Neuroendocrinology Letters Volume 42 No. 4 2021
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Fatigue as the limiting factor for vaginal birth in patients with multiple sclerosis

Kamil Biringer[1], Štefan Sivák[2], Jana Siváková[1], Róbert Ružiňák[2], Martina Martiníková[3], Ema Kantorová[2], Zuzana Biringerová[4], Erik Kúdela[1], Egon Kurča[2]

1 Dpt. of Gynecology and Obstetrics, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovak Republic, European Union
2 Dpt. of Neurology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovak Republic, European Union
3 Second Dpt. of Neurology, Slovak Medical University, F. D. Roosevelt Faculty Hospital, Banská Bystrica, European Union
4 Dpt. of Anesthesiology and Intensive Medicine, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovak Republic, European Union

Correspondence to: Štefan Sivák, Assoc. prof., M.D., Ph.D.,
Dpt. of Neurology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovak Republic, European Union, Kollarova 2, 036 01 Martin
TEL.: 043/4203 209; E-MAIL: stefan.sivak@jfmed.uniba.sk

Submitted: 2021-05-17 Accepted: 2021-07-05 Published online: 2021-07-05

Key words: **Multiple sclerosis; Pregnancy; Fatigue; Childbirth; Caesarean section**

Neuroendocrinol Lett 2021; **42**(4):222–228 **PMID:** 34436842 NEL420421A02 © 2021 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease. This study evaluated pregnancy-related issues in patients with MS in one perinatological centre.
MATERIAL AND METHODS: A single-centre, retrospective study of the perinatal period in patients with MS admitted at the Dpt. of Gynaecology and Obstetrics, Jessenius Faculty of Medicine, Comenius University and the University Hospital in Martin, Slovak Republic, European Union from January 1, 2015 to December 1, 2020 was performed. Selected parameters from personal, obstetric, and neurological histories were analysed.
RESULTS: A cohort of 15 patients (32.5±5.3 years) with a relapsing-remitting form of MS gave birth to 16 children. The mean length of MS at the time of delivery was 9±3.6 years. The severity of the Expanded Disability Status Scale score was 2.0±1.5. Caesarean section (CS) was indicated in 14 deliveries (87.5%). It was elective CS in 10 patients. The most common indication for elective CS was a combination of significant chronic fatigue syndrome and neurological deficit (paresis).
CONCLUSIONS: The basis for the management of pregnancy, childbirth, and the postpartum period in women with MS is a planned pregnancy based on close cooperation among patients, gynaecologists, and neurologists. Vaginal delivery is not primarily contraindicated. Indications for CS should be considered individually. One way to minimise the indications for CS is a more accurate diagnosis and personalised treatment of fatigue in pregnant women with MS. Presumably, both obstetricians and neurologists prefer vaginal delivery as the first choice in patients with fatigue syndrome.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the brain and spinal cord, in which the nerve cells themselves, their axons, and myelin are gradually damaged. The prevalence of MS is 100–130 in 100,000 inhabitants in the Slovak Republic. Women of childbearing potential are the most frequently affected group, as the disease affects approximately three times more women than men with the first symptoms of the disease at the age of 20–40 years (Trojano *et al.* 2012; Hanulíková & Mardešić, 2019). Pregnancy has not been recommended in the past. However, The Pregnancy in Multiple Sclerosis Study published in 1998 confirmed the reduction of MS relapses by up to 70% during pregnancy, with a maximum in the third trimester. In the first three postpartum months, the number of relapses increases (Confavreux *et al.* 1998). Studies have shown that pregnancy is not a long-term risk factor for the worsening overall course of MS (D'hooghe *et al.* 2010). Some studies suggest a possible protective effect of pregnancy and lactation on a more favourable disease course (Pakpoor *et al.* 2012; Ponsonby *et al.* 2012; Vukusic *et al.* 2021).

In our work, pregnancy-related issues in patients with MS were evaluated at one perinatological centre in the Slovak Republic, the European Union, focusing on fatigue syndrome as the main indication for caesarean section (CS).

