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Podcast

Investigation of pregnancy tendency, reproductive characteristics, and disability in women with multiple sclerosis: A secondary data analysis of the national registry in Iran

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Keywords
Multiple Sclerosis; Pregnancy; Parity; Abortion; Disability; Iran

Abstract

Background: Multiple sclerosis (MS) predominantly affects women of childbearing age, significantly impacting their quality of life (QOL).

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The diagnosis of MS can influence pregnancy intention, and the level of disability associated with MS may change before and after pregnancy. This study aims to analyze the reproductive characteristics of Iranian female patients with MS (PwMS) and their association with the Expanded Disability Status Scale (EDSS) and pregnancy tendency, providing valuable insights into disease progression and the development of tailored treatments.

Methods: A cross-sectional study was conducted using data from the nationwide MS registry of Iran (NMSRI) from 2018 to 2021. Patients without a documented history of pregnancy, MS type, or EDSS score were excluded from the study. Various statistical methods, including nonparametric tests, the generalized estimating equation (GEE) model, and multiple logistic regression, were employed to analyze the data.

Results: The study included 1120 PwMS with a median diagnostic age of 31 and a disease duration of 6 years. The majority had relapsing-remitting MS (RRMS) and the mean EDSS score at bassline was 1.5 ± 1.4. A history of pregnancy or abortion was associated with higher EDSS scores. Multiparity before MS diagnosis was linked to EDSS score ≥ 5, while this EDSS range was associated with decreased parity after MS diagnosis (all P-values < 0.05).

Conclusion: Pregnancy and parity can affect the disability in female PwMS irrespective of clinical symptoms, diagnosis age, and MS type. Moreover, the chance of parity may be affected by a higher disability score, which should be considered in the clinical setting.

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disease that also affects women of reproductive age, especially in the third and fourth decades of life.[1] In Iran, the incidence and prevalence of MS in 2017 were 2.4 and 69.5 per 100000, respectively, with an increasing trend over the past 20 years.[2,3] In fact, the disease prevalence in the capital city of Tehran, Iran, is now believed to be as high as world's most prevalent countries having reached a record of 194.62 per 100000 in 2021.[4] The disease is associated with progressive disability in affected individuals when inflammatory activity is high, significantly affecting patients' lifestyles.[5-7] With the approval of disease-modifying therapies (DMTs), there is an opportunity to reduce inflammatory activity, and thus relapse rate and disability of patients with MS (PwMS).[8]

MS has been shown to have no significant impact on woman's fertility compared with the general population, although it may influence the decision to become pregnant due to fear of unexpected consequences.[9] Moreover, since various DMTs are not suitable for use during pregnancy, there is a need to individualize treatment decisions to ensure safe pregnancy in women of childbearing potential.[10] This issue is associated with some changes in the disability level of patients and may correlate with the number of pregnancies.[11] On the other hand, hormonal changes during pregnancy have been found to alter relapse rates and disability in women with MS.[12]

Some studies suggest that the diagnosis of MS may alter the pregnancy tendency resulted from the disability or consuming DMTs.[9,11] In addition, the prevalence of parity or abortion in female PwMS may be different after diagnosis of MS.[9,11] Therefore, we have designed this study to assess the reproductive characteristics (i.e., pregnancy, parity and abortion history, and type of delivery), their trends, and their relationship with disability in female PwMS registered in the nationwide MS registry of Iran (NMSRI).

This study could contribute valuable knowledge to understand the complex nature of the disease. By identifying factors that influence the course of the disease and its progression, such studies can lead to the development of tailored outcome measures, improved access to reproductive health care, informed decision making, reduced disparities in sexual and reproductive health services, and policy and clinical implications that benefit this patient population. Furthermore, this research can contribute to the development of new treatments by understanding disease progression, developing tailored management strategies, improving patient care, informing drug development, and addressing unmet medical needs.[13-15]

Materials and Methods

Study design: This population-based, cross-sectional secondary data analysis was performed using the data of clinically confirmed PwMS registered by NMSRI between December 8, 2018 and October 10, 2021.[16] The NMSRI was launched in 2018 to collect epidemiological and clinical information on PwMS by collecting patient data with the aid of two main questionnaires. While the first one is used in clinics and solely covers the minimum data set,[17] the second one is filled in the MS societies and includes not only the items in the first questionnaire, but also MS risk factors including reproductive characteristics.[18] Among the provinces of Iran that have entered the NMSRI

so far, 9 provinces including Khuzestan, Isfahan, Mazandaran, Guilan, Markazi, Chaharmahal and Bakhtiyari, Kerman, Qom, and Qazvin register the data obtained from the MS societies questionnaires in the System.[19] Experienced neurologists confirm MS diagnosis for all cases using the 2017 McDonald criteria.[20] Meanwhile, continuous training sessions and workshops, online available guidelines and executive committee, and timely response to technical obstacles help the registered data to be consistent throughout the country.[19] Maximum coverage and completeness of patient information are the most important features of our registry.[16] The methodological aspects of NMSRI have been mentioned in detail.[16,18]

