

# Multiple sclerosis in pregnancy. Treatment options and outcomes: a review

Delia Cudalba<sup>2</sup>, Nicolae Gica<sup>1,2</sup>, Gheorghe Peltecu<sup>1,2</sup>, Radu Botezatu<sup>1,2</sup>, Anca Maria Panaitescu<sup>1,2</sup>

<sup>1</sup> "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

<sup>2</sup> Filantropia Clinical Hospital, Bucharest, Romania

## ABSTRACT

**Background.** Women are commonly diagnosed with multiple sclerosis during reproductive age. There is need for disease control management during pregnancy, taking into consideration potential maternal and fetal risks. This review article aims to summarize what is acknowledged so far regarding treatment options of multiple sclerosis and outcomes in pregnancy, providing up-to-date information.

**Methods.** In order to write this review a comprehensive literature electronic search for journal articles and guidelines regarding multiple sclerosis during pregnancy was undertaken.

**Results and conclusion.** Multiple sclerosis management in pregnancy is a challenging issue. The use of disease-modifying drugs has improved both the course of the disease and the attitude towards pregnancy in patients living with multiple sclerosis. Pregnancy appears to have a protective effect on disease activity, particularly during the third trimester.

**Keywords:** multiple sclerosis, pregnancy, disease-modifying therapy, outcomes

## INTRODUCTION

Multiple sclerosis is a degenerative, chronic inflammatory and autoimmune disease characterized by demyelination and axonal damage in the central nervous system, producing gradual physical and cognitive impairment caused by the alteration of the conduction of electrical impulses to muscle groups [1]. It is one of the most common causes of disability in young adults [2].

Multiple sclerosis has a progressive course with different clinical manifestations as spasticity, discoordination, tremor, sensory changes (decreased sensation, tingling), cognitive dysfunction (short-term memory loss, decreased information processing speed), vision deficits, bowel and bladder dysfunction, seizures, pain, mood disorders, sexual dysfunction [3,4].

According to the statistics, 2.8 million people are living with MS. Multiple sclerosis develops in young adults, mostly affecting women of childbearing age

(20-40 years). The ratio of female to male is 2:1, even 4:1 in some countries [5].

Studies report that one in three female patients become pregnant after being diagnosed with MS [6].

The most common clinical form is the relapsing remitting MS. The disease may have a progressive course without remission – secondary progressive MS, although some patients experience the primary progressive MS, with a progressive course from the onset. The best results were seen in treating the relapsing remitting form as monoclonal antibodies and other disease-modifying drugs revolutionized the management of MS [7].

As the incidence of MS is on the rise in the last decades and most of the candidates are women of reproductive age, the management of the disease during, before and after the conception in order to lower the chances of relapse but avoiding the possible adverse outcomes of the disease-modifying therapies remains a controversial and complex issue.

*Corresponding author:*

Anca Panaitescu

*E-mail:* panaitescu.anca@umfcd.ro

*Article history:*

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This review article proposes to review current data regarding the pharmacologic therapeutic considerations and the outcomes for women affected by MS in pregnancy.

## MATERIALS AND METHODS

A systematic literature electronic search for studies and guidelines was undertaken using major electronic databases – PubMed, Cochrane Library. Search words were multiple sclerosis combined with “pregnancy”. Publications were selected based on accessibility to full paper article, quality evaluation, publication year. The publications used are mentioned in References section. This is a literature review.

## DISCUSSIONS

### Current treatment options

Multiple sclerosis management involves treating specific symptoms, reducing frequency of relapses and preventing disease progression. Disease-modifying drugs can be immunomodulators-interferon beta, alemtuzumab, natalizumab, glatiramer acetate, teriflunomide, dimethyl fumarate, ocrelizumab, corticosteroids and immunosuppressants – cladribine, fingolimod.