MATERIALS AND METHODS

The medical records of patients diagnosed with MS were retrospectively studied, focusing on the perinatal period of patients who were hospitalised at our department from January 1, 2015 to December 1, 2020. Descriptive statistics were used to describe the cohort. In patients, selected parameters from personal, obstetric, and neurological histories were monitored. The severity of neurological impairment using the Expanded Disability Status Scale (EDSS) was assessed (Kurtzke, 1983). CS urgency was classified according to the Royal College of Obstetricians and Gynaecologists (2010).

RESULTS

From January 1, 2015 to December 1, 2020, 15 patients gave birth to 16 children with diagnosed MS (Table 1). The mean age of the patients at the time of delivery was 32.5±5.3 years. All patients had a relapsing-remitting form of the disease (RRMS). The mean length of MS at the time of delivery was 9±3.6 years. The EDSS score was 2.0±1.5, which in most cases represents a mild degree of disability (Table 2). Three patients (No. 3, 9, 13) suffered from more severe neurological deficits with EDSS scores of 4.5, 5, and 5.5, respectively, and predominant paraparetic-ataxic gait, severe fatigue syndrome, and the inability to walk for more than 500 meters.

As recommended at that time, discontinuation of disease-modifying treatment (DMT) at a defined time before pregnancy was indicated. Patients received pre-conceptual glatiramer acetate (n=4), interferon β-1a (n=3), natalizumab (n=2), fingolimod (n=2), and interferon β-1b (n=1). Four patients were without DMT due to a stable long-term neurological status (no. 10, 11, 12, and 14). In two patients, three pregnancies were unplanned, and treatment was discontinued only after the diagnosis of ongoing pregnancy (no. 1a, 1b, and 9). These were patients with DMT using glatiramer acetate (no. 1a and 1b) and natalizumab (no. 9). In all three pregnancies, the course of pregnancy was physiological, no relapse of the disease was observed, and pregnancy was terminated by CS due to primary neurological indication. The newborns were healthy (Tables 1 and 2).

A relapse of the disease was observed during pregnancy in two cases (no. 3 and 4).

Of the 16 births, only one mother gave birth spontaneously physiologically (no. 4), and one by forceps for vaginal delivery (no. 7). CS was performed on the remaining 14 cases (87.5%). CS was indicated in 10 patients (no. 1, 2, 3, 5, 6, 9, 10, 12, 13, 14) as elective CS due to primary neurological indication in the underlying disease. The most common reason for elective CS was a combination of significant chronic fatigue syndrome and neurological deficit (paresis) in the underlying disease. In one patient (no. 8), CS was indicated due to primary gynaecological indication for a cephalopelvic disproportion. In three patients (no. 1, 11, 15), CS was emergent for threatened foetal hypoxia.

Due to a higher risk of disease progression during the postpartum period, eight patients were preventively indicated for bolus intravenous immunoglobulin (IVIG) treatment as a single dose of 10–15 mg IVIG on the fourth postpartum day or at a higher risk of relapse repeatedly after one month (1–2 times). This treatment was generally well tolerated.

DISCUSSION

Mode of delivery

In the group of 15 MS patients with 16 births, CS was performed in 87.5% of cases. In 10 births (62.5%), CS was indicated as elective due to primary neurological indication.

When evaluating large cohorts of mothers diagnosed with MS, the CS rate was between 9.6 and 42.4% (Finkelsztejn *et al.* 2011; Kelly *et al.* 2009). In our study, an even higher number of CSs (87.5%) were found compared to the results from the above-mentioned studies. This could be explained by the low number of patients in our cohort and by the fact that in our perinatological centre, the selected population of mothers with presumed complications preferred childbirth. Presumably, a wide variation of CS rates could be

