Effect of MS on pregnancy and the effect of pregnancy on MS patients in Isfahan

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Research

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Abstract

Background Multiple sclerosis is a chronic disease of the central nervous System. Most women with MS are diagnosed during their reproductive ages. This study evaluated the effect of pregnancy on MS and the effect of MS disease on fertility and pregnancy health.

Material & 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 its treatment, and the third part was related to the reproductive system and the history of pregnancy associated with MS. Data were analyzed by SPSS software version 16 using Chi-square, ANOVA and t-test.

Results The mean age of women with MS was 32.4 years. The most common primary symptom was blurred vision (42.7%). 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 subjects in the second trimester.

Discussion 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. Therefore, pregnancy has a protective role against MS.

Background

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 World Health Organization (WHO), it is estimated that more than two 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 have 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 impairment, but in most cases (60-80%) 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 (SLE), it leads to an improvement in another category of autoimmune diseases, such as multiple sclerosis 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 (feto -maternal tolerance).

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 pre-pregnancy. This 70% reduction in disease activity during the third trimester was definitively established through a relatively large multicenter prospective study of 227 pregnant women with MS followed prospectively through the remainder of pregnancy and one year postpartum (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 effect of pregnancy on MS and the effects of MS on pregnancy are important. Therefore, 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.

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 in 2017 in Isfahan city on 110 women suffering from MS with a history of pregnancy. These women were selected from a total of 2328 women with multiple sclerosis in Isfahan who met the inclusion criteria. Samples were selected using the census method for women with MS who experienced pregnancy. All the patients suffering from MS have a case 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, 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, a contraception method) and the history of pregnancy (number of pregnancy care, changes in the symptoms of the disease in each of the trimesters, the gestational age at the time of pregnancy termination) associated with multiple sclerosis (presence of attack, medication changes, changes in symptoms and disease severity), respectively.

The data were analyzed using t-test, chi-square, ANOVA and SPSS software version 16.

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 subjects were married, had undergraduate and graduate education, and were of the normal social class (Table 1).

Table 1: Demographic Characteristics of Research Participants

Studied Variable		Frequency	Percentage
Marital Status	Married	108	98.2
	Abandoned	1	0.9
	Divorced	1	0.9
Occupation	Housekeeper	97	88.2
	Employee	9	8.2
	Worker or and Farmer	0	0.0
	Self-Employed	4	3.6
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

MS disease was diagnosed in 19.5% (21 cases) of subjects under study aged less than 20 years and 70.5% (72 cases) at 21-30 years old and 10.2% at age 31-40. The duration MS incidence in 46.9% was less than 5 years, in 33.3% between 6-10 years, 7.2% from 11-15 years, 8.1% of people aged 16-20 years and 3.6% of them more than 20 years old. The type of disease of the subjects studied is described in Table 2.

Table 2: The Type of MS Disease in Research Participants

Type of MS Disease	Frequency	Percentage
Primary Progressive	8	8.7
Secondary Progressive	6	6.5
relapsing remitting	75	81.5
Recurrent Progressive	3	3.3

The average score was 1.18 EDSS. The most common primary symptom of the disease in the studied population was, respectively, blurred vision with 42.7%, oscillation and numbness of the organs 36.4%, diplopia 10.9%, vibration and imbalance 2.7%, pain, spasticity and muscle stiffness 2.7%, dizziness 1.8%, and speech difficulty 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. Also, 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 to 12 years of infertility). 78% of the population studied had a history of planned and wanted pregnancy and 22% had no planning (Table 3).

Table 3: Reproductive Characteristics of Research Participants

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

The results showed that 56.9% of the subjects 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 one year before pregnancy, 69.2% of the subjects had no attacks, 25.2% had one attack and 5.6% had two to four attacks. During pregnancy, 86.2% of 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 subjects discontinued the medication after the scheduled pregnancy. Of those

who stop the medication, 88.1% had no disease relapses, but 11.9% had relapses of the disease. Among the studied subjects, 89.4% did not take fertility medications for pregnancy, and only 10.6% of these drugs (Clomiphene 60%, 10% Human Menopausal Gonadotropin (HMG), 10% Human Chorionic Gonadotropin (HCG), and other drugs 20%) were used. 76% (73 subjects) did not have any drug changes. And 6.3% of the participants in the research (6 subjects) changed their medication during pregnancy.

The results of the study showed that 24.8% of the participants in their pregnancy received up to 4 care from community health centers or doctors' offices while 19% had 5 to 8 visits, 33.7% had 9 to 10 visits and 22.5% had 11 to 12 times Visited. The results indicate 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%, pain and spasticity 1.8%. Also, 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 subjects 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 this study showed that the average age of the studied subjects was 32.4 years old, and the majority of them had diploma or a lower education and a normal social class. In this study and also in the other studies, in line with the results of our study, 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. (2011) identified fatigue as the first and most common symptom in MS patients (18). The results of our study also indicated that fatigue is the most common symptom that exacerbates during pregnancy, which is expected to increase fatigue during pregnancy in women with MS due to increased progesterone level.