Study population: The target population of the current study included all female PwMS registered in MS societies in the aforementioned nine provinces of Iran. The inclusion criteria were defined as registered women with confirmed MS diagnosis according to the 2017 revisions of McDonald diagnostic criteria. Patients without a documented history of pregnancy, MS type, or Expanded Disability Status Scale (EDSS) score were excluded from the study. Furthermore, due to the religious and cultural context of our country, individuals without a history of official marriage were not considered for the study. This is because in our Iranian Muslim population, it is customary to conceive children only after getting married. Our expert panel in the research and treatment team established a threshold for EDSS scores (EDSS ≥ 5 as severe and EDSS ≤ 4.5 as not severe) to distinguish between the different forms of MS based on their level of disability.

Data collection: Demographic characteristics of subjects were recorded, including gender, age at the study time, date of birth, place of residence in the previous year, family history of MS, and date of visit. In addition, disease characteristics and course including date and age of diagnosis, age at onset of the first symptoms, type of MS, EDSS score, pregnancy history and comorbidity (before and after MS), ambulation, and hospitalization for MS were recorded for further assessment.

The relevant information was collected by personal interview of PwMS in each center by a neurologist or some trained registrants. Following MS diagnosis, the EDSS score was assessed by neurologists and the latest score was used as a standard of disease severity. All collected data were transmitted into the NMSRI through the District Health Information Software 2 (DHIS2). Duplicate records were excluded based on the national identification code.

Continues and categorical variables were described by mean and standard deviation (SD) or median (Q1, Q3) and frequency (%), respectively. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Moreover, the chi-square test, Fisher's exact test, and Monte Carlo method were used to evaluate the relationship between categorical variables. Comparisons between groups were made using the Mann-Whitney, Kruskal-Wallis, and Bonferroni post hoc tests. In addition, to compare reproductive characteristics and chronic diseases before and after MS diagnosis, the McNemar test, Wilcoxon signed rank test, and generalized estimating equation (GEE) method were used.

Variables such as age at diagnosis, disease duration, and walking ability were compared among MS types by nonparametric tests. The time changes of maternal characteristics were investigated using GEE model by logit or log link functions. Additionally, the association of these characteristics before and after diagnosis, separately, and their changes over time with the severity of the disease (EDSS ≥ 5) were investigated using multiple logistic regression model.

To evaluate the association between the reproductive variables and MS severity, the crude and adjusted odds ratios (ORs) were calculated along with their 95% confidence intervals (CIs) based on univariate and multiple logistic regression model, respectively. In all models, the following factors were included: age at time of study, age at first symptoms, age at diagnosis, disease duration, and MS type. All analyses were performed using R 4.0.2 and SPSS software (version 23, IBM Corporation, Armonk, NY, USA). Two-tailed P-values < 0.05 were considered significant.

Ethical consideration: This study was conducted under the supervision of the Ethics Committee of Tehran University of Medical Sciences. The registration code for this study is: IR.TUMS.NI.REC.1400.038. All steps taken in this study are in accordance with the principles of the Declaration of Helsinki.

Results

Sample selection: Among 5349 patients who were registered in NMSRI, 914 were single, 245 did not have pregnancy data, and 3070 did not have EDSS score documentation. Thus, 1120 patients were included in the final analysis (Figure 1).

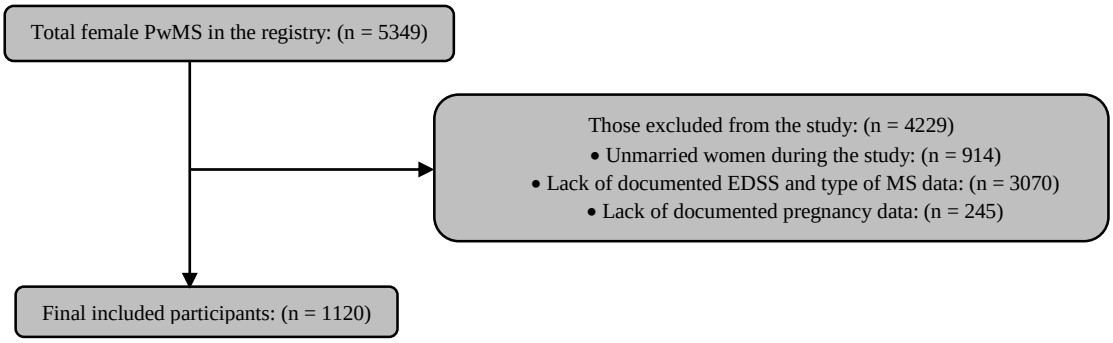

Figure 1. Flowchart of the study
PwMS: Patients with multiple sclerosis; MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale

The demographics: The patients' mean age (± SD) was 34.2 ± 12.6, while their median (Q1, Q3) disease duration was 6 (2, 11) years. The demographics and maternal characteristics of PwMS regarding different MS types are presented in table 1. Relapsing-remitting MS (RRMS) was the most common type of MS, with a prevalence of 90%. Overall, the average diagnosis age, current age, the disease duration, as well as the distribution of different job levels, the number of hospitalizations, and walking ability status were significantly different among the four groups ($P < 0.05$). Bonferroni post hoc pairwise comparisons showed that the diagnosis age in patients with secondary-progressive MS (SPMS) and primary-progressive MS (PPMS) and the disease duration in patients with SPMS and RPMS were significantly higher than that of patients with RRMS ($P < 0.05$). Further, patients with SPMS had a significantly greater disease duration than those with PPMS (Figure 2).

Reproductive and comorbidity history: Table 2 displays the features prior to and subsequent to the onset of MS regarding reproductive history and comorbidities. Most of the included patients had a history of pregnancy (72%) before the MS diagnosis ($P < 0.001$). The observed difference remained significant after modeling with GEE method (73.2% vs. 21.5%, $P < 0.001$). More patients with abortion history were in the pre-MS group than in the post-MS group ($P < 0.001$). In addition, patients had a higher prevalence of cardiovascular disease (CVD) ($P = 0.009$), hypertension (HTN) ($P = 0.003$), diabetes mellitus (DM) ($P = 0.001$), and hypothyroidism ($P = 0.049$) after the diagnosis of MS.

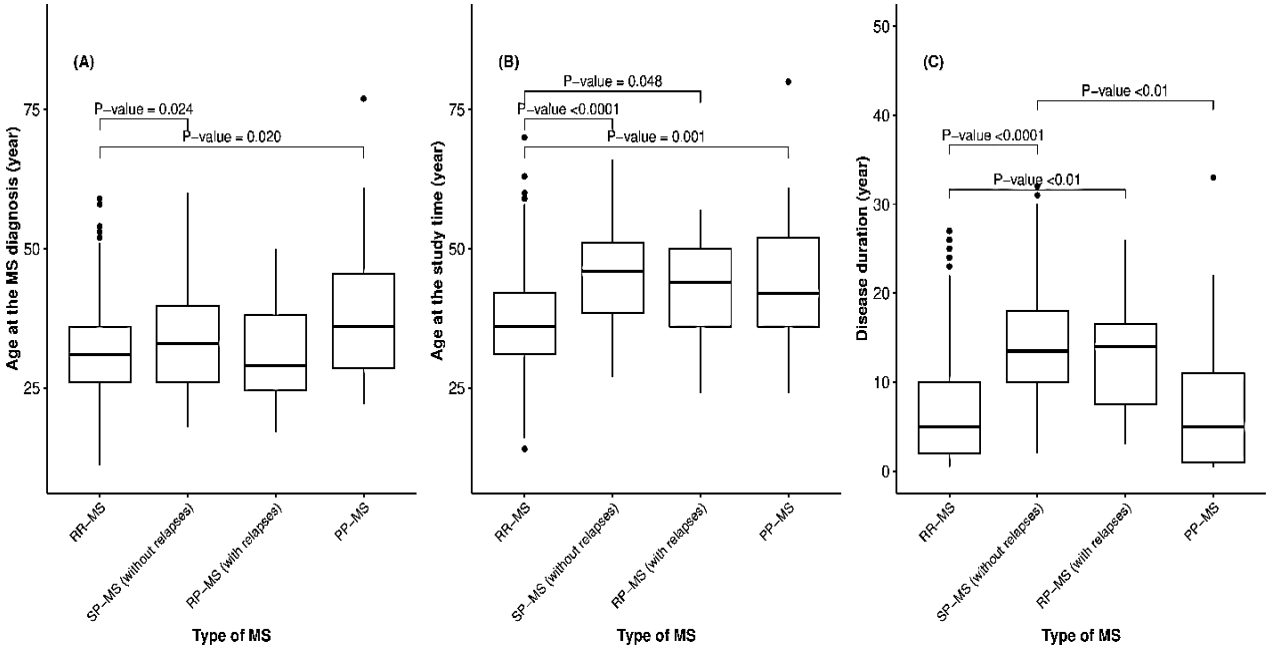

Figure 2. Post-hoc analysis with Bonferroni corrections based on multiple sclerosis (MS) type and age at MS diagnosis (A), age at the study time (B), and disease duration (C)