Tab. 1. Demographic parameters and mode of delivery in patients with MS

No.	Age (years)	Pregnancy/ Parity	GW	Mode of delivery*	EDSS	Indication for operative delivery	BW/BL (g/ cm)	AS
1a	30	1/0	42	CS 1	2	Signs of foetal hypoxia	3910/52	9/9
1b	32	2/1	38	CS 4	2	Severe fatigue syndrome; previous CS	3200/50	9/9
2	31	1/0	40	CS 4	2	Severe fatigue syndrome	3730/53	9/10
3	38	1/0	36	CS 4	5.5	MS relapse—left sensorimotor hemisyndrome, passes 100 m without help, severe fatigue syndrome	3000/51	7/7
4	33	2/1	38	Spontaneous vaginal	2		3830/53	9/9
5	30	4/2	38	CS 4	2.5	Severe fatigue syndrome, quadriparesis, exacerbated sacralgia	3200/51	9/9
6	32	1/0	39	CS 4	1	Severe fatigue syndrome	3530/52	9/9
7	34	1/0	41	Forceps	3		3480/52	9/9
8	29	1/0	40	CS 4	1	Cephalopelvic disproportion	3040/50	9/9
9	31	2/1	40	CS 4	5	Severe fatigue syndrome, paraparesis of the lower extremities	2810/50	9/9
10	34	3/1	39	CS 4	1	Severe fatigue syndrome; pPROM, foetal breech presentation, uterus subseptus	3300/52	9/9
11	36	1/0	40	CS 1	2.5	Signs of foetal hypoxia; PROM	2900/48	10/10
12	38	3/2	40	CS 4	4	Severe fatigue syndrome	3260/51	5/8
13	41	2/1	38	CS 4	4.5	Severe fatigue syndrome, paraparesis of the lower extremities	3720/53	9/9
14	50	3/0	36	CS 4	1	Severe fatigue syndrome, pPROM, IVF+ET in patient history, previous laparoscopic myomectomy	2560/48	9/9
15	32	2/0	36	CS 1	2	Signs of foetal hypoxia	2170/43	9/9

Legend: No.—patient number, GW—week of gestation, EDSS—Expanded Disability Status Scale, BW/BL—birth weight/birth length, AS—Apgar score in 1st and 5th minute, CS—caesarean section, MS—multiple sclerosis, pPROM—preterm premature rupture of membranes, PROM—premature rupture of membranes, IVF+ET—in vitro fertilisation and embryo transfer; *—caesarean section urgency according to RCOG 2010

caused by local habits and rules (10). Patients diagnosed with MS are more likely to give birth by CS compared to the control group of healthy women (Finkelsztejn *et al.* 2011; Kelly *et al.* 2009). The presence or absence of MS should not influence decisions about the mode of delivery or anaesthesia (Dobson *et al.* 2019), which is not always accepted in practice. De Giglio *et al.* (2020) found that in patients diagnosed with MS before pregnancy, acute or elective CS were indicated significantly more often than in healthy controls. This difference in the mode of delivery was not present in mothers with MS confirmed after delivery. MS itself is often subjectively perceived as a risk factor for pregnancy and childbirth.

In addition to obstetric indications, clinical neurological status should be considered when deciding labour management (Dobson *et al.* 2019; Kalinowska *et al.* 2020). The most common reasons for CS in our study were severe fatigue syndrome and significant neurological deficit. Fatigue is considered one of the leading causes of the deteriorating quality of life in patients with MS, regardless of depression or disability (Krupp *et al.* 1988). It is also one of the most common symptoms reported by at least 75% of patients with MS at some point in the disease (Krupp, 2006; Lerdal *et al.* 2007). Standard definitions of fatigue include feeling exhausted or a subjective lack of physical or mental energy interfering with normal or desired activities. However, these terms can be interpreted differently, depending on the cultural or educational environment. Ambiguity also arises from the fact that there is no gold standard by which fatigue can be measured and quantified (Braley & Chervin, 2010). Therefore, fatigue is a controversial indication of CS and should be assessed by an interdisciplinary approach, considering factors other than obstetric factors. In our cohort, significant fatigue was an indication for elective CS in 66.7% of cases (Table 1).

