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Review

Pregnancy and Multiple Sclerosis: A Review

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Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that occurs in people of reproductive age, affecting pregnancy significantly. The purpose of this review is to highlight the effect of MS on pregnancy. The methodology included the search of review and research studies in electronic databases (Google scholar, EBSCO, Elsevier, etc.) related to MS in pregnancy with an emphasis on the recent literature. Pregnancy has a strong influence on disease activity. In particular, there is a significant reduction in the recurrence rate of up to 70% of the disease patients during the third trimester of pregnancy and for the first 3 months after delivery. MS as a disease does not prevent fertility. However, pregnancy planning and full information about the disease, its course and the potential risks of medication are the cornerstone of responsible maternity.

Keywords: multiple Sclerosis, pregnancy, childbirth, breastfeeding

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1 INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory disorder of the Central Nervous System characterized by demyelination and neurodegeneration of neurons in the brain and spinal cord and usually affects young adults with a higher incidence in women[1,2]. The prevalence is two to three times higher in women than in men[3].

MS is the most common demyelinating disease seen in high-income countries, is heterogeneous, and has a global prevalence. It presents higher incidence rates in North America (140/100,000 population) and Europe (108/100,000), and lower rates in East Asia (2.2/100,000 population) and sub-Saharan Africa (2.1/100,000). According to a report of the International Federation of people suffering from MS the global prevalence has increased from 30/100,000 in 2008 to 33/100,000 in 2013[4].

In particular, the prevalence of the disease in Europe has been characterized by a North-South prevalence gradient, where incidence rates are higher in the North and lower in the South. France is located in the middle of Western Europe between areas with a high prevalence of MS such as the Scandinavian countries and the United Kingdom and countries where the prevalence of MS is low such as Italy, Greece, and Spain[4].

According to one series of studies 70-88% of MS patients are still alive 25 years after clinical onset, and the

median time from onset to death ranges from 24 years to >45 years[4].

The ratio between women and men has increased significantly due to the increased incidence of multiple sclerosis in women[5].

2 RISK FACTORS

The etiology of the disease remains unclear, however a combination of genetic and environmental factors may lead to the onset of the disease[6,7].

MS is clearly more common in women. Therefore, hormonal factors are considered to be involved in regulating the course of the disease[8].

Another risk factor is the insufficient exposure of individuals to vitamin D. Vitamin D has important immunological and hormonal functions, and its deficiency is associated with the risk and severity of MS[2]. Studies have shown that the percentage of people who get sick is higher in geographical areas far from the equator, which are less exposed to solar radiation. Conversely, for people living in areas that consume a large amount of fish rich in vitamin D, the disease rates are much lower[7].

Furthermore, while the disease is common in areas inhabited by people from northern Europe the effect is modified depending on where those individuals lived in their early lives. Migration studies since the 1970s show that migration from low-risk areas to high-risk areas in childhood is associated with a low risk of developing multiple sclerosis and vice versa[5].

It is interesting to discuss that environmental factors that mostly appear during childhood seem to play a role in the onset of the disease. Thus, if childhood is the most fragile period for the onset of MS later in life, then preventive measures should be implemented early in childhood (for example, adopting a diet rich in vitamin D, etc.)[4].

In addition, factors implicated as positively influencing the onset of MS are smoking, childhood obesity[6], infectious mononucleosis as well as exposure to the Epstein-Barr virus[4,7]. Obesity in early life is associated with a two-fold increase in the risk of developing the disease in men and women, which could be due to the reduced vitamin D levels of obese individuals[5].

Finally, the increased heritability among MS families provides evidence that genetic factors play a prominent role in the development of MS[5].

3 CLINICAL FEATURES

MS is often accompanied by specific cognitive deficits that affect memory, concentration, speed of information processing, and executive functions[9]. The clinical picture of MS patients depends on the focus on the Central Nervous System, so patients may present symptoms such as muscle weakness resulting in difficulty moving, numbness in the face and lower limbs, visual disturbances, bladder and bowel dysfunction, sexual dysfunction, fatigue and depression[10,11].

The physical manifestations of MS lead to difficulty with balance and gait, which is an important factor in determining the functional status of people with MS. Imbalance usually appears early in the disease and typically worsens as the disease progresses. This implies an increased risk of falls and reduced quality of life[12].

Among the most common mental disorders in MS are depression, anxiety and sleep problems[13]. There is a strong correlation between fatigue and depression and also between depression and anxiety, and these interactions have significant effects on patients' quality of life[14]. Fatigue is the most frequently reported symptom and affects up to 80% of patients [11,13].

