



# Effects of Sex-Related Factors on Disability Risk in Women with Multiple Sclerosis

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## Abstract

**Objective:** It has been reported that estrogen may affect T helper (Th) 1 and Th-2 lymphocytes and the ratio of Th-1 to Th-2, which play an essential role in the immunopathogenesis of multiple sclerosis (MS). Therefore, hormonal changes during transitional periods, such as pregnancy and menopause, may affect the activity of the disease at different phases of the menstrual cycle. This study aimed to determine the association of MS in women with variables, such as menarche age, menstrual order, menopausal age, and disease-related factors, such as disability level and the number of relapses.

**Materials and Methods:** This descriptive study enrolled 281 women with MS. The participants were evaluated using a simple and short survey by the researchers. A neurologist evaluated the Expanded Disability Status Scale (EDSS) score, the number of attacks, and disease duration.

**Results:** Sixty-seven (23.8%) of 281 patients had entered menopause. There was no significant difference in the EDSS score of women with MS with or without menopause ( $p>0.05$ ). Sixty patients (21.4%) had children after MS. There was no significant difference between the number of relapses before ( $1.87\pm 1.46$ ) and after having a child ( $3.15\pm 3.59$ ) ( $p>0.05$ ). Additionally, the last EDSS score ( $2.46\pm 2.07$ ) was not different from the EDSS score after having a child ( $2.35\pm 1.81$ ) ( $p>0.05$ ). It was found that 80.4% of the patients had a regular menstrual cycle, whereas 19.6% of them had an irregular cycle. The EDSS score was significantly higher in women with irregular menstrual cycles than in women with regular menstrual cycles ( $p<0.05$ ). The age at menarche in the study group (13.07) was found to be earlier than the average age at menarche in Turkey (13.3) ( $p<0.05$ ).

**Conclusion:** This study suggested that menopause and childbearing may not affect disability level or the number of attacks in women with MS. Additionally, women with MS have an earlier age at menarche compared with the general population. Future studies should investigate earlier age at menarche as a possible risk factor in MS.

**Keywords:** Multiple sclerosis, women, disability, menarche

## Introduction

Multiple sclerosis (MS) is a chronic, progressive, demyelinating disease that affects over 2.5 million people worldwide and is more common in young adults aged 20-40 years. The incidence of MS is 2-3 times higher in women than in men (1). Pregnancy is an essential clinical condition in individuals with MS since the age of onset of MS usually coincides with the reproductive period in women. While the woman's immune system is modulated to protect the developing fetus during pregnancy, a remission period is frequently observed for autoimmune

diseases due to the effect of hormones during pregnancy (2). It has also been shown that the cure rate is increased in other cell-mediated autoimmune diseases, including psoriasis and rheumatoid arthritis, during pregnancy (3). An increase in estrogens (estradiol, estriol) and progesterone may be responsible for the immunomodulation. These hormones peak in the third trimester of pregnancy, the time when the most significant protection against a disease occurs (4).

Additionally, there are slight changes in other hormones, such as cortisol, during pregnancy. It increases early in pregnancy, is

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short-lived, and contributes less to protection against disease in the last trimester of pregnancy. Estrogen is neuroprotective in various neurological disease models and plays a role in normal cognitive development, and this is assumed to be evolutionary. It is advantageous for a pregnancy factor to be both immunomodulatory and neuroprotective because these properties enable the fetus to survive as an allogeneic and protect the developing brain. It may also be an ideal mechanism to protect the fetus in mothers with MS (5). Additionally, decades of observation have shown that women with MS have fewer attacks during pregnancy, but there is an increase in postpartum relapses later. Clinical observations highlight the fact that the onset of MS in women occurs after delivery. Therefore, pregnancy, childbirth, and the postpartum period are turning points for women with MS (6).

In a study that followed up 227 women with MS prospectively, a 70% decrease in the attack rates was shown in the third trimester of pregnancy. In the same study, the rate of attacks in the postpartum period was higher than that before pregnancy. It has been shown that during the following postpartum year, the frequency of attacks decreased, and the attack rate returned to that of the prepregnancy period (7).