Fatigue syndrome in MS is considered a multidimensional symptom and manifests in several dimensions, such as physical, cognitive, and psychosocial fatigue (Beckerman *et al.* 2020). Separating treatable

Tab. 2. Neurological status and treatment in patients with MS

No.	MS duration (years)	Neurological status	DMT before pregnancy	DMT during pregnancy	Relapse during pregnancy	Postpartum care
1a	6	Left-sided hyperreflexia, mild ocular motor dysfunction, chronic fatigue syndrome	INFβ-1a	At the beginning, discontinuation after confirmed pregnancy	0	IVIG, DMT
1b	8	Mild postural instability, chronic fatigue syndrome	INFβ-1a	At the beginning, discontinuation after confirmed pregnancy	0	IVIG, DMT
2	8	Bilateral hyperreflexia, mild central monoparesis of left lower limb, postural instability, chronic fatigue syndrome	Glatiramer acetate	0	0	DMT
3	13	Relapse in the 3rd trimester–mild left-sided sensorimotor hemisyndrome, reduced left eye visual acuity, able to walk without aid or rest for 100 m only, general weakness, chronic fatigue syndrome	Natalizumab	0	3rd trimester–worsening of left-sided sensorimotor hemisyndrome, reduced left eye visual acuity, able to walk without aid or rest for 100 m only, general weakness, chronic fatigue syndrome (methylprednisolone, subsequent improvement)	MS relapse after childbirth–right-sided hemiparesis–IVIG + methylprednisolone + DMT
4	2	Left-sided hemiparesis, mild postural instability, physically and mentally well composed	Glatiramer acetate	0	2nd trimester–mild upper limb paraparesis with spontaneous improvement	IVIG, relapse in the 2nd month after childbirth–sensory relapse (lower limb paraesthesia) – IVIG, DMT
5	13	Gait ataxia, left hand hypoesthesia, right lower limb hypoaesthesia, chronic fatigue syndrome	INFβ-1b	0	0	IVIG, DMT

causes from non-treatable causes of fatigue can be challenging. When treatable causes are not appropriately managed, it can significantly worsen maternal overall status. However, adequate diagnosis and preventive and personalised treatment of fatigue syndrome during pregnancy could positively improve women's quality of life. At the same time, it will make it possible to avoid CS and minimise the negative consequences of CS for the mother and child with the improvement of women's quality of life in the postpartum period. Because of new findings and recommendations on MS, we presumed that both obstetricians and neurologists prefer vaginal delivery as the method of the first choice in patients with fatigue syndrome. This would reduce the total number of CSs and the number of CSs in category 4, according to RCOG. At the same time, it can be assumed that there could be only a slight increase in CS in category 2. This aim could be achieved by more accurate diagnosis and targeted treatment of fatigue syndrome.

Acute treatment of disease relapses during pregnancy

Disease relapse was observed in two patients (no. 3 and 4) during pregnancy. Patient no. 4 developed mild upper limb paraparesis in the second trimester, which resolved after several days without treatment. Reduced left eye visual acuity, general weakness, mild left-sided sensorimotor hemisyndrome, and the inability to walk for more than 100 meters appeared in patient no. 3 in the third trimester. The patient was treated with an intravenous bolus of methylprednisolone with a gradual improvement in neurological deficit. A new disease relapse with similar neurological symptoms presented in the first days after a planned uncomplicated caesarean delivery in the 36th week of pregnancy. Again, the patient was treated with a bolus of methylprednisolone followed by an IVIG bolus intravenously with a subsequent complete improvement of neurological deficit. An early restart of DMT with natalizumab was planned. The patient had a moderate

