member of advisory boards at Genzyme, Biogen, Merck and Novartis.

BS received academic travel support from Novartis, Teva, Merck and Biogen

RF received academic travel support from Genzyme, Biogen, Merck, Novartis, Roche, Teva and speaker compensations from Teva and Biogen.

CC received academic travel support from Novartis, Genzyme, Merck, Biogen and Roche, has been a member of advisory boards at Genzyme, Biogen, Merck and Novartis, has received PI fees from the ISS “Social Cognition in MS” project at Teva.

Acknowledgements

All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgements and have given us their written permission to be named. If we have not included an Acknowledgements, then that indicates that we have not received substantial contributions from non-authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102682.

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