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Investigating the interaction between fertility, pregnancy, and multiple sclerosis

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Abstract:

BACKGROUND: Multiple sclerosis (MS) is a chronic disease of the central nervous system. Most women with MS are diagnosed during their reproductive ages. The aim of this study was to evaluate the interaction between fertility, pregnancy, and MS.

MATERIALS AND METHODS: A retrospective descriptive–analytic study was conducted on 110 women suffering from MS with a history of pregnancy (between 2007 and 2017 years) in Isfahan, Iran. Samples were selected in a census model. Women completed a researcher-constructed questionnaire by telephone. The questionnaire consisted of three parts: demographic information, MS and its symptoms and treatment, and reproductive system and the history of pregnancy associated with MS. The data were analyzed by SPSS software version 16 using Chi-square, ANOVA, and t-test.

RESULTS: The mean age of women was 32.4 years. In this population, the average number of pregnancies was 1.61, the number of deliveries was 1.35, the number of abortions was 0.24, the history of ectopic pregnancy was 0.01, the number of alive children was 1.36, and the number of dead children was 0.01. The average time of the last MS attack before the pregnancy was 21.36 months. Fatigue (24.5%) was the most common symptom exacerbated during pregnancy. MS symptoms improved in 55.0% of women in the second trimester.

CONCLUSIONS: MS had no effect on the pregnancy status, such as the number of abortions, ectopic pregnancy, alive and dead children, and the duration of pregnancy. Symptoms of the disease improved during pregnancy. Therefore, pregnancy has a protective role against MS.

Keywords:

Health, multiple sclerosis, pregnancy, reproductive, women

Introduction:

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS) of presumed autoimmune origin. It is a chronic disease of CNS characterized by loss of motor and sensory function.^[1] The prevalence of the disease varies in different regions of the globe, ranging from 15/100,000 to 250/100,000.^[2] According to the World Health Organization, it is estimated that >2 million people worldwide suffer from MS

and the disease is one of the most common causes of neurological disability in young adults.^[3,4] The estimated number of people with MS has increased from 2.1 million in 2008 to 2.3 million in 2013.^[4] Studies reported that the incidence of MS is increasing in females.^[5] Iran has a medium-to-high prevalence rate of MS, and the prevalence of MS significantly has increased during recent years. Their results showed that Isfahan is the highest in Iran MS ranking.^[6,7]

Clinically, most MS patients experience recurrent episodes (relapses) of neurological

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impairment, but in most cases, the course of the disease becomes chronic and progressive with time, leading to cumulative motor disability and cognitive deficits.^[3]

The disease is along with a wide range of incidence of physical, mental, and sometimes psychological signs and symptoms. Signs and symptoms are unpredictable and vary from one person to another. Symptoms of MS include vision disorders (nystagmus, diplopia, reduced vision, etc.), pain, fatigue, weakness, dizziness, numbness, neuromuscular disorders in various systems including ataxia and gait abnormalities, paralysis, tremors, spasms, muscle stiffness, speech problems, bladder dysfunction, bowel (constipation and diarrhea), memory loss, sexual problems, and mood swings.^[8,9]

With a typical age of onset in the third or fourth decades,^[10] MS is two times more common in women than in men.^[11] Most women with MS are diagnosed during their reproductive ages.^[12] The results of a study showed the protective role of pregnancy in preventing the progression of the demyelination process.^[13] Although pregnancy is associated with a worsening of a group of autoimmune diseases, such as systemic lupus erythematosus, it leads to an improvement in another category of autoimmune diseases, such as MS and rheumatoid arthritis. Recent evidence suggests that the protective role of pregnancy in these types of diseases may be due to the side effects of the immunological process. This is the result of maternal immunity during pregnancy, which causes the mother to tolerate the fetus as an antigen (fetomaternal tolerance).^[14]

The potential impact of pregnancy on relapse course is of practical importance. It is now well understood that the risk of relapse significantly declines during pregnancy, particularly during the third trimester, only to increase three-fold in the first 3–4 months postpartum compared with prepregnancy. The results of a relatively large prospective study of 227 pregnant women during pregnancy and 1 year after delivery showed a definite 70% reduction in disease activity in the third trimester of pregnancy.^[15]

