



Multiple sclerosis and pregnancy – treatment considerations

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Abstract

Multiple sclerosis is a chronic inflammatory disease which, due to the destruction of the fibres of the central nervous system in the process of demyelination, leads to numerous neurological symptoms and progressive disability. The disease is autoimmune, which means that myelin is destroyed by the patient's own cells, caused by improper functioning and regulation of the immune system. Multiple sclerosis affects more and more people and is therefore a significant clinical problem which, to a large extent, affects women, especially in childbearing age. This presents a big challenge for carrying out pregnancy while continuing the therapy, ensuring the safety of the foetus and simultaneously achieving the best possible therapeutic effect. The decision whether the therapy should be continued or whether it should be eliminated is usually made according to assessment of the possible gains and losses. Despite the lack of clear indications, there are many studies proving the relative safety of the use of individual but not all the drugs during pregnancy. Pregnancy, however, has a fairly good impact on the development of multiple sclerosis, and that safety considerations, especially those concerning the growing foetus, force a decision to change or completely suspend the therapy. In-depth research on the already available and emerging therapeutic pathways in multiple sclerosis bring hope for increasingly better results in the future in the treatment of pregnant patients with multiple sclerosis.

Key words

pregnancy, Multiple sclerosis, neurology, gynecology, treatment considerations

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease leading to demyelination and consequent destruction of nerve fibres in the central nervous system (CNS), which leads to a gradual loss of their function, causing various neurological symptoms and gradually aggravating the patient's disability [1]. The disease is autoimmune, which means that myelin is destroyed by the patient's own cells, caused by the improper functioning and regulation of the immune system [2].

Multiple sclerosis may vary among patients due to the fact that any part of central nervous system can be affected resulting in different symptoms one to another. Three main types of disease can be distinguished that differ in the type of progression and clinical assessment. First, there is relapsing-remitting multiple sclerosis (RRMS), which occurs the most often, characterized by many relapses over time, divided by periods of total or at least significant remission. Relapses are characterized by new neurological symptoms or exacerbations of preexisting neurological symptoms that were preceded by at least one month of clinical stability [3]. Secondly, primary-progressive multiple sclerosis (PPMS), in which no relapses occur. In some cases, the symptoms do not disappear and once disability occurs, it increases. The third type, secondary-progressive multiple sclerosis (SPMS), usually begins 10 years later than RRMS [4]. Prognosis

depends on the type, but the disease undoubtedly decreasing life expectancy from five to 10 years [5].

The incidence of the disease ranges from two to 150 cases per 100,000 of the population, which makes it a significant clinical problem and challenge [6]. Importantly, multiple sclerosis affects women to a large extent, and are from two to three times more likely to be diagnosed [7]. It very often begins between the ages of 20 and 40 [8]. Due to the fact, that this is the reproductive age, the doctor and the patient often have to deal with pregnancy management in conditions of a chronic disease. Although the outcome of healthy pregnant women and those with MS is very often similar, there are several important risk factors. For instance, patients with MS have a higher risk of infection during pregnancy which can affect the life and health of the mother as well as the foetus [9]. Just as multiple sclerosis can influence the course of pregnancy, pregnancy influences the course of the disease and presents new clinical challenges for the medical team. One such challenge is obviously conducting therapy in such a way as not to endanger the life and health of the mother and the foetus, while achieving the best therapeutic effect on MS.

OBJECTIVE

The presented study describes the relationship between pregnancy and multiple sclerosis, focusing on the impact of various forms of therapy on the development and safety of the foetus and the ultimate success of the pregnancy itself. The study is based on a literature review on this topic,

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primarily from the PubMed database, that was searched with the following terms: 'multiple sclerosis' and 'pregnancy'. The most recent papers, preferably not older than eight years, were chosen in order to provide the most appropriate and reliable data.

The influence of pregnancy on the course of multiple sclerosis. Due to the autoimmune background of multiple sclerosis, the immunomodulatory effects caused by pregnancy have a very good effect on the course of the disease. Immunomodulation is necessary to protect the foetus which, being a molecular foreign organism in a woman's body, may be exposed to the harmful and potentially lethal effects of the mother's immune system. Numerous factors, mainly hormonal (progesterone and estrogens are most important), have an inhibitory effect on the functioning of immune cells. This condition allows for the development of the foetus, but it is also somewhat incidental in the relief of MS progression [10].