In addition, among the early symptoms of the disease are disorders of the bladder, bowel and sexual function[15]. All these symptoms affect multiple aspects of life and activity and essentially constitute an obstacle to daily activities, family, social and professional life[16]. Contributing to the complexity of symptoms are changes in mood, personality and cognitive function and, by extension, the impairment of the quality of life of people with MS[17].

4 FATIGUE

Fatigue is a common symptom for the majority of MS patients with a rate of up to 80% and the influence of fatigue is related to functional, family and social life dysfunction [18,19].

Progressive fatigue during the day is typical for this group of patients. It starts soon after they wake up from a night's sleep and is aggravated by various factors, e.g. temperature, pain and physical activity[20,21].

The symptom of fatigue significantly affects the cognitive functions of individuals, thus reducing their concentration and attention. Therefore, fatigue is one of the main reasons for people with MS to leave work[16].

5 DEPRESSION

Depression affects 26-55% of patients, and approximately 50% of patients who experience depression remain with them for life[22-25].

Diagnosing depression in MS patients is imperative because depression worsens motor disability. Additionally, depression has a detrimental effect on patients' cognitive

and physical functions[26] and may contribute to patients' reduced adherence to treatment[27].

Depression, anxiety, the stress of adapting to the disease, fear, side effects from the treatment, anxiety, the impairment of the person's functionality due to the effect of the disease, the lack of a supportive environment, the incomplete planning of the interventions, etc result in patients experiencing social exclusion, frustration, hopelessness and finally, a reduction in the quality of life.

6 MULTIPLE SCLEROSISIN PREGNANCY

The onset of MS usually occurs during the reproductive years. Therefore, pregnancy among MS patients is common[8].

In the past, especially during the first half of the 20th century, female patients were often discouraged from becoming mothers because pregnancy was considered a risk for MS. Although some studies may suggest that MS increases the risk of adverse effects on pregnancy outcomes, the majority of studies demonstrate that the risk of complications during pregnancy and delivery outcomes are the same as in healthy women[28-30].

Pregnancy has a strong influence on disease activity. Therefore, for the period of pregnancy and for a period immediately after delivery, the course of the disease is better controlled than at any other period of the patients' life. In particular, there is a significant reduction in the rate of relapse of up to 70% of patients with the disease during the third trimester of pregnancy and for the first 3 months after delivery, either in the form of relapse or as activity in magnetic resonance imaging (MRI) findings[8,31].

The reasons for the improvement of MS during pregnancy and the activation of the disease after delivery are based on changes in the levels of the female sex hormones, estrogen and progesterone, and the significant changes in the function of the immune system[31,32].

After delivery, the disease often worsens, with frequent relapses and the highest incidence of relapses within 3 months of delivery. The reasons for the increased activity after delivery are not entirely clear, but factors such as the sharp decline in estrogen levels and the rapid return of the mother's immune function to the normal pre-pregnancy state are possible explanations[8].

6.1 Family Planning

Many women with MS want to have children. However, they are often unsure whether the disease and its treatment will allow them to carry a pregnancy to term and whether there will be effects on their health as well as on the fetus. One of the first things women with multiple sclerosis who want to have children want to know is whether there is a risk that their children will develop the disease and if there is anything they can do to prevent this[33].

MS as a disease does not preclude fertility and pregnancy, however, pregnancy planning is considered a prerequisite for responsible motherhood[30]. Family planning is important when choosing an initial treatment for multiple sclerosis, and patients should be advised of the safety of dimethyl fumarate use during pregnancy and advised to plan pregnancy[34]. Female patients during the family planning phase should be informed that MS does not have significant effects on conception, pregnancy outcome and normal fetal development[35]. According to studies women with MS take the same amount of time to get pregnant as the general population. Therefore, neither MS itself nor the use of immunosuppressive drugs reduces fertility[33].

Several studies show that for pregnant women treated with interferons compared to those pregnant women not exposed to interferon, their newborns have a lower average birth weight, shorter length and preterm birth. The results of the studies are not related to birth weight less than 2,500kg, by caesarean section, with congenital anomaly or spontaneous abortion[36].

On the other hand, contraception should be discussed with female patients of childbearing age, especially when drugs such as Figolimod and Teriflunomide are chosen for treatment, which have potentially teratogenic effect[33]. In terms of contraception, not only is there no evidence that contraceptives can adversely affect the clinical course of MS, but it has also been suggested that high-dose estrogen-containing contraceptives can provide an anti-inflammatory effect[30,37].