The mean number of pregnancies in women with MS was 1.61 in the studied population. Ferraro's study in 2017 indicated that MS disease was associated with an increase in the number of unmarried women compared to the general population (22% versus 13%) (19). A study in France also found that 30% of women with MS had no children, although in this study women were still at reproductive ages (20). Of 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 (21,22). In the present study, just one sample person had parity 4, and the rest of the women had 3 and less than 3 pregnancies and the results of this study which is consistent with other studies show that these women do not tend to have many children. Therefore, perhaps part of 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 (23). 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 (24). In the present study, 88.2% of the mothers have been 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 (19). Considering that about 45% of the subjects had university education and most of the subjects of the study enjoyed a moderate economic level, it seems the results of our study also indicate that with increasing social and economic level, the tendency to delay and decrease in childbearing increases.

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 (25). Also, 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 of the present study 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 is no difference in infertility, the use of Assisted Reproductive Technology (ART) fertility means, the time taken for pregnancy until becoming pregnant and abortion in the population of women with MS in relation 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 has been higher than general population (20% versus 12%). In our study, the average decision-making time for pregnancy until maternal pregnancy has been 8.4 months. Therefore, MS disease does not have a negative effect on maternal pregnancy. According to the definition, if people fail to become pregnant after one year of taking action for becoming pregnant, they belong to the definition of infertility, while the average time in our study was less than one 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 result of study showed motherhood does not seem to have negative effects on risk or course of MS, although the interpretations of all these studies need to factor a possible bias as women with severe course of the disease may tend to prevent pregnancies, and rather patients with severe form or late onset

of the disease decide to become pregnant (26). Therefore, the use of fertility medications by 10.6% of the subjects does not mean MS-induced infertility in this population, but probably it has been because of the tendency and acceleration of fertility due to the control of the disease during that time period. Although the results of the study showed that the level of Anti-mullerian hormone, the number of follicles and the volume of ovaries (27) in patients with severe MS were less than those with mild type (28), but 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 (29), but 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 (30). 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 subjects 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% versus 50%).

The mean time interval of the last MS attack before pregnancy has been 21.36 months, and about 69.2% of the subjects had no attacks before the pregnancy. Therefore, given the favorable conditions of the disease before pregnancy, it seems that creating sensitivity to treatment by Neurologists have been appropriate before 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 subjects under the supervision of the doctor had stopped the drug. Of those who stopped, 11.9% had recurrence of MS attacks. The subject indicates that at least amount of medication that the mothers have received and has been careful monitoring and supervision of doctors on MS patients before pregnancy. Therefore, the results suggest that the choice of drugs in a way to have low-risk for pregnancies, while at the same time that leads to minimal recurrence, has been considered by the experts. 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 more than 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. But about 50% have not realized this importance, so that unfortunately, about 30% of people referred to service providing centers 4 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) has 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, 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 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 and reduced 80% of recurrence, especially in the third trimester of pregnancy, which seems to increase the level of hormone, especially in the third trimester of pregnancy creates 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 of the condition of MS in the second trimester of pregnancy may also be attributed to adherence of the pattern of the disease to other chronic diseases, such as cardiovascular and inflammatory diseases get better condition during 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 non-pregnant 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 impact on the pregnancy status, including the number of abortions, ectopic pregnancy, alive and dead children, infertility status and duration of pregnancy. Therefore, MS does not have a negative effect on pregnancy. Also, the symptoms of the disease in pregnancy are improved with respect to before pregnancy and postpartum. The maximum improvement in MS symptoms in the second trimester was for the population under study. Therefore, pregnancy has a protective role against MS disease.

Abbreviations

MS
Multiple Sclerosis
CNS
Central Nervous System
WHO
World Health Organization
SLE
Systemic Lupus Erythematosus
EDSS
Expanded Disability Status Scale
HMG
human menopausal gonadotropin
HCG
Human Chorionic Gonadotropin
ART
Assisted Reproductive Technology

Declarations

Ethics approval and consent to participate

This study was a part of a research project approved in 2017 (research number of 192111) in Isfahan University of Medical Sciences in Iran. The study was approved by the Ethic Committee of Isfahan University of Medical Sciences, Iran. Written informed consent was obtained from all the patients before enrollment. Also consent to publish was obtained from the patients.

Availability of data and materials:

The data generated and used in the analysis of this study are included in this published article. Additional data is available from the authors upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

MF, AF, VM drafted the manuscript. MF, AF, VM designed the study. AF, VM, SM, SH were responsible for the conduct of the study. MF, AF, VM participated in the statistical analyses, interpretation and manuscript revisions. All the authors read and approved the final version and agreed to be accountable for the study.

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