In addition to the general reduction in the severity of the disease, fewer relapses are observed in pregnant women. The study conducted by Confavreux on 227 patients showed a 70% reduction in the frequency of relapses in the third trimester [11]. According to Salemi et al., although during pregnancy, especially in the third trimester, the number of relapses is significantly lower than before pregnancy, there is no significant difference in the number of relapses in relation to the year before pregnancy than during pregnancy, and three months after childbirth [12]. However, the number of relapses may increase slightly immediately after birth, and the positive effect of pregnancy is undeniable. It is also worth noting that a large number of pregnancies improves the overall prognosis of patients, which is manifested primarily by a lower degree of disability as a result of disease progression, or a longer time to achieve it. [13]. Although many studies prove this relationship, it should be noted that women with a more severe course of the disease decide to have a child less often, which may lead to false conclusions.

Effects of multiple sclerosis treatment on pregnancy.

Although pregnancy may have a positive effect on the course of the disease, it is also a specific, high-risk condition requiring verification by existing therapies. Patients suffering from MS and planning children should inform their doctor as soon as possible in order to evaluate and modify the treatment, if necessary, in the interest of the foetus and mother.

The safety of drugs used in pregnancy is assessed using the Food and Drug Administration (FDA) classification (Tab. 1). However, in 2015, the FDA replaced the former pregnancy risk letter categories on drug labeling with new information to make them more comprehensible, although the old, pre-2015 classification it is still in use. There are a number of medications available for the treatment of multiple sclerosis, ranging from ongoing disease-modifying medications to those relieving symptomatic treatment and are the two main pillars of multiple sclerosis therapy.

Table 2 summarizes the most commonly used disease-modifying drugs and their safety categories (prescribing information was downloaded from product websites). These are drugs that are taken irrespective of the occurrence of relapses, often long-term, affecting the immune system of patients in order to reduce the severity of the disease.

Table 1. FDA pregnancy categories

A	No evidence of fetal harm in well- controlled human studies
B	No evidence of fetal harm in animal studies
C	Evidence of fetal harm in animal studies or no available data
D	Evidence of fetal harm in humans, however in some circumstances use may be justified
X	Not indicated for use during pregnancy due to evidence of fetal harm in humans

Table 2. Safety categories of disease-modifying therapies

IFN- β 1b	C
IFN- β 1a	C
Fingolimod	C
Glattiramer acetate	B
Dimethyl fumarate	C
Teriflunomide	X
Alemtuzumab	C
Natalizumab	C
Mitoxantrone	D

Moreover, there is no adequate data on risk in pregnant for both dactalimumab and ocrelizumab; however, dactalimumab may cause embryofetal death and reduced growth at exposures 30 times higher than used in clinical circumstances. Ocrelizumab is proven to put infants at risk of B-cell depletion and lymphocytopenia due to its mechanism of action as an anti-CD20 antibody [14].

Table 3. Safety categories of symptoms management therapies

Corticosteroid	C
Baclofen	C
Diazepam	D
Tizanidine	C
Gabapentine	C
Amantadine	C
Modafinil	C
Oxybutinin	B
Tolterodine	C
Dalfampridine	C

Table 3 lists the medications used to suppress relapses which indicate on the labeling their safety category (prescribing information was downloaded from product websites). Corticosteroids are used to treat acute exacerbation [15]. For dealing with spasticity, baclofen, diazepam or tizanidine are administered [16], as well as gabapentin, which also reduces pain and seizures [17]. Amantadine and modafinil decrease fatigue [18]. Oxybutinin and tolterodine are used when the patient is suffering from an overactive bladder [19]. Dalfampridine may be considered to improve walking speed.

As can be seen, the safety profile of drugs used in multiple sclerosis is not satisfactory. It has been assumed that none of the disease-modifying drugs should be taken during pregnancy, and to-date there are no clear guidelines suggesting appropriate therapeutic solutions, although some drugs appear to be safer than others [14]. Particularly

noteworthy are interferons and glatiramer acetate, which show a small number of side-effects. Newer drugs still require in-depth research, although it is already known that some of them may have an adverse effect on the development of the foetus [20].

DISCUSSION

None of the disease-modifying therapies in pregnant women are approved in the United States, but some countries allow the use of individual drugs in certain conditions and circumstances. Usually, the decision whether the therapy should be continued or whether it should be eliminated results from the assessment of possible gains and losses [21, 22]. Despite the lack of clear indications, there are many studies proving the relative safety of the use of individual but not all the drugs during pregnancy. For instance, glatiramer acetate is approved in the countries of European Union for treating pregnant patients with RRMS. There are studies proving no teratogenicity or increase the risk of miscarriages in patients undergoing therapy with glatiramer acetate during pregnancy [23]. Due to this relatively safe profile, it is the only drug approved by the FDA, classified under the letter B.