Interferon beta is the first disease-modifying therapy used to treat multiple sclerosis. It has satisfying results in reducing relapse rates and delaying the onset of disability [8]. Considering its high molecular weight, interferon beta does not cross the placenta [9]. Since 2019 the European Medicines Agency approved the use of interferon beta in pregnancy. This recommendation was supported after the results of two cohort studies [10,11]. There was a concern around an association between treatment with interferon beta and an increased rate of spontaneous abortions, but it was dismissed in recent large studies [12,13].

Glatiramer acetate is indicated in patients with relapsing-remitting MS, reducing the frequency of relapses. It benefits from same large molecular weight as interferon-beta and does not cross the placental barrier. Concerning exposure to glatiramer acetate in pregnancy, studies proved that its use is safe [14].

Studies report for both interferon beta and glatiramer acetate that postpartum restart after cessation during pregnancy takes several months to come to full potency and may not be useful in lowering rates of relapse until then [15].

Dimethyl fumarate is used for relapsing forms of MS. Although studies reported no teratogenic events or potential risks, there is not sufficient data in order to draw conclusions regarding its use in preg-

nancy. So far, dimethyl fumarate is not recommended in pregnancy [14].

Teriflunomide is an immunomodulator indicated for relapsing forms of MS for its anti-inflammatory effects. It was proved to be teratogenic and embryotoxic in animal studies and therefore was contraindicated in pregnancy. There were a few studies which demonstrated no teratogenic effects, but not enough data to be able to update recommendations [14,16].

Alemtuzumab is usually reserved for cases where there is inadequate response to at least 2 drugs for MS because of its severe autoimmune adverse effects.

Guidelines recommend efficient contraception up to 4 months after using alemtuzumab. The main concerns with its use in pregnancy is a higher risk of developing autoimmune thyroiditis which may further lead to premature birth, neurocognitive disabilities, low birth weight or preeclampsia [17,18].

Fingolimod reduces the frequency of clinical exacerbations and delays the progression to physical impairment. It is recommended to stop Fingolimod two months before conception and while breastfeeding.

Natalizumab is one of the major disease-modifying drugs currently used in MS treatment. It is administered as monotherapy for reducing frequency of relapses and preventing disease progression. Due to its large molecular weight, it does not cross the placenta until the second trimester. It is known that interrupting its use prior or during pregnancy may determine severe disease reactivation. Recent studies proved that cessation of natalizumab in early pregnancy instead before conception would lower rates of relapses. Guidelines recommend continuation of natalizumab until 34 weeks of gestation where permanent treatment is needed. Natalizumab infusions could pass to 8-weekly instead of 4-weekly, resuming postpartum in 8-12 weeks after the last infusion. Exposure to natalizumab in late pregnancy was found to cause minor, self-remitting hematological abnormalities in infants [19].

The major concern when using natalizumab is the risk of progressive multifocal leukoencephalopathy, therefore, routine MR brain imaging monitoring should continue during pregnancy. There were no cases of congenital PML so far. Regarding breastfeeding, there was observed low absorption [20-22,15].

Ocrelizumab is indicated in relapsing or primary progressive forms of MS. It is an immunoglobulin, therefore it is believed that it crosses the placenta and the fetus is exposed if administered during pregnancy. Effective contraception up to 6-12 months is recommended after treatment with ocrelizumab. The use during breastfeeding is contraindicated [15].

Cladribine is an immunosuppressant given for relapsing-remitting disease and active secondary progressive disease, recommended when there is inadequate response to first-line options. Cladribine use during pregnancy was observed in animal studies, where there was demonstrated that it is embryo lethal in female mice and teratogenic to both female and male mice. Although cladribine does not interfere with hormonal contraception, taking into account the potential fetal adverse outcomes, it is recommended to add a barrier method of birth control during treatment and even 4 weeks after the last dose. Women receiving cladribine should defer pregnancy for at least 6 months after treatment. Breastfeeding is contraindicated during treatment and one week after completing it [14,15].