No.	MS duration (years)	Neurological status	DMT before pregnancy	DMT during pregnancy	Relapse during pregnancy	Postpartum care
6	9	Asymmetry of deep tendon reflexes, chronic fatigue syndrome	Glatiramer acetate	0	0	DMT
7	9	Postural instability, gait ataxia, urinary retention	Glatiramer acetate	0	0	DMT
8	4	Bilateral Babinski sign	Fingolimod	0	0	IVIG, DMT
9	11	Spastic quadriparesis, paraparetic-ataxic gait, able to walk for about 300 m using a cane, chronic fatigue syndrome	Natalizumab	Natalizumab once at the beginning, discontinuation after confirmed pregnancy	0	IVIG, DMT
10	12	Babinski sign, chronic fatigue syndrome	0	0	0	0
11	12	Left-sided hypoesthesia, postural instability, mild ataxic gait	0	0	0	0
12	9	Mild postural instability, able to walk for about 600–700 m, chronic fatigue syndrome	0	0	0	0
13	13	Lower limb central paraparesis, able to walk for 200 m, right lower limb hypoesthesia, chronic fatigue syndrome	Fingolimod	0	0	IVIG, in the 2nd month after childbirth–risk of relapse–worsening of gait and lower limb paraesthesia for 48 hours, DMT
14	6	Babinski sign, chronic fatigue syndrome	0	0	0	0
15	3	Asymmetry of deep tendon reflexes, Bilateral Babinski sign	INFβ-1a	0	0	IVIG, DMT, confirmed MRI progression

Legend: No.—patient number, MS—multiple sclerosis, DMT—Disease Modifying Treatment, INF—interferon, IVIG—intravenous immunoglobulin, MRI—Magnetic resonance imaging

neurological deficit (EDSS 5.5) on long-term natalizumab treatment that had been discontinued before the planned pregnancy. Presumably, recurrent relapses could be caused by the abrupt discontinuation of long-term DMT with natalizumab. This could lead to the so-called rebound effect with repeated relapses of neurological deficit. Standard treatment of disease relapses during pregnancy consists of intravenous administration of methylprednisolone up to a dose of 1 gram over 3–5 days. Non-fluorinated glucocorticoids, such as prednisone or methylprednisolone, cross the placenta only to a limited extent. They are metabolised mainly by placental 11-beta-hydroxysteroid dehydrogenase, leading to low foetal blood levels and safe use in the second and third trimesters. If possible, they should be avoided during the first trimester due to a slightly increased risk of orofacial foetal defects and low birth weight (Kalinowska *et al.* 2020; Park-Wyllie *et al.* 2000). Fluorinated glucocorticoids, such as betamethasone and dexamethasone, are not recommended in treating MS relapses due to their good placental transition and relatively high concentrations in foetal blood. Their safe short-term administration is indicated, for example, in an acceleration of lung maturation in preterm births (Kalinowska *et al.* 2020; McGoldrick *et al.* 2020). In treating severe disease relapses that are not responding to corticoid therapy, the administration of IVIG is recommended and considered safe during pregnancy (Kaplan, 2019; Zapletalová, 2014).

Long-term DMT

Planned parenthood is generally recommended for patients with MS, which requires the patient's cooperation with a gynaecologist and neurologist. The neurologist directs the MS treatment and identifies a clinically stable disease period for the planned pregnancy, ideally a year without relapse. The role of the gynaecologist is

to plan and time fertilisation (Hanulíková & Mardešić, 2019; Van Der Walt *et al.* 2019).