Ideally, the time of MS diagnosis and pregnancy planning should not coincide because a window of time is needed to assess disease activity. In addition, the risk of relapse is higher after the first seizure. Since the diagnosis of MS is followed by the initiation of treatment, the woman's desire for a future pregnancy should be taken into account in order to choose the appropriate and safe treatment regimen for herself and the fetus[30]. Therefore, family planning must be carried out before the decision to start pregnancy since the risk of teratogenesis exists in some of the medicinal substances used as treatment[36]. In order to plan a pregnancy the MS disease must be inactive for at least 12 months[38].

In addition, during the pre-pregnancy family planning consultation, immunization (varicella if there is no previous infection, measles, mumps and rubella for those born after 1980) is recommended, taking into account that such live attenuated vaccines are contraindicated while taking immunosuppressants and can only be taken into account 3 months after the break[38].

6.2 Genetic Factors

Susceptibility to MS is based on a complex interaction

between individual genes and the external environment. The risk to offspring is small but may be of concern to prospective parents[37,39].

However, the risk of developing the disease in the child is equal to 4% if only one parent is affected while the rate in the general population is 0.2%. About 15% of all MS patients are closely or distantly related to people who also have MS, but the majority of patients have no family history. In the case where both parents suffer from MS the percentage can vary from 20% to 30%[36,39].

These evidences indicate that there is a strong genetic factor that when combined with possible environmental insults, can lead to the onset of the disease[40].

6.3 Management Of Ms During Pregnancy

Pregnant women with MS should continue to take vitamin D and folic acid supplements, maintain a healthy diet, and refrain from smoking and alcohol[41].

In France, there are national recommendations which emphasize that obstetric follow-up remains unchanged in MS unless there is a stable level of disability. In addition, there is collaboration between neurologist, obstetrician, anesthesiologist and general practitioner necessarily[38].

At least one visit to the neurologist during pregnancy is recommended, either in the first trimester or later in pregnancy[38].

Pregnant women with multiple sclerosis should be informed that urinary tract infections are more common during pregnancy, should be educated in recognizing the initial symptoms of UTI and advised to perform pelvic floor exercises[34].

Most inactivated vaccines can be used normally during pregnancy, while live vaccines should be recommended for use before pregnancy. (mRNA vaccine for COVID-19 is recommended)[41].

If necessary, in case of disease reactivation or safety concerns, MRI without gadolinium can be performed[34]. The application of MRI should be evaluated on a case-by-case basis, and a standardized protocol with a magnetic field strength of 1.5T is recommended for the detection of new or enlarging T2 lesions with active disease[41].

In the third trimester, a visit should be scheduled to take an updated report of the neurological status and plan the postpartum period[34].

6.4 The Effect of Pregnancy on Multiple Sclerosis

Pregnancy has a positive and protective influence on disease activity. The results of the studies report a significant decrease in the relapse rate during pregnancy in women with MS, especially in the third trimester, which is followed by a sharp increase in the number of relapses in the immediate postpartum period and a return to levels of the year before pregnancy[37,42,43].

During pregnancy, data from brain imaging with magnetic resonance imaging are limited. Despite this, in women who underwent MRI there was a marked reduction in the number of active lesions, with the active lesion burden dropping to zero in the third trimester[29,37].

The beneficial effects of pregnancy in MS may be explained by the relative state of immunosuppression induced by the fetoplacental unit during this period[29,44]. The most accepted theory to explain the protective effect of pregnancy on relapse rate and disease activity in women with MS is that, during pregnancy, estrogen and other sex hormones change the immune profile[42,44].

Estrogen is a hormone that has a strong effect on the change of the immune system, the percentages of which increase during pregnancy and especially in the last trimester. This increase suppresses immune activity resulting in a subsequent reduction in disease activity. After delivery, estrogen levels drop immediately and the immune system returns to its normal function and, by extension, the disease continues its course[42,43].

Another possible explanation for the association of pregnancy with spontaneous remission is cytokine secretion by the placenta. With increased cytokine production, an increase in the number of helper T2 cells and a concomitant suppression of helper T1 cells have been observed[29,43,44].

Some patients with existing mobility difficulties may experience further reduced mobility and increased spasticity as pregnancy progresses due to increasing weight and changes in the center of gravity. In these cases women should be informed about possible falls and that they may need further physical therapy than usual[37].

6.5 The Role of Estrogens

Studies that have been performed in rats with autoimmune encephalomyelitis, found the protective role of estrogen where it caused a reduction in insulin and clinical severity. They also demonstrated reduced inflammatory activity and reduction of lesions and demyelination in the white matter of estrogen-treated mice[45].