An increasing incidence for MS observed during the last 50 years cannot be explained by changes in genetic risk factors, emphasizing the importance of environmental factors related to lifestyle. Multiple studies have shown that stressful life is associated with an increased risk of MS.^[16,17] According to the fact that MS occurs at ages of fertility and its prevalence is more in women than men, Study on the interaction between fertility, pregnancy, and multiple sclerosis is important. Despite many studies on MS, this study is the first in Iran to study the interaction between MS and reproductive health and pregnancy for 10 years. There is conflicting information available

about the effects of MS on fertility and reproductive health, which raises concerns among women with MS. For example, research has reported decreased ovarian reserve, decreased sexual desire, and fear of the adverse effects of pregnancy on MS or the adverse effects of MS on fertility. In Iran, a more detailed study was needed in this group of patients. Among the many problems that people with MS experience, the results of a study show that they have a high level of anxiety due to the disease. They face many problems, including physical disability, activity limitations, job loss, inability to pay expenses, and worries about maintaining and continuing their married life, including having children. Therefore, psychological support of the patient and his family is known to be a major necessity.^[18] Therefore, the aim of this study was to investigate the interaction between fertility, pregnancy and MS.

Materials and Methods

The aim of this study was to evaluate the status of MS in reproductive system and pregnant women with MS and the effect of pregnancy on MS disease. This retrospective descriptive–analytic study was conducted on 2328 women suffering from MS in 2017 in Isfahan city (research number of 192111). Since this study was intended to evaluate the effect of MS on pregnancy and fertility in women with MS, 110 patients with inclusion criteria were examined. Inclusion criteria included having a history of pregnancy in the last 10 years in women with MS and consent to participate in the study. There was no output criterion for the samples in this study. Samples were selected using the census method. All the patients suffering from MS have a Medical record in the treatment deputy. Thus, after obtaining the permit using telephone numbers included in the case, women with MS who had their pregnancy (between 2007 and 2017 years) have been called, and after acquiring permission from them, a researcher-constructed questionnaire was completed by telephone for them by telephone. The questionnaire consisted of three parts: the first part included the demographic information (age, marital status, occupation, level of education, economic status of the family, social status, and place of residence); the second part included the MS disease information and its symptoms and the treatment of the disease (age of disease onset, duration of the disease, its first symptom, type of disease, and Expanded Disability Status Scale [EDSS] score); and the third part related to the fertility characteristics (number of pregnancies, delivery, abortion, history of ectopic pregnancy, alive child, dead child, history of infertility, its duration, using fertility medications, and a contraception method) and the history of pregnancy (number of pregnancy care, changes in the symptoms of the disease in each of the trimesters, and the gestational age at the time of

pregnancy termination) associated with MS (presence of attack, medication changes, and changes in symptoms and disease severity).

The data were analyzed using *t*-test, Chi-square, ANOVA, and SPSS software version 19 (Inc., Chicago, IL, USA).

Results

The results of the study on 110 mothers, who suffered from MS, showed that their mean age was 32.4 and most of the women were married, had undergraduate and graduate education, and were of the normal social class [Table 1].

In our study, MS disease was diagnosed in 19.5% (21 cases) of women aged <20 years and 70.5% (72 cases) aged 21–30 years and 10.2% at the age of 31–40 years. The average time from the onset of the MS disease to the time of study in 46.9% of women was <5 years, in 33.3% between 6 to 10 years, in 7.2% of them between 11 to 15 years and in 8.1% of women 16 to 20 years and in 3.6% of them >20 years old. The type of disease of the women studied is described in Table 2.

The average score was 1.18 EDSS. The most common primary symptom of the disease in the studied population was, respectively, blurred vision in 42.7%, oscillation and numbness of the organs in 36.4%, diplopia in 10.9%, vibration and imbalance in 2.7%, pain, spasticity and muscle stiffness in 2.7%, dizziness in 1.8%, and speech difficulty in 0.9%, but none of them expressed nystagmus, gastrointestinal, urinary, sexual, and mood changes as the first symptom of their illness.

In this population, the mean number of pregnancies was 1.61, the number of deliveries was 1.35, the number of abortions was 0.24, the history of ectopic pregnancy was 0.01, the number of alive children was 1.36, and the number of dead children was 0.01. Furthermore, 95.4% of them had no history of infertility, and 4.6% had a history of infertility, with an average infertility duration of 6 years (1–12 years of infertility). 78% of the population studied had a history of planned and wanted pregnancy and 22% had no planning [Table 3].