Table 1. General demographic and maternal characteristics based on type of multiple sclerosis (MS)

Characteristics		Total (n = 1120)	RRMS (n = 1006, 90%)	SPMS (n = 78, 7%)	RPMS (n = 13, 1%)	PPMS (n = 23, 2%)	P
Age at MS diagnosis (year)		31 (26, 36)	31 (26, 36)	33 (26, 40)	29 (23, 40)	36 (27, 46)	0.020*
Age at symptoms onset (year)		29 (25, 35)	29 (25, 35)	29 (24, 38)	27 (22, 36)	34 (25, 45)	0.211*
Age at the study time (year)		36 (31, 43)	36 (31, 42)	46 (38, 51)	44.0 (34.5, 50.5)	42 (35, 53)	< 0.001*
Disease duration (year)		6 (2, 11)	5 (2, 10)	13.5 (9.7, 18.0)	14.0 (6.5, 17.5)	5 (1, 11)	< 0.001*
Marital status	Married	944 (94.0)	21 (91.0)	69 (89.0)	21 (91.0)	944 (94.0)	0.220**
	Widow/divorced	60 (6.0)	1 (4.0)	9 (11.0)	1 (4.0)	60 (6.0)	
Job	Employed	171 (17.0)	4 (17.0)	5 (6.0)	4 (17.0)	171 (17.0)	0.019**
	Unemployed	798 (79.0)	19 (83.0)	65 (83.0)	19 (83.0)	798 (79.0)	
	Retired	11 (1.0)	0 (0)	6 (8.0)	0 (0)	11 (1.0)	
	Student	6 (1.0)	0 (0)	0 (0)	0 (0)	6 (1.0)	
Family history of MS (Yes)		218 (19.0)	198 (20.0)	15 (19.0)	0 (0)	5 (22.0)	0.351**
Comorbidity (Yes)		208 (19.0)	182 (18.0)	16 (21.0)	3 (23.0)	7 (30.0)	0.454**
Hospitalizations number	Never	294 (29.0)	4 (17.0)	5 (6.0)	4 (17.0)	294 (29.0)	< 0.001**
	1 to 4	613 (61.0)	14 (61.0)	50 (64.0)	14 (61.0)	613 (61.0)	
	≥ 5	91 (9.0)	5 (22.0)	23 (29.0)	5 (22.0)	91 (9.0)	
Walking ability	Unlimited	840 (83.0)	9 (39.0)	11 (14.0)	9 (39.0)	840 (83.0)	< 0.001**
	Limited (≥ 300 m)	92 (9.0)	4 (17.0)	6 (8.0)	4 (17.0)	92 (9.0)	
	Limited (100-300 m)	50 (5.0)	4 (17.0)	30 (39.0)	4 (17.0)	50 (5.0)	
	Needing help	18 (2.0)	5 (22.0)	20 (26.0)	5 (22.0)	18 (2.0)	
	Unable	3 (0.3)	1 (4.0)	10 (13.0)	1 (4.0)	3 (0.3)	
Smoking (Yes)		22 (2.0)	21 (2.0)	1 (1.0)	0 (0)	0 (0)	0.863**
Duration of smoking (≥ 10 years)		9 (1.0)	8 (1.0)	1 (1.0)	0 (0)	0 (0)	0.999**

Data are presented as median [interquartile range (IQR)] or number and percentage

*Kruskal-Wallis test or post hoc analysis; **Chi-square, Fisher's exact test, or Monte Carlo method

MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary-progressive multiple sclerosis; RPMS: Relapsing-progressive multiple sclerosis; PPMS: Primary-progressive multiple sclerosis

Table 2. Comparison of the reproductive properties and chronic diseases before and after the multiple sclerosis (MS) diagnosis