However, approximately 40% of pregnancies in MS patients are unplanned and at risk of exposure to chronic DMT during the most vulnerable weeks at the beginning of pregnancy (Fragoso *et al.* 2013). There were 13 planned and 3 unplanned pregnancies in our cohort. Two pregnant patients took glatiramer acetate (no. 1a and 1b) and natalizumab (no. 9) unintentionally during the first trimester. In both patients, the treatment was discontinued immediately after the pregnancy was determined according to the then valid recommendations (Zapletalová, 2014). No complications of this therapy were noticed during pregnancy or in the postpartum period, including newborns' health status. Currently, both drugs can be used during pregnancy in indicated cases. Glatiramer acetate can be administered during pregnancy according to the recommendations of the 2018 European Academy of Neurology (EAN) and European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). In September 2019, the European Medicines Agency approved the administration of interferon β during pregnancy and lactation in a group of SM patients with an increased risk of relapse (Andersen & Magyari, 2020; Zanghi *et al.* 2020). According to EAN / ECTRIMS recommendations, it is recommended to delay pregnancy until a more stable period in patients with persistently high disease activity. If the patient still decides to become pregnant or has an unplanned pregnancy, treatment with the more effective DMT monoclonal antibody natalizumab should be considered (Montalban *et al.* 2018). The benefit of continuing natalizumab during the entire pregnancy may outweigh the risk of recurring disease activity, particularly in women with highly active MS. (Canibano *et al.* 2020) Treatment is not associated with impaired female fertility, embryofoetal development, or changes in pregnancy. However, approximately 75% of neonates exposed to natalizumab after week 30 of gestation experienced mild to moderate haematological changes, such as thrombocytopenia and anaemia. Therefore, in highly active MS forms, its use in a reduced dose can be considered until the 30th week of pregnancy to monitor for possible blood abnormalities and subsequent complications in neonates (Haghikia *et al.* 2014). An early restart of natalizumab therapy after delivery is recommended due to the risk of a rebound effect (Dobson *et al.* 2019). Similarly, in MS patients treated with natalizumab for a long time and planning a pregnancy, the risk of disease relapse after abrupt treatment discontinuation (so-called rebound effect) should be considered. The rebound effect is usually described 12–16 weeks after drug cessation (Portaccio *et al.* 2018). In our cohort, two patients received chronic natalizumab treatment. According to the recommendations of that time, the treatment was discontinued before the attempt to conceive. Two disease relapses occurred in the third trimester and postpartum and were successfully treated with a bolus of methylprednisolone and IVIG in patient no.3. For other medicines used in DMT, concomitant use of effective contraception and discontinuation at the indicated time before a planned pregnancy is recommended due to unknown or insufficient safety. (Andersen & Magyari, 2020)

CONCLUSIONS

Over the last 20 years, the approach to pregnancy in patients with MS of childbearing age has positively changed. The basis is a planned pregnancy based on the close cooperation of the patient, gynaecologist, and neurologist. Vaginal delivery is not primarily contraindicated. Indications for CS should be considered individually from a neurological and obstetric point of view. To minimise the neurological indications of CS, a more accurate diagnosis and preventive and personalised treatment of fatigue in pregnant women with MS is recommended.

ACKNOWLEDGEMENT

This study was supported by the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic – VEGA 1/0301/19.

DISCLOSURE STATEMENT

The authors declare that they have no financial or nonfinancial conflicts to declare.

REFERENCES

1 Andersen JB, Magyari M (2020). Pharmacotherapeutic considerations in women with multiple sclerosis. Expert Opin Pharmacother. **21**(13): 1591–1602.
2 Beckerman H, Eijssen IC, van Meeteren J, Verhulsdonck MC, de Groot V (2020). Fatigue Profles in Patients with Multiple Sclerosis are Based on Severity of Fatigue and not on Dimensions of Fatigue. Sci Rep. **10**(1): 4167.
3 Braley TJ, Chervin RD (2010). Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. SLEEP. **33**(8): 1061–1067.
4 Canibaño B, Deleu D, Mesraoua B, Melikyan G, Ibrahim F, Hanssens Y (2020). Pregnancy-related issues in women with multiple sclerosis: an evidence-based review with practical recommendations. J Drug Assess. **9**(1): 20–36.
5 Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T (1998). Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. **339**(5): 285–291.
6 De Giglio L, Federici S, Ruggieri S, Borriello G, D'Errico Ma, De Angelis C, et al (2020). Cesarean section in women with MS: A choice or a need? Mult Scler Relat Disord. **38**: 101867.
7 D'hooghe MB, Nagels G, Uitdehaag BM (2010). Long-term effects of childbirth in MS. J Neurol Neurosurg Psychiatry. **81**(1): 38–41.
8 Dobson R, Dassan P, Roberts M, Giovannoni G, Nelson-Piercy C, Brex PA (2019). UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. Pract Neurol. **19**(2): 106–114.

9 Finkelsztejn A, Brooks JB, Paschoal FM Jr, Fragoso YD (2011). What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. BJOG. **118**(7): 790–797.

10 Fragoso YD, Adoni T, Alves-Leon SV, Azambuja ND Jr, Barreira AA, Brooks JB, et al (2013). Long-term effects of exposure to disease-modifying drugs in the offspring of mothers with multiple sclerosis: a retrospective chart review. CNS Drugs. **27**(11): 955–961.