The results showed that 56.9% of the population studied had a natural contraception method before pregnancy, 28.4% had condom, 7.3% hormone, 5.5% had intrauterine devices, and 1.8% had no method. The average decision-making time for pregnancy until getting pregnant for this population was 8.47 months.

The average time of the last MS attack before the pregnancy was 21.36 months. During 1 year before

Table 1: Demographic characteristics of research participants

Studied variable	Frequency (%)
Education level	
Illiterate	2 (1.8)
Sub-diploma and diploma	57 (51.8)
Undergraduate and bachelor	45 (40.9)
Masters and higher	6 (5.5)
Economic level of family	
Very low	8 (7.2)
Low	11 (10.0)
Average	81 (73.6)
High	10 (9.1)
Very high	0 (0.0)
Social status	
Non affluent	8 (7.3)
Normal	95 (86.4)
Affluent	4 (3.6)
Place of living	
Leased	41 (37.3)
Personal property	64 (58.2)
Organizational property	3 (2.7)

Table 2: The type of multiple sclerosis disease in research participants

Type of MS disease	Frequency (%)
Primary progressive	8 (8.7)
Secondary progressive	6 (6.5)
Relapsing remitting	75 (81.5)
Recurrent progressive	3 (3.3)

MS=Multiple sclerosis

pregnancy, 69.2% of the women had no attacks, 25.2% had one attack, and 5.6% had 2–4 attacks. During pregnancy, 86.2% of the mothers did not experience any attacks, while 10.1% had an attack, 2.8% two attacks, and 0.9% of the participants had three attacks during pregnancy.

In this population, the drugs taken in the order of frequency are as follows: interferon beta 92.4% and fingolimod 1.9%. Among those who had planned pregnancy, 100% of the women discontinued the medication after the scheduled pregnancy. Of those who stopped the medication, 88.1% had no disease relapses, but 11.9% had relapses of the disease. Among the population studied, 89.4% did not take fertility medications for pregnancy, and only 10.6% of these drugs (clomiphene 60%, 10% human menopausal gonadotropin, 10% human chorionic gonadotropin, and other drugs 20%) were used. 76% (73 women) did not have any drug changes. Moreover, 6.3% of the participants in the research (6 women) changed their medication during pregnancy.

The results of the study showed that 24.8% of the participants in their pregnancy received up to four cares from community health centers or doctors' offices, while 19% had 5–8 visits, 33.7% had 9–10 visits, and 22.5% had

Table 3: Reproductive characteristics of research participants

Variable	Frequency (%)	Mean
Gravid		
1	60 (54.0)	1.61
2	36 (33.0)	
3	10 (9.1)	
4	4 (3.1)	
Para		
0	7 (6.4)	1.35
1	64 (58.2)	
2	33 (30.0)	
3	5 (4.5)	
4	1 (0.9)	
Abortion		
0	87 (79.1)	0.24
1	21 (19.1)	
2	2 (1.8)	
Ectopic pregnancy		
0	109 (99.1)	0.01
1	1 (0.9)	
Alive child		
0	7 (6.4)	1.36
1	63 (57.3)	
2	34 (30.9)	
3	5 (4.5)	
4	1 (0.9)	
Died child		
0	109 (99.1)	0.01
1	1 (0.9)	

11–12 times visited. The results indicated that only 50% of participants received standard service numbers.

According to the report of individuals during the pregnancy, the following symptoms were observed in the order of frequency including 24.5% fatigue and emotional changes 15.5%, anesthesia 11.8%, motor problems 6.4%, urinary tract infection 5.5%, sexual problems 2.7%, and pain and spasticity 1.8%. Furthermore, MS symptoms improved in 55.0% of people in the second trimester, while they improved by 28.8% and 16.3% in the first and third trimester, respectively. The mean age of pregnancy termination in these women was 38.13 weeks. The data used to support the findings of this study are available from the corresponding author upon request.