Interferons, which have not shown any increase in malformations among animal studies, were believed to cause a higher rate of miscarriages. This was observed when using doses higher than established clinical needs, although there are also studies indicating no increase in spontaneous abortions during IFN- β therapy [24, 25]. Also, it has been proved that dimethyl fumarate, when used to treat patients during pregnancy in comparison to the general population, does not cause any harm to the foetus, [26].

The effect of natalizumab on the foetus may slightly increase abnormalities and malformations, but there no particular defects have been observed. Although it is uncommon, in patients with an aggressive type of MS, hematological disorders was detected in 10 of 13 births. All these side-effects indicate the need of for caution, but in some cases the benefits from treatment may be higher than potential damage [27, 28]. Pregnant patients should be treated with natalizumab only by experienced physicians, and due to the mentioned hematological abnormalities, the presence of a pediatrician may be needed [29].

As mentioned, teriflunomide is classified under the letter X, which indicates strong evidence of foetal harm that may be caused by using this drug during pregnancy. Some authors suggest discontinuing the therapy with teriflunomide, as well as dimethyl fumarate and, if necessary, switching to a safer drug should be considered [30]. It is interesting that there are studies proving that this does not have to be the case, and teriflunomide may be used in the treatment of some patients. That being said, one retrospective study should be mentioned that proved no foetal malformations nor miscarriages despite therapy [31]. However, the number of patients was quite low which that may have led to a false conclusion, and in spite of its mentioned potential, the administration of teriflunomide is still not recommended during pregnancy.

CONCLUSION

Multiple sclerosis and pregnancy are quite common coexisting clinical challenges among young women, hence it is extremely important to understand their interaction. Although pregnancy has a fairly good impact on the development of multiple sclerosis, there are occasions when safety considerations, especially those concerning the growing foetus, force a decision to change or completely suspend therapy. However, it happens that pregnancy, by alleviating symptoms, compensates for the lack of drugs, which is a very desirable situation. On the other hand, in the case of more aggressive forms of the disease, administration of drugs may seem necessary. In such cases, the safest possible solutions should be selected from a wide range of available therapeutic options, guided by the latest results of research on the safety of each drug. Although there are no sufficiently clear guidelines for the treatment of MS patients, some drugs seem to be a quite good choice, and some of them are even registered in the European Union.

Whenever possible, discontinuation of disease-modifying therapies is usually recommended. If multiple sclerosis in a pregnant patient is treated with interferon or glatiramer acetate, withdrawal of the drug might be considered, especially in highly active cases. Natalizumab seems to be a beneficial option when the risk of disease reactivation is significant. Women receiving drugs with a worse safety profile, e.g. teriflunomide, may be switched to those mentioned previously (interferon, glatiramer acetate), depending on the particular circumstances.

The welfare of the woman and the foetus should be taken into account before each decision is taken, assessing the gains and losses. In-depth research on the already available and emerging therapeutic pathways in multiple sclerosis bring hope in the future for increasingly better results in the treatment of pregnant patients with MS.

REFERENCES

1. INDS Multiple Sclerosis Information Page. National Institute of Neurological Disorders and Stroke. 2015.
2. Nakahara J, Maeda M, Aiso S, et al. Current concepts in multiple sclerosis: autoimmunity versus oligodendroglial pathology. *Clinical Reviews in Allergy & Immunology*. 2012; 42(1): 26–34.
3. Nazareth TA, Rava AR, Polyakov JL, et al. Relapse prevalence, symptoms, and health care engagement: patient insights from the Multiple Sclerosis in America 2017 survey. *Mult Scler Relat Disord*. 2018; 26: 219–234.
4. Losy J, Bartosik-Psujek H, Członkowska A, et al. Leczenie stwardnienia rozsianego zalecenia Polskiego Towarzystwa Neurologicznego. *Pol Przegl Neurol*. 2016; 12(2): 80–95.
5. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008; 372(9648): 1502–1517.
6. Rosati G. The prevalence of multiple sclerosis in the world: an update. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2001; 22(2): 117–139.
7. Sellner J, Kraus J, Awad A, et al. The increasing incidence and prevalence of female multiple sclerosis – a critical analysis of potential environmental factors. *Autoimmun Rev*. 2011; 10(8): 495–502.
8. Hellwig K. Pregnancy in multiple sclerosis. *Eur Neurol*. 2014; 1: 39–42.
9. MacDonald SC, McEkrath TF, Hernández-Díaz S. Pregnancy Outcomes in Women With Multiple Sclerosis. *Am J Epidemiol*. 2019; 188(1): 57–66.
10. Whitecare CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. *Science*. 1999; 283(5406): 1277–1278.
11. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. *Pregnancy in Multiple Sclerosis Group*. *New England Journal of Medicine*, 1998; 339(5): 259–291.