Corticosteroids prevent and suppress inflammation and are used to treat acute exacerbations.

Corticosteroids should be avoided during the first trimester because of the risk of fetal malformations [23]. During the second and the third trimester's high-dose methylprednisolone courses are the main option in treating particularly severe relapses.

The possibility to use IFN-beta and glatiramer acetate in pregnancy and natalizumab up to 34 weeks has brought a solution for women with high relapse rate in this particular period. Health care providers and also patients should be aware of the disease-modifying drugs which are teratogenic like fingolimod, teriflunomide, alemtuzumab, cladribine or ocrelizumab.

The first large prospective study concerning the natural history MS published in 1998 and so far the main results are confirmed by subsequent studies [24].

The Pregnancy in Multiple Sclerosis (PRIMS) study concluded that the rate of relapses lowers during pregnancy, in particular in the third trimester, but increases during the first three months after birth [25].

The number of relapses is almost halved during pregnancy and approximately doubled in the first three months postpartum. It is believed that pregnancy is associated with less long-term impairment [26, 27].

### **Pregnancy outcomes**

The conceptional perspective of women living with multiple sclerosis changed over the last decades. Until late 1990s women diagnosed with multiple sclerosis were recommended to avoid pregnancy. PRIMS study was of important significance in changing perspectives of conception in patients with multiple sclerosis.

### **Impact of pregnancy on multiple sclerosis course**

Studies on the short-term impact of pregnancy on multiple sclerosis proved that the relapse rate

decreases during pregnancy, particularly during the last trimester but increases postpartum, mainly during the first 3 months following delivery [28,29].

The protective effect of pregnancy on disease activity is explained by the switch in the T helper cell profile from pro-inflammatory cytokines Th1 to anti-inflammatory cytokines – Th2 induced by estrogens and other sex hormones. Following delivery, the disease rebound is influenced by the resuming of the immune system to its pre-pregnancy settings. [30,31].

Important risk factors for early postpartum relapses are higher rate of relapse and no use of disease-modifying therapy in the 2 years before pregnancy, the number of relapses during gestation. Early postpartum relapses are poor prognostic markers for disability progression. There are studies which report lower risk of postpartum relapses in women who were administered at least 8 weeks of therapy during pregnancy [32-35].

The long-term effect of pregnancy on disability progression continues to be a debatable issue. There are controversial findings in the literature. Some studies report no influence of the pregnancy on disability accumulation over time [36]. Other studies show a slower progression toward disability in women who conceived after the diagnosis of multiple sclerosis versus nulliparous women [37].

### **Impact of multiple sclerosis in pregnancy**

Recent data supports the evidence that multiple sclerosis does not have a great impact on pregnancy outcomes.

Studies on multiple sclerosis in pregnancy showed that the rate of ectopic pregnancies and spontaneous abortions and spontaneous pregnancies was similar to the general population. However, the mean number of children per women with multiple sclerosis was proved to be lower than general population [38-41].

Guidelines advice that except for the cases where there is noteworthy disability, the mode of delivery should not be influenced by multiple sclerosis. Still, studies report greater rates of cesarean delivery in women with multiple sclerosis [42,15]. Regarding anesthetic concerns, both epidural and general anesthesia are considered to be safe [43].

Some studies reported a higher incidence of small for gestational age off springs, urinary tract infections, constipation and of induced labor, in particular in cases with greater disability [44].

The rate of hospitalization before and after delivery was reported to be higher in women with multiple sclerosis [45].

## **CONCLUSIONS**

The use of disease-modifying drugs has changed both the course of the disease and the perspective of

pregnancy in patients living with MS. New therapeutic developments made it possible to successfully and safely control disease activity in women with MS during gestation and afterwards.

Multiple sclerosis management in pregnancy is challenging since most disease modifying treatments are contraindicated or not enough documented during this period.

Improved patient care for women living with MS throughout preconception, pregnancy, labor,

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