Discussion

The results of the study showed that the majority of participants had normal social class. In this study and also in other studies, most people having MS were suffering from the “relapsing remitting” type and the most common primary symptom in them was vision impairment like our study. While Kaminska *et al.* identified fatigue as the first and most common symptom in MS patients^[19] The results of our study also

showed that fatigue is the most common symptom that is exacerbated during pregnancy. In women with MS, fatigue increases during pregnancy due to increased progesterone levels. The results of a study showed that people with MS appear to show different personality characteristics than normal people. For example, the rate of depression in this group of patients is high. Therefore, in providing health care, this issue and the like should be considered.^[20]

The mean number of pregnancies in women with MS was 1.61 in the studied population. Ferraro’s study indicated that MS disease was associated with an increase in the number of unmarried women compared to the general population (22% vs. 13%).^[21] A study also found that 30% of women with MS had no children, although in this study women were still at reproductive ages.^[22] The causes of childlessness in women suffering from MS are reduced inclination to become a mother because of disability, fear of future disability, fear of genetic transmission of disease to child, the effect of pregnancy on severity of disease, the effect of illness on pregnancy, fear of stopping or starting treatment during pregnancy, and not encouraging doctors to become pregnant. This issue can be largely controlled by proper awareness of affected women.^[23,24]

In the present study, just one sample person had parity 4, and the rest of the women had 3 and <3 pregnancies, and the results of this study, which is consistent with other studies, showed that these women do not tend to have many children. Therefore the low number of parity in these women can be attributed to postponement of pregnancy or the effect of drugs on infertility and MS-related sexual dysfunction.^[25] The results of the study showed that the reasons for the lack of willingness to have children in these people are depression, reduced social activity, disability because of illness, reduced maternity willingness, and stress associated with coming down with a chronic disease.^[26] In the present study, 88.2% of the mothers are housewives and this indicates a specific social inactivity in this group, which may be due to the reduction of childbearing. Studies also showed that women with a higher socioeconomic level tended to delay pregnancy.^[21] The results of our study also indicated that the increase in social and economic level was accompanied by a tendency to delay and decrease in childbearing.

Although multiparous women are at a lower risk of MS attacks, the average childbearing frequency of mothers with MS in this study was 1.6. In this study, 33.0% of mothers had two pregnancies and only a small percentage of women had third and fourth pregnancy. Regarding this fact, it seems that by expressing the reduction of the risk of MS recurrence in multiparous

women, the good role of pregnancy in MS can be considered. The risk of MS in multiparous women is lower than that of nulliparous women.^[27] Furthermore, the results of the study by Ponsonby *et al.* showed that increasing parity rates plays a protective role against the progression of MS (demyelinating) disease.^[13]

The results showed that MS did not affect the pregnancy status, including the number of abortions, ectopic pregnancy, and the number of alive and dead children. The study by Ferraro *et al.* also indicated that there was no difference in infertility rate, use of assisted reproductive technology, the time taken for becoming pregnant and number of abortions in the population of women with MS compared to the general population and even the time taking action for pregnancy until becoming pregnant in women with MS has been shorter than control group. The frequency of elective abortion in these women was higher than general population (20% vs. 12%). In our study, the average decision-making time for pregnancy until maternal pregnancy was 8.4 months. Therefore, MS disease does not have a negative effect on maternal pregnancy. The average time to become pregnant in our study was <1 year (about 8 months). In our study, also, 95.4% of the population did not have infertility history. Therefore, MS does not have a negative effect on Fertility.

The results of the study showed that motherhood does not seem to have a negative effect on the risk or course of MS. Interpretation and conclusion of studies should take into account the bias that women with severe disease may often prevent pregnancy, while women with a mild form or late onset of symptoms decide to become pregnant.^[23] Therefore, the use of assisted reproductive drugs by 10.6% of the women does not mean infertility caused by MS in this population. The use of these drugs is probably due to the desire and acceleration of pregnancy when the disease is under control. Although the results of the study showed that the level of anti-Mullerian hormone, the number of follicles, and the volume of ovaries^[28] in patients with severe MS were less than those with mild type,^[29] the subject that whether the reduction of ovarian storage reduces the menopause age or fertility rate in women with MS is unknown. Therefore, although there is a controversy over the fertility situation of women with MS,^[30] the decline in ovarian function may affect the fertility potential. A recent epidemiological study has found no evidence of the effect of MS on fertility.^[22] The important note is that 22% of the population had unwanted pregnancy and pregnancy without any plans. Regarding the fact that 56.9% of people have chosen withdrawal contraceptive method and 1.8% have had no contraceptive method, this percentage of unwanted pregnancy was expected. Therefore, considering the importance of controlling the

MS disease before pregnancy and the side effect of drugs on the fetus, more attention is needed and providing proper counseling about contraception in the health centers to these MS women is required. Despite the fact that studies show that hormonal methods are the most appropriate contraceptive method for this target group, just 7.3% of the population studied have had this method in the year before their pregnancy, which seems to be due to the low level of awareness of individuals and the inadequacy of receiving appropriate training from service providers. However, in a cohort study by Karp *et al.*, 55% of the studied population used oral contraceptives.^[10] The results of the study showed that using oral contraceptive reduces the level of anti-Mullerian hormone,^[31] and the use of this contraceptive method in women with MS has attracted lower attention than the general population (24%–28% vs. 50%).