Another study of non-pregnant women with relapsing rheumatoid arthritis who took high-dose estrogen-containing contraceptives and concomitant interferon-b1a therapy for 96 weeks observed a significant reduction of 26.5% in active lesions on brain MRI imaging compared to those women who received only interferon-b1a[42].

In other studies administering the hormone estriol to non-pregnant women at a dose permitted in pregnancy, the results were again a reduction in lesions. Enhancement of lesions returned to pretreatment when estriol was stopped and was significantly reduced again when the hormone was restored[42].

6.6 Postpartum Multiple Sclerosisrelapse Rate

The studies that have been carried out internationally on the effect of MS during pregnancy amount to a large number. Based on these studies, a significant increase in the relapse rate after the first postpartum trimester is demonstrated[46]. From the second trimester onwards for the next two years postpartum, the relapse rate does not differ from that before initiation of pregnancy. Specifically, the relapse rate returns to the prepregnancy rate[43,47,48]. Even in the modern era of treatment, there are no evidence-based interventions to effectively prevent postpartum relapse.

A strong predictor of early postpartum relapse appears to be the annual relapse rate in the pre-pregnancy period, suggesting that minimizing the relapse rate before conception may lead to better early postpartum relapse outcomes[42]. According to Langer-Gould (2013), a higher incidence of relapse before pregnancy and relapses during pregnancy are strongly associated with an increased risk of postpartum relapses. Therefore, the more active the disease is before pregnancy and during pregnancy, the higher the risk of postpartum recurrence[47,49].

It is widely accepted that the months after childbirth are very dangerous for the occurrence of MS relapses. In order to reduce this risk, it has been suggested that modulating and immunosuppressive therapies be started soon after delivery. The present proposal has the disadvantage that lactating patients have no guarantee for the safety of the newborns due to the active substances that pass through breastfeeding[50].

Stability of women's MS before they become pregnant is paramount to avoiding relapses after delivery[51]. The postpartum period is a more difficult time to control disease activity, as treatment with azathioprine, fingolimod, glatiramer acetate, interferon β, mitoxantrone, or natalizumab is not recommended during breast-feeding.

Corticosteroids and intravenous immunoglobulins can be given to treat and prevent postpartum recurrences in patients who are breastfeeding[52,53]. However, considering the low doses of steroids excreted in breast milk, short courses of steroids could be given if several (between two to four hours) injections are separated from breastfeeding[51].

To deal with postpartum relapses, the neurologist should pay special attention to the patient in order to create an individualized treatment plan. In patients with a high rate of recurrence, it should be decided together with the patient to resume medication and delay breastfeeding[41].

6.7 The Role of Vitamin

Reduced vitamin D levels among mothers with MS during pregnancy affect both maternal and newborn health. Vitamin D deficiency in pregnancy has been associated with multiple potential adverse effects on the mother and offspring[54]. In particular, breastfeeding increases the risk of hypovitaminosis D in mothers, and this is known to be a well-described risk factor for MS that is associated with a higher risk of relapse[49].

7 COUNSELING FOR FAMILIES WITH MULTIPLE SCLEROSIS

Patient counseling is important and should be based on the individualized needs of each patient and be tailored and targeted to each patient's clinical, psychological and socioeconomic status[55].

MS patients may have many doubts and concerns during the reproductive cycle and family planning. For this reason, it is useful to divide the childbearing period into the period before pregnancy, during and after childbirth, so that the patient can focus on the corresponding instructions in each case.

In the preconception period expectant parents should be informed about the couple's sexual activity, the effect of MS on fertility, and the risks of MS treatment on fertility. Also, on the use and effect of contraceptive preparations, on the possible risk of developing MS in the offspring and on the possible effects of previous and current treatment on pregnancy and the fetus. And finally about the short and long term effects of pregnancy and MS.

During pregnancy the information is about the management of MS, about the use and results of symptomatic and modifying therapy as well as about the treatment of relapses. In addition to the use of MRI to assess disease activity. Finally about the short and long term effects of pregnancy on MS.

In the postpartum period, the information concerns the prediction of relapses and their treatment. At the time of initiation of the symptomatic and also the modifying treatment of MS. Breastfeeding and its benefits, potential disability parenting and finally long-term planning[55].