Variables		Crude number and percentages		P*	Estimated marginal percentages or rates (95% CI) by GEE model		P**
		Pre-MS	Post-MS		Pre-MS	Post-MS	
Reproductive characteristics							
Pregnancy history (Yes)		810 (72.0)	248 (22.0)	< 0.001	73.20 (70.50-75.80)	21.50 (19.00-24.20)	< 0.001
Parity	0	310 (28.0)	872 (78.0)	< 0.001	1.27 (1.22-1.33)†	0.27 (0.24-0.31)†	< 0.001
	1	354 (31.0)	186 (17.0)				
	≥ 2	456 (41.0)	62 (5.0)				
Abortion history (Yes)		184 (16.0)	74 (7.0)	< 0.001	16.30 (14.20-18.70)	6.50 (5.20-8.20)	< 0.001
Abortions number	0	936 (84.0)	1046 (93.0)	< 0.001	0.22 (0.19-0.25)†	0.08 (0.06-0.10)†	< 0.001
	1	143 (13.0)	58 (5.0)				
	≥ 2	41 (3.0)	16 (2.0)				
Chronic diseases							
Hypertension (Yes)		16 (1.0)	27 (2.0)	0.001	0.70 (0.40-1.30)	1.10 (0.60-2.00)	0.003
Diabetes mellitus (Yes)		16 (1.0)	29 (3.0)	0.001	1.00 (0.50-1.90)	1.80 (1.10-2.80)	0.001
Cardiovascular disease (Yes)		5 (0.4)	13 (1.0)	0.008	0.01 (0.00-1.00)	0.03 (0.00-1.00)	0.009
Pulmonary disease (Yes)		5 (0.4)	6 (0.5)	0.999	0.40 (0.10-0.90)	0.50 (0.20-1.00)	0.560
Hypothyroidism (Yes)		66 (6.0)	76 (7.0)	0.100	5.30 (4.10-6.80)	6.30 (4.90-7.90)	0.049
Hyperthyroidism (Yes)		10 (1.0)	13 (1.0)	0.508	0.80 (0.40-1.50)	1.00 (0.50-1.90)	0.317
Autoimmune disease (Yes)		5 (0.4)	7 (0.6)	0.625	NA	NA	0.082

*Crude P-value(s) were calculated based on McNemar, Wilcoxon signed rank tests; **Adjusted P-value(s) were calculated based on GEE method (the logit and log link functions were used for Binary and Poisson family, respectively); †The marginal rates were estimated based on total number of parity (pre-MS range: 0 to 8; post-MS range: 0 to 4) and total number of abortions (pre-MS range: 0 to 6; post-MS range: 0 to 3), including confounders were: age at the study time, diagnosis age, first symptoms age, disease duration, and MS type

MS: Multiple sclerosis; GEE: Generalized estimating equation; CI: Confidence interval; NA: Not available

Moreover, using the GEE model and adjusting on age, disease duration, and MS type, the percentages (95% CI) of pregnancies [pre: 73.2% (70.5%-75.8%); post: 21.5% (19.0%-24.2%)] and abortions [pre: 16.3% (14.2%-18.7%); post: 6.5% (5.2%-8.2%)] as well as the estimated rates of parities [pre: 1.27 (1.22, 1.33); post: 0.27 (0.24, 0.31)] and abortions [pre: 0.22 (0.19, 0.25); post: 0.08 (0.06, 0.10)] were all significantly decreased after MS diagnosis ($P < 0.001$).

MS severity: In terms of MS severity, 1081 patients (97%) had an EDSS score of 4.5 or lower. The association between EDSS score and reproductive characteristics before and after MS diagnosis is presented in table 3. As observed, the mean EDSS score was significantly higher in patients with a pregnancy (1.67 ± 1.50 vs. 1.43 ± 1.39, $P = 0.020$) or abortion (1.76 ± 1.41 vs. 1.47 ± 1.41, $P = 0.040$) history following their MS diagnosis. Moreover, the logistic regression analysis revealed that prior to MS diagnosis, the odds of reaching an EDSS score ≥ 5 was about 2.5 times higher in patients with parity ≥ 2 compared to those without parity (OR: 2.41, 95% CI: 1.02-5.70, $P = 0.044$). On the other hand, cesarean section was significantly associated with decreased odds of disease severity (EDSS score ≤ 4.5) compared to natural vaginal delivery (OR: 0.26, 95% CI: 0.10-0.67, $P = 0.005$). However, upon adjustment, these associations were no longer statistically significant.

Considering the trends in reproductive characteristics, the mean EDSS score was significantly higher in patients with a positive pregnancy history before or after the MS diagnosis ($P = 0.007$) (Table 4). In addition, logistic regression analysis revealed a significant association between a high EDSS score (≥ 5) and a decrease in parity after the MS diagnosis (OR: 3.35, 95% CI: 1.01-11.09, $P = 0.047$). None of the changes remained statistically significant after adjusting for confounders.