11 Haghikia A, Langer-Gould A, Rellensmann G, Schneider H, Tenenbaum T, Elias-Hamp B, et al (2014). Natalizumab use during the third trimester of pregnancy. JAMA Neurol. **71**(7): 891–895.

12 Hanulíková P, Mardešić T (2019). Roztroušená skleróza a těhotenství z pohledu gynekologa – možnosti asistované reprodukce. [(Multiple sclerosis and pregnancy from a gynecologist's perspective – assisted reproduction options.) (In Czech with English abstract.)] Cesk Slov Neurol N. **82/115**(2): 155–159.

13 Kalinowska A, Kułakowska A, Adamczyk-Sowa M, Czajkowski K, Kurowska K, Pietrzak B, et al (2020). Recommendations for neurological, obstetrical and gynaecological care in women with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. Neurol Neurochir Pol. **54**(2): 125–137.

14 Kaplan TB (2019). Management of Demyelinating Disorders in Pregnancy. Neurol Clin. **37**(1): 17–30.

15 Kelly VM, Nelson LM, Chakravarty EF (2009). Obstetric outcomes in women with multiple sclerosis and epilepsy. Neurology. **73**(22): 1831–1836.

16 Krupp L (2006). Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult Scler. **12**: 367–368.

17 Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC (1988). Fatigue in multiple sclerosis. Arch Neurol. **45**: 435–437.

18 Kurtzke JF (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. **33**(11): 1444–1452.

19 Lerdal A, Celius EG, Krupp L, Dahl AA (2007). A prospective study of patterns of fatigue in multiple sclerosis. Eur J Neurol. **14**: 1338–1343.

20 McGoldrick E, Stewart F, Parker R, Dalziel SR (2020). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews. **12**, CD004454.

21 Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al (2018). ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. **24**(2): 96–120.

22 Pakpoor J, Disanto G, Lacey MV, Hellwig K, Giovannoni G, Ramagopalan SV (2012). Breastfeeding and multiple sclerosis relapses: a meta-analysis. J Neurol. **259**(10): 2246–2248.

23 Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al (2000). Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. **62**(6): 385–392.

24 Ponsonby AL, Lucas RM, van der Mei IA, Dear K, Valery PC, Pender MP, et al (2012). Offspring number, pregnancy, and risk of a first clinical demyelinating event: the AusImmune Study. Neurology. **78**(12): 867–874.

25 Portaccio E, Moiola L, Martinelli V, Annovazzi P, Ghezzi A, Zaffaroni M, et al (2018). Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: II: Maternal risks. Neurology. **90**(10): e832–e839.

26 Royal College of Obstetricians and Gynaecologists. Classification of Urgency of Caesarean Section – a Continuum of Risk (2010). Good Practice No. **11**: 1–4. https://www.rcog.org.uk/globalassets/documents/guidelines/goodpractice11classificationofurgency.pdf

27 Trojano M, Lucchese G, Graziano G, Taylor BV, Simpson S Jr, Lepore V, et al (2012). Geographical variations in sex ratio trends over time in multiple sclerosis. PLoS One. **7**(10): e48078.

28 Van Der Walt A, Nguyen AL, Jokubaitis V (2019). Family planning, antenatal and post partum care in multiple sclerosis: a review and update. Med J Aust. **211**(5): 230–236.

29 Vukusic S, Michel L, Leguy S, Lebrun-Frenay C (2021). Pregnancy with multiple sclerosis. Rev Neurol (Paris). **177**(3): 180–194.

30 Zanghì A, D'Amico E, Callari G, Chisari CG, Borriello G, Grimaldi LME, et al (2020). Pregnancy and the Postpartum Period in Women With Relapsing-Remitting Multiple Sclerosis Treated With Old and New Disease-Modifying Treatments: A Real-World Multicenter Experience. Front Neurol. **11**: 105.

31 Zapletalová O (2014). Roztroušená skleróza a těhotenství. [(Multiple sclerosis and pregnancy.) (In Czech with English abstract.)] Neurol Praxi. **15**(4): 197–201.