8 BREASTFEEDING AND MULTIPLE SCLEROSIS

Breastfeeding should be encouraged, because there is no risk of transmission of the disease through breast milk. The disease itself does not create obstacles to breastfeeding. In particular, it has been observed that mothers who exclusively breastfeed have much lower rates of disease activity than mothers who do not exclusively breastfeed or do not breastfeed at all[43]. Recent publications report that

exclusive breastfeeding is associated with a protective effect in reducing postpartum relapse. According to Anderson et al.[56], exclusive breastfeeding reduces the chances of early damage after delivery for at least 3 months[56]. In addition, prolonged amenorrhea associated with lactation results in a fourfold reduction in postpartum recurrences[49,57].

Exclusive breastfeeding, for at least 2-4 months, reduces the risk of relapse, possibly as a result of hormonal changes[58]. Hormones activated by exclusive breastfeeding provide a possible explanation for the protective effect in breastfeeding mothers with MS. With exclusive breastfeeding, prolactin levels significantly increase resulting in the suppression of ovarian function[43,59]. According to a study by Gregg et al.[60], high prolactin levels promote remyelination[60].

The case for exclusive breastfeeding is extremely attractive because it is available to women worldwide regardless of economic status, thus offering a potential high-impact strategy to reduce the risk of postpartum recurrence and improve offspring health. Breast milk provides infants with antibodies and other factors that aid in the healthy development of their immune system[49].

In a study by Hellwig et al.[61], it is reported that mothers with MS who exclusively breastfed their infants for at least 2 months had a significantly lower risk of relapse during the first 6 months postpartum compared to mothers who did not exclusively breastfeed. Therefore, exclusive breastfeeding appears to act as a moderately effective treatment in MS with an expiration date[61].

In Greece, it is observed that there are no specialized structures for the care of pregnant women with MS. Women with MS are deprived of the care and support they need to relieve the multiple symptoms of the disease while simultaneously feeling anxious and helpless in the early days of their delivery.

9 DISCUSSION AND CONCLUSION

In the present review, MS was studied in relation to pregnancy. The changes that occur during pregnancy and how they affect MS were studied.

MS disease usually manifests itself between the ages of 20 and 40 during the reproductive period and affects women more often than men**.** This differentiation is probably due to hormonal factors as well as lifestyle.

The occurrence of MS does not appear to affect the fertility of patients, who have a normal fertility rate, and also does not affect the fetuses. Studies have shown that the effects on the fetus do not differ between women with MS and healthy women.

Studies show that the rate of recurrence decreases during pregnancy, and specifically during the third trimester, the decrease reaches 70%. What is concluded about the causes of the decrease in recurrences is that an important role is played by the hormonal changes that occur in the body during pregnancy and that hinder the development of the immune system.

In the period immediately after childbirth, the risk of recurrence increases. A possible explanation is exclusive breastfeeding, which appears to have a protective effect on disease activity.

Finally, there is a high probability that pregnant women with MS will experience depression during pregnancy and especially after delivery. The possibility of postpartum depression is very likely since the disease is a risk factor for depression and in combination with the hormonal changes that occur increase the rate. Therefore, it is considered necessary for the team of health professionals to be close to the patient in order to prevent any kind of complication. In addition, it would be important for the patient to be referred to a mental health professional for psychological support.

The rate of developing MS in the offspring of mothers with MS is 3% to 5%. The explanation for this is that the disease has genetic characteristics. On the other hand, this percentage is not particularly high because the probability that they will not develop the disease is 96%.

Many women suffering from MS do not have full knowledge of how MS affects pregnancy and vice versa and for this reason many of them hesitate to proceed with a pregnancy. For this reason, it is considered necessary as soon as MS is diagnosed that patients are informed immediately about the complications of the disease and if they want to have children. In this way, they will be informed about the medication, how it can affect the fetus, as well as the time when the medication should be stopped. Women with MS would be better off having a planned pregnancy. If they do not want to have children, they should be informed about the importance of contraception[38].

In the future, it would be useful to train health professionals about MS and how it affects pregnancy, in order to inform patients about the course of the disease in pregnancy. In this way, women will be able to have full information about their disease and will know in advance that a future pregnancy does not negatively affect the disease, nor is the disease harmful either to the patient or to the fetus.

Finally, it would be useful to organize highly specialized and trained multidisciplinary structures for the care, counseling and psychosocial support of MS patients.

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Conflicts of Interest
The authors declared no conflict of interest.

Data Availability
No additional data are available.

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Author Contribution
Evaggelia S had the initial idea of the manuscript, Evaggelia S, Andriopoulou M and Dimitrios C wrote and drafted the manuscript, and Dimitrios C, Victoria V had final supervision of the manuscript.

Abbreviation List
MS, Multiple sclerosis
MRI, Magnetic resonance imaging

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