Discussion

The present study aimed to investigate the potential association between MS-related severity and various maternal characteristics, and disease history parameters as well as reproductive trends in an Iranian population of female PwMS. Our observations revealed that there might be a decrease in both parity and the likelihood of experiencing abortion following an MS diagnosis. Interestingly, this was found to be irrespective of the MS type, age, or disease duration and was further linked with a higher EDSS score. Notably, our results suggest that MS diagnosis may have a more pronounced effect on pregnancy rates in individuals with higher EDSS scores. To the best of our knowledge, this is the first study to explore the relationship between MS severity and alterations in reproductive patterns among female PwMS.

We observed that the chance of parity might fall by 3.4 folds in PwMS, regardless of their symptoms, diagnosis age, and MS type. It has been established that most of DMTs are not safe for pregnant PwMS;[21] therefore, a pregnancy test is usually taken before starting the treatment.[22] In addition, it is recommended that PwMS use contraceptive tools, which are less complicated than oral contraceptive pills, to prevent pregnancy during their therapy.[23] Moreover, the diagnosis of MS is usually associated with lower quality of life (QOL) and higher anxiety levels.[24] This can influence pregnancy tendency, especially when there is a lack of proper health care assistance, responsible for enhancing the QOL in PwMS.[25] These altogether may justify the results of our study, reporting significantly lower pregnancy rates after MS diagnosis.

It has been shown that women diagnosed with MS demonstrate a comparable degree of physiological competence for pregnancy. However, they may exhibit a higher incidence of reliance on assisted reproductive technologies compared to the general population.[26] This issue can be related to sexual dysfunction[27] and abnormal sex hormone patterns.[28,29] Meanwhile, it was shown that hormonal therapy or assisted reproductive technologies might cause MS exacerbation and increase disability.[30] Vukusic et al. reported a decrease in relapse rate during pregnancy and an increase in relapse rate in the first trimester of the post-partum period.[31] Changing the T-cells from pro-inflammatory forms in the first trimester to anti-inflammatory ones in the third trimester can affect the severity of MS.[32]

The current study found that disability levels did not vary significantly in patients who experienced pregnancy either before or after their MS diagnosis. This observation may be attributed to the pattern of DMT initiation and discontinuation among these patients. Although pregnancy is not contraindicated in PwMS, it is common to advise them to terminate DMTs a few months before conception, which might be associated with a higher rate of MS relapse during the first trimester.[11,33]

Table 3. The association between Expanded Disability Status Scale (EDSS) score and reproductive characteristics before and after multiple sclerosis (MS) diagnosis

Variables		Mean ± SD	P*	EDSS ≤ 4.5 [n (%)]	EDSS ≥ 5 [n (%)]	Crude OR (95% CI)	P**	Adjusted OR (95% CI)	P***
Total		1.50 ± 1.40		1081 (97)	39 (3)				
Reproductive history before MS diagnosis									
Pregnancy history	Yes	1.53 ± 1.44	0.138	778 (72)	32 (82)	1.78 (0.78-4.08)	0.172	0.92 (0.31-2.76)	0.886
	No (reference)	1.37 ± 1.34		303 (28)	7 (18)				
Parity	0 (reference)	1.37 ± 1.34	0.204	303 (28)	7 (18)	-	-	-	-
	1	1.41 ± 1.25		346 (32)	8 (21)	1.00 (0.36-2.79)	0.999	0.77 (0.21-2.81)	0.686
	≥ 2	1.63 ± 1.57		432 (40)	24 (61)	2.41 (1.02-5.70)	0.044	1.05 (0.32-3.40)	0.940
Abortion history	Yes	1.63 ± 1.63	0.502	174 (16)	10 (26)	1.80 (0.86-3.75)	0.119	2.05 (0.79-5.31)	0.140
	No (reference)	1.46 ± 1.37		907 (84)	29 (74)				
Abortions number	0 (reference)	1.46 ± 1.37	0.798	907 (84)	29 (74)	-	-	-	-
	1	1.65 ± 1.67		136 (13)	7 (18)	1.61 (0.69-3.75)	0.269	1.63 (0.55-4.82)	0.378
	≥ 2	1.54 ± 1.50		38 (3)	3 (8)	2.47 (0.72-8.47)	0.151	4.05 (0.83-19.84)	0.084
Delivery type++	Natural (reference)	1.84 ± 1.48	0.001	284 (42)	19 (68)	-	-	-	-
	Cesarean	1.40 ± 1.28		340 (51)	6 (21)	0.26 (0.10-0.67)	0.005	0.50 (0.15-1.74)	0.277
	Both	1.80 ± 1.41		48 (7)	3 (11)	0.93 (0.27-3.28)	0.915	0.74 (0.15-3.55)	0.704
Reproductive history after MS diagnosis									
Pregnancy history	Yes	1.67 ± 1.50	0.02	239 (22)	9 (23)	1.06 (0.49-2.26)	0.886	1.03 (0.36-2.97)	0.959
	No (reference)	1.43 ± 1.39		842 (78)	30 (77)				
Parity	0 (reference)	1.43 ± 1.39	0.06	842 (78)	30 (77)	-	-	-	-
	1	1.71 ± 1.54		178 (17)	8 (21)	1.26 (0.57-2.80)	0.568	1.18 (0.39-3.57)	0.772
	≥ 2	1.55 ± 1.37		61 (6)	1 (3)	0.46 (0.06-3.43)	0.449	0.51 (0.05-5.09)	0.570
Abortion history	Yes	1.76 ± 1.41	0.04	72 (7)	2 (5)	0.76 (0.18-3.21)	0.706	0.64 (0.13-3.20)	0.597
	No (reference)	1.47 ± 1.41		1009 (93)	37 (95)				
Abortions number	0 (reference)	1.47 ± 1.41	0.104	1009 (93)	37 (95)	-	-	-	-
	1	1.69 ± 1.37		57 (5)	1 (3)	0.48 (0.06-3.55)	0.471	0.45 (0.05-3.83)	0.465
	≥ 2	2.03 ± 1.56		15 (1)	1 (3)	1.82 (0.23-14.13)	0.568	1.32 (0.08-18.23)	0.834
Delivery type++	Natural (reference)	2.03 ± 1.58	0.060	62 (29)	4 (50)	-	-	-	-
	Cesarean	1.53 ± 1.36		148 (69)	4 (50)	0.42 (0.10-1.73)	0.229	0.41 (0.08-2.27)	0.309
	Both	2.08 ± 0.80		6 (3)	0 (0)	Not calculated	0.999	Not calculated	0.999