12. Salemi G, Callari G, Gammino M, et al. The relapse rate of multiple sclerosis changes during pregnancy: a cohort study. *Acta Neurol Scand.* 2004; 110(1): 23–26.
13. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol.* 2016; 80(1): 89–100.
14. Voskuhl R, Momtazee C. Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding. *Neurotherapeutics.* 2017; 14(4): 974–984.
15. Smets I, Van Deun L, Bohyn C, et al. Corticosteroids in the management of acute multiple sclerosis exacerbations. *Acta Neurol Belg.* 2017; 117(3): 623–633.
16. Otero-Romero S, Sastre-Garriga J, Comi G, et al. Pharmacological management of spasticity in multiple sclerosis: Systematic review and consensus paper. *Mult Scler.* 2016; 22(11): 1386–1396.
17. Gold R, Oreja-Guevara C. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. *Expert Rev Neurother.* 2013; 13(12 Suppl): 55–59.
18. Generali JA, Cada DJ. Amantadine: multiple sclerosis-related fatigue. *Hosp Pharm.* 2014; 49(8): 710–712.
19. Zonić-Imamović M, Imamović S, Čičkušić A, et al. Effects of Treating an Overactive Urinary Bladder in Patients with Multiple Sclerosis. *Acta Med Acad.* 2019; 48(3): 271–277.
20. Amato MP, Portacio E. Fertility, pregnancy and childbirth in patients with multiple sclerosis: impact of disease-modifying drugs. *CNS Drugs.* 2015; 29(3): 207–220.
21. Levin S, Rimmer K, Vargas WS. Neuroimmunologic disorders in pregnancy. *Handb Clin Neurol.* 2020; 172: 105–123.
22. Batista S, Martins da Silva A, Sá MJ, et al. Recomendações sobre a Abordagem da Esclerose Múltipla na Gravidez, Parto e Pós-Parto: Posição de Consenso do Grupo de Estudos de Esclerose Múltipla [Recommendations about Multiple Sclerosis Management during Pregnancy, Partum and Post-Partum: Consensus Position of the Portuguese Multiple Sclerosis Study Group]. *Acta Med Port.* 2020; 33(9): 611–621.
23. Houtchens MK, Kolb CM. Multiple sclerosis and pregnancy: therapeutic considerations. *Journal of Neurology.* 2013; 260(5): 1202–1214.
24. Thiel S, Langer-Gould A, Rockhoff M, et al. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis-A prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. *Multiple Sclerosis.* 2016; 22(6): 801–809.
25. Coyle PK, Sinclair SM, Scheuerle AE, et al. Final results from the Betaseron (interferon β -1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events. *BMJ Open.* 2014; 4(5).
26. Gold R, Philips JT, Havrdova E, et al. Delayed-Release Dimethyl Fumarate and Pregnancy: Preclinical Studies and Pregnancy Outcomes from Clinical Trials and Postmarketing Experience. *Neurol Ther.* 2015; 4(2): 93–104.
27. Friend S, Richmann S, Bloomgren G, et al. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. *BMC Neurol.* 2016; 16(1): 150.
28. Varytė G, Zakarevičienė J, Ramašauskaitė D, et al. Pregnancy and Multiple Sclerosis: An Update on the Disease Modifying Treatment Strategy and a Review of Pregnancy's Impact on Disease Activity. *Medicina (Kaunas).* 2020; 56(2): 49.
29. Haghikia A, Langer-Gould A, Rellensmann G, et al. Natalizumab use during the third trimester of pregnancy. *JAMA Neurol.* 2014; 71: 891–895.
30. Alroughani R, Altintas A, Al Jumah M, et al. Pregnancy and the Use of Disease-Modifying Therapies in Patients with Multiple Sclerosis: Benefits versus Risks. *Multiple Sclerosis International.* 2016.
31. Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. *Neurol Ther.* 2014; 3(2): 133–138.