The mean time interval of the last MS attack before pregnancy has been 21.36 months, and about 69.2% of the participants had no attacks before the pregnancy. Therefore, disease control before pregnancy plays an important role in the condition of mothers with MS during pregnancy. This shows the importance of the role of neurologists in treating and controlling the disease before attempting to pregnancy.

The most commonly used drug in the year before and after pregnancy was Sinovex and Recigen. After making decision to become pregnant, 97.3% of the women under the supervision of the doctor had stopped the drug. Of those who stopped, 11.9% had recurrence of MS attacks. Therefore, the results of this study showed that receiving minimal medication and strict control of physicians and specialists in mothers with MS before pregnancy. The results also showed that the choice of low-risk drug for pregnancy and the minimum possibility of disease recurrence, had been considered by neurologists. However, in a study, 40% of women before pregnancy have had to modify the dosage of drugs in the year before pregnancy.^[12]

During pregnancy, 93.7% of people did not take any medications, and 6.3% of the participants in the study (6 people) experienced relapses during pregnancy and used glatiramer acetate. Therefore, the results of the study showed that the participants in this study did not have a very active disease and were in a controlled phase of the disease, so only the first-line drugs were received.

In the field of prenatal care, 56.2% of the participants in the study were taken care for >9 sessions; therefore, it seems that only half of the studied population have realized the importance of receiving adequate care and referral to service providing centers. However, about 50% had not realized this importance so about 30% of people

referred to service providing centers times or less during their pregnancy, and perhaps the cases of recurrence of the disease are related to the population who referring to the service-providing centers (public health centers, neurologists, and obstetrics and gynecology clinics) had been below the standard. Therefore, it shows the importance of focusing on raising the awareness of mothers with MS.

Examining the effect of pregnancy on MS disease is very important, especially when it was initially thought that pregnancy would have a negative effect on the disease.^[32] The results of this study showed that fatigue, emotional and mood disorders, limb numbness, and digestive and motor problems were the most common symptoms of exacerbation during pregnancy in women with MS. However, the results showed that 28% of people in the first trimester, 55% in the second trimester, and 16.3% in the third trimester experienced few symptoms of MS. The results of this study, like other studies, showed that the symptoms of the disease in pregnancy would improve compared to prenatal and postpartum. This study showed that in the second trimester, there was a maximum recovery for the population under study too. Other studies showed, in the third trimester, the highest reduction in recurrence and return of MS symptoms compared to before prenatal period.^[10,12]

Another study showed that pregnancy had a protective role against MS. Therefore, pregnancy had been associated with an 80% reduction in disease recurrence, especially in the third trimester of pregnancy. Increased hormone levels, especially in the third trimester of pregnancy, appear to provide this protection.^[14] Perhaps it can be stated that the difference in the results of this study with other existing studies and documentation can be attributed to a smaller number of sample cases.

The improvement in the condition of MS in the second trimester of pregnancy may be attributed to the pattern of other chronic diseases such as cardiovascular and inflammatory diseases that are better in the second trimester. In a study, it was indicated that although pregnancy for women with MS leads to a reduction in symptoms, a long-term 10-year examination showed that pregnant women do not differ with nonpregnant women in terms of long-term outcomes, and therefore, it seems the probability that the pregnancy increases the risk of secondary attacks is very low.^[10] In the present study, it was also showed that patients had fewer symptoms during pregnancy.

Conclusions

MS had no effect on the pregnancy status, such as the

number of abortions, ectopic pregnancy, alive and dead children, and the duration of pregnancy. The symptoms of the disease are improved during pregnancy and that patients had fewer symptoms during pregnancy. Therefore, pregnancy has a protective role against MS.

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Conflicts of interest

There are no conflicts of interest.

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