*P-value(s) are calculated based on Mann-Whitney test or Kruskal-Wallis test; **Unadjusted P-value(s) based on univariate logistic regression; ***Adjusted P-value(s) based on multiple logistic regression [including confounders were: age at the study time, diagnosis age, first symptoms age, disease duration, and multiple sclerosis (MS) type]; ++Analyses were done based on 700 available data on pre-MS delivery type and 224 post-MS delivery type; †Based on the Bonferroni test, the pairwise comparisons between natural and cesarean were statistically significant

MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale; OR: Odds ratio; CI: Confidence interval; SD: Standard deviation

Table 4. The association between reproductive characteristics trends and Expanded Disability Status Scale (EDSS) score

Variables		Total (n = 1120) [n (%)]	EDSS score		Severity of MS disease					
			Mean ± SD	P*	EDSS ≤ 4.5 (n = 1081, 97%) [n (%)]	EDSS ≥ 5 (n = 39, 3%) [n (%)]	Crude OR (95% CI)	P**	Adjusted OR (95% CI)	P***
Pregnancy history (before/after)	Yes/Yes	104 (9)	1.76 ± 1.51	0.007	100 (9)	4 (10)	3.28 (0.59-18.23)	0.175	1.06 (0.14-8.16)	0.953
	Yes/No	706 (63)	1.50 ± 1.43		678 (63)	28 (72)	3.39 (0.80-14.36)	0.098	1.18 (0.22-6.36)	0.846
	No/Yes	144 (13)	1.60 ± 1.49		139 (13)	5 (13)	2.95 (0.56-15.44)	0.200	1.29 (0.20-8.15)	0.788
	No/No	166 (15)	1.17 ± 1.15		164 (15)	2 (5)	-	-	-	-
Parity trend (after minus before)	Decreasing	728 (65)	1.51 ± 1.44	0.132	698 (65)	30 (77)	3.35 (1.01-11.09)	0.047	2.07 (0.41-10.30)	0.376
	Increasing	155 (14)	1.62 ± 1.51		149 (14)	6 (15)	3.14 (0.77-12.75)	0.109	1.52 (0.37-6.31)	0.564
	Not changed	237 (21)	1.31 ± 1.25		234 (22)	3 (8)	-	-	-	-
Abortion history (before/after)	Yes/Yes	11 (1)	1.59 ± 1.70	0.128	10 (1)	1 (3)	3.02 (0.37-24.39)	0.300	1.62 (0.10-25.00)	0.731
	Yes/No	173 (15)	1.63 ± 1.63		164 (15)	9 (23)	1.66 (0.77-3.57)	0.199	2.18 (0.80-5.90)	0.126
	No/Yes	63 (6)	1.79 ± 1.37		62 (6)	1 (3)	0.49 (0.07-3.64)	0.483	0.48 (0.06-4.07)	0.503
	No/No	873 (78)	1.43 ± 1.36		845 (78)	28 (72)	-	-	-	-
Abortions number trend (after minus before)	Decreasing	176 (16)	1.64 ± 1.65	0.054	166 (15)	10 (26)	1.83 (0.87-3.85)	0.108	2.34 (0.89-6.18)	0.085
	Increasing	63 (6)	1.79 ± 1.37		62 (6)	1 (3)	0.49 (0.07-3.67)	0.489	0.49 (0.06-4.12)	0.510
	Not changed	881 (79)	1.43 ± 1.36		853 (79)	28 (72)	-	-	-	-