The effect of the last trimester of pregnancy on the increase in postpartum attacks or permanent disability accumulation has been a controversial issue. While short-term studies that followed up patients for  $\leq 2$  years showed that pregnancy does not affect disability, long-term studies have shown that multiple pregnancies in women with MS cause less disability and/or prolong the time taken to reach a certain level of disability (8-10).

Other turning points for women with MS are menarche age and menopause. Azimi et al. (11) conducted a systematic review to define the role of age at menarche in MS and found that the risk of MS was negatively correlated with age at menarche (11). In contrast, Zuluaga et al. (12) investigated the effects of menarche on the risk of developing MS and found that there was no relationship between age at menarche and the risk of developing MS (12).

Therefore, this study aimed to determine the association of MS in women with menarche age, menstrual order, menopausal age, and disease-related factors such as disability level and the number of attacks. The results of this study will contribute to the literature and provide a different perspective on the effects of sex-related factors on the course of the disease in women with MS.

## Materials and Methods

### Participants and Procedures

This study was conducted in the MS Center of Dokuz Eylul University Hospital, Izmir, Turkey. The research protocol was

approved by the Dokuz Eylul University Ethics Committee (decision number: 2021/28-02, date: 13.10.2021). Written consent was obtained from all participants before the assessment.

The eligibility criteria were diagnosis of definite MS according to current diagnostic criteria, age  $> 18$  years, and being a woman. The exclusion criterion included women unable to follow instructions.

### Outcome Measures

Information, such as age, MS diagnosis year, and disease course of the patients, were obtained from the records in iMed7.0.

### Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) is the most widely used scale for assessing disability in patients with MS. EDSS scoring is based on the neurological examination of the seven functional systems and the patient's ambulation status. Functional systems are ordered as pyramidal, cerebellar, brainstem, sensory, bladder and intestinal, visual, and cerebral. The total score ranges from 0 to 10 (13).

### Semistructured Interview

It consisted of 10 questions investigating the age at menarche, presence of menopause, age at menopause, menstrual cycle, and course of the disease in women with MS before, during, and after pregnancy. A nurse who was an expert in MS performed the semistructured interviews.

### Sample Sizes

It is recommended to include at least 10% of the total population in descriptive studies (14). There are  $\sim 2000$  registered women with MS in the MS Center of Dokuz Eylul University Hospital. Therefore, the smallest sample size to be included in the study was planned as 200.

### Statistics Analyses

Data were analyzed using the IBM SPSS (version 24.0. Armonk, NY: IBM Corp) program. Kolmogorov-Smirnov/Shapiro-Wilk tests and analysis of graphs were used to determine whether the data were normally distributed. Since the variables did not show a normal distribution, all analyzes were performed with nonparametric methods. Descriptive analyses were presented as percentages and median (interquartile range). Mann-Whitney U test was used to analyze differences between groups for continuous variables.

## Results

Most of the participants had a relapsing-remitting disease course (86.8%). The median EDSS score of the participants was 2.0 (range between 0 and 7) (Table 1). Sixty-seven (23.8%) of 281 patients had entered menopause. There was no significant difference in the EDSS score of pwMS with or without menopause ( $p > 0.05$ ). Sixty patients (21.4%) had children after

Age (years)	38.0 (31.0-48.0)
Age at menarche	13.0 (12.0-14.0)
Age at menopause	46.5 (43.0-50.0)
EDSS score	2.0 (1.0-3.5)
Disease duration (years)	8.0 (4.0-14.0)
Number of attacks	3.0 (2.0-5.0)
<b>Disease course</b>	
Relapsing-remitting MS	244 (86.8%)
Secondary-progressive MS	32 (11.4%)
Primer-progressive MS	5 (1.8%)

EDSS: Expanded disability status scale, MS: Multiple sclerosis

MS. There was no significant difference between the number of relapses before ( $1.87 \pm 1.46$ ) and after having a child ( $3.15 \pm 3.59$ ) ( $p > 0.05$ ). Additionally, the last EDSS score ( $2.46 \pm 2.07$ ) was not different from the EDSS score after having a child ( $2.35 \pm 1.81$ ) ( $p > 0.05$ ). According to Adalı and Koç's (15) study, the mean age at menarche was 13.3 in Turkey (15). When comparing the mean age at menarche among women with and without MS in Turkey, a significant difference was found (13.3 versus 13.07) ( $p = 0.007$ ).