*P-value(s) are calculated based on Mann-Whitney test or Kruskal-Wallis test; **Unadjusted P-value(s) based on univariate logistic regression; ***Adjusted P-value(s) based on multiple logistic regression [including confounders are: age at the study time, diagnosis age, first symptoms age, and multiple sclerosis (MS) type]
MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale; OR: Odds ratio; CI: Confidence interval; SD: Standard deviation

This can also increase the disability and the EDSS score in patients, regardless of prior stable disease or age.[34] To overcome this problem, it is recommended that the disease activity be controlled with DMTs such as glatiramer acetate and this therapy continue throughout pregnancy;[35] however, it is worthwhile to note that glatiramer acetate needs time to express its optimal efficacy,[36] and it should be administered at least two months before the pregnancy. It should be noted that the DMT market does not have a universal coverage around the country.[8,25] Moreover, Iranian expectant mothers traditionally are reluctant to use DMTs during pregnancy and also breastfeeding period which we believe has more duration in our country.

Our study revealed that, following MS diagnosis, patients with multiple pregnancies (multiparous) displayed lower EDSS scores when compared to those who had only one pregnancy (monoparous). This observation contrasts with the findings prior to MS diagnosis, where multiparity was linked to higher EDSS scores. Although the difference between these groups was not statistically significant, further research should still take this into account. In fact, a higher EDSS can decrease the chance of multiparity, and multiparity is usually seen in patients with lower disability scores. The present study is not directly comparable to others evaluating the disability in monoparous versus multiparous patients, because we have to consider the overall population; however, this issue is also seen in a study in 2016, which demonstrated higher disability in monoparous PwMS than in multiparous patients.[37] In addition, higher EDSS in those who had several babies before the MS diagnosis can be justified based on the decreased tendency to have a baby after MS diagnosis. Indeed, the protective effect of pregnancy on PwMS may not be present in this group of patients.

We also observed that the abortion after MS diagnosis is associated with higher EDSS scores. This issue can be related to inflammatory rebound changes in the post abortion period and remarkably in the first 12 months post event. In addition, as mentioned above, at the first trimester of pregnancy, the disability may arise, which is also associated with the pro-inflammatory status at the early stages of pregnancy, which can affect the likelihood of abortion.[38] This issue should be considered in the consultation of PwMS who tend to have a baby.

This study exhibits several noteworthy aspects. Firstly, we conducted this research in collaboration with NMSRI, signifying its multicenter nature and inclusion of diverse ethnic groups. Secondly, we evaluated the impact of parity and abortion on disability scores in a large sample size, thereby augmenting the statistical power of our findings. Considering the fact that this study was conducted on the documented registry data, the unknown number of relapses during pregnancy and the lack of data for other confounders such as DMTs may affect our results. In addition, our study was a secondary analysis of the collected data from our national MS registry. It must be noted that our population was a relatively young population (34.2 ± 12.6) with relatively short duration of disease (6 years), making most of them (97%) to have EDSS scores less than 4.5. In fact, the mean EDSS score was 1.5 ± 1.4 in total. Moreover, lack of pregnancy data of unmarried female PwMS is another limitation of this study. Due to religious reasons in Iran, unmarried female PwMS do not get pregnant; otherwise, they would not officially declare it until an official marriage documentation. To better understand the relationship between MS and pregnancy, conducting more prospective studies in PwMS during pregnancy is necessary to achieve more reliable results. Furthermore, it would be better to collect data of unmarried population to compare the results between married and unmarried population. However, this remains a persistent constraint in Muslim countries.

Conclusion

The diagnosis of MS is associated with a decrease in pregnancy tendency in affected individuals. Pregnancy and parity might affect the disability level in PwMS, changing the treatment before, during, and after the pregnancy and during the breastfeeding period. Regardless of their current age, age of diagnosis, age of first symptoms, or type of MS, female PwMS who have had multiple pregnancies and childbirths may experience disability levels that differ from their pre-MS diagnosis status, making it crucial for medical consultants to closely monitor those who plan on becoming pregnant.

Conflict of Interests

The authors declare no conflict of interest in this study.

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