It was found that 80.4% of the patients had a regular menstrual cycle, while 19.6% of them had an irregular cycle. The EDSS score was significantly higher in women with irregular menstrual cycles than in women with regular menstruation cycles ( $p < 0.05$ ). The detailed information is presented in Table 2.

## Discussion

This study was conducted to describe the effects of sex-related factors on disability in women with MS. Our result showed that the average age at menarche was significantly different in women with MS compared to the general population. Additionally, the women with MS who had irregular menstrual cycles had higher EDSS scores than their regular counterparts. However, there were no significant differences between pwMS with or without menopause in terms of clinical characteristics.

There is no consensus related to the effects of earlier age at menarche on the disease course of MS. Antonovsky et al. (16) compared the age at menarche between women with MS and healthy controls and found no significant difference in terms of the average age of menarche. However, the study was conducted in Israel, and participants consisted of a mixed population, which could affect menstruation due to the heterogeneous genetic background (16). Besides, Zuluaga et al. (12) included 501 female pwMS with a clinically isolated syndrome and assessed the age at menarche as a risk of clinically definite MS. They reported that menarche is not a risk factor for MS (12). A recent systematic review demonstrated that late age at menarche might have a protective effect on MS onset. However, the authors highlighted that the mechanism should be investigated in future studies (17). The present study showed that women with MS had an earlier age at menarche than the average age in Turkey. We speculated that earlier age at menarche led to increased estrogen exposure, which may have affected the occurrence of MS. Additionally, women with irregular menstrual cycles had higher disability levels. These findings also support the fact that hormonal instability could be an influential factor in the progression of MS. Moreover, there was no relationship between menopause, childbearing, and clinical characteristics of MS. This could improve the management of the pregnancy period by neurologists in our clinic. When patients decided to have a child, whole process running with the neurologists and the best time is determine together.

## Study Limitations

This study has some limitations. First, we did not include healthy controls to compare the menstruated periods, which could provide detailed information. Second, we used a self-reported method to evaluate the sex-related factors. This method has the disadvantage of being subject to memory bias, especially regarding the age at menarche. Using objective methods to assess hormonal levels may help in understanding the biological mechanisms. Third, the results of the present study cannot be generalized. Therefore, further multicenter studies need to be conducted.

	Menstrual cycle (n=214)				
	Regular (n=171)		Irregular (n=43)		p
	Median	IQR	Median	IQR	
EDSS	1.5	1.0-2.0	2.25	1.0-5.5	<b>0.001*</b>
Disease duration (years)	6.0	3.0-12.0	6.5	3.0-10.25	0.294
Number of attacks	3.0	2.0-5.0	2.5	2.0-4.0	0.746

\*Statistically significant. IQR: Interquartile range, EDSS: Expanded Disability Status Scale

## Conclusion

This study suggested that menopause and childbearing may not affect the disability level or the number of attacks in women with MS. However, women with MS have an earlier age at menarche, which could be linked to an increased risk of MS or an earlier age at MS symptom onset.

## Ethics

**Ethics Committee Approval:** The research protocol was approved by the Dokuz Eylul University Ethics Committee (decision number: 2021/28-02, date:13.10.2021).

**Informed Consent:** Written consent was obtained from all participants before the assessment.

**Peer-review:** Internally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: S.O., U.S., T.A., Concept: Y.S., A.T.O., S.O., U.S., T.A., Design: Y.S., A.T.O., S.O., U.S., T.A., Data Collection or Processing: Y.S., A.T.O., Analysis or Interpretation: A.T.O., Literature Search: Y.S., A.T.O., S.O., U.S., T.A., Writing: Y.S., A.T.O., S.O., U.S., T.A.

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